Published in final edited form as:

Curr Opin Hematol. 2009 March ; 16(2): 112–123. doi:10.1097/MOH.0b013e3283257a87.

Second Hematopoietic Stem Cell Transplantation in Myeloid Malignancies

Lisa M. Arfons, MD¹, Marcie Tomblyn, MD, MS², Vanderson Rocha, MD, PhD³, and Hillard M. Lazarus, MD, FACP¹

¹ Department of Medicine, Case Comprehensive Cancer Center, University Hospitals Case Medical Center, 11100 Euclid Ave. Cleveland, OH 44106 USA

² Adult Blood and Marrow Transplant Program, Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, MN 55455 USA

³ Hematology Bone Marrow Transplant Department, Hopital Saint-Louis, Acute Leukemia Working Party of European Group for Blood and Marrow Transplantation and Eurocord, 1 Av Claude Vellefaux, 75010, Paris, France

Abstract

Purpose of Review—Hematopoietic stem cell and umbilical cord blood (UCB) transplantation can be a life-saving procedure for many patients with myeloid malignancies. The post-transplant period, however, can be complicated by graft failure and disease relapse, prompting the need for further therapy. Herein we review examine the data of second allogeneic stem cell transplant after autologous, allogeneic and UCB transplantation.

Recent Findings—While large, prospective, multi-center trials are lacking, certain factors such as younger patient age, lower disease burden and a longer interval between first transplantation and relapse appear to portend a better prognosis for second transplant.

Summary—Currently, only a select group of patients without important co-morbidities should be considered for second allogeneic transplantation. Strategies such as new immunosuppressive agents, anti-leukemia monoclonal antibodies, graft modification and use of molecularly targeted therapy are needed to decrease the morbidity and increase the efficacy of transplantation.

Keywords

Second allogeneic stem cell transplantation; myeloid malignancy; umbilical cord blood transplantation; graft failure; disease relapse

Introduction

Allogeneic stem cell transplantation (AlloSCT) provides the only potential long-term curative option for patients affected by myeloid malignancies (AML, CML, MDS, CMML, JMML), especially those with high-risk features. A subset of patients, however, fail to achieve durable

Address correspondence to: Hillard M. Lazarus, MD, FACP, Department of Medicine, University Hospitals Case Medical Center, Case Western Reserve University, 11100 Euclid Avenue, Cleveland, OH 44106, Telephone 216-844-3629, FAX 216-844-5979, hillard.lazarus@case.edu.

Disclosures: L. Arfons, M. Tomblyn, V. Rocha and H. Lazarus have no conflicts of interest.

Disclaimer regarding the data provided by the CIBMTR: The data presented here are preliminary and were obtained from the Statistical Center of the Center for International Blood and Marrow Transplant Research. The analysis has not been reviewed or approved by the Advisory or Scientific Committee of the CIBMTR. The data may not be published without the approval of the Advisory Committees.

remissions due to graft failure or disease relapse after autologous stem cell transplantation (autoSCT), alloSCT and umbilical cord blood transplantation (UCBT). Such patients, in theory, can be considered for second alloSCT. The Center for International Blood and Marrow Transplant Research (CIBMTR) reported that during the years 2000 to 2006, 323 patients received a second alloSCT for AML, the majority within 12 months of the first SCT (W Perez and T Petersen, personal communication). In Europe, the Acute Leukemia Working Party (ALWP) registry of the European Blood and Marrow Transplant (EBMT) in the same period reported 614 second alloSCT for adults with AML, the majority for relapse (V Rocha, personal communication). In this review, we examine the data of using second alloSCT after graft failure or disease relapse after autoSCT, alloSCT and UCBT for patients with myeloid malignancies. We discuss the challenges associated with this procedure and highlight predictors of outcome, allowing for optimizing patient selection criteria.

Graft Failure After First AlloSCT

Graft failure and rejection after alloSCT, while uncommon except after UCBT, are associated with a high mortality. Several factors such as underlying disease state, donor-recipient graft incompatibility, infusion of low numbers of nucleated or CD34+ cell dose, viral infections, defective marrow microenvironment or incomplete ablation of host immune cells have all been implicated [1]. In the papers we reviewed, the definition of engraftment is an absolute neutrophil count greater than $0.5 \times 10^9/L$ for three consecutive days any time after transplantation which may or may not be defined also in the setting of a mixed or full donor chimerism. Never attaining these threshold blood counts defines primary graft failure. Graft rejection, or secondary graft failure, generally is defined as recurrent neutropenia less than $0.5 \times 10^9/L$ after initial count recovery without a reversible etiology such as infection or medication-induced myelosuppression; again, this finding may be in the setting of mixed or full donor chimerism. In fact, the literature defining neutrophil recovery and neutrophil engraftment is changing. Confusion in this definition has arisen after the era of reduced-intensity conditioning regimen (RIC), in which a period of bone marrow aplasia does not necessarily occur and therefore the definition of neutrophil recovery, as stated above, cannot be followed. One could argue that to fulfill the definition of engraftment, chimerism data are needed to demonstrate the presence of donor cells. The use of chimerism analysis, especially a mixed chimeric state, as a marker of graft failure, rejection, disease relapse or stable remission, however, has not been clearly delineated and therefore cannot be recommended to define disease states or guide therapeutic decisions [2**]. Moreover, the definition of engraftment using chimerism in a registry-based point of view also is difficult due to the heterogeneity of chimerism techniques and different evaluation times after transplantation. For these and other reasons, in this review, we exercise caution when interpreting the results of graft failure or non-engraftment in the field of RIC.

Outcomes after allogeneic second transplants for graft failure or rejection

Several studies examined patient outcomes after a second alloSCT performed for graft failure or rejection (Table 1) [3–11]. Unfortunately, however, most reports are from single-institutions describing small numbers of patients, varied conditioning regimens and differing donor graft sources, both for first and second transplantation. GVHD prophylaxis also is not standardized between centers.

The largest series reported by Guardiola *et al.* [3] retrospectively examined 82 patients who underwent second alloSCT, but the authors do not specifically state the numbers of patients with acute myeloid leukemia within the acute leukemia group. TRM at 100 days was 53% and a 3-year overall survival (OS) was 30% for the entire cohort, irrespective of underlying disease. Patients with an inter-transplant time of more than 80 days had a better OS; 73% of patients

had neutrophil counts greater than $0.5 \times 10^9/l$ for at least three days by day +40. The authors postulated that a high neutrophil recovery rate contributed to improved outcomes. The GVHD prophylaxis regimen also contributed positively to OS, as those patients more than 80 days from first transplantation who received cyclosporine alone had a 54% 3-year OS compared to only 8% in the non-cyclosporine therapy group. Prednisone use appeared to contribute to early deaths from fungal infections and lower neutrophil recovery rates. The data did not discern whether to use the same or different donor.

A second, large series from Platzbecker and colleagues [11] reported on the outcomes of 70 patients who underwent a second alloSCT using peripheral blood stem cells (PBSC) or bone marrow from the same donor. Fifty-three of the patients had a myeloid malignancy. Primary graft failure was the reason for the second transplant in 34 patients while the remainder had disease relapse. The median OS was three months for all patients. Patients who were re-transplanted because of graft failure, however, had a 37% OS at 40 months as compared to the 7% OS at 40 months for those patients re-transplanted for disease relapse ($p=0.02$). Patient age less than 50 years also portended a better outcome. Underlying disease did not impact survival.

