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Effects of all-trans retinoic acid (ATRA) in addition to chemotherapy for adults with acute myeloid leukaemia (AML) (non-acute promyelocytic leukaemia (non-APL)) (Review)

Küley-Bagheri Y, Kreuzer KA, Monsef I, Lübbert M, Skoetz N

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[Intervention Review]

Effects of all-trans retinoic acid (ATRA) in addition to chemotherapy for adults with acute myeloid leukaemia (AML) (non-acute promyelocytic leukaemia (non-APL))

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ABSTRACT

Background

Acute myeloid leukaemia (AML) is the most common acute leukaemia affecting adults. Most patients diagnosed with AML are at advanced age and present with co-morbidities, so that intensive therapy such as stem cell transplantation (SCT) is impossible to provide or is accompanied by high risks for serious adverse events and treatment-related mortality. Especially for these patients, it is necessary to find out whether all-trans retinoic acid (ATRA), an intermediate of vitamin A inducing terminal differentiation of leukaemic cell lines, added to chemotherapy confers increased benefit or harm when compared with the same chemotherapy alone.

Objectives

This review aims to determine benefits and harms of ATRA in addition to chemotherapy compared to chemotherapy alone for adults with AML (not those with acute promyelocytic leukaemia (non-APL)).

Search methods

We searched the Central Register of Controlled Trials (CENTRAL), MEDLINE, study registries and relevant conference proceedings up to July 2018 for randomised controlled trials (RCTs). We also contacted experts for unpublished data.

Selection criteria

We included RCTs comparing chemotherapy alone with chemotherapy plus ATRA in patients with all stages of AML. We excluded trials if less than 80% of participants were adults or participants with AML, and if no subgroup data were available. Patients with myelodysplastic syndrome (MDS) were included, if they had a refractory anaemia and more than 20% of blasts.

Data collection and analysis

Two review authors independently extracted data and assessed the quality of trials. We contacted study authors to obtain missing information. We used hazard ratios (HR) for overall survival (OS) and disease-free survival (DFS; instead of the pre-planned event-free survival, as this outcome was not reported), and we calculated risk ratios (RR) for the other outcomes quality of life, on-study mortality and adverse events. We presented all measures with 95% confidence intervals (CIs). We assessed the certainty of evidence using GRADE methods.

Main results

Our search resulted in 2192 potentially relevant references, of which we included eight trials with 28 publications assessing 3998 patients. Overall, we judged the potential risk of bias of the eight included trials as moderate. Two of eight trials were published as abstracts only. All the included trials used different chemotherapy schedules and one trial only evaluated the effect of the hypomethylating agent decitabine, a drug known to affect epigenetics, in combination with ATRA.

The addition of ATRA to chemotherapy resulted in probably little or no difference in OS compared to chemotherapy only (2985 participants; HR 0.94 (95% confidence interval (CI) 0.87 to 1.02); moderate-certainty evidence). Based on a mortality rate at 24 months of 70% with chemotherapy alone, the mortality rate with chemotherapy plus ATRA was 68% (95% CI 65% to 71%).

For DFS, complete response rate (CRR) and on-study mortality there was probably little or no difference between treatment groups (DFS: 1258 participants, HR 0.99, 95% CI 0.87 to 1.12; CRR: 3081 participants, RR 1.02, 95% CI 0.96 to 1.09; on-study mortality: 2839 participants, RR 1.02, 95% CI 0.81 to 1.30, all moderate-certainty evidence).

Three trials with 1428 participants reported the adverse events 'infection' and 'cardiac toxicity': There was probably no, or little difference in terms of infection rate between participants receiving ATRA or not (RR 1.05, 95% CI 0.96 to 1.15; moderate-certainty evidence). We are uncertain whether ATRA decreases cardiac toxicity (RR 0.46, 95% CI 0.24 to 0.90; $P = 0.02$, very low certainty-evidence, however, cardiac toxicity was low).

