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Autologous hematopoietic stem cell transplantation following high dose chemotherapy for non-rhabdomyosarcoma soft tissue sarcomas

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ABSTRACT

Background

Soft tissue sarcomas (STS) are a highly heterogeneous group of rare malignant solid tumors. Non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) comprise all STS except rhabdomyosarcoma. In patients with advanced local or metastatic disease, autologous hematopoietic stem cell transplantation (HSCT) applied after high-dose chemotherapy (HDCT) is a planned rescue therapy for HDCT-related severe hematologic toxicity. The rationale for this update is to determine whether any randomized controlled trials (RCTs) have been conducted and to clarify whether HDCT followed by autologous HSCT has a survival advantage.

Objectives

To assess the effectiveness and safety of HDCT followed by autologous HSCT for all stages of non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) in children and adults.

Search methods

For this update we modified the search strategy to improve the precision and reduce the number of irrelevant hits. All studies included in the original review were considered for re-evaluation in the update. We searched the electronic databases CENTRAL (2012, Issue 11) in *The Cochrane Library*, MEDLINE and EMBASE (05 December 2012) from their inception using the newly developed search strategy. Online trials registers and reference lists of systematic reviews were searched.

Selection criteria

Terms representing STS and autologous HSCT were required in the title or abstract. In studies with aggregated data, participants with NRSTS and autologous HSCT had to constitute at least 80% of the data. Single-arm studies were included in addition to studies with a control arm because the number of comparative studies was expected to be very low.

Data collection and analysis

Two review authors independently extracted study data. Some studies identified in the original review were re-examined and found not to meet the inclusion criteria and were excluded in this update. For studies with no comparator group, we synthesized the results for studies reporting aggregate data and conducted a pooled analysis of individual participant data using the Kaplan-Meier method. The primary outcomes were overall survival (OS) and treatment-related mortality (TRM).

Main results

The selection process was carried out from the start of the search dates for the update. We included 57 studies, from 260 full text articles screened, reporting on 275 participants that were allocated to HDCT followed by autologous HSCT. All studies were not comparable due to various subtypes. We identified a single comparative study, an RCT comparing HDCT followed by autologous HSCT versus standard chemotherapy (SDCT). The overall survival (OS) at three years was 32.7% versus 49.4% with a hazard ratio (HR) of 1.26 (95% confidence interval (CI) 0.70 to 2.29, P value 0.44) and thus not significantly different between the treatment groups. In a subgroup of patients that had a complete response before treatment, OS was higher in both treatment groups and OS at three years was 42.8% versus 83.9% with a HR of 2.92 (95% CI 1.1 to 7.6, P value 0.028) and thus was statistically significantly better in the SDCT group. We did not identify any other comparative studies. We included six single-arm studies reporting aggregate data of cases; three reported the OS at two years as 20%, 48%, and 51.4%. One other study reported the OS at three years as 40% and one further study reported a median OS of 13 months (range 3 to 19 months). In two of the single-arm studies with aggregate data, subgroup analysis showed a better OS in patients with versus without a complete response before treatment. In a survival analysis of pooled individual data of 80 participants, OS at two years was estimated as 50.6% (95% CI 38.7 to 62.5) and at three years as 36.7% (95% CI 24.4 to 49.0). Data on TRM, secondary neoplasia and severe toxicity grade 3 to 4 after transplantation were sparse. The one included RCT had a low risk of bias and the remaining 56 studies had a high risk of bias.

Authors' conclusions

A single RCT with a low risk of bias shows that OS after HDCT followed by autologous HSCT is not statistically significantly different from standard-dose chemotherapy. Therefore, HDCT followed by autologous HSCT for patients with NRSTS may not improve the survival of patients and should only be used within controlled trials if ever considered.

PLAIN LANGUAGE SUMMARY

High-dose chemotherapy followed by autologous hematopoietic stem cell transplantation for non-rhabdomyosarcoma soft tissue sarcomas

Review question

We reviewed the evidence about the effect of high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation compared to standard-dose chemotherapy on overall survival in people with non-rhabdomyosarcoma soft tissue sarcomas. We found one randomized controlled trial (RCT) comparing both treatments and 48 studies with results from transplantation only.

Background

Non-rhabdomyosarcoma soft tissue sarcomas are a group of rare cancers. People with inoperable or metastatic disease have a poor prognosis. It was believed that higher doses of chemotherapy might improve patients' survival. However, high doses of chemotherapy stop the production of blood cells in the bone marrow and are not compatible with life. Stem cells collected from people before high-dose chemotherapy can be transplanted back to the patient if the blood cell count gets too low. Due to a lack of research studies, it has not been proven that patients treated with this procedure live any longer than patients treated with standard chemotherapy. We wanted to determine whether using high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation was better or worse than standard-dose chemotherapy.

Study characteristics

The evidence is current to 5 December 2012. The single RCT that was identified compared 38 patients in the transplantation group versus 45 patients in the chemotherapy only group and was judged to have a low risk of bias (high methodological quality). The participants were 18 to 65 years old, had various types of non-rhabdomyosarcoma soft tissue sarcomas and were observed for a median follow-up time of 55 months. The rest of the studies reported results for a series of or individual transplanted patients only, with various

ages, tumor types and follow up times; they all had a high risk of bias. The treatment period among studies ranged from 1994 to 2008. The single RCT and some of the other studies were funded by non-profit organizations. Three studies reported financial support by biopharmaceutical companies. Most studies did not give details of funding.

Key results

In the single RCT, the overall survival (OS) at three years was 32.7% in the transplantation group versus 49.4% in the chemotherapy only group, and this was not found to be significant. There was one case of treatment-related mortality in the transplantation group and none in the chemotherapy only group.

Quality of evidence

The overall quality of the data was based on a single RCT, which had a low risk of bias. The rest of the studies had a high risk of bias due to single-arm and retrospective study design and were not useful for comparing two treatments. Currently the research evidence indicates that patients with non-rhabdomyosarcoma soft tissue sarcomas should not be treated with high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation. If this treatment is offered it should be done only within clinical controlled trials and after careful consideration.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [\[Explanation\]](#)

Autologous hematopoietic stem cell transplantation following high-dose chemotherapy for non-rhabdomyosarcoma soft tissue sarcoma						
Patient or population: patients with non-rhabdomyosarcoma soft tissue sarcoma Settings: Spezialized hospital Intervention: Autologous hematopoietic stem cell transplantation following high-dose chemotherapy Comparison: standard-dose chemotherapy						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard-dose chemotherapy	Autologous hematopoietic stem cell transplantation following high-dose chemotherapy				
Overall survival Follow-up: median 55 months	489 per 1000	571 per 1000 (375 to 785)	HR 1.26 (0.7 to 2.29)	83 (1 study)	⊕⊕⊕⊕ high	
Progression-free survival Follow-up: median 55 months	756 per 1000	849 per 1000 (681 to 955)	HR 1.34 (0.81 to 2.2)	83 (1 study)	⊕⊕⊕⊕ high	
Treatment-related mortality	See comment	See comment	Not estimable	163 (12 studies ¹)	⊕○○○ very low	case series; 15 events in 0 subjects
Health-related quality of life	See comment	See comment	Not estimable	-	See comment	not reported
Disease-free survival Follow-up: 3 years	See comment	See comment	Not estimable	0 (1 study ¹)	⊕○○○ very low ¹	case series; 0 events in 0 subjects

Non-hematological toxicity grade 3 to 4	See comment	See comment	Not estimable	105 (9 studies ¹)	⊕○○○ very low ¹	case series; 38 events in 0 subjects
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*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; HR: Hazard ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ case series

BACKGROUND

Description of the condition

Soft tissue sarcomas (STS) are a highly heterogeneous group of rare malignant solid tumors of non-epithelial extraskelatal body tissue and are classified on a histogenetic basis (Enzinger 2001). STS have a significant risk of distant metastasis in addition to the potential for locally destructive growth and recurrence. Non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) comprise all STS except rhabdomyosarcoma, which primarily affects children and young adults. In this review we investigated NRSTS which are categorized as malignant according to the World Health Organization (WHO) 2002 classification (Fletcher 2002) as adopted by the European Society for Medical Oncology (ESMO) Guidelines Working Group (ESMO 2012). This latter classification excludes the Ewing family of tumors (EFT).

NRSTS usually originate *de novo* and rarely from benign tumors. In most cases the pathogenesis is unknown; however, some factors have been found to be associated with the development of NRSTS (Enzinger 2001). These include exposure to ionizing radiation, environmental carcinogenic substances, oncogenic viruses and immunologic factors. Genetic factors can also play a role since some inherited diseases such as neurofibromatosis type 1 are associated with a higher risk of NRSTS (Tsao 2000).

In Western countries about four new cases of NRSTS are estimated per 100,000 population every year (ESMO 2012), with rhabdomyosarcoma and the Ewing family of tumors excluded from this statistic. STS constitute about 1% of malignancies in adults and 7% in children (NCI 2009a). Rhabdomyosarcoma represents about 50% of STS in children (Gurney 1997; Miller 1995). NRSTS are rare in both children and adults and the distribution of NRSTS differs significantly between children and adults (Table 1) according to Spunt 2006.

Based on the Surveillance, Epidemiology and End Results (SEER) cancer statistics review (1975 to 2007) of the National Cancer Institute (NCI), in the US 10,520 new cases and 3920 deaths from STS were estimated for the year 2010 (NCI 2010a). Separate data were not available for rhabdomyosarcoma and NRSTS. The distribution of STS increased with age according to SEER data from 2001 to 2005. Of all STS cases, 10.3% were in children and young adults less than 20 years of age (NCI 2008a). The median age at diagnosis of STS, including tumors of the heart, was 57 years (NCI 2008b).

Staging

Disease progression may be dichotomized into the two categories of limited and extensive disease. Limited disease is typically a localized, small-sized, low-grade and operable and accessible tumor that has no regional lymph node involvement and no distant metastases. Extensive disease can also be denoted as advanced disease,

defined as localized, large-sized and high-grade tumor that may not be completely removed by surgery, may be invasive and may have regional lymph node involvement or distant metastases. Both categories differ significantly in terms of prognosis and treatment. Where many patients with limited disease may be cured by surgery, extensive disease is associated with a poor outcome and many patients receive chemotherapy as palliative therapy.

The American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system combines grade, depth and size of the tumor as well as regional lymph node involvement and distant metastases and describes the extent of a cancer's spread from stage 0 to IV (AJCC 2002). A review reported the five-year overall survival (OS) estimates for stage I (low-grade, superficial and deep), II (high-grade, superficial and deep), III (high-grade, large and deep) and IV (any metastasis to lymph nodes or distant sites) as approximately 90%, 70%, 50% and 10% to 20%, respectively; information on treatment was not given (Clark 2005). A multicenter study a total of 2185 participants with advanced STS revealed a median survival of 12 months (Van Glabbeke 1999). In the same study, of the 1922 (26%) eligible participants who responded to chemotherapy the five-year OS was 10%; in univariate analyses the response to chemotherapy was not predicted by the same factors as was OS.

Symptoms

The location of the primary tumor can involve any area of the body. The distribution is 40% lower limb and girdle, 20% upper limb and girdle, 20% abdominal sites, 10% trunk and 10% head and neck (Clark 2005). NRSTS can involve any type of tissue and typically affect muscles, tendons, adipose tissue, blood vessels and joints (Sondak 2001) and commonly present as a painless mass. The symptoms depend on the anatomical site of origin, the size of the mass and other aspects. Retroperitoneal sarcomas are most often asymptomatic, until the mass grows large enough to be clinically obvious or presses on vital organs and causes pain (Dileo 2005).

Patients who relapse or suffer progressive disease after therapy or metastasis are commonly called high-risk patients because these signs are associated with shorter survival time. Spontaneous recovery from NRSTS is unknown.

Description of the intervention

Standard therapy

Surgery is the standard treatment for localized NRSTS (ESMO 2012) and can be curative if distant dissemination is not present (Kotilingam 2006). Chemotherapy is a standard treatment for patients with distant metastasis (ESMO 2012) and is regarded mainly as a palliative treatment for high-risk patients who are characterized by inoperable, locally advanced and metastatic disease.

Doxorubicin, ifosfamide, gemcitabine, dacarbazine, docetaxel and trabectedin are used in monotherapy or in combinations (ESMO 2012). Riedel 2012 provides an overview of current systemic therapies and discusses possible novel therapeutic agents and treatment strategies.

High-dose chemotherapy (HDCT) followed by autologous hematopoietic stem cell transplantation (HSCT)

Autologous hematopoietic stem cell transplantation (HSCT) is defined as the transplantation of stem cells that have been collected previously from bone marrow or peripheral blood of the same person. High-dose chemotherapy (HDCT) uses higher doses of chemotherapeutic agents than are usually applied in standard-dose chemotherapy. HDCT may be tolerated by the patient or it may ablate the patient's bone marrow reserves and create an absolute requirement for stem cell rescue. Instead of HDCT, high-dose radiation therapy may be used to treat NRSTS patients. Autologous HSCT applied after HDCT or high-dose radiation is a planned rescue therapy for HDCT-related severe hematologic toxicity (Banna 2007). Ideally, a mega-therapy regimen should be used consisting of several non-cross resistant agents that have a steep dose-response curve and little extramedullary toxicity (Ladenstein 1997).

HDCT and autologous HSCT are not standard treatment options; they are an experimental approach mainly used to treat high-risk people with an unfavorable prognosis (stage IV with distant metastases). HDCT and autologous HSCT may be used in special cases after careful consideration, usually for patients who respond well to standard chemotherapy according to Response Evaluation Criteria in Solid Tumors (RECIST) (Therasse 2000) criteria (Kasper 2005; Kasper 2007b). Carboplatin, cisplatin, cyclophosphamide, etoposide, ifosfamide, melphalan, mitoxantrone and thiotepa, for example, have been used in HDCT regimens. Independent of the disease status, HDCT and autologous HSCT are hazardous interventions that carry the risk of life-threatening organ failure.

Adverse events

Non-hematological adverse events, such as short-term and long-term organ toxicities, must be considered when using HDCT (Ladenstein 1997). Hematological adverse events as a result of autologous HSCT are usually manageable but life-threatening consequences of pancytopenia. They generally affect all patients and include, for example, graft failure, severe infections and bleeding.

Frequency

Of a total of 20,017 autologous HSCTs that were registered in Europe in the year 2010, by the European Group for Blood and Marrow Transplantation (EBMT), 45 were indicated for STS (Passweg 2012).

How the intervention might work

HDCT followed by autologous HSCT was adopted to treat high-risk patients because it was believed that escalating doses in chemotherapy might increase survival by capturing putatively remnant malignant cells and might overcome resistance to standard-dose chemotherapy (Banna 2007). High-dose chemotherapy may cause severe hematologic and non-hematologic toxicity and autologous HSCT is a planned rescue therapy for the HDCT-related demise of hematopoietic stem cells.

Why it is important to do this review

In the last two decades, from 1986 to 2007, the lack of evidence and need to conduct randomized controlled trials (RCTs) was stated by authors seeking to clarify the relevance of HDCT followed by autologous HSCT in high-risk patients with STS (Blay 2000; Carvajal 2005; Dumontet 1992; Ek 2006; Elias 1998; Kasper 2007a; Ladenstein 1997; Pinkerton 1986; Reichardt 2002; Rosti 2002; Schlemmer 2006; Seeger 1991; Woods 1999). Some authors have warned against the use of HDCT followed by autologous HSCT, indicating the possibility of repositioning of malignant cells (Woods 1999). Others have questioned the use of HDCT with reference to the potential existence of refractory cancer stem cells (Banna 2007; Bonnet 1997; Sanchez-Garcia 2007). The rationale for this review update is to review the latest available evidence and to clarify whether RCTs have been conducted and whether results of any study show evidence of a survival advantage.

OBJECTIVES

To assess the effectiveness and safety of high-dose chemotherapy (HDCT) followed by autologous hematopoietic stem cell transplantation (HDCT) for all stages of non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) in children and adults.

METHODS

Criteria for considering studies for this review

Types of studies

Inclusion criteria

- Randomized controlled trials (RCTs).

Since we expected to find few if any RCTs, non-RCTs were also included as follows.

- Prospective non-randomized controlled trials (denoted quasi-RCTs in the first version), other non-RCTs such as prospective and retrospective cohort studies, case-control studies, phase I and II prospective studies, case series and case reports.

Results from RCTs and controlled clinical trials (CCTs) may provide data for estimation of effects on overall survival (OS) and answer the question: does the intervention provide a significantly better survival than the control and does the quality of the studies fit with the assumption that the intervention is better than the control? Data from non-comparative studies (phase I and II prospective studies, case series and case reports) were collected to estimate treatment-related mortality (TRM) within a cohort of participants. Due to the lack of a control group these studies do not provide data for estimation of treatment effect.

Exclusion criteria

None

Rationale for including non-RCTs

Authors of studies on HDCT with autologous HSCT have stated that RCTs are both necessary and feasible. However, NRSTS is a rare disease and, according to the results of a previous literature search, currently there are no published RCTs available. In addition, CCTs or studies with any comparative data may be unlikely or rare. If they do exist they may be of low methodological quality. Based on the assumption that it is unlikely that the intervention has been or will be studied in RCTs in the near future, this systematic report of the findings and the limitations of all available published studies will be useful, for example for informing the design of appropriate RCTs and providing a summary of all of the evidence on the topic to date.

Types of participants

Inclusion criteria

We have adopted the World Health Organization (WHO) classification of soft tissue tumors to define the population of patients with NRSTS (Fletcher 2002) with the exception of the Ewing family of tumors (see 'Exclusion criteria' below). Studies were included as long as at least 80% of patients had NRSTS. Children as well as adults were investigated and age limits did not apply. Participants were included regardless of the severity of the disease and the clinical staging information, as long as they received autologous (from either a peripheral or bone marrow source, or both) HSCT.

Exclusion criteria

Whilst the WHO classification of NRSTS includes the Ewing family of tumors, that is extraosseous tumor types, we excluded these types because they are primarily bone sarcomas. Because extraosseous types are rarely diagnosed and share common features, they were regarded as one entity with osseous types and were excluded.

The clear delineation of soft tissue sarcomas to be included in the present report and the grounds for exclusion of some tumor types was hindered by the presence of more than 30 heterogeneous tumor entities, the distinction between malignant tumors and two categories of intermediate malignancies as described in the WHO classification (Fletcher 2002), and a complicated histology and terminology. Therefore, we present the designation of tumors that were regarded as (malignant) soft tissue sarcomas in the present review (Table 2) and we present the terms for tumors that were not considered (Table 3).

Types of interventions

Intervention: autologous hematopoietic stem cell transplantation (HSCT), stem cells from a peripheral source or the bone marrow, serving as a rescue therapy usually applied after high-dose chemotherapy (HDCT).

Comparison: standard-dose chemotherapy, which is defined as chemotherapy at a lower dose than HDCT without the need for stem cell rescue.

Types of outcome measures

Primary outcomes

- Overall survival (OS): the event was death by any cause, from diagnosis or start of HDCT and autologous HSCT.
- Treatment-related mortality (TRM): incidence of deaths that were classified as treatment related or the participants died of treatment complications.

Secondary outcomes

- Disease-free survival (DFS): time free of disease after diagnosis or start of HDCT and autologous HSCT. We provided the definitions reported in the studies.
- Progression-free survival (PFS): time staying free of disease progression after diagnosis or start of HDCT and autologous HSCT. We provided the definitions reported in the studies.
- Event-free survival (EFS): time staying free of any of a particular group of defined events after diagnosis or start of HDCT and autologous HSCT. We provided the definitions reported in the studies.
- Non-hematological toxicity grade 3 to 4: adverse events classified according to the common toxicity criteria (NCI 2009b)

within 90 days of start of HDCT and autologous HSCT; grades 3 and 4 of toxicity were extracted for non-hematological (nausea, mucositis, kidney, liver, nervous system, heart, other) toxicities.

- Secondary neoplasia: as classified by the study authors.
- Health-related quality of life measured by validated questionnaires.

Search methods for identification of studies

Electronic searches

We conducted an electronic database search of MEDLINE (Ovid), including articles published between 1946 and 5 December 2012, by using the search strategy shown in [Appendix 1](#). We searched EMBASE (Ovid), including articles published between 1980 and 5 December 2012, by using the search strategy shown in [Appendix 2](#). We searched *The Cochrane Library*, including articles published from inception to 5 December 2012, by using the search strategy shown in [Appendix 3](#). The original strategies which were run on 5 February 2010 and are shown in [Appendix 4](#) for MEDLINE (Ovid), in [Appendix 5](#) for EMBASE (Ovid), and in [Appendix 6](#) for *The Cochrane Library*. For this update we considered all studies that were included in the original review and re-evaluated them. We searched for ongoing trials by scanning the online registries ClinicalTrials.gov ([ClinicalTrials.gov 2012](#)) and the World Health Organization International Clinical Trials Registry Platform ([ICTRP 2012](#)) on 5 December 2012 for additional completed or ongoing studies using the search strategy “sarcoma AND chemotherapy AND transplantation”. For the update of the present review we searched abstracts of annual meetings of the following societies via EMBASE (Ovid): American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), Bone Marrow Transplantation (BMT) Tandem Meeting of the American Society for Blood and Marrow Transplantation (ASBMT) and the Center for International Blood and Marrow Transplant Research (CIBMTR), and European Group for Blood and Marrow Transplantation (EBMT).

The search strategies used have been developed and executed by the author team.

Searching other resources

We located information about trials not registered in electronic databases by searching the reference lists of relevant articles and review articles such as [Banna 2007](#), [Ek 2006](#), [Pedrazzoli 2006](#), and [Verma 2008a](#). For the update, we did not identify more recent reviews. We contacted authors to replenish missing information.

Data collection and analysis

Selection of studies

We endorsed the PRISMA statement, adhered to its principles and conformed to its checklist ([Moher 2009](#)). We re-ran the whole selection process including all records retrieved from the inception of each database. We retrieved all titles and abstracts by electronic searching and downloaded them to the reference management database EndNote Version X3 ([Thomson Reuters Corp 2012](#)). We removed duplicates and two review authors examined the remaining references independently (FP, CB). We excluded those studies that clearly did not meet the inclusion criteria and we obtained copies of the full texts of potentially relevant references. Two authors (FP, CB) assessed the eligibility of retrieved papers independently. We resolved disagreement by discussion and it was not necessary to consult a third review author. We considered studies written in languages other than English and asked peers familiar with the particular language and with the principles of study evaluation to translate major methodological issues. We also used the [Google Translate 2012](#) program. We documented reasons for the exclusion of studies.

Data extraction and management

We re-extracted the data from all selected studies identified from the inception of each database. Two review authors (FP, CB) independently abstracted data on study characteristics, patients and interventions, duration of follow up, outcomes, and deviations from the protocol. In addition, two review authors (FP, CB) independently assessed the risk of bias. We resolved differences between review authors by discussion or by appeal to a third review author (LS). All included studies were full-text publications. We extracted the following data.

- General information on author, title, source, publication date.
- Study characteristics: trial design, setting, inclusion and exclusion criteria, comparability of patients' characteristics between groups, treatment allocation, blinding, subgroup analysis, length of follow-up.
- Participant characteristics: age; gender; number of participants recruited, /allocated, affected, analyzed; additional diagnoses; participants lost to follow-up.
- Interventions: type of high-dose chemotherapy, source of stem cells, and type of standard-dose chemotherapy.
- Outcomes: overall survival, treatment-related mortality, disease-free survival, progression-free survival, event-free survival including type of event, toxicity, secondary neoplasia, health-related quality of life.

Assessment of risk of bias in included studies

Two review authors (FP, CB) independently assessed the risk of bias in the included studies using six criteria. We have used four criteria of The Cochrane Collaboration's tool for assessing risk of bias ([Higgins 2011a](#)):

1. random sequence generation (selection bias);
2. allocation concealment (selection bias);
3. blinding of outcome assessment (detection bias);
4. selective reporting such as not reporting pre-specified outcomes (reporting bias).