Jabbour and colleagues [6] and Chewning and co-workers [7] specifically examined fludarabine-based preparative regimens in twenty-five patients undergoing second alloSCT for primary or secondary graft failure. While both groups demonstrated high rates of engraftment (6 of 9 patients and all 16 patients, respectively), in their prospective study of only patients with myeloid malignancies Jabbour *et al* [6] had high rates of aGVHD and TRM and a lower OS with the combination of fludarabine and anti-thymocyte globulin. In a larger series of patients, 11 of whom had myeloid malignancies, Chewning and colleagues [7] reported a 35% 3-year OS and DFS of 18%; patients age 20 years or younger had a statistically significant better OS than older patients (5 of 8 patients younger than 20 years survived more than 6 months as compared to 1 of 8 subjects older than 20 years $p=0.02$).

Unrelated UCBT

Unrelated UCBT is associated with delayed neutrophil recovery and a higher incidence (10–30%) of engraftment failure as compared to bone marrow or PBSC [12]. Explanations include: the low number of hematopoietic progenitor cells present in an UCB unit and lower nucleated and CD34+ cell dose infused; the influence of HLA disparities; different biologic properties such as lack of some adhesion molecules for homing; greater immaturity of cord blood hematopoietic cells; and usually more advanced disease status at time of transplantation [13*–14].

The majority of the literature addressing use of UCBT for second alloSCT after graft failure is limited to case reports, making widely-applicable statements regarding outcomes difficult [4,5], see Table 1.

Satoh *et al.* [15], Nakamura and co-workers [16] and Ohwada and colleagues [17] in three separate case reports identify three patients, two 44 years old and one 16 years old, with AML. All three underwent myeloablative conditioning and UCBT of one unit, all mismatched at two HLA-loci. Two suffered from primary graft failure (diagnosed on day +31 and day +27) while the other had graft rejection on day +28, confirmed by complete loss of donor chimerism, neutropenia and a hypocellular marrow. All three received a different RIC regimen and underwent a second UCBT with one cord unit and all engrafted with the second UCBT less than 30 days after second transplantation. The 16 year old patient remained in CR through 19 months after the second UCBT while one 44 year old patient was in CR for at least 5 months after second UCBT. All three patients had 100% second donor chimerism after repeat transplantation.

The Eurocord group analyzed outcomes of UCBT after second transplants as a salvage therapy in the setting of primary graft failure after one or two units of cord blood for hematologic diseases. From May 1995 to July 2007, the results of 1115 UCBT for hematological diseases were reported to the Eurocord registry. At total of 113 of these transplants were diagnosed as primary graft failures (failure to achieve a neutrophil count $> 500 \times 10^6/L$ until 60 days after UCBT or having received a treatment for graft failure in this period). From this group, 34 patients did not received treatment, 25 received an autologous rescue from pre-cryopreserved stem cells and 54 received a second HSCT. Median age of these 54 patients at transplant was 12 (1–51) years and 17 patients had AML or MDS. Median time between first and second transplants was 56 (33–116) days. Source of stem cells for the second transplant was 5 mismatched unrelated bone marrow (MMUD), 13 haploidentical related grafts, 26 single UCB and 10 double UCB grafts. T-cell depletion was used in 12 cases. RIC regimens (often fludarabine-based) were used in the majority of cases. Low-dose TBI was administered to 33 patients and serotherapy (ALG/ATG/other monoclonal antibody) was used in 39 patients (5 patients received no preparatory conditioning). Twenty-nine of 54 patients engrafted: 5 of 26 receiving a single and 8 of 10 receiving a double UCB unit while 16 of 18 received other alternative donor grafts. Eighteen patients (35%) developed acute graft-versus-host disease (GVHD) grades II–IV; chronic GVHD was observed in 8 of 24 evaluable patients (33%). Two-year OS was $24 \pm 6\%$ which varied according to cell source. At 2 years after transplant: 3/5 patients receiving MMUD, 10/13 receiving haploidentical grafts, 5/10 given double UCB and 2/26 receiving single UCB units were alive and well (Eurocord, unpublished data). Thus, second transplants may be considered as a salvage therapy for primary graft failure after unrelated UCBT. Choice of the best conditioning regimen and best cell source still are open questions. Based on these preliminary results, patients can be rescued with double UCBT or haploidentical donors.

One problem in the daily practice of treating UCBT recipients is when to decide that the patient must undergo a second transplant. Given the small numbers of patients studied, no reliable recommendations can be made regarding the treatment of UCBT-associated graft failure and rejection and use of UCB as a graft source for a second alloSCT; these case reports and the Eurocord preliminary analysis suggest this option is feasible. Currently, patients live longer in aplasia due to improved supportive care and better control of infections. Neutrophil recovery after UCBT can occur as late as 60 days after transplantation. In fact, among 350 unrelated UCBT for adults with AML performed between 2000–2006 and reported to Eurocord, 265 patients engrafted at a median days of 21 days; 5% of patients who engrafted had neutrophil recovery after day 45 (Eurocord, unpublished data). At Hopital Saint-Louis, a bone marrow aspiration and chimerism test is performed at day + 30 for those patients without signs of engraftment and no response to hematopoietic growth factors and a second graft search commences.

Currently, at the University of Minnesota patients who have a persistent ANC less than $0.5 \times 10^9/L$ and a day +21 bone marrow with less than 5% cellularity prompts a search for a second graft. If by day +28 there is no change in the ANC or bone marrow cellularity, a second conditioning regimen is started. If there is evidence of early hematopoietic recovery on day +28, growth factors are continued and a repeat bone marrow is performed on day +35.

Multi-institutional studies, however, are needed to evaluate the cell dose and administration route of cord blood [18*,19], including the utility of double UCBT after graft failure or rejection.

Relapse after autoSCT

While autoSCT procedures have a low TRM, this modality is associated with high relapse rates and increased likelihood of second malignancies. Thus, there are a number of studies examining patients (Table 2) who received an alloSCT for relapse after an autoSCT [20–26].

There are no data in the literature reporting outcomes of unrelated UCBT for relapse after autoSCT. In a survey of the Eurocord registry, among 350 UCBT performed for adult AML patients, autoSCT was performed in 76 patients (23%). Median age was 40 (18–65) years. At UCBT, 67% of the patients were in second complete remission and 33% not in remission. Median time from autoSCT to UCBT was 15 months for those patients given an UCBT in remission and 10 months for those transplanted not in remission. A majority of the transplants used a single UCB unit (70%) with one or two HLA disparities. As a preparative regimen, half the patients received a non-myeloablative regimen. At a median follow-up of 12 months, 2-year OS was 28±6%, 38% for those transplanted in remission and 10% if not in remission. A risk factor analysis was not possible due to the short follow-up and limited number of patients but the data show that UCBT can rescue almost 40% of those who relapsed after autoSCT when remission is obtained before UCBT.

Relapse after alloSCT

Historically, alloSCT relied solely on myeloablative conditioning prior to transplantation, precluding many patients with end-organ damage from being offered a second alloSCT. RIC and improved GVHD prophylaxis enables more patients to undergo a second alloSCT (Table 3) [27–34]. Studies examining the outcomes of patients after second alloSCT are summarized in Table 3.