Rates and severity of diarrhoea and nausea/vomiting were assessed in two trials with 337 patients and we are uncertain whether there is a difference between treatment arms (diarrhoea: RR 2.19, 95% CI 1.07 to 4.47; nausea/vomiting: RR 1.46, 95% CI 0.75 to 2.85; both very low-certainty evidence).

Quality of life was not reported by any of the included trials.

Authors' conclusions

We found no evidence for a difference between participants receiving ATRA in addition to chemotherapy or chemotherapy only for the outcome OS. Regarding DFS, CRR and on-study mortality, there is probably no evidence for a difference between treatment groups. Currently, it seems the risk of adverse events are comparable to chemotherapy only.

As quality of life has not been evaluated in any of the included trials, further research is needed to clarify the effect of ATRA on quality of life.

PLAIN LANGUAGE SUMMARY

Treatment with all-trans retinoic acid in addition to chemotherapy for adult patients with acute myeloid leukaemia (non-APL)

What is the aim of this review?

This review aims to determine benefits and harms of all-trans retinoic acid (ATRA) in addition to chemotherapy compared with chemotherapy alone for adults with AML. We did not evaluate participants with acute promyelocytic leukaemia (APL). We collected and analysed all relevant studies to answer this question and found eight studies.

Key messages

The addition of ATRA to chemotherapy did not show relevant differences in terms of overall survival (OS), but the subgroup analyses showed that there is potential benefit for ATRA in combination with a certain chemotherapeutic called decitabine, for older patients (over 60 years) and for patients who already had successful chemotherapy and now receive therapy for maintenance. We assessed the certainty of evidence as moderate for OS, disease-free-survival and on-study mortality.

Rates of toxicities were low, therefore certainty of evidence is 'very low' to 'low' for the adverse events diarrhoea, nausea/vomiting and cardiac toxicity. For the adverse event infection, we judged the certainty of evidence as moderate. Currently, it seems the risk of adverse events with additional ATRA are comparable to chemotherapy only.

Quality of life was not reported by any of the included trials.

What was studied in this review?

Acute myeloid leukaemia is a life-threatening type of cancer that starts in the blood-forming cells of the bone marrow and can cause many different signs and symptoms. It is classified into several subtypes, of which one subtype, acute promyelocytic leukaemia (APL) is treated differently to the other subtypes.

Almost 60% of patients are older than 65 years at the time of diagnosis. Because of advanced age and accompanying diseases an intensive therapy with high-dose chemotherapy and stem cell transplantation often is not possible or is accompanied by high risks for serious

adverse events and treatment-related mortality. For these reasons it would be important to know a less intensive and dangerous therapy for older patients.

All-trans retinoic acid (ATRA), an intermediate product of vitamin A, had been integrated into treatment regimens for APL by the end of the 1980s. It is administered orally and is generally well tolerated but can induce a severe, life-threatening complication called differentiation syndrome, which includes breathing difficulties and fever.

The literature provides contradictory data about the benefit of ATRA for patients with AML. It has been reported to increase the sensitivity of AML cell lines to chemotherapy by reducing one protein, which is associated with poor response to chemotherapy and therefore is related to a poor prognosis. These reports have led to the assumption that ATRA added to chemotherapy may improve outcomes and might replace or reduce the intensity of chemotherapy for patients with AML.

What are the main results of this review?

We found eight relevant studies with almost 4000 patients in total, conducted in the UK, Germany and France. These studies compared chemotherapy in combination with ATRA with chemotherapy alone in adult patients (over 18 years) with AML. All the included trials used different chemotherapy schedules, as there are several types of chemotherapy regimens for AML. Only in one trial did participants receive a newer drug, decitabine, which has been licensed for the treatment of AML since 2012.

Adding ATRA to chemotherapy probably makes little or no difference to OS. ATRA may be potentially beneficial in combination with decitabine, for older patients (over 60 years) and for patients who receive therapy for maintenance, but these findings need to be explored by further research.

For disease-free-survival, complete response rate and on-study mortality there was probably no or little difference between treatment groups.