We extended the tool for assessing risk of bias with five additional criteria that are specific for the inclusion criteria for the present review and that are critical for confidence in the results:

1. prospective design;
2. comparable baseline characteristics;
3. assignment of patients to treatment groups;
4. concurrent control;
5. loss to follow-up.

We applied The Cochrane Collaboration's criteria for judging risk of bias (Higgins 2011b). In general, a 'low risk' of bias is judged if the bias is unlikely to seriously alter the results, for example, participants and investigators enrolling participants could not foresee assignment. A 'high risk' of bias is judged if the bias seriously weakens confidence in the results, for example, participants or investigators enrolling participants could possibly foresee assignments. 'Unclear' risk of bias is judged if the bias raises some doubt about the results, for example, the method of concealment is not described or not described in sufficient detail to allow a definite judgement.

We judged studies as prospective if an explicit statement was reported or there were clues suggesting a prospective design (for example prior approval of treatment, informed consent). We judged studies as retrospective if an explicit statement was reported or was implied by a description that data were reviewed from an existing source. We regarded each of the following items as an indication of a retrospective design: registry reports and reviewing of medical records.

Measures of treatment effect

The primary effect measure was the hazard ratio (HR) for time-to-event data. If the HR was not directly given in the publication, we planned to estimate HRs according to methods proposed by Parmar 1998 and Tierney 2007.

We planned to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous outcomes. In the case of rare events, we planned to use Peto odds ratio instead. We planned to analyze continuous data and to present them as mean differences, if all results were measured on the same scale (for example length of hospital stay). If this was not the case (for example pain or quality of life), we planned to use standardized mean differences.

Studies reporting aggregate data that combined the results of several participants (including results from separately reported subpopulations that fulfilled the inclusion criteria) were distinguished from studies with individual data of single participants. Data from these studies were described as narrative summaries. In some studies diagnoses of NRSTS were mixed with non-NRSTS solid tumors and rhabdomyosarcomas to such an extent that the propor-

tion of NRSTS participants was less than 80% of the study population. In this case, if data on single participants were identified that fulfilled the inclusion criteria of the present review we included the study and data for the individual participant in our data analysis.

Estimates of OS were considered for the evaluation if the use of the Kaplan-Meier method was reported in the study. We described survival estimates from studies reporting aggregate data independent of the start of the follow-up period on the condition that these estimates were not pooled with those of other studies.

A survival analysis was conducted of individual participant level data based on the Kaplan-Meier method. Pooling required binary information on OS (0 = alive; 1 = dead) and on follow-up. In the majority of cases, the starting point of follow-up was the beginning of treatment. However, we accepted other starting points such as the time when the diagnosis or indication for treatment was established. Statistical analyses of time to event data were performed using SAS Version 9.2 (SAS Institute Corp 2012).

Unit of analysis issues

None

Dealing with missing data

We conformed to The Cochrane Collaboration's principal options for dealing with missing data and analysed only the available data (Higgins 2011c). If data were missing or only imputed data were reported we contacted trial authors to request data on the outcomes among participants who were assessed. We contacted the authors of the studies by Bui-Nguyen 2012, Ivanova 2010, Jordan 2010, Philippe-Chomette 2012, Schlemmer 2006 to ask for missing data about the histologic types that were combined as 'others'. The authors responded well and as a consequence we could base the inclusion or exclusion of patient data on the additional data.

Assessment of heterogeneity

We planned to assess heterogeneity between studies by visual inspection of forest plots; by estimation of the percentage heterogeneity between trials which cannot be ascribed to sampling variation (I^2 statistic) (Higgins 2003); by a formal statistical test of the significance of the heterogeneity (Cochran's Q) (Deeks 2011); and, if possible, by subgroup analyses (see 'Subgroup analysis and investigation of heterogeneity'). We planned to investigate and report possible reasons if there was evidence of substantial heterogeneity. We planned to use the random-effects model with inverse variance weighting for statistical pooling (DerSimonian 1986). We did not pool estimates.

Assessment of reporting biases

We conformed to The Cochrane Collaboration's criteria and planned to evaluate reporting biases such as publication bias, time

lag bias, multiple (duplicate) publication bias, location bias, citation bias, language bias and outcome reporting bias (Sterne 2011). We did not assess reporting bias because of the low number of identified studies.

Data synthesis

One review author (FP) entered the data into [Review Manager 2011](#). Another review author (CB) checked the entered data. Methods of synthesizing the studies depended on the quality, design and heterogeneity of the studies identified.

We planned to synthesize data on mortality (HDCT and autologous HSCT versus SDCT) by using the hazard ratio (HR) as effect measure in a random-effects model. However, data were too scarce to be reasonably pooled. Aggregate data were synthesized as narrative. In contrast, individual data were pooled and available time-to-event data were analyzed in a Kaplan-Meier survival analysis.

We used the software GRADEpro 3.2 ([GRADEpro 2008](#)) to create the 'Summary of findings' table 1 as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Schünemann 2011](#)).

Subgroup analysis and investigation of heterogeneity

We had planned subgroup analyses based on age, stage, and time period of treatment. However, we found no appropriate data to conduct these analyses.

Sensitivity analysis

We had planned sensitivity analyses to compare the results of studies with low versus high risk of bias. As all included studies had a high risk of bias, no sensitivity analyses were carried out.

RESULTS

Description of studies

Clinical heterogeneity was substantial because tumor subdiagnosis varied considerable between patients. Furthermore, tumor stage

was not reported for all participants. Study design was tenuously reported due to the identification of either aggregate data or individual patient data in one-arm studies. Overall, the likelihood of bias was very high except in the single randomized controlled trial (RCT). All studies were not comparable due to various subtypes.

Results of the search

For this update we modified the search strategy to improve the precision and reduce the number of irrelevant hits. In the original review, we applied a search strategy that was designed to include all solid tumors including the Ewing family of tumors and rhabdomyosarcoma. This strategy resulted in the retrieval of a large number of documents (4782) including a very high fraction of not relevant retrieved documents. We revised the search strategy and this retrieved a considerably reduced number of retrieved documents (1035) from the inception of each electronic databases. The new strategy did not identify some single-arm studies with individual data that were included in the original review. Some individual cases are hidden in articles that do not mention soft tissue sarcomas and transplantation in the title or abstract. Some of those are missed by the new strategy. It is impossible to identify all published cases of transplanted patients with NRSTS. Therefore, the number of identified relevant cases will vary with different strategies. The retrieval information confirmed that the number of studies with comparative data and aggregate data did not vary and the number of these types of identified studies was robust. The new search strategy was more economical in terms of spending resources for study selection for the present review, and also for future updates. We did not ignore the results of the original review and re-evaluated all studies that were identified by the old strategy and were included in the original review.

We retrieved 1035 records applying the new search strategy. We also retrieved six ongoing studies. We imported 15 studies that were included in the original review but were not identified with the new search strategy. We screened 773 different articles after removal of duplicates ([Figure 1](#)). The titles and abstracts of 513 articles did not fulfil the inclusion criteria or they reported about ongoing studies. A total of 260 of the retrieved articles were evaluated in detail using the full text. Of these, a total of 62 records reporting about 57 studies were included in the present review and the other 198 references were excluded. We identified one randomized controlled trial (RCT), six single-arm studies with aggregate data, and 50 single-arm studies with individual data.

Figure 1. Literature search and study flow.

Eight studies were published after the original retrieval and were added to the included studies (Bisogno 2010; Buerk 2010; Bui-Nguyen 2012; Cook 2012; Etienne-Mastroianni 2002; Houet 2010; Jordan 2010; Philippe-Chomette 2012). Nine further studies were included in the original review but were not identified by the new search strategy (Fang 2008; Graham 1997; Hawkins 2002; Kretschmar 1996; Krskova 2007; Matsuzaki 2002; Peters 1986; Peters 1989; Sleas 1988) (Table 4). These 15 studies were included in the update in addition to the results of the new search strategy. Three studies were included in the original review and identified in the update but were excluded after re-evaluation (Ivanova 2010; Kaminski 2000; Kuehne 2000). Three studies were excluded in the original review and identified in the update but were included after re-evaluation (Blay 2000; Fetscher 1996; Mingo 2005). Six further studies were included in the original review and not identified in the update but were excluded after re-evaluation. Four studies reported about undifferentiated sarcoma, which is not included (Endo 1996; Frapier 1998; Mesia 1994; Nakamura 2008). One study reported about rhabdoid tumor but without information about the localisation, which is required for identification of the extrarenal and the extracerebral rhabdoid tumors (Ronghe 2004). One study reported on undifferentiated sarcoma and rhabdoid tumor without information about the localisation (Shaw 1996). We retrieved a total of 49 studies in ClinicalTrials.gov 2012 and found 14 potentially relevant studies. We identified six ongoing studies, whereof two studies are currently recruiting (NCT00638898; NCT01288573) and four studies are not recruiting participants (NCT00002601; NCT00002854; NCT00141765; NCT00623077). We identified three completed studies, one terminated study that was withdrawn due to slow accrual, and four studies with unknown status and information that has not been verified recently. The investigators did not provide results via the registry and we did not find a publication in PubMed 2012 matching the data shown in the registry. Of the rest of the 35 studies, 15 studies did not include the diagnosis of interest, 15 studies did not include the intervention of interest, and five did not include the outcome of interest. We did not identify other relevant studies searching in the two trials registries ICTRP 2012 and ISRCTN 2012. We did not identify any additional studies from screening the reference lists of included studies and reviews.

Included studies

We identified 57 studies including a total of 275 participants that received HDCT and autologous HSCT. The characteristics of all 57 included studies are described in the section [Characteristics of included studies](#). We have provided a tabulated overview of seminal characteristics in Table 5.

Design

We included one RCT with two parallel treatment groups, HDCT and autologous HSCT versus SDCT (Bui-Nguyen 2012). It was an open, multicenter, randomized phase III study. All patients received the same baseline treatment. Patients were eligible for randomization if they had responded to chemotherapy or, for stable disease, if a complete surgical resection of all disease sites could be carried out. Randomization was carried out centrally. The intention-to-treat (ITT) modified population included all randomly assigned patients excluding patients found to be ineligible at central histology review.

We included six single-arm studies that reported aggregate data of participants that received HDCT and autologous HSCT and that consisted of at least 80% with relevant NRSTS (Bertuzzi 2003; Bisogno 2010; Blay 2000; Bokemeyer 1997; Cook 2012; Philippe-Chomette 2012). Three of the studies collected the data prospectively (Bertuzzi 2003; Bisogno 2010; Blay 2000) and three retrospectively (Bokemeyer 1997; Cook 2012; Philippe-Chomette 2012). The remaining 50 studies comprised single-arm studies without appropriate aggregate data. Relevant participants were considered in the survival analysis of pooled individual data.

Sample sizes

The authors of the RCT (Bui-Nguyen 2012) conducted an ITT analysis of 38 participants in the HDCT arm versus 41 participants in the SDCT arm. Six single-arm studies reported aggregate data of 10 (Bertuzzi 2003), 14 (Bisogno 2010), 24 (Blay 2000), 16 (Bokemeyer 1997), 36 (Cook 2012), and 14 (Philippe-Chomette 2012) participants with NRSTS who received HDCT and autologous HSCT. Fifty studies reported on 123 individual relevant participants. Overall survival and follow-up data were reported for 80 participants in 41 studies and subsequently those data could be considered in survival analysis of the pooled individual data.

Setting

The 57 studies were set in 12 different countries, eight countries in Europe (Czech Republic, France, Germany, Greece, Italy, Netherlands, Spain, United Kingdom), two in North America (Canada, United States), and two in Asia (Korea, Japan). Most of the transplanted patients were studied in the USA (79 of 260) and France (79 of 260). In four countries (France, Germany, Italy, USA) 10 or more patients were studied. The only RCT (Bui-Nguyen 2012) was set in France.

Participants

We included 275 patients with 15 different relevant histological diagnoses in 57 studies. Most patients (N = 109) had desmoplastic small round-cell tumor; 10 or more patients were reported for

angiosarcoma, desmoplastic small round-cell tumor, leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma, and synovial sarcoma.

Bui-Nguyen 2012 reported the age in the HDCT arm in a range of 18.5 to 65.0 years (median 45.8 years) and a comparable age in the SDCT arm with a range of 18.7 to 65.0 years (median 43.3 years). Males were 58.5% of participants (24 of 41) in the HDCT arm and 50% (23 of 46) in the CDCT arm.

Bertuzzi 2003 reported a range of 15 to 60 years of age (median 29 years) for the 10 male patients that were included. Bisogno 2010 included 13 males and one female, the age range was 2 to 17.8 years (median 10.3 years). Blay 2000 reported on 30 patients of which 17 were males and 13 females. The age ranged from 17 to 57 years (median 34 years). Bokemeyer 1997 reported the age range between 25 and 57 years with a median of 45 years. Gender was not specified. Cook 2012 reported the age range between 8 and 46 years with a median of 19 years; 29 were males and 7 were females. Philippe-Chomette 2012 reported an age range of 4 to 22.6 years for 14 transplanted patients in the HDCT arm; 12 of those patients were males and 2 females.

Age was provided for 113 of 123 individual patients ranging from 1 to 65 years with a median of 27 years. Gender was provided for 83 individual patients, of which 55 were male and 28 were female. Follow-up was provided for 80 individual patients, ranging from 0 to 120 months with a median of 17 months.

Interventions

Components and the dosage of various chemotherapeutic regimens are described in the [Characteristics of included studies](#).

In the study by Bui-Nguyen 2012, 87 patients received courses one to five of standard-dose chemotherapy. Forty-one patients were randomized to receive HDCT and transplantation of autologous peripheral stem cells as course six in the HDCT arm. Of these, 38 patients were analyzed in a modified ITT analysis. Forty-six patients were randomized to again receive standard-dose chemotherapy as course six. Of these, 45 patients were analyzed in a modified ITT analysis.

In the study by Bertuzzi 2003, after a four-course induction phase 10 patients in complete or partial response received HDCT and autologous HSCT using peripheral blood as the stem cell source. In the study by Bisogno 2010, after an induction phase of nine weeks 14 patients at various clinical stages received three consecutive intensified-dose combinations and autologous HSCT using peripheral blood as the stem cell source. In the study by Blay 2000, after induction chemotherapy for most of the patients 24 patients with an advanced clinical stage including 87% with metastasis received HDCT and autologous HSCT. The stem cell source was mainly bone marrow (N = 25) and a few patients received stem

cells from peripheral blood (N = 5). In the study by Bokemeyer 1997, 16 patients received HDCT and autologous HSCT from peripheral blood. In the study by Cook 2012, 36 patients received HDCT and autologous HSCT mainly from peripheral blood (N = 33) and a few from bone marrow (N = 2), with information missing in one patient. In the study by Philippe-Chomette 2012, 14 patients received various regimens of HDCT and autologous HSCT. The source of stem cells was not reported.

Primary outcome

All seven included studies with aggregate data (Bertuzzi 2003; Bisogno 2010; Blay 2000; Bokemeyer 1997; Bui-Nguyen 2012; Cook 2012; Philippe-Chomette 2012) reported overall survival (OS). Among the 50 studies with individual data from 123 patients, OS and follow-up were reported for 80 patients. Ten studies reported treatment-related mortality (TRM), five of seven studies with aggregate data and five of 50 studies with individual data. There were 13 events in nine and zero events in one study.

Secondary outcomes

One study reported disease-free survival, five studies reported progression-free survival, nine reported non-hematological toxicity grade 3 to 4, and one study reported secondary neoplasia. Five studies reported on five severe adverse events.

Excluded studies

A total of 198 references of the potentially relevant articles were excluded (Figure 1) based on:

- not diagnosis of interest, NRSTS according to Table 2 or relevant data not reported separately (n = 95);
- not intervention of interest, not HDCT and autologous HSCT (n = 69);
- not outcome of interest or not reported separately (n = 2);
- not publication type of interest, a review, editorial, letter, duplicate data, or congress abstract (n = 32).

Excluded studies are described in the [Characteristics of excluded studies](#) table.

Risk of bias in included studies

We have identified one comparative study with a randomized design (Bui-Nguyen 2012). We think that this trial stands out and has substantially less risk of bias than the rest of the studies. Fifty-six of 57 studies were single-arm studies that subsequently had a very high risk of bias, see [Characteristics of included studies](#). An overview of the risk of bias is shown in Figure 2 and the risk of bias for each study is shown in Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of outcome assessment (detection bias)	Selective reporting (reporting bias)	Prospective design	Comparable baseline characteristics	Assignment of patients to treatment groups	Concurrent control	Lost to follow-up
Al Balushi 2009	●	●	●	●	●	●	●	●	●
Andres 2006	●	●	●	●	●	●	●	●	●
Bernbeck 2007	●	●	●	●	●	●	●	●	●
Bertuzzi 2003	●	●	●	●	●	●	●	●	●
Bisogno 2010	●	●	●	●	●	●	●	●	●
Bilay 2000	●	●	●	●	●	●	●	●	●
Bley 2004	●	●	●	●	●	●	●	●	●
Boelke 2005	●	●	●	●	●	●	●	●	●
Bokemeyer 1997	●	●	●	●	●	●	●	●	●
Buerk 2010	●	●	●	●	●	●	●	●	●
Bui-Nguyen 2012	●	●	●	●	●	●	●	●	●
Cole 1999	●	●	●	●	●	●	●	●	●
Cook 2012	●	●	●	●	●	●	●	●	●
Doros 2008	●	●	●	●	●	●	●	●	●
Engelhardt 2007	●	●	●	●	●	●	●	●	●
Ebner-Mastroianni 2002	●	●	●	●	●	●	●	●	●
Fang 2008	●	●	●	●	●	●	●	●	●
Farrugia 2008	●	●	●	●	●	●	●	●	●
Fetscher 1996	●	●	●	●	●	●	●	●	●
Fetscher 1997	●	●	●	●	●	●	●	●	●
Fraser 2006	●	●	●	●	●	●	●	●	●
Garrido 1998	●	●	●	●	●	●	●	●	●
Graham 1997	●	●	●	●	●	●	●	●	●
Hara 2010	●	●	●	●	●	●	●	●	●
Hawkins 2002	●	●	●	●	●	●	●	●	●
Hoogerbrugge 1997	●	●	●	●	●	●	●	●	●
Houel 2010	●	●	●	●	●	●	●	●	●
Jordan 2010	●	●	●	●	●	●	●	●	●
Kasper 2007a	●	●	●	●	●	●	●	●	●
Kasper 2010	●	●	●	●	●	●	●	●	●
Kozuka 2002	●	●	●	●	●	●	●	●	●
Kretschmar 1996	●	●	●	●	●	●	●	●	●
Krskova 2007	●	●	●	●	●	●	●	●	●
Kurre 2000	●	●	●	●	●	●	●	●	●
Kushner 1996	●	●	●	●	●	●	●	●	●
Kushner 2001	●	●	●	●	●	●	●	●	●
Kushner 2008	●	●	●	●	●	●	●	●	●
Lafay-Cousin 2000	●	●	●	●	●	●	●	●	●
Lashkari 2009	●	●	●	●	●	●	●	●	●
Lippe 2003	●	●	●	●	●	●	●	●	●
Livadi 2006	●	●	●	●	●	●	●	●	●
Madigan 2007	●	●	●	●	●	●	●	●	●
Matsuzaki 2002	●	●	●	●	●	●	●	●	●
Mazurk 1998	●	●	●	●	●	●	●	●	●
Mingo 2005	●	●	●	●	●	●	●	●	●
Mitchell 1994	●	●	●	●	●	●	●	●	●
Navid 2006	●	●	●	●	●	●	●	●	●
Patel 2004	●	●	●	●	●	●	●	●	●
Peters 1986	●	●	●	●	●	●	●	●	●
Peters 1989	●	●	●	●	●	●	●	●	●
Philippe-Chomette 2012	●	●	●	●	●	●	●	●	●
Recchia 2006	●	●	●	●	●	●	●	●	●
Saab 2007	●	●	●	●	●	●	●	●	●
Sleese 1988	●	●	●	●	●	●	●	●	●
Sung 2003	●	●	●	●	●	●	●	●	●
Yamamura 2003	●	●	●	●	●	●	●	●	●
Yonemoto 1999	●	●	●	●	●	●	●	●	●

Allocation

We have identified true randomization including highly probable adequate random sequence generation for [Bui-Nguyen 2012](#) and judged a low risk of bias for this study. We judged a high risk of bias for the rest of the studies.

Assignment of patients to treatment groups

In the study by [Bui-Nguyen 2012](#), patients were assigned to two different treatment arms in a randomized fashion. Thus we judged a low risk of bias for this study. The rest of the studies were single-arm studies with an observational design and we judged a high risk of bias for these studies.

Blinding

Blinding of outcome assessment was not addressed in all included studies. Thus, we judged a high risk of bias for all studies.

Incomplete outcome data

[Bui-Nguyen 2012](#) conducted a modified ITT analysis. The exclusion of histologically ineligible patients after randomization affected three of 41 patients in the HDCT arm and one of 46 patients in the SDCT arm. All other studies analyzed the patients as treated. Thus we judged a low risk of bias for [Bui-Nguyen 2012](#) and a high risk of bias for the rest.

Selective reporting

In the study by [Bui-Nguyen 2012](#), allocation was carried out centrally, though masking of allocation was not described in full detail. Thus we judged an unclear risk of bias for this study. We judged a high risk of bias for the rest of the studies.

Other potential sources of bias

Prospective design

The one RCT was prospective ([Bui-Nguyen 2012](#)), three of the six single-arm studies with aggregate data ([Bertuzzi 2003](#); [Bisogno 2010](#); [Blay 2000](#)) and 12 of the 50 single-arm studies with individual data ([Fraser 2006](#); [Graham 1997](#); [Hawkins 2002](#); [Jordan 2010](#); [Kasper 2010](#); [Kushner 1996](#); [Kushner 2001](#); [Lafay-Cousin 2000](#); [Lashkari 2009](#); [Patel 2004](#); [Peters 1986](#); [Peters 1989](#)) had prospective parts. The prospective design may be advantageous for studies that present aggregate data from a series of patients treated in a certain time period. The prospective design is not relevant for individual data. Thus, we judged a low risk of bias for [Bui-Nguyen](#)

[2012](#), [Bertuzzi 2003](#), [Bisogno 2010](#), and [Blay 2000](#) and we judged a high risk of bias for the rest.

Comparable baseline characteristics

[Bui-Nguyen 2012](#) had a randomized controlled design and the baseline characteristics of both treatment groups were comparable. Thus, we judged a low risk of bias for [Bui-Nguyen 2012](#) and a high risk of bias for the rest.

Concurrent control

We identified a concurrent control group in [Bui-Nguyen 2012](#) and judged a low risk of bias. The rest of the studies did not report a control group and we judged a high risk of bias. Note: [Philippe-Chomette 2012](#) reported the results of some cases with conventional chemotherapy. The data for those cases were probably observed and not part of an experimental design, collected retrospectively in different time periods.

Loss to follow-up

[Bui-Nguyen 2012](#) conducted a modified ITT analysis. The exclusion of histologically ineligible patients after randomization affected three of 41 patients in the HDCT arm and one of 46 patients in the SDCT arm. All other studies analyzed the participants as treated. Thus we judged a low risk of bias for [Bui-Nguyen 2012](#) and a high risk of bias for the rest.

Effects of interventions

See: [Summary of findings for the main comparison](#) Autologous hematopoietic stem cell transplantation following high-dose chemotherapy for non-rhabdomyosarcoma soft tissue sarcoma

Primary outcome

Overall survival

Overall survival (OS) was not statistically significantly different between HDCT and autologous HSCT versus SDCT at three years in the RCT by [Bui-Nguyen 2012](#): 32.7% versus 49.4% with a HR of 1.26 (95% CI 0.70 to 2.29, $P = 0.44$) ([Table 6](#)). The authors separately analyzed patients that had achieved a complete response to induction therapy before HDCT. OS was higher in the complete response patients compared to all patients and OS was statistically significantly different between the treatment arms. The OS among the patients that have achieved a complete response

at three years before HDCT was 42.8% versus 83.9% with a HR of 2.92 (1.1 to 7.6, $P = 0.028$) (Table 6).