Eapen *et al.* [30], for the CIBMTR, reported on 279 patients (75% with a myeloid malignancy) who relapsed after alloSCT and underwent a second transplant. Time from first transplant to relapse was the most important prognostic indicator. Specifically, time to relapse more than 6 months after first alloSCT was associated with lower TRM and relapse rates, fewer treatment failures and better OS. Patients who relapsed between 7 and 12 months had similar outcomes to those patients who relapsed more than one year after first transplantation. Also, age 20 years or younger portended a lower TRM, treatment failure and overall mortality. Improved disease control at second transplant was associated with a lower relapse rate and lower treatment failure rate. Patients given a RIC regimen had higher relapse rates. There was no difference between those patients with AML *versus* ALL *versus* CML in any outcome.

Shaw and colleagues [34] retrospectively examined the outcomes of 71 patients (half with myeloid malignancies) who underwent RIC prior to a second alloSCT for relapsed disease. Early relapse rate within 11 months of initial transplantation negatively affected TRM and OS during the second transplant. Development of cGVHD lowered the probability of relapse at 2 years (44% *versus* 63% for those with and without cGVHD, respectively, $p=0.15$) and also improved OS at 2 years, 54% for those with cGVHD as compared to 29% for those without cGVHD ($p=0.014$). Those patients with lymphoproliferative disorders fared significantly better than those patients with ALL, AML, CML or MDS; this finding may have reflect a less aggressive disease course in these patients. Age, disease status, aGVHD and use of TBI did not impact patient outcomes. They conclude that second alloSCT may be appropriate for a subset of patients relapsing beyond 11 months after initial transplantation but warn that this retrospective study has selection bias.

In a survey of the ALWP of EBMT, 244 patients transplanted in first complete remission, who subsequently relapsed and received a second alloSCT in European centers during the period 2000 to 2006, were analyzed. The SCT donor used in the first transplantation was an HLA

identical sibling in 172 cases, an unrelated donor in 55 and a syngeneic, haploidentical or unrelated UCB unit in the remainder. Conditioning was myeloablative in 70% of the cases. Interval from first to second transplant was 368 (range 63–2162) days for HLA identical siblings and 377 (range 578–1895) days for unrelated donors. The stem cell source for the second transplant was PBST in 94% and BM in 6%. Seventy-eight (32%) patients were transplanted in remission and 166 (68%) were not in remission. Conditioning regimen was non myeloablative in 60% of the cases. Median follow-up after second transplant was only 7 months. Neutrophil recovery was observed in 89% of the patients. At 2 years, the probability of survival after HLA identical sibling and unrelated donors SCT were $23\pm 4\%$ and $15\pm 6\%$, respectively. If remission was obtained before the second transplant, 2 year OS was $38\pm 7\%$ compared to $16\pm 4\%$ for those patients not in remission ($p<0.001$). Median time from first alloSCT to relapse in this population was 11 months. Two year OS was $17\pm 5\%$ for patients relapsing after first alloSCT and $26\pm 6\%$ for those transplanted after this time ($p=0.002$). Age at second transplantation was not associated with OS.

Successful transplantation/prognostic factors

While there are no large, randomized, controlled trials to assess the prognostic factors and outcomes associated with second alloSCT after graft failure or disease relapse, examining all studies allows for review of risk factors. Disease in remission at time of transplant, younger recipient age and longer time from first transplant to relapse portend the greatest successful outcomes for second alloSCT (Table 4).

Other options → DLI

While alloSCT is performed for curative intent in hematologic malignancies, disease relapse occurs in approximately 40% of patients after transplantation. Median age of leukemia patients is approximately 70 years and by that time many may have co-morbid conditions that preclude an alloSCT, even in the era of RIC; furthermore, many younger patients who underwent an initial alloSCT may have end-organ damage or transplant-related morbidities prohibiting a second transplant. Options for disease control in these patients include DLI for GVL effect which avoids the morbidity of further conditioning and immune suppression. Additionally, DLI often is used for patients with a high risk of relapse as a planned procedure after alloSCT, especially in those patients without GVHD.

DLI for CML relapse has been shown to be effective; however, the data for DLI in AML are less convincing, especially for patients in frank leukemic relapse. Tomblyn and Lazarus [35] recently reviewed the use of DLI in a variety of conditions including relapsed CML. In a collective cohort of over 500 patients, there were variations in cell dose and escalation schedule among the studies; 77% of patients achieved a molecular CR with an OS ranging from 53% to 95% over three years. In the only large-scale review restricted to patients with AML, Schmid *et al.* [36] reported on 399 patients from EBMT centers who received DLI ($n=171$) or other treatment ($n=228$) for relapsed AML after alloSCT. Patients who received DLI had a better 2-year OS, 21% *versus* 9%, than those who did not. Factors associated with a better survival were relapse time more than 5 months from initial alloSCT, age less than 37 years and the use of DLI. In the cohort of patients who received DLI, patients in remission or with favorable cytogenetics had a 56% 2 year OS as compared to 21% for females not in remission but with a lower tumor burden. All other patients had only a 9% 2-year OS after DLI. Those subjects with aGVHD had a lower OS due to early mortality; however, patients with cGVHD had a better OS in those patients who had DLI. The authors suggest that DLI for relapsed disease be used in conjunction with chemotherapy to attempt remission and should be considered in a subset of patients. The lack of large, randomized controlled trials make further recommendations difficult.

Factors important to a successful outcome with DLI are similar to the good prognostic indicators for a second alloSCT. The ideal indication, cell dose, dosing schedule and necessity of chemotherapy prior to infusion of DLI cannot be established with the data currently available for those myeloid malignancy patients. Moreover, some other strategies to consolidate the remission obtained after DLI are not reported and more questions than answers remain.

Conclusions

Both autologous and allogeneic SCT can be a curative procedure for a majority of patients with myeloid malignancies; however, graft failure and disease relapse occur, necessitating further therapy. The ideal salvage treatment is unknown, but second alloSCT deserves consideration given the availability of less toxic preparative regimens and better supportive care (antibiotics, aGVHD prophylaxis) during the transplantation period. The published data are limited due to small sample size as many of the studies are single-institution, retrospective reviews. These data indicate that second alloSCT is not feasible in all patients and it is difficult to make recommendations regarding patient and disease selection for a procedure still associated with high TRM. Benefits and risks of second transplants have must be discussed with patients and their families. Variables such as underlying disease, patient age, co-morbid conditions, disease status at the time of transplantation, conditioning and GVHD regimens, donor type as well as graft source introduce uncertainty and make application to a wide patient population challenging. There are no well-designed, retrospective studies that include large numbers of homogenous groups of patients and importantly, there is no prospective study addressing the question of the feasibility of second transplants for graft failure or relapse after SCT. For patients in relapse, the best candidates for the procedure are younger, have late-relapsed disease and are in remission at time of consideration of second alloSCT, but larger, multi-center trials are needed. On the other hand, for SCT recipients who experience graft failure and rejection, it is unclear how to optimally treat these patients. As UCBT is increasing in recent years, the role of second transplants for graft failure after this procedure will be investigated.