The combination of ATRA probably did not lead to a higher infection rate. Regarding cardiac toxicity and diarrhoea, the certainty of the evidence was assessed as very low, so we are uncertain whether the addition of ATRA is beneficial.

Quality of life was not reported by any of the included trials.

How up-to-date is this review?

We searched for studies that had been published up to July 2018.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. ATRA in addition to chemotherapy compared to chemotherapy only for adults with acute myeloid leukaemia (AML) (non-acute promyelocytic leukaemia (APL))

ATRA in addition to chemotherapy compared to chemotherapy alone for adults with acute myeloid leukaemia (AML) (non-acute promyelocytic leukaemia (APL))

Patient or population: adults with acute myeloid leukaemia (AML) (non-acute promyelocytic leukaemia (APL))

Setting: hospital, clinics or ambulatory

Intervention: ATRA, an intermediate of vitamin A inducing terminal differentiation of leukaemic cell lines or all trans , in addition to chemotherapy (Idarubicin, cytarabine, etoposide, mitoxantrone, cytarabine, decitabine, daunorubicin, fludarabine, thioguanine, amsacrine, mitoxantrone)

Comparison: chemotherapy only

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with chemotherapy only	Risk with ATRA in addition to chemotherapy				
Mortality (instead of overall survival) follow-up: 24 months	Moderate 700 per 1.000	 678 per 1.000 (649 to 707)	HR 0.94 (0.87 to 1.02)	2985 (7 RCTs)	⊕⊕⊕⊖ MODERATE ¹	Data calculated for mortality instead of for overall survival, due to technical reasons
Quality of life						not reported
Mortality, relapse and progresses (instead of disease- or relapse-free survival)	Moderate 800 per 1.000	 797 per 1.000 (753 to 835)	HR 0.99 (0.87 to 1.12)	1258 (3 RCTs)	⊕⊕⊕⊖ MODERATE ²	Data calculated for mortality, progress and relapse instead of for disease- or relapse-free survival, due to technical reasons
On-study mortality	Study population 84 per 1.000	 85 per 1.000 (68 to 109)	RR 1.02 (0.81 to 1.30)	2839 (5 RCTs)	⊕⊕⊕⊖ MODERATE ³	
Infection grade III/IV	Study population 528 per 1.000	 555 per 1.000 (507 to 608)	RR 1.05 (0.96 to 1.15)	1428 (3 RCTs)	⊕⊕⊕⊖ MODERATE ²	

Diarrhoea grade III/IV	Study population		RR 2.19 (1.07 to 4.47)	337 (2 RCTs)	⊕⊕⊕⊕ VERY LOW ^{2 4}
	60 per 1.000	130 per 1.000 (64 to 266)			
Nausea/vomiting grade III/IV	Study population		RR 1.46 (0.75 to 2.85)	337 (2 RCTs)	⊕⊕⊕⊕ VERY LOW ^{2 4}
	77 per 1.000	113 per 1.000 (58 to 221)			
Cardiac toxicity grade III/IV	Study population		RR 0.46 (0.24 to 0.90)	1428 (3 RCTs)	⊕⊕⊕⊕ VERY LOW ^{2 4}
	37 per 1.000	17 per 1.000 (9 to 34)			

***The risk in the intervention group** (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; **RR:** Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Abbreviations: AML: acute myeloid leukaemia; APL: acute promyelocytic leukaemia; ATRA: all-trans retinoic acid

¹ Downgraded by one due to heterogeneity ($I^2 = 67\%$) (inconsistency)

² Downgraded by one due to unblinded study design, unblinded outcome assessors (risk of bias)

³ Downgraded by one due to small number of events (imprecision)

⁴ Downgraded by two due to very small number of included patients (imprecision)

BACKGROUND

Description of the condition

Acute myeloid leukaemia (AML) is a heterogeneous group of clonal malignant myeloid disorders. The disease is characterized by overproduction of immature white blood cells, called myeloblasts or leukaemic blasts, within the bone marrow. Immaturity of white cells and displacement of other cells evolving from the myeloid cell line (i.e. erythrocytes, thrombocytes, granulocytes and monocytes) lead to typical symptoms such as fatigue and weakness, haemorrhage, infection and fever (Lowenberg 1999).