The single-arm studies with aggregate data reported an OS at two years ranging from 20% to 51.4% and at three years ranging from 38.9% to 40% (Table 6). Blay 2000 and Cook 2012 compared patients that had achieved versus not achieved a complete response before HDCT. Blay 2000 reported an OS at two years of 63% versus 27%, and Cook 2012 reported an OS at three years of 57% versus 28% (Table 6). Again, the achievement of a complete response before HDCT was favorable with respect to OS. We conducted a survival analysis using individual data on the condition that survival status and time to event were reported. This was true for 65% (80 of 123) of the patient data; for 43 patients, follow-up data were not available. We estimated an OS at two years of 50.6% (95% CI 38.7 to 62.5) and at three years of 36.7% (95%

CI 24.4 to 49.0) (Table 6). Both estimates were within the range of the other studies. We provided the OS for each individual case in Table 7. The graphical presentation of the Kaplan-Meier graph of all 80 included patients at risk is shown in Figure 4. We also analyzed the subgroup of patients with the diagnosis of desmoplastic small round-cell tumor because this diagnosis constituted the largest proportion, 34% (27 out of 80), of individual patients considered for the survival analysis (Figure 5). Of the individual data from patients with desmoplastic small round-cell tumor, 77% (27 of 35) had follow-up information. Both survival curves do not appear to be considerably different, though the median survival was 2.8 years within the subgroup of 27 patients with desmoplastic small round-cell tumor versus 2.2 years within the total population of 80 patients.

Figure 4. Kaplan-Meier analysis of overall survival of individual cases data from patient with various NRSTS
X-axis below line: years
X-axis above line: number of patients at risk
Y-axis: probability of overall survival
 The Kaplan-Meier analysis of overall survival was conducted using individual data of patients with NRSTS with available follow-up information (total 80, failed 46, censored 34) from 41 case series and case reports. Information about outcome (dead or alive) and follow-up (time of survival after diagnosis or begin of treatment) was required for each individual. Number of subjects at risk after each additional year of follow up. Abbreviations: NRSTS: non-rhabdomyosarcoma soft tissue sarcoma

Figure 5. Kaplan-Meier analysis of overall survival of individual cases data from patient with DSRCT only
X-axis below line: years
X-axis above line: number of patients at risk
Y-axis: probability of overall survival
The Kaplan-Meier analysis of overall survival was conducted using individual data of patients with NRSTS with available follow-up information (total 27, failed 13, censored 14) from case series and case reports. Information about outcome (dead or alive) and follow-up (time of survival after diagnosis or begin of treatment) was required for each individual. Number of subjects at risk after each additional year of follow up.
Abbreviations:
DSRCT: desmoplastic small round cell tumor

Treatment-related mortality

Treatment-related mortality (TRM) was addressed in 12 studies (163 transplanted participants). Ten of 12 studies reported a procedure-related death for 15 participants and two of 12 studies reported zero treatment-related deaths (Table 8). A conservative estimate of TRM was 5.5% (15 procedure-related deaths of a total of 275 transplanted patients).

Secondary outcomes

Disease-free survival

Cook 2012 reported an OS at three years of 23% regarding all patients and 40% versus 9% regarding patients with and without a complete response before HDCT respectively (Table 9).

Progression-free survival

Progression-free survival (PFS) was not statistically significantly different between HDCT and autologous HSCT versus SDCT in the RCT by Bui-Nguyen 2012 at three years (9.3% versus 21.6% with a HR of 1.34 (95% CI 0.81 to 2.20, $P = 0.25$)) (Table 10). The authors separately analyzed patients that had achieved a complete response to induction therapy before HDCT. PFS was higher in the complete response patients compared to all patients and OS was statistically significantly different between the treatment arms: OS among the patients that have achieved complete response at three years before HDCT was 20.0% versus 62.3% with a HR of 2.87 (95% CI 1.3 to 6.3, $P = 0.009$) (Table 10). Blay 2000 reported a considerable difference between the PFS of patients with complete response before HDCT at two and five years (62% versus 5%).

Non-hematological toxicity grade 3 to 4

Non-hematological toxicity grade 3 to 4 was addressed in nine studies and a serious adverse event was described for 38 participants in nine studies (Table 11). A conservative estimate was 13.8% (38 events of non-hematological toxicity grade 3 to 4 in a total of 275 transplanted patients).

Secondary neoplasia

Secondary neoplasia was addressed in one case report (Table 12).

Health-related quality of life

Health-related quality of life scales were not addressed in the included studies.

DISCUSSION

Summary of main results

Unlike in the first Cochrane systematic review published in 2011, we identified a randomized controlled trial (RCT) comparing HDCT followed by autologous HSCT to standard chemotherapy (SDCT) (Bui-Nguyen 2012). The authors reported a difference in overall survival (OS) after the treatment in favor of SDCT (32.7% versus 49.4%) but the difference was not statistically significant (HR 1.26, 95% CI 0.70 to 2.29, $P = 0.44$). Progression-free survival was also in favor of SDCT (9.3% versus 21.6%) but again the difference was not significant (HR 1.34, 95% CI 0.81 to 2.20, $P = 0.25$). Therefore, there is evidence that patients may not have a better survival after HDCT followed by autologous HSCT. If at all, this intervention should only be offered after careful consideration and only within controlled clinical trials. Of the participants, 20% have diagnoses not relevant to the present review and the 80% of participants with relevant diagnoses have 12 different types of NRSTS. The heterogeneity of types of NRSTS may be important because the OS may differ between the tumor types and the results of frequent types may overlay those of infrequent types.

We identified six case series reporting aggregate data that represented at least 80% of patients with NRSTS. These results described observed survival after a single experimental treatment. The results do not allow conclusions about an effect or benefit of this treatment that is not established. Of the six studies, four case series reported on transplanted patients with desmoplastic small round-cell tumors. OS at two years ranged between 20% and 51.4%. Two case series had a variety of NRSTS. Unfortunately they did not report Kaplan-Meier survival estimates. Our estimated OS of 50.6% at two years for the remaining studies with participant level data falls slightly below the upper limit of

the range of 20% to 51.4% reported for six studies with aggregate data. Follow-up information was available for 65% (80 out of 123) of participants that could be included in the survival analysis.

For treatment-related mortality (TRM), even the more conservative estimate of 5.5% (15 out of 275 transplanted patients) is considerably higher than the 2.0% TRM within the first days following HSCT reported by the European Group for Blood and Marrow Transplantation (EBMT) Registry (EBMT 2009) for the year 1998 (Rosti 2002). Secondary neoplasia was reported for just one participant, which was probably an extreme underestimation of the true frequency because of the relatively short follow-up in the included studies and the fact that the included studies were not designed to specifically detect secondary neoplasia. The detection of secondary neoplasia depends on a long follow-up, which might be provided by cancer registers. This reported incidence compares with a frequency of 4.0% for secondary neoplasia based on register data (Neglia 2001) and 6.9% (Baker 2003) after a long observation period of 20 years. Non-hematological severe organ toxicity grade 3 to 4 was reported for 36% (38 of 105) transplanted patients with relevant NRSTS in nine studies. Lower grade and hematological toxicity were not included and should be accounted for to get a full picture of adverse events.

Overall completeness and applicability of evidence

Many of the studies we identified had to be excluded because they included participants with different heterogeneous tumors without separate reporting, or the proportion of participants with NRSTS was fewer than 80%. Furthermore, some treatments were performed 10 to 20 years ago. Thus, the results may not be applicable to patients who are treated today. It is also a possibility that the results reflect the course of the disease and a consequence of the prior therapy rather than a consequence of the test intervention.

Quality of the evidence

The one RCT has a low risk of bias, whereas the remaining 48 studies were judged as having a high risk of bias. The characteristics of these single-arm studies showed that there are many different tumor types of NRSTS treated by transplantation, though each individual NRSTS entity was scarce. We found that a pooled survival analysis of individual participant data was considerably hampered. Specifically, the required follow-up information was incomplete or missing for 34% (37 out of 108) of participants and, therefore, corresponding data could not be included in the survival analysis. Each tumor type may carry an individual risk profile and, therefore, ideally should be evaluated separately. The body of evidence does not allow robust conclusions to be made in relation to the objectives of the review.

Potential biases in the review process

Strengths

The search strategy was broad and it is very likely that all relevant studies were identified. The WHO classification of NRSTS was adopted and modified to define a clear terminology for the study selection process. Studies were excluded if the proportion of non-eligible participants were greater or equal to 20% of the total population. Authors were contacted to ask for additional data.

Limitations

The results of studies may be difficult to compare because follow-up started at different time points, that is at diagnosis or at start of treatment. The delay between diagnosis and starting high-dose chemotherapy can be considerable. The median delay between diagnosis and intensification was four to 39 months in a study on 22 participants with STS including 11 NRSTS and 11 rhabdomyosarcoma patients (Dumontet 1992). We did a sensitivity analysis restricting the pooled analysis to individual cases that were followed from the start of the treatment and we excluded cases that were followed from diagnosis. However, we found only a very marginal difference in survival estimates.

We identified one RCT with a low risk of bias. This means that the results of this RCT may be used as evidence for the evaluation of the efficacy of autologous HSCT following HDCT for NRSTS. All other identified studies were single-arm studies with an inherent very high risk of bias. This means that the results of the single-arm studies are not helpful to decide whether autologous HSCT following HDCT for NRSTS is a meaningful treatment option. Many studies were excluded because participants with NRSTS were mixed with participants with other malignant diseases. The heterogeneity of NRSTS and the possible different terminology used in publications may have led us to overlook studies with eligible participants. This may be more an issue for case series but it is highly unlikely for controlled trials. The pooled survival analysis of individual data was based on less than half of all the individual data available and the exclusion of these data, whilst intending to reduce bias, may also have introduced bias.

Agreements and disagreements with other studies or reviews

We agree with Pedrazzoli 2006 that the potential benefit of this treatment option has not been investigated sufficiently in comparative studies. A systematic review (Verma 2008a) was performed to determine whether first-line dose-intensive chemotherapy supported by growth factor or autologous bone marrow or stem cell transplantation improves outcomes compared with standard-dose chemotherapy in patients with inoperable, locally advanced or metastatic soft tissue sarcoma. Verma 2008a included only one case series (Schlemmer 2006) with HDCT followed by autologous HSCT, which was excluded from the present review because 40% of patients were not diagnosed with the disease of interest. Kasper 2005 concluded that the use of HDCT for locally advanced or metastatic adult (soft tissue and bone) sarcomas still remains highly investigational and should not be performed outside clinical trials.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence base does not support the use of HDCT followed by autologous HSCT in high-risk patients with NRSTS. If this treatment is offered it should only be after careful consideration and integrated within a prospective concurrent, preferably randomized, controlled trial.

Implications for research

It is doubtful whether further studies are necessary to clarify the relevance of HDCT followed by autologous HSCT in patients with NRSTS. If non-randomized controlled studies are conducted, a low risk of bias should be achieved. Single-arm studies are not helpful. Criteria for the included tumor types should adhere to the WHO classification.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Al Balushi 2009

Methods	Duration: 2000 to 2007 Study design: retrospective report of cases without control Treatment: number of arms: 1 Follow-up time: 18, 24, and 72 months for 3 transplanted participants	
Participants	Setting: single center in Canada Eligibility criteria: patients with desmoplastic small round-cell tumor Number of participants: 5 patients with desmoplastic small round-cell tumor <ul style="list-style-type: none">3 transplanted patients with metastatic desmoplastic small round-cell tumor (included in the present review)not included in the present review: 2 patients without HSCT Age: not specified Gender: not specified	
Interventions	High-dose chemotherapy (HDCT): all 5 patients were treated with a total of 4 cycles of chemotherapy regimen that includes doxorubicin 270 to 375 mg/m ² , ifosfamide 36000 to 58000 mg/m ² , cyclophosphamide 12500 to 21000 mg/m ² , and etoposide 2700 to 4350 mg/m ² total doses Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none">Stem cell source: bone marrow	
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: toxicity reported as individual data	
Notes	Financial support: not addressed	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective

Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Andres 2006

Methods	Duration: August to October 2002 Study design: retrospective report of a single cases without control Treatment: number of arms: 1 Follow-up time: 10 months for 1 transplanted participant
Participants	Setting: single center in Spain Eligibility criteria: 1 patient with desmoplastic small round-cell tumor, no metastases Number of participants: 1 patient <ul style="list-style-type: none"> 1 transplanted patient with desmoplastic small round-cell tumor (included in the present review) Age: 21 years old Gender: 1 female
Interventions	High-dose chemotherapy (HDCT): thiotepa 1200 mg/m ² , carboplatin 2000 mg/m ² , and cyclophosphamide 9600 mg/m ² , total doses Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> Stem cell source: not specified ("stem cell rescue")
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: toxicity reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available

Andres 2006 (Continued)

Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Bernbeck 2007

Methods	Duration: 2001 to 2005 Study design: retrospective report of cases without control Treatment: number of arms: 1 Follow-up time: not reported
Participants	Setting: single center in Germany Eligibility criteria: high-risk soft tissue sarcomas, that means patients that are refractory to conventional therapy (incomplete response or relapse) or may have metastases Number of participants: 9 patients <ul style="list-style-type: none"> • 2 transplanted patients with synovial sarcoma with metastases (included in the present review) • not included in the present review: 6 patients with rhabdomyosarcoma • not included in the present review: 1 patient with Ewing sarcoma Age: 21 and 21 years old Gender: 1 male, 1 female
Interventions	High-dose chemotherapy (HDCT): topotecan 3.75 mg/m ² , etoposide 500 mg/m ² , carboplatin 500 mg/m ² , and cyclophosphamide 1000 mg/m ² , total doses Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> • Stem cell source: peripheral blood
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: toxicity reported as individual data
Notes	Financial support: the authors have no conflict of interest to disclose

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment

Bernbeck 2007 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Bertuzzi 2003

Methods	Duration: 1997 to 2002 Study design: prospective study of consecutive cases without control Treatment: number of arms: 1 Follow-up time: time to event analysis with 2 year follow-up of transplanted participants, median follow-up 35 months
Participants	Setting: single center in Italy Eligibility criteria: advanced desmoplastic small round-cell tumor at various clinical stages including 4 patients with metastases Number of participants: 10 patients <ul style="list-style-type: none"> 10 transplanted patients with desmoplastic small round-cell tumor (included in the present review) Age: median 29 years of age (range 15 to 60 years) Gender: 10 males
Interventions	High-dose chemotherapy (HDCT): after a four-course induction phase, patients in complete or partial response received HDCT with melphalan 160 mg/m ² plus mitoxantrone 60 mg/m ² or thiotepa 600 mg/m ² , total doses Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> Stem cells source: peripheral blood
Outcomes	Primary outcomes: overall survival and treatment-related mortality ("no toxic deaths were observed") reported as aggregate data Secondary outcomes: progression-free survival reported as aggregate data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	Low risk	Prospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Bisogno 2010

Methods	<p>Duration: 1999 to 2008</p> <p>Study design: prospective study of cases without control</p> <p>Treatment: number of arms: 1</p> <p>Follow-up time: time to event analysis with 3 year follow-up of transplanted participants with a median follow-up of 27 months for survivors</p>
Participants	<p>Setting: multi-center study in Italy</p> <p>Eligibility criteria: desmoplastic small round-cell tumor at various clinical stages including 4 patients with metastases</p> <p>Number of participants: 14 patients</p> <ul style="list-style-type: none"> 14 transplanted patients with desmoplastic small round-cell tumor (included in the present review) <p>Age: median 10.3 years of age (range 2 to 17.8 years)</p> <p>Gender: 13 males, 1 female</p>
Interventions	<p>High-dose chemotherapy (HDCT): after an induction phase of nine weeks, three consecutive intensified-dose combinations were applied: thiotepa 300 mg/m², melphalan 60 mg/m², cyclophosphamide 4000 mg/m², thiotepa 300 mg/m², and melphalan 80 mg/m², total doses</p> <p>Autologous hematopoietic stem cell transplantation (HSCT)</p> <ul style="list-style-type: none"> stem cell source: peripheral blood

Bisogno 2010 (Continued)

Outcomes	Primary outcomes: overall survival reported as aggregate data Secondary outcomes: progression-free survival reported as aggregate data; toxicity reported as individual data	
Notes	Conflict of interest: “The authors have no conflict of interest to disclose.” Support: “This research was partially supported by a grant from the Fondazione Citta della Spiranza.”	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	Low risk	Prospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Blay 2000

Methods	Duration: 1988 to 1994 Study design: prospective study of cases without control Treatment: number of arms: 1 Follow-up time: time to event analysis with 5 year follow-up of transplanted participants with a median follow-up of 94 months for survivors
Participants	Setting: single center in France Eligibility criteria: advanced soft tissue sarcomas Number of participants: 30 patients, 26 patients had distant metastases and the rest of 4 had a locally advanced stage <ul style="list-style-type: none"> 24 transplanted patients analyzed in a subgroup of patients with adult-type sarcomas excluding rhabdomyosarcoma and Ewing family of tumors; this subgroup

	<p>analysis compared patients who have achieved a complete response before HDCT with those who had a partial or minor response (included in the present review, 80% of all participants)</p> <ul style="list-style-type: none">○ 22 transplanted patients with NRSTS: 5x leiomyosarcoma, 4x synovial sarcoma, 4x undifferentiated sarcoma, 3x unclassified sarcoma, 2x angiosarcoma, 2x liposarcoma, 1x fibrosarcoma, 1x hemangiopericytoma○ not included in the present review: 1x paraganglioma, 1x Schwannosarcoma● not included in the present review: 5 patients with rhabdomyosarcoma● not included in the present review: 1 patient with extraskeletal permeative neuroectodermal tumor (PNET) <p>Age: median 34 years of age (range 17 to 57 years)</p> <p>Gender: 17 males, 13 female</p>	
Interventions	<p>High-dose chemotherapy (HDCT): the majority of patients had received induction chemotherapy, afterwards HDCT was applied that comprised etoposide 800 mg/m², cisplatin 200 mg/m², ifosfamide 12000 mg/m², total doses</p> <p>Autologous hematopoietic stem cell transplantation (HSCT)</p> <ul style="list-style-type: none">● stem cell source: bone marrow (N = 25) or peripheral blood (N = 5)	
Outcomes	<p>Primary outcomes: overall survival reported as aggregate data, treatment-related mortality “one sudden toxic death”</p> <p>Secondary outcomes: progression-free survival and toxicity reported as aggregate data</p>	
Notes	Financial support: not addressed	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	Low risk	Prospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control

Blay 2000 (Continued)

Loss to follow-up	Unclear risk	Possible but not reported
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Bley 2004

Methods	Duration: no information on observation period available Study design: retrospective report of a single case without control Treatment: number of arms: 1 Follow-up time: 7 months for 1 transplanted participant
Participants	Setting: single center in Germany Eligibility criteria: liposarcoma Number of participants: 1 patient <ul style="list-style-type: none"> 1 transplanted patient with liposarcoma and with autologous HSCT (included in the present review) Age: 22 years of age Gender: 1 female
Interventions	High-dose chemotherapy (HDCT): melphalan and busulfan Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: not specified
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: toxicity reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study

Bley 2004 (Continued)

Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Boelke 2005

Methods	Duration: in 1993 Study design: retrospective report of a single case without control Treatment: number of arms: 1 Follow-up time: 89 months for 1 transplanted participant
Participants	Setting: single center in Germany Eligibility criteria: malignant fibrous histiocytoma Number of participants: 1 patient <ul style="list-style-type: none"> 1 transplanted patient with recurrent malignant fibrous histiocytoma and with autologous HSCT (included in the present review) Age: 33 years of age Gender: 1 female
Interventions	High-dose chemotherapy (HDCT): melphalan and busulfan Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: peripheral blood
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: adverse events reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control

Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Bokemeyer 1997

Methods	Duration: no information on observation period available Study design: retrospective report of cases without control Treatment: number of arms: 1 Follow-up time: not specified
Participants	Setting: patients were presumably treated in 3 centers in Germany according to author affiliation Eligibility criteria: histologically proven metastatic or advanced adult soft tissue sarcoma without prior treatment, age between 18 and 60 years, a Karnofsky index greater than or equal to 50%, adequate liver, kidney, and bone marrow function Number of participants: 18 patients <ul style="list-style-type: none"> 16 transplanted patients with NRSTS and with autologous HSCT: 5x malignant fibrous histiocytoma, 4x hemangiopericytoma, 3x synovial sarcoma, 2x leiomyosarcoma, 2x mesenchymal sarcoma (included in the present review) not included in the present review: 2x malignant Schwannoma Age: median 45 (range 25 to 57) years of age Gender: not specified
Interventions	High-dose chemotherapy (HDCT): doxorubicin, 75 mg/m ² , ifosfamide at different dose levels 8000, 10000, 12000, 14000, or 16000 mg/m ² , total dose Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: peripheral blood
Outcomes	Primary outcomes: overall survival reported as aggregate data Secondary outcomes: progression-free survival, toxicity reported as aggregate data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment

Bokemeyer 1997 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Buerk 2010

Methods	Duration: not specified Study design: retrospective report of a single case without control Treatment: number of arms: 1 Follow-up time: 6 weeks for 1 transplanted participant
Participants	Setting: single center in Germany Eligibility criteria: angiosarcoma Number of participants: 1 patient <ul style="list-style-type: none"> 1 transplanted patient with epithelioid angiosarcoma of the scapula without distant metastases (included in the present review) Age: 48 years of age Gender: 1 male
Interventions	High-dose chemotherapy (HDCT): not specified Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: peripheral blood
Outcomes	Primary outcomes: overall survival reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment

Buerk 2010 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Bui-Nguyen 2012

Methods	<p>Duration: 2000 to 2008</p> <p>Study design: randomized controlled trial: “<i>This open, multicenter, randomized phase III study [...]. “All patients eligible for preenrollment received the same baseline treatment [...]. “[...] eligible for randomization if they had responded to chemotherapy or, for stable disease, if a complete surgical resection of all disease sites could be carried out. Patients were ineligible for randomization if they had progressed or had only stable disease with no possibility for complete resection of the primary and/or metastatic tumor”. “Randomization was stratified by center using a blocked method with block size of four and was carried out centrally”. “The intention to treat (ITT)-modified population included all randomly assigned patients excluding patients found to be ineligible at central histology review.”</i></p> <p>Treatment: number of arms: 2</p> <p>Follow-up time: time to event analysis at 3 years with a median follow-up of 55 months for survivors</p>
Participants	<p>Setting: multicenter trial in 16 centers in France</p> <p>Eligibility criteria: patients aged 18 to 65 years with histologically confirmed, inoperable locally advanced or metastatic soft tissues sarcomas; Eastern Cooperative Oncology Group performance status of 0 or 1; normal cardiac, hepatic, and renal function, adequate bone marrow reserve; patients had received no prior chemotherapy or concurrent therapy; patients for whom it was possible to perform potentially curative locoregional treatments and patients with uterine, bone, or digestive tumors were excluded</p> <p>Number of participants: 264</p> <ul style="list-style-type: none"> • 264 patients pre-enrolled • 207 patients received first 4 of 6 chemotherapy courses • 87 patients were randomized to HDCT plus autologous HSCT (N = 41, but data from 38 analyzed in ITT) and to SDCT (N = 46, but data from 45 analyzed in ITT) <ul style="list-style-type: none"> ◦ 69 patients with NRSTS: 16x leiomyosarcoma, 16x malignant fibrous histiocytoma, 10x others (2x undifferentiated sarcoma, 2x malignant myoepithelioma, 1x leiomyosarcoma, 1x fibrosarcoma, 1x myofibrosarcoma, 1x unclassified sarcoma, 1x