Future directions

Second transplants for graft failure, mainly after unrelated UCBT and for relapse after SCT, have shown disappointed results. Importantly, only a selected group of patients without important co-morbidities or those obtaining remission should be considered for second transplants. More experimental data, including animal models, may be helpful and trigger new approaches to improve the dismal results of second transplants. To improve the results of second transplants, the development of strategies that decrease the toxicity of the procedure, increase the engraftment rate and the GVL effect as well as decrease acute GVHD after second transplants are needed. Among those strategies, one could speculate: i) use of new immunosuppressive drugs with low toxicity to be used in the conditioning regimen ii) use of monoclonal antibodies that target leukemia cells and avoid the host-*versus*-graft reaction, iii) better understanding of homing and tolerance with an intelligent modification of the composition of the graft, such as the increase of specific NK cells, veto cells [37*] or T regulatory cells; iv) modification of the route of administration of hematopoietic cells; v) new immunosuppressive drug combinations to avoid GVHD after second transplants such as MMF, sirolimus, or even use of cyclophosphamide early after transplant [38]; v) use of post-transplant therapy with new molecular drugs to reinforce the molecular and hematologic remission of some AML subtypes. All these approaches only will be realistic and may improve results of second transplants in well-designed, multi-center, prospective clinical trials.

Abbreviations

aGVHD

	acute graft- <i>versus</i> -host disease
AlloSCT	allogeneic stem cell transplantation
ALWP	Acute Leukemia Working Party
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
AutoSCT	autologous stem cell transplantation
cGVHD	chronic graft- <i>versus</i> -host disease
CIBMTR	Center for International Blood and Marrow Transplant Research
CML	chronic myelogenous leukemia
CMML	chronic myelomonocytic leukemia
CR	complete remission
DFS	disease-free survival
DLI	donor lymphocyte infusion
EBMT	European Group for Blood and Marrow Transplantation
EFS	event free survival
GVHD	graft- <i>versus</i> -host disease
GVL	graft- <i>versus</i> -leukemia
JMML	juvenile myelomonocytic leukemia
MDS	myelodysplastic syndrome
MMF	mycophenolate mofetil

NRM	non-relapse mortality
OS	overall survival
PBSC	peripheral blood stem cells
PR	partial remission
RIC	reduced-intensity conditioning
SCT	stem cell transplantation
TBI	total body irradiation
TRM	treatment-related mortality
UCB	umbilical cord blood
UCBT	umbilical cord blood transplantation

References

1. Wolff SN. Second hematopoietic stem cell transplantation for the treatment of graft failure, graft rejection or relapse after allogeneic transplantation. *Bone Marrow Transplant* 2002;29:545–552. [PubMed: 11979301]
- 2**. Liesveld JL, Rothberg PG. Mixed chimerism in SCT: conflict or peaceful coexistence? *Bone Marrow Transplant* 2008;42:297–310. [PubMed: 18660844] This review discusses the different methods of chimerism analysis, and the role of chimerism in both malignant and non-malignant disease states. The authors also discuss the role of graft type, lineage-specific chimerism and the clinical application of the analysis
3. Guardiola P, Kuentz M, Garban F, et al. Second early allogeneic stem cell transplantations for graft failure in acute leukaemia, chronic myeloid leukaemia and aplastic anemia. *Br J Haematol* 2000;111:292–302. [PubMed: 11091216]
4. Narimatsu H, Kami M, Miyakoshi S, et al. Graft failure following reduced-intensity cord blood transplantation for adult patients. *Br J Haematol* 2005;132:36–41. [PubMed: 16371018]
5. Fernandes J, Rocha V, Robin M, et al. Second transplant with two unrelated cord blood units for early graft failure after haematopoietic stem cell transplantation. *Br J Haematol* 2007;137:248–251. [PubMed: 17408466]
6. Jabbour E, Rondon G, Anderlini P, et al. Treatment of donor graft failure with nonmyeloablative conditioning of fludarabine, antithymocyte globulin and a second allogeneic hematopoietic transplantation. *Bone Marrow Transplant* 2007;40:431–435. [PubMed: 17603511]
7. Chewning JH, Castro-Malaspina H, Jakubowski A, et al. Fludarabine-based conditioning secures engraftment of second hematopoietic stem cell allografts (HSCT) in the treatment of initial graft failure. *Biol Blood Marrow Transplant* 2007;13:1313–1323. [PubMed: 17950918]
8. Lang P, Mueller I, Greil J, et al. Retransplantation with stem cells from mismatched related donors after graft rejection in pediatric patients. *Blood Cells Mol Dis* 2008;40:33–39. [PubMed: 17884640]

9. Byrne BJ, Horwitz M, Long GD, et al. Outcomes of a second non-myeloablative allogeneic stem cell transplantation following graft rejection. *Bone Marrow Transplant* 2008;41:39–43. [PubMed: 17982503]
- 10*. Heinzlmann F, Lang PJ, Ottinger H, et al. Immunosuppressive total lymphoid radiation-based reconditioning regimens enable engraftment after graft rejection or graft failure in patients treated with allogeneic hematopoietic stem cell transplantation. *Int J Radiation Oncology Biol Phys* 2008;70:523–528. This retrospective trial evaluated 14 patients with hematologic malignancies who underwent a second transplant for graft failure. The authors postulate that a TLI-based conditioning regimen would be efficacious with a low toxicity profile. The seven pediatric patients (16 years or younger) fared better than the older cohort with a DFS and OS of 85.7% each after 681 days median follow-up. Treatment related toxicity was minimal without major complications. The adult cohort all died from infectious complications, GVHD, disease relapse and treatment related complications
11. Platzbecker U, Binder M, Schmid C, et al. Second donation of hematopoietic stem cells from unrelated donors for patients with relapse or graft failure after allogeneic transplantation. *Haematologica* 2008;93:1276–1278. [PubMed: 18519515]
12. Rocha V, Labopin M, Sanz G, et al. Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. *N Engl J Med* 2004;351:2276–85. [PubMed: 15564544]
- 13*. Tse WW, Zang SL, Bunting KD, Laughlin MJ. Umbilical cord blood transplantation in adult myeloid leukemia. *Bone Marrow Transplant* 2008;41:465–472. [PubMed: 18246116] This review discusses the immunologic properties, clinical application and outcomes of umbilical cord blood transplantation
14. Rocha V, Sanz G, Gluckman E, et al. Umbilical cord blood transplantation. *Curr Opin Hematol* 2004;11:375–85. [PubMed: 15548991]
15. Satoh N, Takenouchi S, Hashimoto S, et al. Switching of donor cells after urgent second cord blood transplantation for suspected graft failure. *Int J Hematol* 2007;86:451–454. [PubMed: 18192115]
16. Nakamura Y, Tanaka Y, Ando T, et al. Successful engraftment of the second reduced-intensity conditioning cord blood transplantation (UCBT) for a patient who developed graft rejection and infectious complications after the first UCBT for AML. *Bone Marrow Transplant* 2007;40:395–396. [PubMed: 17572713]
17. Ohwada C, Nakaseko C, Ozawa S, et al. Second cord blood transplantation (UCBT) with reduced-intensity conditioning for graft failure after the first UCBT for AML. *Bone Marrow Transplant* 2004;34:999–1000. [PubMed: 15448661]
- 18*. Frasson F, Gualandi F, Podesta M, et al. Direct intrabone transplant of unrelated cord-blood cells in acute leukaemia: a phase I/II study. *Lancet Oncol* 2008;9:831–839. [PubMed: 18693069] This clinical trial examined the outcomes of 32 patients who underwent direct intrabone marrow cord blood transplantation. Sixteen patients were alive at a median follow-up of 13 months; there were no treatment related complications with the method of administration. The majority of the patients had neutrophil and platelet recovery by a median time of 23 days and 36 days, respectively. There was a lower rate of acute and chronic GVHD as compared to intravenous administration of cord blood. The authors postulate that intrabone marrow infusion of cord blood is an acceptable method of transplantation and further larger studies are warranted
19. Brunstein C, Barker J, Weisdorf D, DeFor T, et al. Intra-bone marrow injection of umbilical cord blood: no impact on rate of haematopoietic recovery. *Bone Marrow Transplant* 2008;41 (Suppl):S22.
20. Blau IW, Basara N, Bischoff M, et al. Second allogeneic hematopoietic stem cell transplantation as a treatment for leukemia relapsing following a first transplant. *Bone Marrow Transplant* 2000;25:41–45. [PubMed: 10654013]
21. Radich JP, Gooley T, Sanders JE, et al. Second allogeneic transplantation after failure of first autologous transplantation. *Biol Blood Marrow Transplant* 2000;6:272–279. [PubMed: 10871152]
22. Ringden O, Labopin M, Gorin NC, et al. The dismal outcome in patients with acute leukemia who relapse after an autograft is improved if a second autograft or a matched allograft is performed. *Bone Marrow Transplant* 2000;25:1053–1058. [PubMed: 10828865]
23. Devine SM, Sanborn R, Jessop E, et al. Fludarabine and melphalan-based conditioning for patients with advanced hematological malignancies relapsing after a previous hematopoietic stem cell transplant. *Bone Marrow Transplant* 2001;28:557–562. [PubMed: 11607768]