	<p>desmoplastic small round cell sarcoma), 10x liposarcoma, 9x synovial sarcoma, 6x angiosarcoma, 1x clear cell sarcoma, 1x desmoplastic round cell sarcoma (included in the present review)</p> <ul style="list-style-type: none"> not included in the present review: 18 patients (20%) with diagnoses other than NRSTS: 9x rhabdomyosarcoma, 2x malignant peripheral nerve sheath tumor, 1x osteosarcoma, 1x melanoma, 5x others (3x endometrial stromal sarcoma, 1x gastrointestinal stromal tumor, 1x triton tumor) 83 patients were included in modified intention to treat analysis (ITT) to compare overall survival and progression-free survival between treatment groups; histologically ineligible patients were excluded from primary group of analysis, 3 from the HDCT plus autologous HSCT group with data from 38 patients used for ITT analysis and 1 from the SDCT group with data from 45 patients used for ITT analysis 62 patients received the assigned treatment and were included in the toxicity analysis <p>Age: range 18.5 to 65.0 years of age, median 45.8, in the HDCT arm and 18.7 to 65.0 years of age, median 43.3, in the SDCT arm</p> <p>Gender: 58.5% (24 of 41) males in the HDCT arm and 50% (23 of 46) males in the CDCT arm</p>				
Interventions	<p>All participants received 5 times standard-dose chemotherapy: doxorubicin 60 mg/m², ifosfamide 7500 mg/m², dacarbazine 900 mg/m², total doses; the sixth course was different between arm 1 and 2:</p> <p>Randomized to arm 1, sixth course:</p> <ul style="list-style-type: none"> High-dose chemotherapy (HDCT): ifosfamide 10000 mg/m², carboplatin, and etoposide 1200 mg/m², total doses Autologous hematopoietic stem cell transplantation (HSCT): stem cell source: peripheral blood actually 22 of 41 randomized patients received HDCT followed by HSCT <p>Randomized to arm 2, sixth course:</p> <ul style="list-style-type: none"> Standard-dose chemotherapy: doxorubicin 60 mg/m², ifosfamide 7500 mg/m², dacarbazine 900 mg/m², total doses actually 40 of 46 randomized patients received standard-dose chemotherapy 				
Outcomes	<p>Primary outcomes:</p> <ul style="list-style-type: none"> Overall survival reported as aggregate data; individual data were not reported <p>Secondary outcomes:</p> <ul style="list-style-type: none"> Progression-free survival reported as aggregate data; individual data were not reported Toxicity reported as individual data 				
Notes	<p>Financial support: Programme Hospitalier de Recherche Clinique, French Health Ministry (non-profit organization); French National Federation for Comprehensive Cancer Centers (non-profit organization)</p> <p>Information about the histological type of sarcoma designated as “others” in the article were communicated by personal contact with the first author</p>				
<i>Risk of bias</i>					
Bias	<table border="1"> <thead> <tr> <th>Authors' judgement</th><th>Support for judgement</th></tr> </thead> <tbody> <tr> <td></td><td></td></tr> </tbody> </table>	Authors' judgement	Support for judgement		
Authors' judgement	Support for judgement				

Random sequence generation (selection bias)	Low risk	<i>“Randomization was stratified by center using a blocked method with block size of four and was carried out centrally”</i>
Allocation concealment (selection bias)	Unclear risk	Allocation was carried out centrally, though, masking of allocation was not described in full detail
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome. It was denoted as an <i>“open, multicenter, randomized phase III study”</i> .
Selective reporting (reporting bias)	Low risk	We did not detect reporting of outcomes that might be selective
Prospective design	Low risk	Randomized controlled trial
Comparable baseline characteristics	Low risk	Baseline data including pretreatment were comparable. <i>“All patients eligible for pre-enrollment received the same baseline treatment”</i> .
Assignment of patients to treatment groups	Low risk	Randomized controlled trial
Concurrent control	Low risk	Randomized controlled trial
Loss to follow-up	Low risk	Loss to follow-up was described and modified intention-to-treat analysis was performed

Cole 1999

Methods	Duration: not specified Study design: retrospective report of a single case without control Treatment: number of arms: 1 Follow-up time: 6 months for 1 transplanted participant
Participants	Setting: single center in the United States Eligibility criteria: synovial sarcoma Number of participants: 1 patient <ul style="list-style-type: none"> 1 transplanted patient with synovial sarcoma (included in the present review) Age: 26 years of age Gender: 1 male
Interventions	High-dose chemotherapy (HDCT): not specified Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: peripheral blood

Cole 1999 (Continued)

Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: adverse events reported as individual data	
Notes	Financial support: not addressed	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Cook 2012

Methods	Duration: 1999 to 2007 Study design: retrospective registry analysis of cases without control reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) Treatment: number of arms: 1 Follow-up time: median of 44 months (range 4 to 89) for survivors
Participants	Setting: analysis of registry data from 29 centers reported to CIBMTR located in North America except for 3 patients Eligibility criteria: desmoplastic small round cell tumor Number of participants: 36 patients <ul style="list-style-type: none"> • 36 transplanted patients (included in the present review) Age: median 19 years of age (range 8 to 46 years) Gender: 29 males, 7 females

Interventions	High-dose chemotherapy (HDCT): the most common agents were thiotepa, etoposide, melphalan, cyclophosphamide, and carboplatin Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: bone marrow (N = 2) or peripheral blood (N = 33), information missing in 1 patient
Outcomes	Primary outcomes: overall survival and treatment-related mortality reported as aggregate data Secondary outcomes: disease-free survival reported as aggregate data
Notes	Financial support of CIBMTR: Grants from non-profit organizations: <ul style="list-style-type: none"> Blue Cross and Blue Shield Association Children's Leukemia Research Association National Cancer Institute (NCI) National Heart, Lung and Blood Institute (NHLBI) National Institute of Allergy and Infectious Diseases (NIAID) Office of Naval Research Grants from biopharmaceutical companies <ul style="list-style-type: none"> Allos, Inc Amgen, Inc. Celgene Corporation CellGenix, GmbH Fresenius-Biotech North America, Inc. Gamida Cell Teva Joint Venture Ltd.; Genentech, Inc. Genzyme Corporation GlaxoSmithKline Kiadis Pharma Millennium Pharmaceuticals, Inc. Milliman USA, Inc. Miltenyi Biotec, Inc. Optum Healthcare Solutions, Inc. Otsuka America Pharmaceutical, Inc. Seattle Genetics Sigma-Tau Pharmaceuticals Soligenix, Inc. Swedish Orphan Biovitrum AB THERAKOS, Inc. Wellpoint, Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment

Cook 2012 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Doros 2008

Methods	Duration: not specified Study design: retrospective report of a single case without control Treatment: number of arms: 1 Follow-up time: 0 months for 1 transplanted participant
Participants	Setting: single center in the United States Eligibility criteria: desmoplastic small round-cell tumor Number of participants: 1 patient <ul style="list-style-type: none"> 1 transplanted patient with desmoplastic small round-cell tumor (included in the present review) Age: 14 years of age Gender: 1 male
Interventions	High-dose chemotherapy (HDCT): not specified Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: not specified ("autologous stem cell rescue")
Outcomes	Primary outcomes: overall survival and treatment-reported mortality reported as individual data Secondary outcomes: adverse events reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization

Doros 2008 (Continued)

Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Engelhardt 2007

Methods	<p>Duration: 1992 to 2003</p> <p>Study design: retrospective report of a consecutive series of cases without controls</p> <p>Treatment: number of arms: 1</p> <p>Follow-up time: not specified for individual participants</p>
Participants	<p>Setting: an international multicenter study, the number of centers and the name of participating countries were not specified and presumably included Germany and the United States</p> <p>Eligibility criteria: high-risk Ewing sarcoma and soft tissue sarcomas, 18 years or older, tumor diameter 5 cm or more, extensive local or distant recurrence and/or metastatic disease, histologically moderately differentiated or undifferentiated tumors</p> <p>Number of participants: 35 patients</p> <ul style="list-style-type: none"> 23 transplanted patients with NRSTS including anaplastic soft tissue sarcoma, angiosarcoma, fibrosarcoma, leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma, malignant hemangiopericytoma, synovial sarcoma (included in the present review) not included in the present review: 8 patients with Ewing sarcoma not included in the present review: 3 patients with rhabdomyosarcoma not included in the present review: 1 patient with Schwannoma <p>Age: range 21 to 56 years of age of 23 patients with NRSTS</p> <p>Gender: 12 males and 11 females of 23 patients with NRSTS</p>
Interventions	<p>High-dose chemotherapy (HDCT): various regimens for individual patients</p> <p>Autologous hematopoietic stem cell transplantation (HSCT)</p> <ul style="list-style-type: none"> stem cell source: peripheral blood

Engelhardt 2007 (Continued)

Outcomes	Primary outcomes: overall survival and treatment-related mortality reported as individual data	
Notes	The reported aggregate data were not considered because the proportion of participants with NRSTS was 67% (23 of 35). A proportion of at least 80% is required for extracting aggregate data Financial support: not addressed	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Etienne-Mastroianni 2002

Methods	Duration: 1970 to 1999 Study design: retrospective report of cases without controls Treatment: number of arms: 1 Follow-up time: 3 to 144 months (mean 42)
Participants	Setting: single center in France Eligibility criteria: primary sarcoma of the lung, metastatic pulmonary sarcomas, as well as mediastinal, thoracic wall, pleural, and cardiac primary sarcomas were excluded; 15 years of age or older Number of participants: 12 patients <ul style="list-style-type: none"> • 1 transplanted patient with leiomyosarcoma (included in the present review) • not included in the present review: 11 patients without transplantation

Etienne-Mastroianni 2002 (Continued)

	Age: 50 years of age Gender: 1 male	
Interventions	High-dose chemotherapy (HDCT): not specified Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none">stem cell source: bone marrow	
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: not reported individually	
Notes	Financial support: not addressed	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Fang 2008

Methods	Duration: in 2006 Study design: retrospective report of cases without control Treatment: number of arms: 1 Follow-up time: not specified	
Participants	Setting: single center in the United States Eligibility criteria: high-risk solid tumor of childhood Number of participants: 2 patients <ul style="list-style-type: none"> 1 transplanted patient with desmoplastic small round-cell tumor (included in the 	

	present review) <ul style="list-style-type: none">not included in the present review: 1 patient with desmoplastic small round-cell tumor but no autologous HSCT Age: 23 years of age Gender: 1 female	
Interventions	High-dose chemotherapy (HDCT): not specified Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none">stem cell source: peripheral blood	
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: not reported individually	
Notes	Financial support: not addressed	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Farruggia 2008

Methods	Duration: not specified Study design: retrospective report of a single case without control Treatment: number of arms: 1 Follow-up time: 36 months
Participants	Setting: single center in Italy Eligibility criteria: synovial sarcoma Number of participants: 1 patient <ul style="list-style-type: none"> 1 transplanted patient with synovial sarcoma (included in the present review) Age: 10 years of age Gender: 1 male
Interventions	High-dose chemotherapy (HDCT): carboplatin 500 mg/m ² , epirubicine 150 mg/m ² , vincristine 1.5 mg/m ² / ifosfamide 3000 mg/m ² , vincristine 1.5 mg/m ² , etoposide 150 mg/m ² , total doses Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: peripheral blood
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: toxicity reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Fetscher 1996

Methods	Duration: not specified Study design: retrospective report of a single case without control Treatment: number of arms: 1 Follow-up time: 1 month
Participants	Setting: single center in Germany Eligibility criteria: nuchal leiomyosarcoma Number of participants: 1 patient <ul style="list-style-type: none"> 1 transplanted patient with leiomyosarcoma (included in the present review) Age: 53 years of age Gender: 1 male
Interventions	High-dose chemotherapy (HDCT): not specified Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: peripheral blood
Outcomes	Primary outcomes: overall survival reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Fetscher 1997

Methods	Duration: in 1994 Study design: retrospective report of a single case without control Treatment: number of arms: 1 Follow-up time: 36 months
Participants	Setting: single center in Germany Eligibility criteria: gastric leiomyosarcoma Number of participants: 1 patient <ul style="list-style-type: none"> 1 transplanted patient with metastatic leiomyosarcoma (included in the present review) Age: 23 years of age Gender: 1 female
Interventions	High-dose chemotherapy (HDCT): etoposide 1500 mg/m ² , ifosfamide 12000 mg/m ² , carboplatin 1500 mg/m ² , epirubicine 150 mg/m ² , total doses Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: peripheral blood
Outcomes	Primary outcomes: overall survival reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Fraser 2006

Methods	<p>Duration: 1995 to 2004</p> <p>Study design: prospective series of cases without control</p> <p>Treatment: number of arms: 1</p> <p>Follow-up time: not specified for individual data</p>
Participants	<p>Setting: single center in the United States</p> <p>Eligibility criteria: patients with a range of high-risk solid and brain tumors who had achieved a complete or partial response with non-progressive disease; patients had high-risk tumors that were either metastatic at diagnosis or had relapsed following therapy; adequate organ function was documented</p> <p>Number of participants: 36 patients</p> <ul style="list-style-type: none"> 4 transplanted patients with desmoplastic small round-cell tumor (included in the present review) not included in the present review: 32 patients with other solid tumors such as 16x Ewing's sarcoma, 3x rhabdomyosarcoma, 2x Wilm's tumor, 2x ovarian tumor, 2x medulloblastoma, 1x hepatoblastoma, 1x retinoblastoma, 1x osteosarcoma, 1x glioblastoma multiforme, 1x ependymoma, 1x chordoma, 1 patient with cerebral rhabdoid tumor <p>Age: 8, 10, 14, 20 years of age</p> <p>Gender: not specified</p>
Interventions	<p>High-dose chemotherapy (HDCT): busulfan 12 mg/kg, melphalan 100 mg/m², thiopeta 500 mg/m², total doses</p> <p>Autologous hematopoietic stem cell transplantation (HSCT)</p> <ul style="list-style-type: none"> stem cell source: bone marrow or peripheral blood
Outcomes	<p>Primary outcomes: overall survival reported as individual data</p> <p>Secondary outcomes: toxicity reported as individual data</p>
Notes	<p>Financial support: "This work was supported in part by a grant from the Children's Cancer Research Fund." (national nonprofit organization)</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Prospective but no relevant aggregate data

Fraser 2006 (Continued)

Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Garrido 1998

Methods	Duration: 1991 to 1995 Study design: retrospective report of 2 cases without control Treatment: number of arms: 1 Follow-up time: not specified for individual data
Participants	Setting: single center in the United States Eligibility criteria: neuroleptic malignant syndrome after transplantation Number of participants: 2 patients <ul style="list-style-type: none"> 1 transplanted patient with metastatic liposarcoma (included in the present review) not included in the present review: 1 transplanted patient with breast carcinoma Age: 45 years of age Gender: 1 male
Interventions	High-dose chemotherapy (HDCT): busulfan 12 mg/kg total dose, melphalan 100 mg/m ² total dose, thiotepa 500 mg/m ² , total doses Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: not specified
Outcomes	Primary outcomes: not reported Secondary outcomes: adverse events reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome

Garrido 1998 (Continued)

Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Graham 1997

Methods	Duration: 1991 to 1995 Study design: prospective report of a cases without control Treatment: number of arms: 1 Follow-up time: not specified
Participants	Setting: single center in the United States Eligibility criteria: recurrent and high-risk pediatric brain tumors after transplantation Number of participants: 49 patients <ul style="list-style-type: none"> 1 transplanted patient with fibrosarcoma (included in the present review) not included in the present: 48 patients with diagnoses other than NRSTS: 19x medulloblastoma, 12x glial tumors, 7x pineoblastoma, 5x ependymoma, 3x Ewing family of tumors, 2x germ cell tumor Age: not specified Gender: not specified
Interventions	Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: bone marrow
Outcomes	Primary outcomes: overall survival Secondary outcomes: toxicity
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment

Graham 1997 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Prospective but no relevant aggregate data
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Hara 2010

Methods	Duration: 2003 to 2009 Study design: retrospective report of a single case without control Treatment: number of arms: 1 Follow-up time: 67 months
Participants	Setting: single center in Japan Eligibility criteria: angiosarcoma Number of participants: 1 patient <ul style="list-style-type: none"> 1 transplanted patient with splenic angiosarcoma (included in the present review) Age: 48 years of age Gender: 1 female
Interventions	High-dose chemotherapy (HDCT): ifosfamide 9000 mg/m ² , etoposide 900 mg/m ² , and carboplatin 1200 mg/m ² , total doses Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: peripheral blood
Outcomes	Primary outcomes: overall survival reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization

Hara 2010 (Continued)

Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Hawkins 2002

Methods	Duration: 1996 to 1998 Study design: prospective report of cases without control Treatment: number of arms: 1 Follow-up time: not specified
Participants	Setting: 3 centers in the United States Eligibility criteria: children and adolescents with metastatic sarcomas Number of participants: 23 patients <ul style="list-style-type: none"> 4 transplanted patients with NRSTS (included in the present review): 2x desmoplastic small round-cell tumor, 1x leiomyosarcoma, 1x fibromyxoid sarcoma not included in the present: 17 patients with diagnoses other than NRSTS: 9x Ewing family of tumors, 6x rhabdomyosarcoma, 2x undifferentiated sarcoma, 1x anaplastic Wilms tumor, 1x malignant peripheral nerve sheath tumor Age: 5 to 19 years of age Gender: 5 male, 1 female
Interventions	High-dose chemotherapy (HDCT): vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: peripheral blood
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: toxicity reported as individual data
Notes	Financial support: not addressed
Risk of bias	

Hawkins 2002 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Prospective but no relevant aggregate data
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Hoogerbrugge 1997

Methods	Duration: 2003 to 2009 Study design: retrospective report of a single case without control Treatment: number of arms: 1 Follow-up time: 8 months
Participants	Setting: single center in the Netherlands Eligibility criteria: fibrosarcoma Number of participants: 1 patient <ul style="list-style-type: none"> 1 transplanted patient with disseminated fibrosarcoma (included in the present review) Age: 1 year of age Gender: not specified
Interventions	High-dose chemotherapy (HDCT): etoposide 1500 mg/m ² , carboplatin 1500 mg/m ² and melphalan 140 mg/m ² , total doses Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: bone marrow
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: toxicity reported as individual data

Hoogerbrugge 1997 (Continued)

Notes	Financial support: Amgen, Inc. (biopharmaceutical company) and Roche Inc. (pharmaceutical company) were acknowledged for their support of the study	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Houet 2010

Methods	Duration: not specified Study design: retrospective report of a single case without control Treatment: number of arms: 1 Follow-up time: more than 10 years
Participants	Setting: single center in Germany Eligibility criteria: desmoplastic small round-cell tumour Number of participants: 1 patient <ul style="list-style-type: none"> 1 transplanted patient with advanced intra-abdominal desmoplastic small round-cell tumour and lymph node involvement (included in the present review) Age: 31 years of age Gender: not specified
Interventions	High-dose chemotherapy (HDCT): not specified Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: peripheral blood

Houet 2010 (Continued)

Outcomes	Primary outcomes: overall survival reported as individual data	
Notes	Financial support: grants from the Deutsche Krebshilfe (nonprofit organization)	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Jordan 2010

Methods	Duration: 2004 to 2006 Study design: prospective series of cases without control Treatment: number of arms: 1 Follow-up time: 3 to 36 months
Participants	Setting: single center in Germany Eligibility criteria: histologically confirmed metastatic sarcoma or germ cell cancer, refractory to standard chemotherapy, no prior high-dose chemotherapy, Eastern Cooperative Oncology Group (ECOG) performance status of at least two and adequate hematologic, hepatic, and renal functions; exclusion criteria: newly diagnosed venous thrombosis, significant cardiovascular disease or surgery within 21 days; presence of cerebral metastases was not an exclusion criterion Number of participants: 16 patients <ul style="list-style-type: none"> • 7 transplanted patients: 2x epitheloid sarcoma, 1x synovial sarcoma, 1x spindle cell sarcoma, 1x leiomyosarcoma, 1x angiosarcoma, 1x hemangiopericytoma (included in the present review)

	<ul style="list-style-type: none">not included in the present review: 5 transplanted patients: 3x osteosarcoma, 2x chondrosarcoma, 1x undifferentiated sarcomanot included in the present review: 3 transplanted patients: germ cell tumor (non-seminoma) Age: range 25 to 58 years of age Gender: not specified	
Interventions	High-dose chemotherapy (HDCT): ifosfamide 9000 mg/m ² , etoposide 900 mg/m ² , carboplatin 900 mg/m ² , and bevacizumab 7.5 to 10.0 mg/kg, total doses Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none">stem cell source: peripheral blood	
Outcomes	Primary outcomes: overall survival reported as individual data	
Notes	Financial support: Two authors have received compensation as a member of the scientific advisory board of Roche AG (pharmaceutical company). The remaining authors declared that they have no conflict of interest	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Prospective but no relevant aggregate data
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Kasper 2007a

Methods	<p>Duration: 1998 to 2007</p> <p>Study design: retrospective series of cases without control</p> <p>Treatment: number of arms: 1</p> <p>Follow-up time: 0 to 54 months (for each included case reported: 0, 2, 4, 4, 6, 11, 14, 16, 19, 20, 20, 21, 26, 54 months)</p>
Participants	<p>Setting: single center in Germany</p> <p>Eligibility criteria: patients with bone and soft tissue sarcomas receiving high-dose chemotherapy and autologous stem cell support</p> <p>Number of participants: 38 patients</p> <ul style="list-style-type: none"> 11 transplanted patients: 5x synovial sarcoma, 3x leiomyosarcoma, 2x liposarcoma 1x malignant fibrous histiocytoma (included in the present review) not included in the present review: 20 transplanted patients: 10x Ewing family of tumors, 6x osteosarcoma, 1x chondrosarcoma, 3x not otherwise specified sarcoma not included in the present review: 7 transplanted patients: 4x malignant peripheral nerve sheath tumors, 2x rhabdomyosarcomas, 1x meningiosarcoma <p>Age: range 23 to 65 years of age</p> <p>Gender: not specified</p>
Interventions	<p>High-dose chemotherapy (HDCT): 23 patients: ifosfamide 12000 mg/m², carboplatin 1200 mg/m², and etoposide 1200 mg/m², total doses; 7 patients: melphalan 420 mg/m², busulfan 1800 mg/m², total doses; 4 patients: melphalan 180 mg/m² and etoposide 3000 mg/m², total doses; 2 patients: melphalan 200 mg/m²; 2 patients: carboplatin 600 mg/m², etoposide 600 mg/m², total doses</p> <p>Autologous hematopoietic stem cell transplantation (HSCT)</p> <ul style="list-style-type: none"> stem cell source: peripheral blood
Outcomes	<p>Primary outcomes: overall survival reported as individual data</p> <p>Secondary outcomes: toxicity reported as individual data</p>
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective

Kasper 2007a (Continued)

Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Kasper 2010

Methods	<p>Duration: 2003 to 2008</p> <p>Study design: prospective nonrandomized controlled clinical trial</p> <p>Treatment: number of arms: 2</p> <p>Follow-up time: follow up was not reported; overall survival was assessed from the time of study inclusion and ranged from 0 to 34 months</p>
Participants	<p>Setting: single center in Germany</p> <p>Eligibility criteria: primary or recurrent metastatic soft tissues sarcoma; no patients with unresectable disease were included; normal creatinine, normal cardiac function and normal bilirubin levels were required before high-dose chemotherapy</p> <p>Number of participants: 34 patients</p> <ul style="list-style-type: none"> 9 patients had partial response to induction chemotherapy and received HDCT and autologous HSCT: <ul style="list-style-type: none"> 4 patients had NRSTS: 2x malignant fibrous histiocytoma, 1x leiomyosarcoma, 1x synovial sarcoma (included in the present review) not included in the present review: 5 patients had other diagnosis (56%): 3x not otherwise specified tumor, 1x primitive neuroectodermal tumor, 1x rhabdomyosarcoma 25 patients received SDCT: <ul style="list-style-type: none"> 16 patients had NRSTS 9 patients with other tumors than NRSTS including including not otherwise specified tumor (36%); 1 of the 9 patients had partial response to induction chemotherapy but refused HDCT and autologous HSCT. <p>Age: not specified</p> <p>Gender: not specified</p>
Interventions	<p>Arm 1:</p> <ul style="list-style-type: none"> High-dose chemotherapy (HDCT): ifosfamide 12000 mg/m², carboplatin 1200 mg/m² and etoposide 1200 mg/m², total doses Autologous hematopoietic stem cell transplantation (HSCT): stem cell source: peripheral blood <p>Arm 2:</p> <ul style="list-style-type: none"> Standard-dose chemotherapy: doxorubicin 75 mg/m² and ifosfamide 6000 mg/m², total doses
Outcomes	<p>Primary outcomes:</p> <ul style="list-style-type: none"> Overall survival: aggregate data included less than 80% NRSTS patient data; individual data reported