24. Meshinchi S, Leisenring WM, Carpenter PA, et al. Survival after second hematopoietic stem cell transplantation for recurrent pediatric acute myeloid leukemia. *Biol Blood Marrow Transplant* 2003;9:706–713. [PubMed: 14652854]
25. Baron F, Storb R, Storer BE, et al. Factors associated with outcomes in allogeneic hematopoietic cell transplantation with nonmyeloablative conditioning after failed myeloablative hematopoietic cell transplantation. *J Clin Oncol* 2006;24:4150–4157. [PubMed: 16896000]
26. Grulich C, Bertz H, Spyridonidis A, et al. A fludarabine, thiopeta reduced toxicity conditioning regimen designed specifically for allogeneic second haematopoietic cell transplantation after failure of previous autologous or allogeneic transplantation. *Bone Marrow Transplant* 2008;41:845–850. [PubMed: 18209719]
27. Michallet M, Tanguy ML, Socie G, et al. Second allogeneic haematopoietic stem cell transplantation in relapsed acute and chronic leukaemias for patients who underwent a first allogeneic bone marrow transplantation: a survey of the Societe Francaise de Greffe de Moelle (SFGM). *Br J Haematol* 2000;108:400–407. [PubMed: 10691873]
28. Pawson R, Potter MN, Theocharous P, et al. Treatment of relapse after allogeneic bone marrow transplantation with reduced intensity conditioning (FLAG ± Ida) and second allogeneic stem cell transplant. *Br J Haematol* 2001;115:622–629. [PubMed: 11736947]
29. Bosi A, Laszlo D, Labopin M, et al. Second allogeneic bone marrow transplantation in acute leukemia: results of a survey by the European Cooperative Group for Blood and Marrow Transplantation. *J Clin Oncol* 2001;19:3675–3684. [PubMed: 11504749]
30. Eapen M, Giralt SA, Horowitz MM, et al. Second transplant for acute and chronic leukemia relapsing after first HLA-identical sibling transplant. *Bone Marrow Transplant* 2004;34:721–727. [PubMed: 15322568]
31. Duus JE, Stiff PJ, Choi J, et al. Second allografts for relapsed hematologic malignancies: feasibility of using a different donor. *Bone Marrow Transplant* 2005;35:261–264. [PubMed: 15558039]
32. Pollyea DA, Artz AS, Stock W, et al. Outcomes of patients with AML and MDS who relapse or progress after reduced intensity allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2007;40:1027–1032. [PubMed: 17846595]
33. Sica RA, Vosganian GS, Tuscano JM, et al. Reduced intensity stem cell transplant (RIST) as salvage treatment for relapse following myeloablative allogeneic transplantation in adult acute myeloid leukemia. *Biol Blood Marrow Transplant* 2007;13 (suppl):133.
34. Shaw, BE.; Mufti, GJ.; Mackinnon, S., et al. Outcome of second allogeneic transplants using reduced-intensity conditioning following relapse of haematological malignancy after an initial allogeneic transplant. *Bone Marrow Transplant*. 2008 Aug 25. Available from: URL: http://www.ncbi.nlm.nih.gov/pubmed/18724393?ordinalpos=6&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum
35. Tomblyn, M.; Lazarus, HM. Donor lymphocyte infusions: the long and winding road: how should it be traveled?. *Bone Marrow Transplant*. 2008 Aug 18. Available from: URL: http://www.ncbi.nlm.nih.gov/pubmed/18711351?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
36. Schmid C, Labopin M, Nagler A, et al. Donor lymphocyte infusion in the treatment of first hematological relapse after allogeneic stem-cell transplantation in adults with acute myeloid leukemia: a retrospective risk factors analysis and comparison with other strategies by the EBMT Acute Leukemia Working Party. *J Clin Oncol* 2007;25:4938–4945. [PubMed: 17909197]
- 37*. Reich-Zeliger S, Bachar-Lustig E, Bar-Ilan A, Reisner Y. Tolerance induction in presensitized bone marrow recipients by veto CTLs: effective deletion of host anti-donor memory effector cells. *J Immunol* 2007;179:6389–94. [PubMed: 17982025] This paper examines the ability of veto cells to induce apoptosis in pre-sensitized CD8 T cells *in vitro*. The authors then demonstrate that in a mouse model bone marrow veto cells also effectively overcame CD8 T cells, theoretically allowing for reduced capacity of graft *versus* host disease
38. Symons HJ, Fuchs EJ. Hematopoietic SCT from partially HLA-mismatched (HLA-haploidentical) related donors. *Bone Marrow Transplant* 2008;42:365–77. [PubMed: 18679375]

Table 1

Selected studies of second allogeneic HSCT or UCBT after HSCT or UCBT graft failure.