Kasper 2010 (Continued)

	Secondary outcomes: <ul style="list-style-type: none">● Progression-free survival: aggregate data included less than 80% NRSTS patient data Adverse events reported as individual data	
Notes	The authors declared that they have no conflict of interest.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Prospective but no relevant aggregate data
Comparable baseline characteristics	High risk	Comparative trial but only individual data were relevant
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Kozuka 2002

Methods	Duration: 1999 to 2000 Study design: retrospective report of 2 cases without control Treatment: number of arms: 1 Follow-up time: not specified
Participants	Setting: single center in Japan Eligibility criteria: recurrent soft tissues sarcoma Number of participants: 2 patients <ul style="list-style-type: none"> 2 transplanted patients: 1x malignant fibrous histiocytoma, 1x malignant hemangiopericytoma (included in the present review) Age: 21 and 37 years of age Gender: 2 males

Kozuka 2002 (Continued)

Interventions	High-dose chemotherapy (HDCT): ifosfamide 15000 mg/m ² , carboplatin 1200 mg/m ² , and etoposide 1500 mg/m ² , total doses Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: peripheral blood
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: adverse events reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Kretschmar 1996

Methods	Duration: not specified Study design: retrospective report of 3 cases without control Treatment: number of arms: 1 Follow-up time: not specified
Participants	Setting: single center in the United States Eligibility criteria: desmoplastic small round-cell tumor Number of participants: 3 patients <ul style="list-style-type: none"> 1 transplanted patients: desmoplastic small round-cell tumor (included in the present review)

Kretschmar 1996 (Continued)

	<ul style="list-style-type: none"> not included in the present review: 2x desmoplastic small round-cell tumor not transplanted Age: 13 years of age Gender: 1 male
Interventions	High-dose chemotherapy (HDCT) Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: bone marrow
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: toxicity reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Krskova 2007

Methods	Duration: in 1998 Study design: retrospective report of a single case without control Treatment: number of arms: 1 Follow-up time: not specified
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Participants	Setting: single center in the Czech Republic Eligibility criteria: desmoplastic small round-cell tumor Number of participants: 1 patients <ul style="list-style-type: none">1 transplanted patients: synovial sarcoma (included in the present review) Age: 9 years of age Gender: 1 male	
Interventions	High-dose chemotherapy (HDCT) Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none">stem cell source: not specified	
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: adverse events reported as individual data	
Notes	Financial support: not addressed	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Kurre 2000

Methods	Duration: 1994 to 1998 Study design: retrospective report of 3 cases without control Treatment: number of arms: 1 Follow-up time: 26 and 42 months after diagnosis
Participants	Setting: single center in the United States Eligibility criteria: desmoplastic small round-cell tumor Number of participants: 3 patients <ul style="list-style-type: none"> • 2 transplanted patients: 2x desmoplastic small round-cell tumor (included in the present review) • not included in the present review: 1x desmoplastic small round-cell tumor, no transplantation Age: 5 and 2.5 years of age Gender: 1 male and 1 female
Interventions	High-dose chemotherapy (HDCT): doxorubicin 75 mg/m ² , cyclophosphamide 1800 mg/m ² , ifosfamide 9000 mg/m ² , and etoposide 500 mg/m ² , total doses Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> • stem cell source: peripheral blood
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: adverse events reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control

Loss to follow-up	Unclear risk	Possible but not reported
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Kushner 1996

Methods	Duration: not specified Study design: prospective series of cases and controls Treatment: number of arms: 2 Follow-up time: 13 to 34 months
Participants	Setting: single center in the United States Eligibility criteria: desmoplastic small round-cell tumor Number of participants: 12 patients <ul style="list-style-type: none"> 4 transplanted patients with desmoplastic small round-cell tumor (included in the present review) not included in the present review: 8 patients with desmoplastic small round-cell tumor that were not transplanted Age: 10, 11, 11, and 14 years of age
Interventions	Arm 1: Chemotherapy: cyclophosphamide 4200 mg/m ² , doxorubicin 75 mg/m ² , vincristine 2000 mg/m ² , ifosfamide 9000 mg/m ² , and etoposide 500 mg/m ² , total doses Arm 2: Additional high-dose chemotherapy (HDCT): thiotepa 900 mg/m ² and carboplatin 1500 mg/m ² , total doses Autologous hematopoietic stem cell transplantation (HSCT): <ul style="list-style-type: none"> stem cell source: bone marrow
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: toxicity reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available

Kushner 1996 (Continued)

Prospective design	High risk	Prospective but no relevant aggregate data
Comparable baseline characteristics	High risk	Controls but only individual data relevant
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Kushner 2001

Methods	Duration: not specified Study design: preliminary results of a prospective series of cases Treatment: number of arms: 1 Follow-up time: 2 years	
Participants	Setting: single center in the United States Eligibility criteria: diagnosis of a cancer that had 25% cure rate with conventional therapies; adequate function of kidneys, heart, and liver Number of participants: 21 patients <ul style="list-style-type: none">1 transplanted patients with desmoplastic small round-cell tumor (included in the present review)not included in the present review: 20 transplanted patients with diagnoses other than NRSTS: 11x neuroblastoma, 3x Ewing family of tumors, 3x medulloblastoma, 1x glioblastoma multiforme, 1x astrocytoma, 1x ovarian teratoma Age: 29 years of age Gender: 1 male	
Interventions	High-dose chemotherapy (HDCT): topotecan 10 mg/m ² , thiotepa 900 mg/m ² , carboplatin 1500 mg/m ² , total doses Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none">stem cell source: peripheral blood	
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: toxicity reported as individual data	
Notes	Financial support: This work was supported in part by grants from the National Cancer Institute (non-profit organization), the Robert Steel Foundation (non-profit organization), the Katie Find A Cure Fund (non-profit organization), and the Justin Zahn Fund (non-profit organization)	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Kushner 2001 (Continued)

Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Prospective but no relevant aggregate data
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Kushner 2008

Methods	Duration: not specified Study design: retrospective report of a single case without control Treatment: number of arms: 1 Follow-up time: 26 months
Participants	Setting: single center in the United States Eligibility criteria: desmoplastic small round-cell tumor Number of participants: 1 patient <ul style="list-style-type: none"> 1 transplanted patient with desmoplastic small round-cell tumor (included in the present review) not included in the present review: 1x desmoplastic small round-cell tumor, no transplantation Age: 18 years of age Gender: 1 male
Interventions	High-dose chemotherapy (HDCT): whole abdominal-pelvic radiation therapy 3000 Gy and irinotecan 250 mg/m ² , total doses Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: peripheral blood
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: adverse events reported as individual data

Kushner 2008 (Continued)

Notes	Financial support: Supported in part by grants from the National Cancer Institute (non-profit organization), Food and Drug Administration (non-profit organization), Hope St Kids (non-profit organization), Katie Find A Cure Fund (non-profit organization), and Robert Steel Foundation (non-profit organization)	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Lafay-Cousin 2000

Methods	Duration: 1986 to 1998 Study design: prospective report of 18 cases without control Treatment: number of arms: 1 Follow-up time: 8 to 31 months (for each included case 8, 13, 16, 31 months reported)
Participants	Setting: 4-center study in France Eligibility criteria: recurrent mesenchymal tumors Number of participants: 18 patients <ul style="list-style-type: none"> • 2 transplanted patients: 2x desmoplastic small round-cell tumor (included in the present review) • not included in the present review: 14x transplanted patients with rhabdomyosarcoma, 2x undifferentiated sarcoma Age: 11 and 16 years of age Gender: 2 females

Lafay-Cousin 2000 (Continued)

Interventions	High-dose chemotherapy (HDCT): thiotepa 900 mg/m ² total dose Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none">stem cell source: bone marrow or peripheral blood (not specified for each included case)	
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: adverse events reported as individual data	
Notes	Financial support: not addressed	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Prospective but no relevant aggregate data
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Lashkari 2009

Methods	Duration: 1995 to 1999 Study design: prospective report of 13 cases without control Treatment: number of arms: 1 Follow-up time: 99 and 138 months
Participants	Setting: single center in the United States Eligibility criteria: locally advanced or metastatic sarcoma Number of participants: 13 patients <ul style="list-style-type: none"> 1 transplanted patients: 1x malignant fibrous histiocytoma, (included in the present review)

	<ul style="list-style-type: none"> not included in the present review: 11x transplanted patients with diagnoses other than NRSTS: 7x Ewing family of tumors, 4x rhabdomyosarcoma, 1x undifferentiated sarcoma Age: 40 years of age Gender: 1 male
Interventions	High-dose chemotherapy (HDCT): doxorubicin 150 mg/m ² , ifosfamide 14000 mg/m ² , melphalan 150 mg/m ² , cisplatin 200 mg/m ² , total doses Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: peripheral blood
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: progression-free survival reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Prospective but no relevant aggregate data
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Lippe 2003

Methods	Duration: not specified Study design: retrospective report of 2 cases without control Treatment: number of arms: 1 Follow-up time: 34 months after diagnosis
Participants	Setting: single center in Italy Eligibility criteria: desmoplastic small round-cell tumor Number of participants: 2 patients <ul style="list-style-type: none"> • 1 transplanted patient with desmoplastic small round-cell tumor (included in the present review) • not included in the present review: 1x desmoplastic small round-cell tumor without transplantation Age: 27 years of age Gender: 1 male
Interventions	High-dose chemotherapy (HDCT): cyclophosphamide 7000 mg/m ² , total dose Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> • stem cell source: peripheral blood
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: toxicity reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Livaditi 2006

Methods	Duration: not specified Study design: retrospective report of 5 cases without control Treatment: number of arms: 1 Follow-up time: 11 months and 15 months
Participants	Setting: single center in Greece Eligibility criteria: desmoplastic small round-cell tumor Number of participants: 5 patients <ul style="list-style-type: none"> • 2 transplanted patients with desmoplastic small round-cell tumor (included in the present review) • not included in the present review: 3x desmoplastic small round-cell tumor without transplantation Age: 7 and 13 years Gender: 1 male and 1 female
Interventions	High-dose chemotherapy (HDCT): not specified Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> • stem cell source: peripheral blood
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: adverse events reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Madigan 2007

Methods	Duration: 1983 to 2003 Study design: retrospective report of 14 cases without control Treatment: number of arms: 1 Follow-up time: 34 months and 104 months after diagnosis
Participants	Setting: single center in the United States Eligibility criteria: extracranial rhabdoid tumors Number of participants: 14 patients <ul style="list-style-type: none"> • 1 transplanted patients with extracranial, extrarenal rhabdoid tumor (included in the present review) • not included in the present review: 12x extracranial rhabdoid tumors without transplantation, 1x extracranial but renal rhabdoid tumor with transplantation Age: 30 months of age Gender: 1 female
Interventions	High-dose chemotherapy (HDCT): not specified Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> • stem cell source: not specified
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: adverse events reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Matsuzaki 2002

Methods	Duration: in 1999 Study design: retrospective report of a single case without control Treatment: number of arms: 1 Follow-up time: not specified
Participants	Setting: single center in Japan Eligibility criteria: synovial sarcoma Number of participants: 1 patients <ul style="list-style-type: none"> • 1 transplanted patients with synovial sarcoma (included in the present review) Age: 11 years of age Gender: 1 female
Interventions	High-dose chemotherapy (HDCT): not specified Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> • stem cell source: peripheral blood
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: adverse events reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Mazuryk 1998

Methods	Duration: in 1996 Study design: retrospective report of a single case without control Treatment: number of arms: 1 Follow-up time: 19 months
Participants	Setting: single center in Canada Eligibility criteria: desmoplastic small round-cell tumor Number of participants: 1 patient <ul style="list-style-type: none"> 1 transplanted patients with desmoplastic small round-cell tumor (included in the present review) Age: 19 years of age Gender: 1 female
Interventions	High-dose chemotherapy (HDCT): busulfan 16 mg/kg and melphalan 140 mg/m ² , total doses Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: peripheral blood
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: adverse events reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Mingo 2005

Methods	Duration: not stated Study design: retrospective report of a single case without control Treatment: number of arms: 1 Follow-up time: 12 months
Participants	Setting: single center in Spain Eligibility criteria: desmoplastic small round-cell tumor Number of participants: 1 patient <ul style="list-style-type: none"> 1 transplanted patients with desmoplastic small round-cell tumor (included in the present review) Age: 4 years of age Gender: 1 male
Interventions	High-dose chemotherapy (HDCT): etoposide, vincristine, ifosfamide, dactinomycin, and doxorubicin Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: peripheral blood
Outcomes	Primary outcomes: overall survival reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Mitchell 1994

Methods	<p>Duration: not specified</p> <p>Study design: report of 11 cases without control, unclear if retrospective or prospective study</p> <p>Treatment: number of arms: 1</p> <p>Follow-up time: 6 months regarding the included patient</p> <p>Unclear if retrospective or prospective study without controls in a single centre, observed in the United Kingdom; information on observation period not available</p>
Participants	<p>Setting: single center in the United Kingdom</p> <p>Eligibility criteria: malignant disease</p> <p>Number of participants: 11 patients</p> <ul style="list-style-type: none"> • 1 transplanted patients with angiosarcoma (included in the present review) • not included in the present review: 5x Ewing family of tumors, 3x rhabdomyosarcoma, 1x acute myeloid leukemia, 1x T-cell lymphoma <p>Age: 16 years of age</p> <p>Gender: 1 male</p>
Interventions	<p>High-dose chemotherapy (HDCT):</p> <p>Autologous hematopoietic stem cell transplantation (HSCT)</p> <ul style="list-style-type: none"> • stem cell source: bone marrow and peripheral blood in addition
Outcomes	<p>Primary outcomes: overall survival reported as individual data</p> <p>Secondary outcomes: toxicity reported as individual data</p>
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Unclear if retrospective and no relevant aggregate data
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control

Mitchell 1994 (Continued)

Loss to follow-up	Unclear risk	Possible but not reported
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Navid 2006

Methods	Duration: 1996 to 2000 Study design: retrospective report of 24 cases without control Treatment: number of arms: 1 Follow-up time: not specified
Participants	Setting: single center in the United States Eligibility criteria: high-risk sarcomas Number of participants: 24 patients <ul style="list-style-type: none"> 2 transplanted patients with desmoplastic small round-cell tumor (included in the present review) not included in the present review: 2 patients with desmoplastic small round-cell tumor not transplanted not included in the present review: 20 patients with diagnoses other than NRSTS: 11x Ewing family of tumors, 9x rhabdomyosarcoma Age: 14 and 21 years Gender: 2 males
Interventions	High-dose chemotherapy (HDCT): cyclophosphamide and targeted topotecan Autologous hematopoietic stem cell transplantation (HSCT): <ul style="list-style-type: none"> stem cell source: bone marrow
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: adverse events reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective

Navid 2006 (Continued)

Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Patel 2004

Methods	Duration: 1994 to 2001 Study design: prospective report of 37 cases without control Treatment: number of arms: 1 Follow-up time: not specified
Participants	Setting: single center in the United States Eligibility criteria: skeletal osteosarcoma and variant bone tumors with poor prognosis Number of participants: 37 patients <ul style="list-style-type: none"> 6 transplanted patients with malignant fibrous histiocytoma (included in the present review) not included in the present review: 29 patients with diagnoses other than NRSTS: 29x osteosarcoma, 2x chondrosarcoma Age: not specified Gender: not specified
Interventions	High-dose chemotherapy (HDCT): cisplatin 120 mg/m ² , ifosfamide 10000 mg/m ² , and doxorubicin 75 mg/m ² , total doses Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: peripheral blood
Outcomes	Primary outcomes: overall survival was not reported for the 6 individual cases Secondary outcomes: toxicity reported as individual data
Notes	Financial support: not addressed The following conclusion might not clearly substantiated by the presented data: Supplemental table 2: 14 HDCT plus autologous HSCT; 18 conventional chemotherapy. Text: "HDC seemed to delay relapse, but did not appear to prolong survival: 2-year EFS 17.9 +/- 11.3% versus 13.2 +/- 8.1%, P < 0.035 and OS 51.4 +/- 14.4% versus 50.9 +/- 11.6%, P value 0.99. Two-year survival was 51.4 +/- 14.4% versus 48.6 +/- 16.7% P value 0.57 for patients treated with HDC (24 pts) versus conventional adjuvant chemotherapy (12 pts), respectively."

Risk of bias

Bias	Authors' judgement	Support for judgement
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Patel 2004 (Continued)

Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Prospective but no relevant aggregate data
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Peters 1986

Methods	Duration: not specified Study design: prospective report of cases without control Treatment: number of arms: 1 Follow-up time: not specified
Participants	Setting: single center in the United States Eligibility criteria: metastatic cancer and sarcoma Number of participants: 29 patients <ul style="list-style-type: none"> 2 transplanted patients with NRSTS: 1x fibrosarcoma, 1x leiomyosarcoma (included in the present review) not included in the present review: 27 patients with diagnoses other than NRSTS Age: 24 and 38 years Gender: 2 females
Interventions	High-dose chemotherapy (HDCT): not specified Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: bone marrow
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: toxicity reported as individual data
Notes	Financial support: not addressed
<i>Risk of bias</i>	

Peters 1986 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Prospective but no relevant aggregate data
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Peters 1989

Methods	Duration: not specified Study design: prospective report of cases without control Treatment: number of arms: 1 Follow-up time: not specified
Participants	Setting: single center in the United States Eligibility criteria: metastatic cancer and sarcoma Number of participants: 23 patients <ul style="list-style-type: none"> 2 transplanted patients synovial sarcoma (included in the present review) not included in the present review: 23 patients with diagnoses other than NRSTS Age: 15 and 26 years Gender: not specified
Interventions	High-dose chemotherapy (HDCT): not specified Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: bone marrow
Outcomes	Secondary outcomes: adverse events reported as individual data
Notes	Financial support: not addressed
<i>Risk of bias</i>	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Prospective but no relevant aggregate data
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Philippe-Chomette 2012

Methods	<p>Duration: 1995 to 2006</p> <p>Study design: retrospective of cases without concurrent control</p> <p>Treatment: number of arms: 1</p> <p>Follow-up time: median of 49 months (range 9 to 108) for survivors</p>
Participants	<p>Setting: multicenter study in France and Belgium</p> <p>Eligibility criteria: desmoplastic small round-cell tumor (DSRCT) diagnosed by the presence of the diagnostic genetic marker designated the Ewing sarcoma and Wilms tumor (EWS-WT1) fusion transcript originating at a chromosomal translocation breakpoint specific for DSRCT; patients under the age of 30 years; clinical data available</p> <p>Number of participants: 14 patients</p> <ul style="list-style-type: none"> 14 transplanted patients (included in the present review) <p>Age: range (4 to 29.7 years for 38 participants)</p> <p>Gender: 12 males and 2 females</p>
Interventions	<p>High-dose chemotherapy (HDCT): various regimens</p> <p>Autologous hematopoietic stem cell transplantation (HSCT)</p> <ul style="list-style-type: none"> stem cell source: not specified
Outcomes	<p>Primary outcomes: overall survival as aggregate data; treatment-related mortality as individual data</p> <p>Secondary outcomes: event-free survival as aggregate data; the first event of progression</p>

	or relapse was taken into account for calculation of event-free survival	
Notes	Financial support: not addressed	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Recchia 2006

Methods	Duration: not specified Study design: retrospective report of a single case without control Treatment: number of arms: 1 Follow-up time: 48 months
Participants	Setting: single center in Italy Eligibility criteria: malignant fibrous histiocytoma Number of participants: 1 patient <ul style="list-style-type: none"> 1 transplanted patients with malignant fibrous histiocytoma (included in the present review) Age: 40 years of age Gender: 1 male
Interventions	High-dose chemotherapy (HDCT): cyclophosphamide 4500 mg/m ² , carboplatin 1000 mg/m ² , and etoposide 1500 mg/m ² , total doses Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: peripheral blood

Recchia 2006 (Continued)

Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: toxicity reported as individual data	
Notes	Financial support: not addressed	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Saab 2007

Methods	Duration: not specified Study design: retrospective report of 11 cases without control Treatment: number of arms: 1 Follow-up time: from diagnosis
Participants	Setting: single center in the United States Eligibility criteria: desmoplastic small round-cell tumor Number of participants: 11 patients <ul style="list-style-type: none"> • 4 transplanted patients with desmoplastic small round-cell tumor (included in the present review) Age: 5, 14, 18, and 21 years Gender: 4 males

Interventions	High-dose chemotherapy (HDCT) <ul style="list-style-type: none"> • 2 patients: cyclophosphamide and topotecan • 1 patient: cyclophosphamide and etoposide • 1 patient: busulphan and melphalan Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> • stem cell source: not specified
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: toxicity reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Sleese 1988

Methods	Duration: not specified Study design: retrospective report of cases without control Treatment: number of arms: 1 Follow-up time: not specified
Participants	Setting: single center in the United States Eligibility criteria: refractory malignant solid tumors Number of participants: 26 patients

	<ul style="list-style-type: none">• 3 transplanted patients: 2x malignant fibrous histiocytoma, 1x leiomyosarcoma (included in the present review)• not included in the present review: 23 patients with diagnoses other than NRSTS Age: 41, 45, 47 years Gender: 3 males	
Interventions	High-dose chemotherapy (HDCT): not specified Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none">• stem cell source: bone marrow	
Outcomes	Primary outcomes: overall survival Secondary outcomes: adverse events reported as individual data	
Notes	Financial support: not addressed	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Sung 2003

Methods	Duration: 1998 to 2001 Study design: prospective report of 26 cases without control Treatment: number of arms: 1 Follow-up time: 19, 45, and 45 months regarding the included patients	
Participants	Setting: single center study in Korea Eligibility criteria: high-risk malignant solid tumors Number of participants: 26 patients <ul style="list-style-type: none">2 transplanted patients: 1x clear cell sarcoma; 1x malignant fibrous histiocytoma (included in the present review)not included in the present review: 24 patients with diagnoses other than NRSTS: 15x neuroblastoma, 3x medulloblastoma, 2x brain stem glioma, 1x glioblastoma multiforme, 1x Ewing family of tumors, 1x astrocytoma, 1x rhabdoid sarcoma, primary location not specified Age: 20 and 48 months of age Gender: 2 males	
Interventions	High-dose chemotherapy (HDCT): successive double HDCT <ul style="list-style-type: none">clear cell sarcoma: melphalan, etoposide, carboplatin, total body irradiation/cyclophosphamide, etoposiderhabdoid sarcoma: melphalan, etoposide, carboplatin/ifosfamide, carboplatin, etoposidemalignant fibrous histiocytoma: carboplatin, etoposide, melphalan/ifosfamide, carboplatin, etoposide Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none">stem cell source: peripheral blood	
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: adverse events reported as individual data	
Notes	Financial support: not addressed	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Prospective but no relevant aggregate data

Sung 2003 (Continued)

Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Yamamura 2003

Methods	Duration: in 1996 Study design: retrospective report of a single case without control Treatment: number of arms: 1 Follow-up time: 4 months following diagnosis
Participants	Setting: single center study in Japan Eligibility criteria: rhabdoid sarcoma Number of participants: 1 patient <ul style="list-style-type: none"> 1 transplanted patients with malignant fibrous histiocytoma (included in the present review) Age: 33 years of age Gender: 1 male
Interventions	High-dose chemotherapy (HDCT): tandem HDCT: ifosfamide 6000 mg/m ² , carboplatin 1200 mg/m ² , etoposide 1200 mg/m ² , total doses Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: peripheral blood
Outcomes	Primary outcomes: overall survival reported as individual data Secondary outcomes: adverse events (development of chronic myelocytic leukemia following chemotherapy) reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome

Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Yonemoto 1999

Methods	Duration: in 1995 Study design: retrospective report of 3 cases without control Treatment: number of arms: 1 Follow-up time: 6, 6, and 8 months regarding the included patients
Participants	Setting: single center study in Japan Eligibility criteria: sarcomas Number of participants: 10 patients <ul style="list-style-type: none"> 3 transplanted patients with synovial sarcoma (included in the present review) not included in the present review: 7 patients with diagnoses other than NRSTS: 6x Ewing family of tumors, 1x osteosarcoma Age: 17, 28, and 40 years of age regarding the included patients Gender: 3 males regarding the included patients
Interventions	High-dose chemotherapy (HDCT): tandem HDCT: busulfan 16 mg/kg, melphalan 140 mg/m ² , thiotepa 600 mg/m ² , total doses Autologous hematopoietic stem cell transplantation (HSCT) <ul style="list-style-type: none"> stem cell source: peripheral blood
Outcomes	Secondary outcomes: adverse events reported as individual data
Notes	Financial support: not addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No allocation concealment

Yonemoto 1999 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessor was not reported for any outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Prospective design	High risk	Retrospective
Comparable baseline characteristics	High risk	Cases without control
Assignment of patients to treatment groups	High risk	Single-arm study
Concurrent control	High risk	No control
Loss to follow-up	Unclear risk	Possible but not reported

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abdel-Dayem 1999	not intervention of interest
Abrahamsen 2000	not diagnosis of interest (histological types of sarcoma not specified)
Aleinikova 2002	not diagnosis of interest
Amarti 1995	not intervention of interest
Antman 1990	not diagnosis of interest (data not reported separately)
Arancibia 2009	not diagnosis of interest (data not reported separately)
Atra 1996	not diagnosis of interest
Atra 2002	not diagnosis of interest
Ayash 1991	not publication type of interest (review)
Baker 1987	not intervention of interest
Banna 2007	not publication type of interest (review)
Beaujean 1987	not diagnosis of interest (data not reported separately)

(Continued)

Bechter 2009	not publication type of interest (review)
Bien 2007	not diagnosis of interest
Bokemeyer 1994a	not intervention of interest
Bokemeyer 1994b	not intervention of interest
Borden 1987	not intervention of interest
Borinstein 2009	not intervention of interest
Bouligand 2007	not diagnosis of interest
Bramwell 1986	not diagnosis of interest (data not reported separately)
Bramwell 1987	not intervention of interest
Brugger 1993	not intervention of interest
Chandrakasan 2011	not intervention of interest
Chang 1988	not intervention of interest
Chen 2004	not diagnosis of interest
Childs 2004	not publication type of interest (review)
Chitalkar 2009	not diagnosis of interest (data not reported separately)
Chuman 2000	not publication type of interest (review)
Chuman 2004	not diagnosis of interest (data not reported separately)
Church 2006	not intervention of interest
Clamon 1983	not intervention of interest
Coulibaly 2008	not intervention of interest
Crist 1987	not intervention of interest
Cunningham 1994	not intervention of interest
Czyzewski 1999	not diagnosis of interest (data not reported separately)
Dantonello 2010	not diagnosis of interest (data not reported separately)

(Continued)

Devalck 1992	not publication type of interest (review)
Duffaud 2005	not diagnosis of interest
Dumontet 1992	not diagnosis of interest (data not reported separately)
Edmonson 1993	not intervention of interest
Ehlert 2012	not diagnosis of interest (data not reported separately)
Ek 2006	not publication type of interest (review)
Elias 1998	not publication type of interest (review)
Endo 1996	not diagnosis of interest (undifferentiated sarcoma)
Ettinghausen 1986	not intervention of interest
Fayette 2009	not intervention of interest
Ferrari 2005	not intervention of interest (one patient with HSCT not reported separately)
Figuerres 2000	not diagnosis of interest (data not reported separately)
Fine 2007	not intervention of interest
Florine 1988	not diagnosis of interest
Frapier 1998	not diagnosis of interest (undifferentiated sarcoma)
Frustaci 2001	not intervention of interest
Gadner 1992	not diagnosis of interest (data not reported separately)
Gadner 2002	not diagnosis of interest
Gamillscheg 1991	not diagnosis of interest (data not reported separately)
Garcia-del-Muro 2011	not intervention of interest
Ghavamzadeh 2011	not diagnosis of interest (data not reported separately)
Gooskens 2011	not diagnosis of interest
Gorin 1981	not diagnosis of interest
Gortzak 2001	not intervention of interest

(Continued)

Goto 2004	not publication type of interest (review)
Gratwohl 2004a	not diagnosis of interest (data not reported separately)
Gratwohl 2004b	not diagnosis of interest (data not reported separately)
Gratwohl 2006	not diagnosis of interest (data not reported separately)
Gu 2004	not diagnosis of interest
Halperin 1984	not intervention of interest
Hara 1998	not diagnosis of interest (rhabdomyosarcoma)
Harada 1982	not diagnosis of interest (data not reported separately)
Hartmann 1984	not diagnosis of interest
Hartmann 1997	not diagnosis of interest (data not reported separately)
Hayes-Jordan 2009	not publication type of interest (review)
Hayes-Jordan 2012	not publication type of interest (review)
He 1999	not intervention of interest
Hernandez 1999	not intervention of interest
Herzog 2005	not publication type of interest (review)
Hibi 1993	not intervention of interest
Hoeffken 1997	not diagnosis of interest (data not reported separately)
Honda 2011	not diagnosis of interest
Horiuchi 2005	not diagnosis of interest
Hubbard 1977	not intervention of interest
Hutspardol 2012	not diagnosis of interest
Ivanova 2010	not diagnosis of interest (data not reported separately)
Iyer 2013	not intervention of interest
Jamil 2004	not diagnosis of interest (data not reported separately)

(Continued)

Jebson 2004	not intervention of interest
Jelic 1997	not intervention of interest
Kabickova 2003	not diagnosis of interest (data not reported separately)
Kallianpur 2012	not publication type of interest (review)
Kaminski 2000	not diagnosis of interest (intracranial)
Kampe 1993	not intervention of interest
Kasper 2005	not publication type of interest (review)
Kasper 2006	not publication type of interest (duplicate data included in follow-up paper Kasper 2008)
Katzenstein 2003	not diagnosis of interest
Kingston 1984	not diagnosis of interest
Kinsella 1988	not diagnosis of interest (data not reported separately)
Kinugawa 1995	not intervention of interest
Kiss 2009	not diagnosis of interest (data not reported separately)
Klein 1983	not intervention of interest
Klingebiel 2008	not diagnosis of interest (data not reported separately)
Koscielniak 1997	not diagnosis of interest
Koscielniak 1999	not intervention of interest
Koscielniak 2002	not publication type of interest (review)
Kuehne 2000	not diagnosis of interest
Kushner 2000	not intervention of interest (data not reported separately)
Kwon 2010	not diagnosis of interest
Ladenstein 1997	not diagnosis of interest (data not reported separately)
Lal 2005	not intervention of interest (data not reported separately)
Lasalvia-Prisco 2012	not diagnosis of interest (data not reported separately)

(Continued)

Le Cesne 2000	not intervention of interest
Leyvraz 2006	not intervention of interest
Lorigan 2007	not intervention of interest
Macak 2003	not intervention of interest
Makris 2009	not intervention of interest
Maraninchi 1984	not diagnosis of interest
Maurel 2009	not intervention of interest
Mesia 1994	not diagnosis of interest (undifferentiated sarcoma)
Minard-Colin 2004	not intervention of interest
Mohensy 2011	not intervention of interest
Mueller 2002	not diagnosis of interest
Nachbaur 1994	not diagnosis of interest
Nag 1995	not intervention of interest (radiotherapy)
Nakamura 2008	not diagnosis of interest (undifferentiated sarcoma)
Nath 2005	not diagnosis of interest
Nemet 1990	not diagnosis of interest
Nemet 1999	not diagnosis of interest
Nickerson 2004	not intervention of interest
Nieboer 2005	not diagnosis of interest
Nieto 1999	not publication type of interest (review)
Nieto 2004	not publication type of interest (review)
Nieto 2007	not diagnosis of interest (data not reported separately)
Ninomiya 1988	not diagnosis of interest (data not reported separately)
Nivison-Smith 2005	not diagnosis of interest (data not reported separately)

(Continued)

Odile 2008	not intervention of interest
Ortega 1991	not diagnosis of interest
Oue 2010	not diagnosis of interest
Ozkaynak 2008	not diagnosis of interest
Palumbo 1997	not intervention of interest
Pasetto 2003	not publication type of interest (review)
Passweg 2012	not outcome of interest
Patel 1992	not publication type of interest (review)
Patel 1998	not intervention of interest
Perez-Gracia 2001	not diagnosis of interest (data not reported separately)
Perez-Martinez 2003	not intervention of interest
Perez-Martinez 2011	not intervention of interest
Pick 1988	not publication type of interest (review)
Pinkerton 1991	not diagnosis of interest
Pohlodek 1994	not outcome of interest
Radulescu 2008	not diagnosis of interest
Rapidis 2008	not publication type of interest (review)
Ray-Coquard 2001	not publication type of interest (review)
Reichardt 1998	not intervention of interest
Rich 1980	not diagnosis of interest
Ronghe 2004	not diagnosis of interest (rhabdoid tumor without information about localisation)
Rupolo 2001	not intervention of interest
Rzepecki 2006	not diagnosis of interest (data not reported separately)
Samma 1994	not diagnosis of interest

(Continued)

Sano 2012	not intervention of interest
Santoro 1995	not diagnosis of interest
Sawyer 1999	not publication type of interest (review)
Schellong 1981	not publication type of interest (review)
Schilder 1999	not diagnosis of interest
Schilder 2001	not diagnosis of interest
Schimmer 2002	not diagnosis of interest (data not reported separately)
Schlegel 2009	not intervention of interest
Schlemmer 2006	not diagnosis of interest (data not reported separately)
Schuster 2008	not diagnosis of interest (data not reported separately)
Schwartzberg 1993	not diagnosis of interest
Schwella 1998	not diagnosis of interest (data not reported separately)
Seibel 2004	not intervention of interest
Seynaeve 1999	not publication type of interest (review)
Shaw 1996	not diagnosis of interest (undifferentiated sarcoma; rhabdoid tumor without information about localisation)
Shen 1993	not diagnosis of interest
Shenoy 2010	not diagnosis of interest
Shvarova 2009	not intervention of interest
Slovacek 2007	not publication type of interest (review)
Somers 2006	not diagnosis of interest (histologic type not specified for individual data)
Sudo 1991	not intervention of interest
Tajima 1983	not diagnosis of interest
Tajima 1988	not diagnosis of interest
Takeda 1995	not disease of interest

(Continued)

Taskinen 1998	not diagnosis of interest
Termuhlen 2006	not disease of interest
Tursz 1996	not intervention of interest
Unruh 1979	not intervention of interest
Van Glabbeke 1993	not intervention of interest
Verma 2002	not publication type of interest (review)
Verma 2008a	not publication type of interest (systematic review)
Verma 2008b	not publication type of interest (review)
Verweij 2000	not intervention of interest
Walker 2004	not intervention of interest
Watanabe 2006	not diagnosis of interest (rhabdoid tumor without information about localisation)
Webber 2007	not intervention of interest
Weh 1996	not intervention of interest
Woods 1999	not publication type of interest (review)
Yamada 1999	not diagnosis of interest
Yaqoob 2006	not publication type of interest (review)
Yeung 1994	not diagnosis of interest
Yokoyama 1993	not intervention of interest
Yumura-Yagi 1998	not diagnosis of interest
Zoubek 1994	not intervention of interest

Characteristics of ongoing studies *[ordered by study ID]*

NCT00002601

Trial name or title	Title: Combination chemotherapy and peripheral stem cell transplantation in treating patients with sarcoma Official Title: High-dose doxorubicin and ifosfamide followed by melphalan and cisplatin for patients with high-risk and recurrent sarcoma
Methods	Study start date: September 1994 Estimated primary completion date: March 2013 Study design: Intervention model: single group assignment; Masking: open label; Primary purpose: treatment Treatment: number of arms: 1 Follow-up time: 2 years after completion of treatment
Participants	Setting: single center in the United States: City of Hope Eligibility criteria: 10 to 55 years of age; patients with high risk or advanced soft tissue sarcoma, osteosarcoma, Ewing family of tumors, or rhabdomyosarcoma; Karnofsky performance status 80% to 100%; other criteria apply Estimated enrollment: 20 patients
Interventions	High-dose chemotherapy (HDCT): cisplatin, doxorubicin, ifosfamide, melphalan Autologous hematopoietic stem cell transplantation (HSCT): stem cell source: peripheral blood
Outcomes	Overall survival, disease-free survival, response, toxicity, feasibility of administration of 2 cycles of high-dose chemotherapy followed by autologous HSCT
Starting date	September 1994 This study is ongoing, but not recruiting participants
Contact information	Study chair: George Somlo, MD, City of Hope, Beckman Research Institute, Duarte, California, United States
Notes	Financial support: non-profit organization

NCT00002854

Trial name or title	Title: High-dose combination chemotherapy plus peripheral stem cell transplantation in treating patients with advanced cancer Official Title: Phase I pilot study of sequential high-dose cycles of cisplatin, cyclophosphamide, etoposide and ifosfamide, carboplatin and taxol with autologous stem cell support
Methods	Study start date: December 1994 Estimated primary completion date: February 2013 Study design: Intervention model: single group assignment; Masking: open label; Primary purpose: treatment Treatment: number of arms: 1 Follow-up time: for at least 5 years after completion of treatment
Participants	Setting: single center in the United States: City of Hope Eligibility criteria: 18 to 55 years of age; patients with primary soft tissue sarcoma with high-grade disease greater than 10 cm or that is metastatic, osteosarcoma, breast carcinoma, ovarian cancer, malignant melanoma,

NCT00002854 (Continued)

	metastatic small cell bone carcinoma, metastatic Ewing family of tumors, metastatic gastrointestinal malignancy or recurrent Wilms tumor; Karnofsky performance status 80% to 100%; other criteria apply Estimated enrollment: 6 patients
Interventions	High-dose chemotherapy (HDCT): cisplatin, cyclophosphamide, etoposide and ifosfamide, carboplatin and taxol Autologous hematopoietic stem cell transplantation (HSCT): stem cell source: peripheral blood
Outcomes	Toxicity, feasibility of administration of 2 cycles of high-dose chemotherapy followed by autologous HSCT
Starting date	September 1994 This study is ongoing, but not recruiting participants
Contact information	Study chair: George Somlo, MD, City of Hope, Beckman Research Institute, Duarte, California, United States
Notes	Financial support: non-profit organization

NCT00141765

Trial name or title	Title: Study of high-dose chemotherapy with bone marrow or stem cell transplant for rare poor-prognosis cancers Official Title: High-dose doxorubicin and ifosfamide followed by melphalan and cisplatin for patients with high-risk and recurrent sarcoma
Methods	Study start date: January 1997 Estimated primary completion date: January 2014 Study design: Intervention model: single group assignment; Masking: open label; Primary purpose: treatment Treatment: number of arms: 1 Follow-up time: 1 year after completion of treatment
Participants	Setting: single center in the United States: The University of Michigan Eligibility criteria: 21 years old or younger, histologically-confirmed Wilms tumor, liver cancer, recurrent brain tumor of childhood, nasopharyngeal carcinoma, fibrosarcoma, desmoplastic small round cell tumor, germ cell tumor or other small round cell tumor, which: is metastatic and has <25% cure rate with conventional treatment or progressed after prior chemotherapy and has <25% salvage rate with non-myeloablative therapies; other criteria apply Estimated enrollment: not stated
Interventions	High-dose chemotherapy (HDCT): cyclophosphamide, ifosfamide, carboplatin and thiotepa Autologous hematopoietic stem cell transplantation (HSCT): stem cell source: peripheral blood
Outcomes	Disease-free survival
Starting date	January 1997 This study is ongoing, but not recruiting participants

NCT00141765 (Continued)

Contact information	Principal investigator: John E Levine, MS MD, The University of Michigan, Ann Arbor, Michigan, United States
Notes	Financial support: non-profit organization

NCT00623077

Trial name or title	Title: Total marrow irradiation added to an alkylator-intense conditioning regimen for patients with high risk or relapsed solid tumors Official Title: Dose escalation of total marrow irradiation added to an alkylator-intense conditioning regimen for patients with high risk or relapsed solid tumors
Methods	Study start date: August 2005 Estimated primary completion date: June 2014 Study design: Endpoint classification: safety/efficacy study; Intervention model: single group assignment; Masking: open label; Primary purpose: treatment Treatment: number of arms: 1 Follow-up time: not stated
Participants	Setting: single center in the United States: University of Minnesota, Masonic Cancer Center Eligibility criteria: up to 70 years; patients with high risk or relapsed malignancies that include: Ewing family of tumors, Wilms tumor, clear cell sarcoma, rhabdoid tumor, hepatoblastoma, rhabdomyosarcoma, soft tissue sarcoma, primary malignant brain neoplasm, retinoblastoma; other criteria apply Estimated enrollment: 45 patients
Interventions	Total marrow irradiation with tomotherapy High-dose chemotherapy (HDCT): busulfan, melphalan, thiotepa Autologous hematopoietic stem cell transplantation (HSCT): stem cell source: peripheral blood
Outcomes	Primary Outcome Measures: Maximum tolerated dose of tomotherapy up to 12 Gy Secondary Outcome Measures: Overall survival, disease-free survival, rate of treatment-related mortality
Starting date	August 2005 This study is ongoing, but not recruiting participants
Contact information	Principal investigator: Michael R Verneris, MD, University of Minnesota, Masonic Cancer Center, Minneapolis, Minnesota, United States
Notes	Financial support: non-profit organization

NCT00638898

Trial name or title	Title: Busulfan, melphalan, topotecan hydrochloride, and a stem cell transplant in treating patients with newly diagnosed or relapsed solid tumor Official Title: Pilot study of high-dose chemotherapy with busulfan, melphalan, and topotecan followed by autologous hematopoietic stem cell transplant in advanced stage and recurrent tumors
Methods	Study start date: December 2006 Estimated primary completion date: April 2019 Study design: Endpoint classification: efficacy study; Intervention model: single group assignment; Masking: open label; Primary purpose: treatment Treatment: number of arms: 1 Follow-up time: After completion of study treatment, patients are followed every 3 months for 1 year and then annually thereafter
Participants	Setting: single center in the United States: City of Hope Eligibility criteria: up to 70 years; patients with relapsed neuroblastoma, rhabdomyosarcoma, Ewing family of tumor, brain tumor, soft tissue sarcomas Wilms tumor, germ cell tumor or other solid tumor who achieved at least partial response to chemotherapy, surgery, or radiotherapy; other criteria apply Estimated enrollment: 25 patients
Interventions	High-dose chemotherapy (HDCT): busulfan, melphalan, topotecan Autologous hematopoietic stem cell transplantation (HSCT): stem cell source: peripheral blood
Outcomes	Primary Outcome Measures: Treatment feasibility in terms of investigational agent-related adverse events of a novel treatment combination followed by peripheral blood stem cell rescue Secondary Outcome Measures: Overall survival, disease-free survival, Incidence of myeloid and platelet engraftment
Starting date	December 2006 This study is currently recruiting participants
Contact information	Principal investigator: Anna Pawlowska, MD, City of Hope, Duarte, California, United States
Notes	Financial support: non-profit organization

NCT01288573

Trial name or title	Title: A combined study in pediatric cancer patients for dose ranging and efficacy/safety of plerixafor plus standard regimens for mobilization versus standard regimens alone Official Title: A phase 1/2 combined dose ranging and randomized, open-label, comparative study of the efficacy and safety of plerixafor in addition to standard regimens for mobilization of haematopoietic stem cells into peripheral blood, and subsequent collection by apheresis, versus standard mobilization regimens alone in pediatric patients, aged 2 to <18 years, with solid tumours eligible for autologous transplants
Methods	Study start date: February 2011 Estimated primary completion date: May 2017 Study design: Allocation: randomized; Endpoint classification: safety/efficacy study; Intervention model: parallel assignment; Masking: open label; Primary purpose: treatment Treatment: number of arms: 2

	Follow-up time: up to 24 months after completion of study treatment
Participants	Setting: multicenter trial in France, Germany, Italy, and the United Kingdom Eligibility criteria: 2 to 18 years of age; patients with Ewing family of tumor, soft tissue sarcoma, neuroblastoma, brain tumors or other malignancy (excluding any form of leukemia) requiring treatment with high dose chemotherapy and autologous transplant as rescue therapy; other criteria apply Estimated enrollment: 67 patients
Interventions	High-dose chemotherapy (HDCT): not specified Autologous hematopoietic stem cell transplantation (HSCT): stem cell source: peripheral blood
Outcomes	Primary Outcome Measures: Proportion of patients achieving at least a doubling of peripheral blood CD34+ count during Stage 2 Secondary Outcome Measures: Survival rates
Starting date	February 2011 This study is currently recruiting participants
Contact information	Study director: Medical Monitor, Genzyme Corporation (sponsor of the trial)
Notes	Financial support: Genzyme Corporation (biotechnology company)

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Frequency of subtypes of included NRSTS in patients of young versus advanced age

Young age (< 20 years)		Advanced ($\geq$ 20 years)	
Subtype	%	Subtype	%
Synovial sarcoma	7.7	Leiomyosarcoma	13.7
Malignant fibrous histiocyoma	4.9	Malignant fibrous histiocyoma	10.1
Fibrosarcoma	4.5	Liposarcoma	8.0
Liposarcoma	2.8	Hemangiosarcoma	2.5
Epithelioid sarcoma	2.0	Spindle cell sarcoma	2.3

Estimates in the table according to [Spunt 2006](#)

Table 2. Included non-rhabdomyosarcoma soft tissue sarcomas (NRSTS)

Diagnosis(*)
Alveolar soft part sarcoma
Anaplastic soft tissue sarcoma
Angiosarcoma <ol style="list-style-type: none"> 1. Angiosarcoma of soft tissue 2. Hemangiosarcoma 3. Hemangiopericytoma 4. Lymphangiosarcoma
Clear cell myomelanocytic tumor
Clear cell sarcoma of soft tissue
Desmoplastic small round cell tumor
Epithelioid sarcoma

Table 2. Included non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) (Continued)

Fibrosarcoma <ul style="list-style-type: none"> 1. Adult fibrosarcoma 2. Myxofibrosarcoma 3. Low grade fibromyxoid sarcoma; hyalinizing spindle cell tumor 4. Sclerosing epithelioid fibrosarcoma
Fibromyxoid sarcoma
Epithelioid hemangioendothelioma
Intimal sarcoma
Leiomyosarcoma <ul style="list-style-type: none"> 1. Leiomyosarcoma (excluding skin)
Liposarcoma <ul style="list-style-type: none"> 1. Dedifferentiated liposarcoma 2. Myxoid liposarcoma 3. Round cell liposarcoma 4. Pleomorphic liposarcoma 5. Mixed-type liposarcoma 6. Liposarcoma, not otherwise specified (added by authors: chondroid liposarcoma)
Malignant fibrous histiocyoma <ul style="list-style-type: none"> 1. Pleomorphic malignant fibrous histiocyoma; undifferentiated pleomorphic sarcoma 2. Giant cell malignant fibrous histiocyoma; undifferentiated pleomorphic sarcoma with giant cells 3. Inflammatory malignant fibrous histiocyoma; undifferentiated pleomorphic sarcoma with prominent inflammation 4. Undifferentiated pleomorphic sarcoma 5. Spindle cell sarcoma
Malignant glomus tumor
Malignant haemangiopericytoma
Malignant mesenchymoma
Mesenchymal sarcoma
Neoplasms with perivascular epithelioid cell differentiation (PEComa)
Rhabdoid sarcoma <ul style="list-style-type: none"> 1. Extra-renal rhabdoid tumor 2. Extra-cerebral rhabdoid tumor
Synovial sarcoma