Reference/ Year/Study Type	N	Median Age, years (Range)	Myeloid Malignancies	1 st Graft Source	Same Donor Used	Characteristics of & Outcomes after 2 nd Transplant for All Patients					
						Conditioning	Engraftment ^a	GVHD/cGVHD	TRM or NRM	Relapse Rate	PFS/OS
Guardiola <i>et al.</i> 2000 [3]	82	25 (2 mo–25yr)	Unknown N=33 acute leukemia N=20 CML	MRD=63 Other = 19	68%	ATS±TBI or TLI; ATG±other drugs not specified	62%	41± 7%/17 ± 5%	53 ± 6% 3yr 22 ± 9% ^d	3yr EFS 26 ± 5%/30 ± 5%	
Narimatsu <i>et al.</i> 2005 [4]	4	57 (17–58) ^b	N=3 AML N=1 MDS ^c	UCBT All RIC	N/A	Flud/Mel/TBI or Flud/BU/TBI	3 of 4	NR	2 of 3	1 of 4 NR ^d	
Fernandes <i>et al.</i> 2007 [5]	4	14.5 (5–38)	N=2 AML N=1 CML	MMUD=1 UCBT=3	0	Cy/Flud/TBI or Cy/ATG/TBI	3 of 4 ^e	3 of 4/3 of 4	1 of 4	0 12mo–25mo 3 of 4/3 of 4	
Jabbour <i>et al.</i> 2007 [6]	9	42 (26–75)	N=2 AML N=5 CML N= 1 CMML N=1 MDS	MRD=3 MMRD=3 HID=1 MUD=2	8 of 9	Flud/ATG	6 of 9	6 of 9/1 of 9 ^f	7 of 9	1 of 9 OS 1 of 9 ^g	
Chewning <i>et al.</i> 2007 [7]	16	22 (4–59)	N=3 AML N=2 CML N=6 MDS	MRD=3 MMRD=2 MUD=5 MMUD=6	6 of 16	Flud/ATG or Flud/Cy/ATG or Flud/Thio/ATG or Flud/Thio/Cam	16 of 16	3 of 16/1 of 10	9 of 16	3 of 16 3yr DFS 18%/35%	
Lang <i>et al.</i> 2007 [8]	11	8 (3 to 39)	N=1 AML N=1CML N=1 JMML N=1 MDS	UCBT =1 MMRD=5 MUD=5	0	TLI/Flud/ATS± Thio or Cy/Flud/ATS±TBI	11 of 11	2 of 11/1 of 11	2 of 11	1 of 11 1yr EFS 72%	
Byrne <i>et al.</i> 2008 [9]	11	47 (20–68)	N=5 AML N=1 CML	MRD=2 MMRD=5 HID=4	4 of 11	Flud/Cy/Cam	9 of 11	5 of 9/1 of 9	2 of 11	4 of 11 7mo–5yr 5 of 11	
Heinzelmann <i>et al.</i> 2008 [10]	14	21.5 (4–53)	N=1 AML N=6 CML N=1 MDS	MRD=2 MMRD=1 HID=4 MUD=4 MMUD=3	NR	TLI/ATS±Flud or TLI/ATS/Flud± Thio	11 of 14	2 of 11/NR	6 of 11	2 of 11 681 days 86%/86% ^h	
Platzbecker <i>et al.</i> 2008 [11]	70 ⁱ	30 (1–59)	N=31 AML/MDS N=22 CML/MPD	MUD=51 MMUD=19	70 of 70	Myeloablative Dose-reduced None/Unknown	NR	NR	63%	16% Median OS was three months	

Abbreviations: AML = acute myelogenous leukemia; ATG = anti-thymocyte globulin; ATS = anti-T-cell serotherapy; BM = bone marrow; BU = busulphan; Cam = Campath; UCBT = umbilical cord blood transplant; CML = chronic myelogenous leukemia; CMML = chronic myelomonocytic leukemia; Cy = cyclophosphamide; DFS = disease free survival; EFS = event free survival; Flud = fludarabine; aGVHD = acute graft *versus* host disease; cGVHD = chronic graft *versus* host disease; HID = haplo-identical donor; HSCT = hematopoietic stem cell transplant; JMML = juvenile myelomonocytic leukemia; Mel = melphalan; MDS = myelodysplastic syndrome; MMRD = mismatched related donor; MMUD = mismatched unrelated donor; MPD = myeloproliferative disorder; MRD = matched related donor; MUD = matched unrelated donor; NR = not reported; NRM = non-relapse mortality; OS = overall survival; P = prospective; PBSC = peripheral blood stem cells; PFS = progression free survival; R = retrospective; RIC = reduced-intensity conditioning; TBI = total body irradiation; Thio = thiotepa; TLI = total lymphoid irradiation; TRM = treatment related mortality

^aSeven of 53 patients with malignant disease (acute leukemia or CML) relapsed at a median of 6 months (range 1mo–5yr) from second transplant.

^bMedian age of patients with graft failure; this is not statistically significantly different from the median age of patients who engrafted after first UCBT (55 yr, range 20–79 yr).

^cThe authors report on 123 patients who underwent reduced-intensity UCBT; nine of those patients did not engraft. Four of the nine received a second UCBT. Of the nine patients who did not engraft, 44% of them had myeloid malignancies but it is unclear who proceeded to second UCBT.

^dSeven of the nine patients died after the second transplant, with a median survival of 3.8 months (range 0.9–15.4 mo).

^eThe fourth patient recovered neutrophils, not platelets, but achieved 100% donor chimerism by day +30.

^fFour patients achieved a complete remission after HSCT, but three of them died “from GVHD and infection; only one remained alive ... but with extensive GVHD.” It is not clear if the three patients died of aGVHD or cGVHD.

^gThe median survival from the first HSCT was 7 months (range 2–24 mo) for all nine patients; only one patient was “alive at the last follow-up.”

^hThe reported PFS/OS are for the seven pediatric patients only. All of the adult patients died. Three died prior to engraftment; the remaining four died prior to day +200. The median overall survival and disease free survival for the entire cohort was 140 days (range 5–1,268).

ⁱThirty-six patients had relapsed disease after alloSCT while 34 patients had graft failure.

Selected studies of allogeneic HSCT after autologous HSCT disease relapse.

Reference/ Year/Study Type	N	Median Age, years (Range)	Myeloid Malignancies	Characteristics of & Outcomes after 2 nd Transplant for All Patients					
				Conditioning	Engraftment	aGVHD/cGVHD	TRM or NRM	Relapse Rate	PFS/OS
Blau <i>et al.</i> 2000 [20]	27 ^d	37 (22–49)	N=17 AML N=4 CML	TBI/Cy or BU/Cy or BU/VP-16	27 of 27	NR	7 of 27	12 of 27	OS 30%/OS for auto followed by allo 43% ^b
Radich <i>et al.</i> 2000 [21]	59	28 (1–57)	N=24 AML N=1 CML	TBI-containing regimen or chemotherapy-only regimen	47 of 59	7 of 32/4 of 32 ^c	2 yr 8 of 24 AML patients/0 of 1 CML patient	12 yr 6 of 24 AML patients/1 of 1 CML patient	2 yr DFS 10 of 24 AML patients/0 of 1 CML patients
Ringdén <i>et al.</i> 2000 [22]	90 ^d	24 (1–56) ^e	N=55 AML	TBI or BU/Cy or other or missing	60 of 62 ^f	5 of 62 ^f	0 of 62 ^f	12 of 62	2 yr OS 32 ± 5% for all allo HSCT transplant patients ^g
Devine <i>et al.</i> 2001 [23]	11 ^h	41 (22–58)	N=9 AML	Flud/Mel±ATG	10 of 11	2 of 10/4 of 7	6 of 11	4 of 11	1 yr OS probability 0.18
Meschinshi <i>et al.</i> 2003 [24]	25 ^h	4.1 ⁱ (1.1–17.2)	N=25 AML	TBI/Cy±ATG	25 of 25	19 of 25/10 of 21	10 yr 20%	10 yr 36%	10 yr DFS 44%/100 d, 1 yr and 10 yr OS 88%,56% and 48%
Baron <i>et al.</i> 2006 [25]	147 ^j	46 (9–73)	N=16 AML N=3 CML N=14 MDS N=2 MPD	TBI±Flud	141 of 147	aGVHD: 56% related, 65% unrelated/ cGVHD 48% related, 60% unrelated	100 d 18%, 3 yr 32% in related; 100 d 6%, 3 yr 28% in unrelated	3 yr probability 48% in related, 44% in unrelated	3 yr PFS 20% in related, 28% in unrelated (29% in myeloid malignancies)/3 yr OS 27% in related, 44% in unrelated (29% in myeloid malignancies)
Grunlich <i>et al.</i> 2008 [26]	49 ^k	52 (27–68)	N=18 AML N=1 CML	Flud/Thio	46 of 49	15 of 46/17 of 39	1 yr 29%	1 yr 55.1%	1 yr OS 25.9% for subgroup with AML