* category of malignant tumors according to the *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Soft Tissue and Bone* (Fletcher 2002)

Table 3. Excluded tumor types

Diagnosis	Reason for exclusion(*)
Atypical teratoid/rhabdoid tumors	WHO classification of tumors of the central nervous system
Chondrosarcoma 1. Mesenchymal chondrosarcoma 2. Extraskelatal myxoid chondrosarcoma ('chordoid type')	Extraskelatal types are difficult to separate
Clear cell sarcoma of the kidney	Excluded by the authors of the present review
Dermatofibrosarcoma protuberans	WHO classification of tumors of the skin
Endometrial stroma sarcoma	WHO classification of tumors: pathology and genetics of tumors of the breast and female genital organs
Ewing family of tumors 1. Ewing sarcoma 2. Skeletal Ewing's sarcoma 3. Extraskelatal Ewingsarcoma 4. Peripheral primitive neuroectodermal tumour (pPNET) 5. Extraskelatal peripheral primitive neuroectodermal tumor (pPNET) 6. Askin tumor	Extraskelatal types are difficult to separate; the Ewing family of tumors is one entity
Extragonadal germ cell sarcoma	WHO classification of tumors: pathology and genetics of tumors of the urinary system and male genital organs WHO classification of tumors: pathology and genetics of tumors of the breast and female genital organs
Follicular dendritic cell sarcoma	WHO classification of tumors of hematopoietic and lymphoid tissues
Ganglioneuroblastoma	WHO classification of nervous system tumors
Gastrointestinal stromal tumor	WHO classification of tumors: pathology and genetics of tumors of the digestive system
Giant cell fibroblastoma	WHO classification of tumors of the skin
Giant cell tumour of bone	WHO classification for tumors of bone tissue
Histiocytic sarcoma	WHO classification of tumors of hematopoietic and lymphoid tissues
Interdigitating dendritic cell sarcoma	WHO classification of tumors of hematopoietic and lymphoid tissues

Table 3. Excluded tumor types (Continued)

Interdigitating reticulum cell sarcoma	WHO classification of tumors of hematopoietic and lymphoid tissues
Kaposi sarcoma	Intermediate malignancy (rarely metastasizing)
Lymphoblastic lymphosarcoma	WHO classification of tumors of hematopoietic and lymphoid tissues
Malignant ectomesenchymoma	Excluded by the authors of the present review
Medulloblastoma	WHO classification of tumors of the central nervous system
Myeloid sarcoma	WHO classification of tumors of hematopoietic and lymphoid tissues
Myxosarcoma (cardiac tumor)	WHO classification of tumors: pathology and genetics of tumors of the lung, pleura, thymus and heart
Nephroblastoma	WHO classification of tumors: pathology and genetics of tumors of the urinary system and male genital organs
Neuroblastoma (Wilms tumor)	WHO classification of tumors: pathology and genetics of tumors of the urinary system and male genital organs
Osteosarcoma 1. Extraskelatal osteosarcoma	Extraskelatal types are difficult to separate
Paraganglioma	WHO classification of nervous system tumors
Peripheral nerve sheath tumor, malignant (neurofibrosarcoma)	WHO classification of nervous system tumors
Rhabdoid tumor, renal	WHO classification of tumors: pathology and genetics of tumors of the urinary system and male genital organs
Rhabdoid tumor, cerebral	WHO classification of tumors of the central nervous system
Rhabdomyosarcoma 1. Embryonal rhabdomyosarcoma (including spindle cell, botryoid, anaplastic) 2. Alveolar rhabdomyosarcoma (including solid, anaplastic) 3. Pleomorphic rhabdomyosarcoma 4. Undifferentiated rhabdomyosarcoma	A soft tissue sarcoma that is excluded to separate rhabdomyosarcomas from non-rhabdomyosarcoma soft tissue sarcomas
Schwannoma, malignant (Schwannosarcoma)	WHO classification of nervous system tumors
Stromal cell sarcoma	Not part of the WHO classification of soft tissue sarcomas, malignant tumors

Table 3. Excluded tumor types (Continued)

Unclassified sarcoma	It is not clear that the tumor is a non-rhabdomyosarcoma soft tissue sarcoma
Undifferentiated sarcoma	It is not clear that the tumor is a non-rhabdomyosarcoma soft tissue sarcoma
Uterine endometrial stromal sarcoma	WHO classification of tumors: pathology and genetics of tumors of the breast and female genital organs

* WHO: World Health Organization

Table 4. Included studies identified by only one search strategy

Old strategy (original)	New strategy (update)
	Bisogno 2010
	Buerk 2010
	Bui-Nguyen 2012
	Cook 2012
	Etienne-Mastroianni 2002
Fang 2008	
Graham 1997	
Hawkins 2002	
	Houet 2010
	Jordan 2010
Kretschmar 1996	
Krskova 2007	
Matsuzaki 2002	
Peters 1986	
Peters 1989	
	Philippe-Chomette 2012

Table 4. Included studies identified by only one search strategy (Continued)

Slease 1988

Eight studies were published after the original retrieval and were added to the included studies: Bisogno 2010; Buerk 2010; Bui-Nguyen 2012; Cook 2012; Etienne-Mastroianni 2002; Houet 2010; Jordan 2010; Philippe-Chomette 2012.

Nine further studies were included in the original review but were not identified by the new search strategy: Fang 2008; Graham 1997; Hawkins 2002; Kretschmar 1996; Krskova 2007; Matsuzaki 2002; Peters 1986; Peters 1989; Slease 1988. These 15 studies were included in the update in addition to the results of the new search strategy.

Three further studies were included in the original review and identified in the update but excluded after re-evaluation: Ivanova 2010; Kaminski 2000; Kuehne 2000.

Three further studies were excluded in the original review and identified in the update but included after re-evaluation: Blay 2000; Fetscher 1996; Mingo 2005.

Six further studies were included in the original review and not identified in the update but excluded after re-evaluation: Four studies reported about undifferentiated sarcoma, which is not included: Endo 1996; Frapier 1998; Mesia 1994; Nakamura 2008. One study reported about rhabdoid tumor but without information about the localisation, which is required for identification of the extra-renal and the extra-cerebral rhabdoid tumors: Ronghe 2004. One study reported about undifferentiated sarcoma and rhabdoid tumor without information about the localisation: Shaw 1996.

Table 5. Overview of included studies

Study	Total, N	Diagnosis			Start of follow up	Prospective	HDCT vs. SDCT, N analyzed
		Not rel, N (%)	Rel, N	Affected patients, N; type of included diagnosis			
Aggregate comparative data (HDCT & autologous HSCT vs. SDCT)							
Bui-Nguyen 2012	87	18 (20)	69	16x LMS, 16x MFH, 10x LPS, 9x SYN, 6x ANG, 2x UDS, 2x MME, 2x DSRCT, 2x FIB, 1x LMS, 1x UCS, 1x CCS	Randomization	YES	38 vs. 45 in ITT ^(*)
Subtotal comparative data in 1 study							38 vs. 45
Aggregate case series data (HDCT & autologous HSCT only)							
Bertuzzi 2003	10	0 (0)	10	10x DSRCT	Therapy	YES	10
Bisogno 2010	14	0 (0)	14	14x DSRCT	Diagnosis	YES	14
Blay 2000	24	2 (10)	22	24x NRSTS	Therapy	YES	24

Table 5. Overview of included studies (Continued)

Bokemeyer 1997	18	2 (11)	16	5x MFH, 4x HAP, 3x SYN, 2x LMS, 2x MES	Therapy	no	16
Cook 2012	36	0 (0)	36	36x DSRCT	Therapy	no	36
Philippe-Chomette 2012	14	0 (0)	14	14x DSRCT	Diagnosis	no	14
<i>Subtotal case series in 6 studies</i>							<i>114</i>
Individual cases data (HDCT & autologous HSCT only)							
Al Balushi 2009	3			3x DSRCT		no	3
Andres 2006	1			1x DSRCT		no	1
Bernbeck 2007	2			2x SYN		no	2
Bley 2004	1			1x LIP		no	1
Boelke 2005	1			1x MFH		no	1
Buerk 2010	1			1x MFH		no	1
Cole 1999	1			1x SYN		no	1
Doros 2008	1			1x DSRCT		no	1
Engelhardt 2007	35			ANA, ANG, FIB, LMS, LIP, MFH, MHP, SYN		no	23
Etienne-Mastroianni 2002	12			1x LMS		no	1
Fang 2008	2			1x DSRCT		no	1
Farruggia 2008	1			1x SYN		no	1
Fetscher 1996	1			1x LMS		no	1
Fetscher 1997	1			1x LMS		no	1

Table 5. Overview of included studies (Continued)

Fraser 2006	36			4x DSRCT		YES	4
Garrido 1998	2			1x LIP		no	1
Graham 1997	49			1x FIB		YES	1
Hara 2010	1			1x ANG		no	1
Hawkins 2002	23			2x DSRCT, 1x FMS, 1x LMS		YES	6
Hoogerbrugge 1997	1			1x FIB		no	1
Houet 2010	1			1x DSRCT		no	1
Jordan 2010	16			2x EPI, 1x SYN, 1x SCS, 1x LMS, 1x ANG, 1x HAP		YES	7
Kasper 2007a	38			5x SYN, 3x LMS, 2x LIP 1x MFH		no	11
Kasper 2010	9			2x MFH, 1x LMS, 1x SYN		YES	4
Kozuka 2002	2			1x MFH, 1x MHP		no	2
Kretschmar 1996	3			1x DSRCT		no	1
Krskova 2007	1			1x SYN		no	1
Kurre 2000	2			2x DSRCT		no	2
Kushner 1996	12			4x DSRCT		YES	4
Kushner 2001	21			1x DSRCT		YES	1
Kushner 2008	1			1x DSRCT		no	1
Lafay-Cousin 2000	18			2x DSRCT		YES	2
Lashkari 2009	13			1x MFH		YES	1
Lippe 2003	2			1x DSRCT		no	1

Table 5. Overview of included studies (Continued)

Livaditi 2006	5			2x DSRCT		no	2
Madigan 2007	14			1x RHA		no	1
Matsuzaki 2002	1			1x SYN		no	1
Mazuryk 1998	1			1x DSRCT		no	1
Mingo 2005	1			1x DSRCT		no	1
Mitchell 1994	11			1x ANG		no	1
Navid 2006	24			2x DSRCT		no	2
Patel 2004	37			6x MFH		YES	6
Peters 1986	29			1x FIB, 1x LMS		YES	2
Peters 1989	23			2x SYN		YES	2
Recchia 2006	1			1x MFH		no	1
Saab 2007	4			4x DSCRT		no	4
Slease 1988	26			2x MFH, 1x LMS		no	3
Sung 2003	26			1x CCS, 1x MFH		no	2
Yamamura 2003	1			1x MFH		no	1
Yonemoto 1999	10			3x SYN		no	3
<i>Subtotal individual cases in 50 studies</i>							<i>123</i>
Summary of patient count							
<i>Subtotal HDCT & autologous HSCT in 57 studies</i>							<i>275</i>
<i>Subtotal SDCT in 1 study</i>							<i>45</i>
<i>Total in 57 studies</i>							<i>320</i>

(*) modified ITT: histologically ineligible patients excluded from primary group of analysis; HDCT group: 3 of 41 randomized data excluded; SDCT group: 1 of 46 randomized data excluded

Abbreviations: Diag: diagnosis; HDCT: high-dose chemotherapy (& autologous hematopoietic stem cell transplantation); HR: hazard ratio; HSCT: hematopoietic stem cell transplantation; ITT: intention to treat; N: number of participants; Nspe: not specified; Prosp: prospective study design; Rand: randomization Rel: relevant; SDCT: standard-dose chemotherapy; Ther: therapy; vs.: versus
Diagnoses: ANA: anaplastic soft tissue sarcoma; ANG: angiosarcoma; CCS: clear cell sarcoma; DSRCT: desmoplastic small round-cell tumor; EPI: epitheloid sarcoma; FIB: fibrosarcoma; FMS: fibromyxoid sarcoma; HAP: hemangiopericytoma; LIP: liposarcoma; LMS: leiomyosarcoma; MES: mesenchymal sarcoma; MFH: malignant fibrous histiocytoma; MHP: malignant hemangiopericytoma; MME: malignant myoepithelioma; NRSTS: various types of non-rhabdomyosarcoma soft tissues sarcomas; RHA: rhabdoid tumor; SCS: spindle cell sarcoma; SYN: synovial sarcoma; UCS: unclassified sarcoma; UDS: undifferentiated sarcoma

Table 6. Overall survival (OS)

Study	OS, % (95% CI)		
	All patients assessed	Complete response before the time of HSCT	Not complete response before the time of HSCT
Aggregate comparative data (HDCT & autologous HSCT vs. SDCT)			
Bui-Nguyen 2012	3 years: 32.7% vs. 49.4%, HR 1.26 (0.70 to 2.29, P = 0.44)	3 years: 42.8% vs. 83.9%, HR 2.92 (1.1 to 7.6, P = 0.028)	Not reported
Aggregate case series data (HDCT & autologous HSCT only)			
Bertuzzi 2003	2 years: 20%	Not reported	Not reported
Bisogno 2010	2 years: 48% 3 years: 38.9%	Not reported	Not reported
Blay 2000	Not reported	2 years: 62% 5 years: 62%	2 years: 27% 5 years: 5%
Bokemeyer 1997	Median 13 months (range 3 to 19)	Not reported	Not reported
Cook 2012	3 years: 40% (24 to 58)	3 years: 57% (29 to 83)	3 years: 28% (9 to 51)
Philippe-Chomettte 2012	2 years: 51.4% (23.2 to 79.6)	Not reported	Not reported
Individual cases data (HDCT & autologous HSCT only)			
50 studies	2 years: 50.6% (38.7 to 62.5) 3 years: 36.7 (24.4 to 49.0) 5 years: 29.9 (16.7 to 43.1)	Not reported	Not reported

Some estimates were deduced from Kaplan-Meier plot.

Bisogno 2010: 1 of 14 patients was reported to have achieved complete response before HDCT

Blay 2000: all patients in subgroup N = 24, patients that achieved complete remission before HDCT N = 8, patients that did not achieve complete remission before HDCT N = 16

Bui-Nguyen 2012: all patients N = 38 vs. N = 45, patients that achieved complete remission before HDCT N = 20 vs. N 19
Cook 2012: all patients N = 36, patients that achieved complete remission before HDCT N = 13, patients that did not achieve complete remission before HDCT N = 18
Abbreviation: CI: confidence interval; HDCT: high-dose chemotherapy; HR: hazard ratio; HSCT: hematopoietic stem cell transplantation; OS: overall survival; SDCT: standard-dose chemotherapy

Table 7. Overall survival: Individual cases data

Study	Diagnosis	Overall survival ^(*) , 0 = alive, 1= dead	Follow up ^(**) , months
Al Balushi 2009	DSRCT	0	72
	DSRCT	0	24
	DSRCT	0	18
Andres 2006	DSRCT	0	10
Bernbeck 2007	SYN	1	
	SYN	0	
Bley 2004	LPS	0	7
Boelke 2005	MFH	0	89
Buerk 2010	ANG	0	1
Cole 1999	SYN	0	6
Doros 2008	DSRCT	1	0
Engelhardt 2007	LPS	0	
	LPS	1	
	LPS	0	
	ANA	1	
	ANA	1	
	ANA	0	
	ANA	0	
	ANA	1	
	LMS	0	
	LMS	1	

Table 7. Overall survival: Individual cases data (Continued)

	LMS	1	
	LMS	1	
	SYN	0	
	SYN	1	
	SYN	1	
	SYN	1	
	SYN	1	
	MFH	0	
	FIB	1	
	FIB	1	
	ANG	0	
	ANG	1	
	MHP	1	
Etienne-Mastroianni 2002	LMS	0	78
Farruggia 2008	SYN	0	36
Fetscher 1996	LMS	0	
Fetscher 1997	LMS	0	36
Fraser 2006	DSRCT	0	
	DSRCT	0	
	DSRCT	0	
	DSRCT	0	
Garrido 1998	LPS	0	
Hara 2010	ANG	1	67
Hoogerbrugge 1997	FIB	1	8
Houet 2010	DSRCT	0	120

Table 7. Overall survival: Individual cases data *(Continued)*

Jordan 2010	SYN	1	8
	MHP	1	29
	ANG	1	6
	EPI	1	7
	EPI	1	6
	LMS	1	3
	SCS	1	15
Kasper 2007	LPS	1	11
	MFH	0	6
	LPS	0	54
	SYN	1	0
	SYN	1	14
	SYN	1	19
	LMS	1	26
	LMS	1	4
	SYN	1	4
	SYN	1	16
	LMS	0	2
Kasper 2010	SYN	1	22
	MFH	1	27
	LMS	0	33
	MFH	1	12
Kozuka 2002	MFH	1	32
	MHP	0	23
Kurre 2000	DSRCT	0	26

Table 7. Overall survival: Individual cases data (Continued)

	DSRCT	0	42
Kushner 2008	DSRCT	0	48
Kushner 2001	DSRCT	0	8
Kushner 1996	DSRCT	0	23
	DSRCT	1	21
	DSRCT	0	13
	DSRCT	0	34
Lafay-Cousin 2000	DSRCT	1	8
	DSRCT	1	31
Lashkari 2009	MFH	0	99
Lippe 2003	DSRCT	1	34
Livaditi 2006	DSRCT	1	15
	DSRCT	1	11
Madigan 2007	RHA	0	104
Mazuryk 1998	DSRCT	0	19
Mingo 2005	DSRCT	1	36
Mitchell 1994	ANG	0	6
Navid 2006	DSRCT	1	3
	DSRCT	1	15
Patel 2004	MFH	0	
	MFH	1	
	MFH	1	
	MFH	1	
	MFH	1	
	MFH	1	

Table 7. Overall survival: Individual cases data (Continued)

Recchia 2006	MFH	1	48
Saab 2007	DSRCT	1	16
	DSRCT	1	2
	DSRCT	1	4
	DSRCT	0	17
Sung 2003	MFH	0	19
	CCS	0	45
Watanabe 2006	RHA	0	36
Yamamura 2002	MFH	1	60
Yonemoto 1999	SYN	1	6
	SYN	1	6
	SYN	0	8
Total: 42 studies	Patients: 108	Alive: 49 Dead: 59	FU reported: 71

(*) Overall survival is dichotomized in alive (0) vs. dead (1) at follow up. Alive includes outcomes such as no evidence of disease, alive with disease, and alive with no further information about disease status. Dead includes outcomes such as died of disease, died of complications, and died with no further information of the cause of death. 45% (49 of 108) patients were reported as alive after a wide range of follow up time. This proportion remained 46% (33 of 71) after limiting to patients with follow up data.

(**) Follow up was reported for 66% (71 of 108) patients and varied between 0 and 108 months after the period between diagnosis and beginning of HDCT. The time to event data of these 71 patients were used in a Kaplan Meier survival analysis. For 34% (37 of 108) patients, follow up was not reported and the data of those 37 patients could not be included in the survival analysis.

Abbreviation: FU: follow-up; OS: overall survival

Diagnoses: ANA: anaplastic soft tissue sarcoma; ANG: angiosarcoma; CCS: clear cell sarcoma; DSRCT: desmoplastic small round-cell tumor; EPI: epitheloid sarcoma; FIB: fibrosarcoma; HAP: hemangiopericytoma; LIP: liposarcoma; LMS: leiomyosarcoma; MES: mesenchymal sarcoma; MFH: malignant fibrous histiocytoma; MHP: malignant hemangiopericytoma; RHA: rhabdoid sarcoma; SCS: spindle cell sarcoma; SYN: synovial sarcoma

Table 8. Treatment-related mortality (TRM)

Study	Events (N)	Cause of death
Aggregate comparative data (HDCT & autologous HSCT vs. SDCT)		
Bui-Nguyen 2012	1	Treatment-related leukemia death 2 years after HDCT

Table 8. Treatment-related mortality (TRM) (Continued)

Aggregate case series data (HDCT & autologous HSCT only)		
Bertuzzi 2003	0	
Bisogno 2010	0	
Blay 2000	1	Sudden toxic death of unknown cause at day 29
Cook 2012	2	Not specified
Philippe-Chomettte 2012	1	Died of treatment toxicity 12 months after HDCT
Individual cases data (HDCT & autologous HSCT only)		
Doros 2008	1	Not specified
Engelhardt 2007	3	Sepsis, sepsis, pulmonary metastases
Kasper 2007	1	Cardiac arrest of unknown origin
Navid 2006	1	Hepatic and renal failure
Saab 2007	2	Acute myocardial infarction, veno-occlusive disease
Sleese 1988	2	Staphylococcus sepsis, progressive encephalopathy
Sum in 12 studies	15	

Blay 2000: The authors did not specify, whether the patient was among the 24 patients with adult-type sarcomas or among the 6 patients with rhabdomyosarcoma and Ewing's sarcoma both of which are not included in the present review.

Cook 2012: 1 death within 100 days

Table 9. Disease-free survival (DFS)

Study	Disease-free survival, % (95% CI)		
	Total assessed	Complete response before the time of HSCT	Not complete response before the time of HSCT
Aggregate case series data (HDCT & autologous HSCT only)			
Cook 2012	3 years: 23% (10 to 39)	3 years: 40% (15 to 69)	3 years: 9% (0 to 29)

Cook 2012: all patients N = 36, patients that achieved complete remission before HDCT N = 13, patients that did not achieve complete remission before HDCT N = 18

Abbreviation: CI: confidence interval; HDCT: high-dose chemotherapy; HSCT: hematopoietic stem cell transplantation; DFS: disease-free survival

Table 10. Progression-free survival (PFS)

Study	Progression-free survival (95% CI)		
	Total assessed	Complete response before the time of HSCT	Not complete response before the time of HSCT
Aggregate comparative data (HDCT & autologous HSCT vs. SDCT)			
Bui-Nguyen 2012	3 years: 9.3% vs. 21.6%, HR 1.34 (0.81 to 2.20, P = 0.25)	3 years: 20.0% vs. 62.3%, HR 2.87, (1.3 to 6.3, P = 0.009)	Not reported
Aggregate case series data (HDCT & autologous HSCT only)			
Bertuzzi 2003	2 years: 0%	Not reported	Not reported
Bisogno 2010	2 years: 23% 3 years: 15.5%	Not reported	Not reported
Blay 2000	Not reported	2 years: 62% 5 years: 62%	2 years: 5% 5 years: 5%
Bokemeyer 1997	Median 8 months (range 2 to 19)	Not reported	Not reported

Some estimates were deduced from Kaplan-Meier plot. Disease-free survival (DFS), event-free survival (EFS), failure-free survival (FFS), or health-related quality of life (HRQL) not reported.

Bisogno 2010: Definition of endpoint: "For event-free survival (EFS), the interval between diagnosis and the date of latest follow-up, relapse or death was considered." In figure 1 of the article, the endpoint was designated as progression-free survival, which also is meaningful regarding the definition.

(*) Blay 2000: including 5 patients with rhabdomyosarcoma and 1 patient with primitive neuroectodermal tumor

Abbreviation: CI: confidence interval; HDCT: high-dose chemotherapy; HR: hazard ratio; HSCT: hematopoietic stem cell transplantation; PFS: progression-free survival; SDCT: standard-dose chemotherapy

Table 11. Non-hematological toxicity grade 3 to 4

Study	Non-hematological toxicity (N)							Notice
	Nausea	Mucositis	Kidney	Liver	Nerv	Heart	Other	
Aggregate comparative data (HDCT & autologous HSCT only)								
Bui-Nguyen 2012	3	4					3	Other: 2 infection, 1 pain
Aggregate case series data (HDCT & autologous HSCT only)								
Bisogno 2010		1						No grade IV organ dysfunctions

Table 11. Non-hematological toxicity grade 3 to 4 (Continued)

Blay 2000	8		5		1	0		
Bokemeyer 1997		2	2		1		1	Nerv: central neurotoxicity; Other: septic episode
Individual cases data (HDCT & autologous HSCT only)								
Garrido 1998					1			Neuroleptic malignant syndrome
Kozuka 2002	1							
Kushner 2001					1			
Patel 2004			1	1			1	Other: respiratory distress
Yonemoto 1999				1				
Sum	12	7	8	2	4	0	5	38 events in 105 patients of 9 studies

Single-arm studies, only transplanted patients. Mucositis not included.

Toxicity defined by National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE), [NCI 2009b](#).

Table 12. Secondary neoplasia

Study	Events	Diagnosis
Individual cases data (HDCT & autologous HSCT only)		
Yamamura 2003	1	Chronic myelogenous leukemia

Single-arm studies, only transplanted patients.

APPENDICES

Appendix I. New MEDLINE/Ovid search strategy

1. soft tissue sarcoma?.mp.
2. ((advanced or malignant) adj3 solid tumo?r?).mp.
3. exp SARCOMA, ALVEOLAR SOFT PART/
4. (alveolar soft part sarcoma? or alveolar soft tissue sarcoma?).mp.
5. exp HEMANGIOSARCOMA/
6. (angiosarcoma? or h?emangiosarcoma? or h?emangiopericytoma? or lymphangiosarcoma?).mp.
7. exp SARCOMA, CLEAR CELL/
8. (clear cell adj3 (sarcoma? or tumo?r?)).mp.
9. exp DESMOPLASTIC SMALL ROUND CELL TUMOR/
10. desmoplastic small round cell tumo?r?.mp.
11. epithel?oid sarcoma?.mp.
12. exp FIBROSARCOMA/
13. (fibrosarcoma? or myxofibrosarcoma?).mp.
14. fibromyxoid sarcoma?.mp.
15. exp HEMANGIOENDOTHELIOMA/
16. h?emangioendothelioma?.mp.
17. exp HEMANGIOSARCOMA/
18. h?emangioendotheliosarcoma?.mp.
19. intimal sarcoma?.mp.
20. exp LEIOMYOSARCOMA/
21. leiomyosarcoma?.mp.
22. exp LIPOSARCOMA/
23. liposarcoma?.mp.
24. exp HISTIOCYTOMA, MALIGNANT FIBROUS/
25. (malignant fibrous histiocyte? or spindle cell sarcoma?).mp.
26. malignant glomus tumor.mp.
27. exp HEMANGIOPERICYTOMA/
28. malignant h?emangiopericytoma?.mp.
29. MESENCHYMOMA.sh.
30. malignant mesenchymoma?.mp.
31. PERIVASCULAR EPITHELIOID CELL NEOPLASMS.sh.
32. perivascular epithelioid cell tumor.mp.
33. exp RHABDOID TUMOR/
34. (rhabdoid tumo?r? or rhabdoid sarcoma?).mp.
35. exp SARCOMA, SYNOVIAL/
36. synovial sarcoma?.mp.
37. exp HEMATOPOIETIC STEM CELL TRANSPLANTATION/
38. TRANSPLANTATION, AUTOLOGOUS.sh.
39. and/37-38
40. (autologous adj6 transplant\$).mp.
41. bone marrow rescue.mp.
42. bone marrow support.mp.
43. bone marrow cell.mp.
44. stem cell rescue.mp.
45. stem cell support.mp.
46. peripheral blood stem cell.mp.
47. high dose chemotherapy.mp.
48. myeloablative chemotherapy.mp.
49. intensive chemotherapy.mp.

50. dose intensive treatment.mp.
51. high dose combination.mp.
52. (ANIMALS not (ANIMALS and HUMANS)).sh.
53. or/1-36
54. or/39-51
55. and/53-54
56. 55 not 52

Appendix 2. New EMBASE/Ovid search strategy

1. soft tissue sarcoma?.mp.
2. ((advanced or malignant) adj3 solid tumo?r?).mp.
3. exp ALVEOLAR SOFT PART SARCOMA/
4. (alveolar soft part sarcoma? or alveolar soft tissue sarcoma?).mp.
5. exp ANGIOSARCOMA/
6. (angiosarcoma? or h?emangiosarcoma? or h?emangiopericytoma? or lymphangiosarcoma?).mp.
7. exp CLEAR CELL SARCOMA/
8. (clear cell adj3 (sarcoma? or tumo?r?)).mp.
9. exp DESMOPLASTIC SMALL ROUND CELL TUMOR/
10. desmoplastic small round cell tumo?r?.mp.
11. exp EPITHELIOID SARCOMA/
12. (epithelioid sarcoma? or epitheloid sarcoma?).mp.
13. exp FIBROSARCOMA/
14. (fibrosarcoma? or myxofibrosarcoma?).mp.
15. fibromyxoid sarcoma?.mp.
16. exp HEMANGIOENDOTHELIOMA/
17. h?emangioendothelioma?.mp.
18. exp HEMANGIOENDOTHELIOUSARCOMA/
19. h?emangioendotheliosarcoma?.mp.
20. intimal sarcoma?.mp.
21. exp LEIOMYOSARCOMA/
22. leiomyosarcoma?.mp.
23. exp LIPOSARCOMA/
24. liposarcoma?.mp.
25. exp MALIGNANT FIBROUS HISTIOCYTOMA/
26. (malignant fibrous histiocyte? or spindle cell sarcoma?).mp.
27. malignant glomus tumor.mp.
28. exp HEMANGIOPERICYTOMA/
29. malignant h?emangiopericytoma?.mp.
30. MESENCHYMOMA.sh.
31. malignant mesenchymoma?.mp.
32. mesenchymal sarcoma?.mp.
33. PERIVASCULAR EPITHELIOID CELL TUMOR.sh.
34. perivascular epithelioid cell tumor.mp.
35. RHABDOID TUMOR.sh.
36. (rhabdoid tumo?r? or rhabdoid sarcoma?).mp.
37. exp SYNOVIAL SARCOMA/
38. synovial sarcoma?.mp.
39. exp AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION/
40. (autologous adj6 transplant\$).mp.
41. bone marrow rescue.mp.
42. bone marrow support.mp.

43. bone marrow cell.mp.
44. stem cell rescue.mp.
45. stem cell support.mp.
46. peripheral blood stem cell.mp.
47. high dose chemotherapy.mp.
48. myeloablative chemotherapy.mp.
49. intensive chemotherapy.mp.
50. dose intensive treatment.mp.
51. (ANIMAL not (ANIMAL and HUMAN)).sh.
52. or/1-38
53. or/39-50
54. and/52-53
55. 54 not 51

Appendix 3. New Cochrane/Wiley search strategy

1. soft tissue sarcoma?
2. (advanced or malignant) adj3 solid tumo?r?
3. MeSH descriptor: [Sarcoma, Alveolar Soft Part] explode all trees
4. (alveolar soft part sarcoma?) or (alveolar soft tissue sarcoma?)
5. MeSH descriptor: [Hemangiosarcoma] explode all trees
6. angiosarcoma? or h?emangiosarcoma? or h?emangiopericytoma? or lymphangiosarcoma?
7. MeSH descriptor: [Sarcoma, Clear Cell] explode all trees
8. (clear cell adj3 (sarcoma? or tumo?r?))
9. MeSH descriptor: [Desmoplastic Small Round Cell Tumor] explode all trees
10. desmoplastic small round cell tumo?r?
11. epithel?oid sarcoma?
12. MeSH descriptor: [Fibrosarcoma] explode all trees
13. (fibrosarcoma? or myxofibrosarcoma?)
14. fibromyxoid sarcoma?
15. MeSH descriptor: [Hemangioendothelioma] explode all trees
16. h?emangioendothelioma?
17. MeSH descriptor: [Hemangiosarcoma] explode all trees
18. h?emangioendotheliosarcoma?
19. intimal sarcoma?
20. MeSH descriptor: [Leiomyosarcoma] explode all trees
21. leiomyosarcoma?
22. MeSH descriptor: [Histiocytoma, Malignant Fibrous] explode all trees
23. (malignant fibrous histiocytoma? or spindle cell sarcoma?)
24. malignant glomus tumor
25. MeSH descriptor: [Hemangiopericytoma] explode all trees
26. malignant h?emangiopericytoma?
27. MeSH descriptor: [Mesenchymoma] explode all trees
28. malignant mesenchymoma?
29. MeSH descriptor: [Perivascular Epithelioid Cell Neoplasms] explode all trees
30. perivascular epithelioid cell tumor
31. MeSH descriptor: [Rhabdoid Tumor] explode all trees
32. (rhabdoid tumo?r? or rhabdoid sarcoma?)
33. MeSH descriptor: [Sarcoma, Synovial] explode all trees
34. synovial sarcoma?
35. MeSH descriptor: [Hematopoietic Stem Cell Transplantation] explode all trees
36. MeSH descriptor: [Transplantation, Autologous] explode all trees

37. (autologous adj6 transplant*)
38. bone marrow rescue
39. bone marrow support
40. bone marrow cell
41. stem cell rescue
42. stem cell support
43. peripheral blood stem cell
44. high dose chemotherapy
45. myeloablative chemotherapy
46. intensive chemotherapy
47. dose intensive treatment
48. high dose combination
49. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34
50. #35 and #36
51. #50 or #37 or #38 or #39 or #40 or #41 #42 or #43 or #44 or #45 or #46 or #47 or #48
52. #49 and #51

Appendix 4. Original MEDLINE/Ovid search strategy

1. exp SARCOMA/
2. (sarcom\$ or sarkom\$).mp.
3. exp LIPOSARCOMA/
4. liposar#om\$.mp.
5. exp FIBROSARCOMA/
6. fibrosar#om\$.mp.
7. exp HISTIOCYTOMA, MALIGNANT FIBROUS/
8. malign\$ fibrous histio#ytom\$.mp.
9. exp LEIOMYOSARCOMA/
10. leiomyosar#om\$.mp.
11. malign\$ glom\$ tumo\$.mp.
12. exp RHABDOMYOSARCOMA/
13. rhabdomyosar#om\$.mp.
14. exp HEMANGIOENDOTHELIOMA/
15. (hemangioendotheliom\$ or haemangioendotheliom\$).mp.
16. exp HEMANGIOSARCOMA/
17. (angiosar#om\$ or hemangiosar#om\$ or haemangiosar#om\$).mp.
18. exp SARCOMA, SYNOVIAL/
19. synovia\$ sar#om\$.mp.
20. epithelioid sar#om\$.mp.
21. exp SARCOMA, ALVEOLAR SOFT PART/
22. (alveolar soft part sar#om\$ or alveolar soft tissue sar#om\$).mp.
23. exp SARCOMA, CLEAR CELL/
24. clear cell sar#om\$.mp.
25. exp SARCOMA, SMALL CELL/
26. (desmoplastic and small round cell tumo\$ or small cell tumo\$).mp.
27. exp RHABDOID TUMOR/
28. ((extrarenal or extra-renal) and rhabdoid tumo\$).mp.
29. (malignan\$ and mesenchymom\$).mp.
30. clear cell myomelano#ytic tumo\$.mp.
31. intima\$ sar#om\$.mp.
32. exp STEM CELL TRANSPLANTATION/

33. exp BONE MARROW TRANSPLANTATION/
34. exp TRANSPLANTATION, AUTOLOGOUS/
35. exp TRANSPLANTATION, HOMOLOGOUS/
36. exp TRANSPLANTATION, CONDITIONING/
37. (autolog\$ hemato\$ or autolog\$ haemato\$ or autolog\$ stem cell or autolog\$ bone marrow or autolog\$ periph\$ or autolog\$ transplant\$ or autolog\$ graft\$ or autotransplant\$ or auto-transplant\$ or autograft\$ or auto-graft\$).mp.
38. (homolog\$ hemato\$ or homolog\$ haemato\$ or homolog\$ stem cell or homolog\$ bone marrow or homolog\$ cord or homolog\$ umbilical or homolog\$ peripheral or homolog\$ transplant\$ or homolog\$ graft\$ or homolog\$ transplant\$).mp.
39. (stem cell transplant\$ or bone marrow transplant\$ or periph\$ blood stem cell or periph\$ stem cell or cord blood transplant\$).mp.
40. (reduced intens\$ or myeloablat\$ or nonmyeloablat\$ or non-myeloablat\$).mp.
41. high dose chemotherapy.mp.
42. or/1-31
43. or/32-41
44. and/42-43
45. (ANIMALS not (ANIMALS and HUMANS)).sh.
46. 44 not 45

Appendix 5. Original EMBASE/Ovid search strategy

1. exp SARCOMA/
2. (sarcom\$ or sarkom\$).mp.
3. exp LIPOSARCOMA/
4. liposar#om\$.mp.
5. exp FIBROSARCOMA/
6. fibrosar#om\$.mp.
7. exp MALIGNANT FIBROUS HISTIOCYTOMA/
8. malign\$ fibrous histio#ytom\$.mp.
9. exp LEIOMYOSARCOMA/
10. leiomyosar#om\$.mp.
11. malign\$ glom\$ tumo\$.mp.
12. exp RHABDOMYOSARCOMA/
13. rhabdomyosar#om\$.mp.
14. exp HEMANGIOENDOTHELIOMA/
15. (hemangioendotheliom\$ or haemangioendotheliom\$).mp.
16. exp HEMANGIOENDOTHELIO SARCOMA/
17. (hemangioendotheliosar#om\$ or haemangioendotheliosar#om\$).mp.
18. exp ANGIOSARCOMA/
19. angiosar#om\$.mp.
20. exp SYNOVIAL SARCOMA/
21. synovia\$ sar#om\$.mp.
22. exp EPITHELIOID SARCOMA/
23. (epithelioid\$ sar#om\$ or epithelioid\$ sar#om\$).mp.
24. exp ALVEOLAR SOFT PART SARCOMA/
25. (alveolar soft part sar#om\$ or alveolar soft tissue sar#om\$).mp.
26. exp CLEAR CELL SARCOMA/
27. clear cell sar#om\$.mp.
28. exp DESMOPLASTIC SMALL ROUND CELL TUMOR/
29. exp SMALL CELL SARCOMA/
30. (desmoplastic and (small round cell tumo\$ or small cell tumo\$)).mp.
31. ((extrarenal\$ or extra-renal\$) and rhabdoid\$ tumo\$).mp.
32. (malign\$ and mesenchymom\$).mp.
33. clear cell myomelano#yt\$ tumo\$.mp.

34. intima\$ sar#om\$.mp.
35. exp STEM CELL TRANSPLANTATION/
36. exp BONE MARROW TRANSPLANTATION/
37. exp NONMYELOABLATIVE STEM CELL TRANSPLANTATION/
38. exp NONMYELOBLATIVE CONDITIONING/
39. exp REDUCED INTENSITY CONDITIONING/
40. exp MYELOABLATIVE CONDITIONING/
41. (autolog\$ hemato\$ or autolog\$ haemato\$ or autolog\$ stem cell or autolog\$ bone marrow or autolog\$ periph\$ or autolog\$ transplant\$ or autolog\$ graft\$ autotransplant\$ or auto-transplant\$ or autograft\$ or auto-graft\$).mp.
42. (homolog\$ hemato\$ or homolog\$ haemato\$ or homolog\$ stem cell or homolog\$ bone marrow or homolog\$ cord or homolog\$ umbilical or homolog\$ periph\$ or homolog\$ transplant\$ or homolog\$ graft\$).mp.
43. (stem cell transplant\$ or bone marrow transplant\$ or periph\$ blood stem cell or periph\$ stem cell or cord blood transplant\$).mp.
44. (reduced intens\$ or myeloablat\$ or nonmyeloablat\$ or non-myeloablat\$).mp.
45. high dose chemotherapy.mp.
46. or/1-34
47. or/35-45
48. and/46-47
49. (ANIMALS not (ANIMALS and HUMANS)).sh.
50. 48 not 49

Appendix 6. Original Cochrane/Wiley search strategy

1. exp SARCOMA/
2. (sarcom\$ or sarkom\$).mp.
3. exp LIPOSARCOMA/
4. liposar#om\$.mp.
5. exp FIBROSARCOMA/
6. fibrosar#om\$.mp.
7. exp HISTIOCYTOMA, MALIGNANT FIBROUS/
8. malign\$ fibrous histio#ytom\$.mp.
9. exp LEIOMYOSARCOMA/
10. leiomyosar#om\$.mp.
11. malign\$ glom\$ tumo\$.mp.
12. exp RHABDOMYOSARCOMA/
13. rhabdomyosar#om\$.mp.
14. exp HEMANGIOENDOTHELIOMA/
15. (hemangioendotheliom\$ or haemangioendotheliom\$).mp.
16. exp HEMANGIOSARCOMA/
17. (angiosar#om\$ or hemangiosar#om\$ or haemangiosar#om\$).mp.
18. exp SARCOMA, SYNOVIAL/
19. synovia\$ sar#om\$.mp.
20. (epithelioid sar#om\$ or epithelioid sar#om\$).mp.
21. exp SARCOMA, ALVEOLAR SOFT PART/
22. (alveolar soft part sar#om\$ or alveolar soft tissue sar#om\$).mp.
23. exp SARCOMA, CLEAR CELL/
24. clear cell sar#om\$.mp.
25. exp SARCOMA, SMALL CELL/
26. (desmoplastic and (small round cell tumo\$ or small cell tumo\$)).mp.
27. exp RHABDOID TUMOR/
28. ((extrarenal or extra-renal) and rhabdoid tumo\$).mp.
29. (malignan\$ and mesenchymom\$).mp.
30. clear cell myomelano#ytic tumo\$.mp.

31. intima\$ sar#om\$.mp.
32. exp STEM CELL TRANSPLANTATION/
33. exp BONE MARROW TRANSPLANTATION/
34. exp TRANSPLANTATION, AUTOLOGOUS/
35. exp TRANSPLANTATION, HOMOLOGOUS/
36. exp TRANSPLANTATION, CONDITIONING/
37. (autolog\$ hemato\$ or autolog\$ haemato\$ or autolog\$ stem cell or autolog\$ bone marrow or autolog\$ periph\$ or autolog\$ transplant\$ or autolog\$ graft\$ or autotransplant\$ or auto-transplant\$ or autograft\$ or auto-graft\$).mp.
38. (homolog\$ hemato\$ or homolog\$ haemato\$ or homolog\$ stem cell or homolog\$ bone marrow or homolog\$ cord or homolog\$ umbilical or homolog\$ periph\$ or homolog\$ transplant\$ or homolog\$ graft\$).mp.
39. (stem cell transplant\$ or bone marrow transplant\$ or periph\$ blood stem cell or periph\$ stem cell or cord blood transplant\$).mp.
40. (reduced intens\$ or myeloablat\$ or nonmyeloablat\$ or non-myeloablat\$).mp.
41. high dose chemotherapy.mp.
42. or/1-31
43. or/32-41
44. and/42-43
45. (ANIMALS not (ANIMALS and HUMANS)).sh.
46. 44 not 45

WHAT'S NEW

Last assessed as up-to-date: 5 December 2012.

Date	Event	Description
21 September 2016	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 1, 2010

Review first published: Issue 2, 2011

Date	Event	Description
1 April 2015	Amended	Contact details updated.
24 February 2015	Amended	Contact details updated.
11 February 2015	Amended	Contact details updated.
27 March 2014	Amended	Contact details updated.
10 June 2013	New citation required and conclusions have changed	We identified a single randomized controlled trial and judged it to have a low risk of bias. The results did not support high-dose chemotherapy followed by autolo-

(Continued)

		gous hematopoietic stem cell transplantation compared to standard-dose chemotherapy in patients with non-rhabdomyosarcoma soft tissue sarcoma
5 December 2012	New search has been performed	Searches re-run and one new study included.

CONTRIBUTIONS OF AUTHORS

FP: designing and coordinating the review, data collection for the review, designing search strategies, undertaking searches, screening search results, organizing retrieval of papers, screening retrieved papers against eligibility criteria, appraising quality of papers, extracting data from papers, writing to authors of papers for additional information, data management for the review, entering data into RevMan, analysis of data, interpretation of data, writing the update

LAS: providing methodological advice, appraising quality of papers

CB: screening retrieved papers against eligibility criteria, extracting data from papers, screening included papers to verify data, interpretation of data

DECLARATIONS OF INTEREST

The authors declare that they have no competing interests.

SOURCES OF SUPPORT

Internal sources

- University of Cologne, Germany.
Provision of fulltexts

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between the recent version and the updated version of the review

It is not clear that the unclassified and the undifferentiated tumor types are non-rhabdomyosarcoma soft tissue sarcomas. Therefore, we did not consider these tumor types for the present review and relocated both types from the list of included to the list of excluded tumor types. As a result, the following seven studies were included in the original review but excluded in the update: [Endo 1996](#); [Frapier 1998](#); [Mesia 1994](#); [Nakamura 2008](#); [Ronghe 2004](#); [Shaw 1996](#); [Watanabe 2006](#).

In contrast to the recent version, we excluded the article by [Ivanova 2007](#). According to e-mail correspondence with the author AB Shvarova of a related article ([Ivanova 2010](#)) and co-worker at the same research institution, the proportion of patients with NRSTS was less than 50%. Most of the retrospectively observed patients were children diagnosed with rhabdomyosarcoma. In contrast to the recent version, we included the study by [Blay 2000](#) because we accepted the results of a subgroup analysis comprising 91% (22 out of 24) relevant patients. In agreement with the recent version, the exclusion of the study by [Schlemmer 2006](#) based on a proportion of NRSTS patients below 80% was confirmed according to a recent author contact.

We complemented PFS estimates. We conducted an updated search and included five further studies ([Bisogno 2010](#); [Buerk 2010](#); [Hara 2010](#); [Houet 2010](#); [Jordan 2010](#)) that were identified in the update and therefore not reported in the recent version. One study reported aggregate data of 14 participants ([Bisogno 2010](#)) and three studies reported individual data of nine participants which were suitable for inclusion in the meta-analysis ([Buerk 2010](#); [Hara 2010](#); [Jordan 2010](#)).

Concerning the two articles by [Kasper 2007a](#) and [Kasper 2010](#), we stated in the recent version that some participants were reported in both articles. In the present updated version, we evaluated these duplicate data and identified six participants by coincidental information on age, histology, and metastatic sites. We included eight instead of 14 participants reported by [Kasper 2007a](#) and seven participants reported by [Kasper 2010](#). Consequently, we removed the duplicate data of six participants from the pooled analysis. We did not find additional reviews in the updated search.

We changed the search strategy to increase the fraction of the identified relevant documents of all identified relevant and not relevant documents (precision). The new search strategy is more economical in terms of spending resources for study selection for the present review and also for future updates. The new search strategy was not only used for the time period to be updated but was used from inception of all electronic databases searched. The screening process was redone regarding the complete retrieved records. All identified studies were evaluated in detail regardless of being part of the original review. We considered and re-evaluated all studies that were included in the original review. Therefore, the search strategy is composed of two parts. The new more narrow strategy is spanning the time from inception to 5 December 2012. The old more broad strategy is spanning from inception to 5 February 2010.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Combined Chemotherapy Protocols [*administration & dosage; adverse effects]; Hematopoietic Stem Cell Transplantation [*methods; mortality]; Salvage Therapy [*methods; mortality]; Sarcoma [*drug therapy; mortality]; Transplantation, Autologous

MeSH check words

Adult; Humans