Abbreviations: AML = acute myelogenous leukemia; ATG = anti-thymocyte globulin; ATS = anti-T-cell serotherapy; BU = busulphan; CML = chronic myelogenous leukemia; CMML = chronic myelomonocytic leukemia; Cy = cyclophosphamide; DFS = disease free survival; EFS = event free survival; Flud = fludarabine; aGVHD = acute graft *versus* host disease; cGVHD = chronic graft *versus* host disease; HSCT = hematopoietic stem cell transplant; JMML = juvenile myelomonocytic leukemia; Mel = melphalan; MDS = myelodysplastic syndrome; MPD = myeloproliferative disorder; NR = not reported; NRM = non-relapse mortality; OS = overall survival; P = prospective; PFS = progression free survival; R = retrospective; RIC = reduced-intensity conditioning; TBI = total body irradiation; Thio = thiotept; TL1 = total lymphoid irradiation; TRM = treatment related mortality; UCBT = umbilical cord blood transplant

^aSixteen patients received an autologous HSCT and eleven received an allogeneic HSCT initially.

^bStatistically significant ($P=0.049$).

^cOverall incidence of aGVHD and cGVHD is not reported, only the number of deaths due to each are given.

^dThe authors report on a total of 2748 patients, ninety of which underwent an allogeneic HSCT after a failed autologous HSCT.

^eMedian age of the patients in the allogeneic group; this group tended to be younger than the chemotherapy alone group (26 years, range 1–77, $p=0.06$).

^fThe authors do not give data regarding total numbers of engraftment, aGVHD or cGVHD, rather the data are reported as causes of death following relapse after first transplantation. Two patients died due to graft failure or rejection in the allogeneic HSCT arm.

^gTwo-year OS for HLA-mismatched allogeneic HSCT recipients was 13 ± 8% *versus* 37 ± 7% in those patients who received an HLA-matched allogeneic HSCT.

^hPatients were either s/p autologous HSCT or allogeneic HSCT as their first transplant.

ⁱAge at second transplant.

^jOne-hundred thirty-five of the 147 patients were s/p autologous HSCT while only twelve patients underwent an allogeneic or syngeneic HSCT as their first transplant.

^kOf the 49 patients in the study, 29 received an autologous HSCT and 20 received an allogeneic HSCT as their first HSCT.

Table 3

Selected studies of second allogeneic HSCT for disease relapse.

Reference/ Year/Study Type	N	Median Age, years (Range)	Myeloid Malignancies	1 st Graft Source	Same Donor Used	Characteristics of & Outcomes after 2 nd Transplant for All Patients					
						Conditioning	Engraftment	aGVHD/cGVHD	TRM or NRM	Relapse Rate	PFS/OS
Michallet <i>et al.</i> 2000 [27]	150	25 (1.5–46)	N=61 AML N=42 CML	MRD=134 MMRD=3 MUD=4 Syn=9	83%	TBI/Cy±VP16 or TBI/Mel or TBI/AraC/Mel/ VP16 or BU/Cy or BU/Mel or Mel or BEAM	93%	69 of 120/34 of 93	5 yr 45 ± 9%	5 yr 44 ± 12%	5 yr DFS 30 ± 8%/OS 32 ± 8%
Pawson <i>et al.</i> 2001 [28]	14	30.5 (9–48)	N=7 AML N=2 MDS	MRD=13 MMRD=1	14 of 14 ^d	Flud/AraC/GCSF± Ida	13 of 14	7 of 14/8 of 11	0 of 14	10 of 14	2–58+ mo DFS 26%/3–58+ mo OS 60%
Bosi <i>et al.</i> 2001 [29]	170	22 (1–46)	N=85 AML	MRD=154 MMRD=6 MUD=3 Syn=7	91%	TBI-based regimen in 68%/non-TBI-based regimen in 32%	90%	59%/32%	5 yr 46%	5 yr 59%	5 yr DFS 25%/5 yr OS 26%
Eapen <i>et al.</i> 2004 [30]	279	NR ^b	N=125 AML N=82 CML	MRD=279	85%	Combination of myeloablative and non-myeloablative regimens	86% ^c	100 d 29%/1 yr and 5 yr 39% and 41%	1 yr and 5 yr 26% and 30%	1 yr and 5 yr 36% and 42%	1 yr and 5 yr DFS 38% and 28%/1 yr and 5 yr OS 41% and 28%
Duus <i>et al.</i> 2005 [31]	6	45.5 ^d (18–51)	N=1 AML N=2 CML N=1 MDS	MRD=3 URD=3	0 of 6	BEAM or Bu/Cy or TBI/Cy±VP16	5 of 6 ^e	2 of 6/4 of 6	0%	2 of 6	Median OS 23mo (3–72 mo)
Pollyea <i>et al.</i> 2007 [32]	13 ^f	52 (20–67)	N=12 AML N=1 MDS	Related=14 Unrelated=11 ^g	13 of 13	BU/Cy/Thio±Cam or Flud/BU/Cam or BU/Cy or TBI/Thio/Flud or Clad	NR	1 of 13 ^h	2 of 13	9 of 13	2 of 9 were alive in remission 939 and 504 days after second HSCT
Sica <i>et al.</i> 2007 [33]	9	NR (21–57)	N=7 AML N=2 MDS	MRD=8 MUD=1	9 of 9	Flud/Cy/GCSF±Ida or Flud/TBI	NR	3 patients had GVHD at the time of death	0%	6 of 9	3 of 9 survive at days +100, +635 and +1795
Shaw <i>et al.</i> [34]	71	39 ^j (8–69)	N=26 AML N=10 MDS N=7 CML N=3 MPD	MRD=68 MUD=3	80%	Flud/AraC/GCSF± Ida or Flud/Mel/BU or Flud/TBI or other non-Flud or other Flud or unknown	98%	26%/42%	100d and1 yr 15% and 23%	1 yr 62% in AML, 57% in CML, 21% in MDS	2 yr OS 18% in AML, 0% in CML and MPD and 18% in MDS

Abbreviations: AML = acute myelogenous leukemia; ATG = anti-thymocyte globulin; ATS = anti-T-cell serotherapy; BM = bone marrow; BU = busulphan; Cam = Campath; Clad = cladribine; CML = chronic myelogenous leukemia; CMML = chronic myelomonocytic leukemia; Cy = cyclophosphamide; DFS = disease free survival; EFS = event free survival; Flud = fludarabine; aGVHD = acute graft *versus* host disease; HSCCT = hematopoietic stem cell transplant; Ida = idarubicin; JMML = juvenile myelomonocytic leukemia; Mel = melphalan; MDS = myelodysplastic syndrome; MMRD = mismatched related donor; MMUD = myeloproliferative disorder; MRD = mismatched unrelated donor; MPD = myeloproliferative disorder; MRD = mismatched related donor; MUD = matched unrelated donor; NR = not reported; NRM = non-relapse mortality; OS = overall survival; P = prospective; PBST = peripheral blood stem cells; PFS = progression free survival; R = retrospective; RIC = reduced-intensity conditioning; Syn = syngeneic donor; TBI = total body irradiation; Thio = thiotepea; TLI = total lymphoid irradiation; TRM = treatment related mortality; UCBT = cord blood transplant; URD = unrelated donor

^a All fourteen patients received BM cells as their first transplant. For the second, twelve of 14 were PBSC, only 2 were BM.

^b Age is given as ≤ 10 years (51), 11–20 years (55), 21–30 years (65), or > 30 years (108).

^c Cumulative incidences of ANC > 500 at day 100 was 86% and platelets >20,000 at 1 year was 83%.

^d Age at second transplant.

^e Five of six patients achieved full engraftment while one patient recovered only neutrophils.

^f This study examined a total of 70 patients who received allogeneic HSCT. Twenty-five patients relapsed, and 13 of them received a second allogeneic HSCT as salvage treatment.

^g Related and unrelated donors could have no more than one antigen or allelic mismatch.

^h One patient died from GVHD. Otherwise the rates are not specified.

ⁱ Age at first transplant.

Table 4

Factors Predicting Successful Second HSCT or UCBT (only from studies with > 60 patients)

Factor	Prognostic Utility	Citations Supporting	Citations Not Supporting or Unable to Assess
Disease status at time of second transplant	Useful	Baron[24] – PR or CR at the time of second alloSCT resulted in higher OS, higher PFS and a lower relapse rate Bosi [32] – patients in CR had higher OS, LFS and lower TRM and relapse rate than those who were in untreated relapse or with refractory disease at the time of second alloSCT (most important factor); patients with AML specifically had higher rates of LFS if in CR as compared to those with persistent disease Eapen [33] – patients with relapsed or persistent disease had a higher relapse rate and a higher treatment failure rate than those in remission Ringdén [25] – patients in first remission at second autograft had better survival	Michallet [31] – authors state that the small number of patients did not allow a comparison between patients with chemosensitive disease and refractory disease Platzbecker [7] Shaw [34] – there was no difference in OS based on disease status
Longer interval from time of first transplant to relapsed disease	Useful, but unclear what time interval is ideal	Bosi [32] – an interval of >292 days between first alloSCT and relapse was associated with lower TRM and relapse rates, and higher LFS and OS Eapen [33] – patients who relapsed more than 6 months from first alloSCT had lower overall mortality, treatment failure rates, relapse rates and TRM (most important factor) Guardiola [6] – an intertransplant time of more than 80 days was a significant predictor of a higher neutrophil recovery rate, lower day 100 TRM and a higher 3 year OS Michallet [31] – patients who relapsed more than 1 year after first alloSCT had higher 5 year OS and DFS and lower TRM as compared to patients who relapsed within 1 year of first alloSCT Ringdén [25] – those patients with a greater than 5 month time between autoSCT and relapse had better OS Shaw [34] – TRM and OS were negatively impacted in those patients who relapsed within 11 months of initial transplant	Platzbecker [7]
Age	Useful, but unclear what age is ideal	Eapen [33] – patients ≤ 20 years had a lower TRM, treatment failure rate and overall mortality rate compared to patients over 20 Guardiola [6] – a recipient age of < 34 years was associated with a lower day 100 TRM and a higher 3 year OS Michallet [31] – age less than 16 years was associated with a better 5 year OS and lower TRM; it was not associated with a better 5 year DFS Platzbecker [7] – age less than 50 years was associated with a better OS Ringdén [25] – patients younger than 26 years had better OS	Baron [24] Shaw [34] there was no difference in OS based on age
Different donor for second transplantation	Not Useful		Eapen [33] Guardiola [6] Shaw [34] – there was no difference in OS based on alternate donor for second alloSCT
Related/unrelated or matched donor	Not Useful		Baron [24] – OS not statistically different in patients with related <i>versus</i> unrelated donors Bosi [32] – DFS was the same for those with non-HLA identical sibling donors as compared to those with an HLA matched sibling donor Ringdén [25] – patients who underwent an HLA-mismatched alloSCT had a lower OS as compared to patients who were treated with chemotherapy alone for relapsed disease Platzbecker [7] – HLA disparity was not associated with OS Shaw [34] – there was no difference in OS based on donor type
Acute GVHD	Equivocal	Bosi [32] – patients with aGVHD at second alloSCT had better LFS and lower relapse rates Shaw [34] – only the subset of patients relapsing within 11 months from first transplant had improved OS with development of aGVHD during the second alloSCT	Baron [24] – the presence of at least grade 2 aGVHD was associated with a higher TRM, and a trend towards lower OS Michallet [31] – absence of aGVHD was associated with higher 5 year OS and DFS Platzbecker [7]
Chronic GVHD	Useful	Baron [24] – those patients who developed cGVHD had lower rates of relapse without impacting TRM and OS Michallet [31] – presence of cGVHD was associated with higher 5 year OS and DFS and lower TRM Shaw [34] – patients with cGVHD had lower relapse rates and higher OS than those without cGVHD after the second alloSCT	Bosi [32] Platzbecker [7]

Factor	Prognostic Utility	Citations Supporting	Citations Not Supporting or Unable to Assess
Donor gender	Equivocal	Michallet [31] female donor transplants were associated with higher 5 year OS, 5 year DFS and lower TRM	
BM vs PBSC	Equivocal	Bosi [32] – patients who received bone marrow stem cells had lower rates of relapse than those who received peripheral blood stem cells Guardiola [6] – the use of peripheral blood stem cells was a significant predictor of a higher neutrophil recovery rate but did not change OS due to the small number of evaluable patients	Eapen [33] Michallet [31] – study not powered to assess this effect Shaw [34] – there was no difference in OS based on BM <i>versus</i> PBSC
Underlying malignancy	Equivocal	Baron [24] – patients with multiple myeloma, myeloid malignancies and Hodgkin's disease were more likely to relapse and had a lower PFS than those with non-Hodgkin's lymphoma Bosi [32] – patients with ALL had higher relapse rates than patients with AML	Eapen [33] Platzbecker [7]
Conditioning regimen	Equivocal	Bosi [32] – patients who received TBI at second alloSCT had higher rates of OS and LFS and lower rates of TRM Eapen [33] – those patients who underwent reduced intensity conditioning had a higher relapse rate than those who received TBI containing regimens	Shaw [34] Platzbecker [7] – in those patient with graft failure there was no difference in OS between those who underwent second conditioning and those who did not
GVHD prophylaxis	Equivocal	Bosi [32] – the use of cyclosporine alone was associated with a better LFS and OS compared to other prophylaxis Guardiola [6] – the use of cyclosporine alone was associated with a lower day 100 TRM and a higher 3 year OS compared to other cyclosporine containing regimens	

aGVHD = acute graft *versus* host disease; ALL = acute lymphoblastic leukemia; alloSCT = allogeneic stem cell transplantation; AML = acute myelogenous leukemia; BM = bone marrow; cGVHD = chronic graft *versus* host disease; CR = complete remission; DFS = disease free survival; LFS = leukemia free survival; OS = overall survival; PBSC = peripheral blood stem cell; PFS = progression free survival; TBI = total body irradiation; TRM = treatment related mortality