The disease is classified into several subtypes by the French-American-British (FAB) classification and by the newer World Health Organization (WHO) classification, which was revised in 2008. The FAB classification system was published in the 1970s and divides AML into eight subtypes - M0 through M7 - on the basis of cytomorphological aspects (Bennett 1976). The WHO has developed a newer system that includes factors now known to affect prognosis and therapy provided for patients with AML (Harris 1999; Vardiman 2009). Subtypes are categorised on the basis of their underlying cytogenetic or molecular genetic abnormalities. Bone marrow aspiration is part of the routine diagnostic workup for a patient with suspected AML. For a diagnosis of AML, a marrow or blood blast count of 20% or more is required, except for cases of AML with translocation t(15;17), t(8;21), inv(16) or t(16;16).

Acute promyelocytic leukaemia (APL), a distinct subtype of AML, is classified as AML M3 by the FAB system, and as APL with translocation between chromosomes 15 and 17 (i.e. t(15;17)) in the WHO classification system. APL is worth mentioning because treatment of patients with this subtype differs from treatment of the others, as per the statement below.

The most common acute leukaemia affecting adults is AML, and its incidence increases with age. In the USA, the annual incidence of AML is approximately 4.1 per 100,000 inhabitants; in Europe, the incidence rate is 3.7 per 100,000 per year. The five-year relative survival rate is 19% for AML. Almost 60% of patients are older than 65 years at the time of diagnosis (Howlader 2013; Visser 2012).

About 60% to 70% of adults with AML can be expected to achieve complete remission (CR) status after receiving appropriate induction therapy, whereupon remission rates are inversely related to patient age. More than 25% of adults with AML (about 45% of those who achieve CR) can be expected to survive three years or longer and may be cured (National Cancer Institute 2015).

Intensive treatment, such as high-dose therapy and stem cell transplantation (SCT), could improve survival among these patients but often is not possible because of advanced age and co-morbidities (Rathnasabapathy 2003).

Description of the intervention

Depending on performance status and co-morbid medical conditions, in addition to patient age, different therapy regimens are used for acute myeloid leukaemia (non-APL).

For patients younger than 60 years, standard therapy includes induction therapy with cytarabine and anthracycline, consolidation therapy with or without allogeneic SCT and post-remission therapy with cytarabine or allogeneic SCT (Fernandez 2009; Lowenberg

2011; Rolig 2015). Allogeneic SCT is an option only when a matched sibling or an alternative donor is available. Otherwise, autologous SCT can be an option (Jing 2013; Sabty 2013).

Patients over 60 years of age often receive low-intensity chemotherapy with subcutaneous cytarabine, 5-azacytidine and decitabine as a result of co-morbidities (Al-Ali 2014; Passweg 2014; Tawfik 2014).

To evaluate the probability of complete response and early death after receipt of standard induction therapy among elderly patients, a Web-based scoring tool is available (Krug 2010). This tool may be helpful in the decision-making process when standard therapy appears too risky because of co-morbidities, leading to contemplation of low-intensity chemotherapy.

Treatment of most patients with APL differs from usual AML treatment. Initial treatment often includes the non-chemotherapy drugs all-trans retinoic acid (ATRA) and arsenic trioxide (Shen 2004).

How the intervention might work

All-trans retinoic acid (ATRA), a metabolite of retinol (vitamin A), had been integrated into treatment regimens for APL by the end of the 1980s. Chromosomal translocation in APL cells leads to rearrangement of retinoic acid receptor α (RARA), an encoded protein of the retinoic acid gene. This gene plays an important role in the development of hematopoiesis-like differentiation and apoptosis (Wang 2008). ATRA induces terminal differentiation of leukaemic cell lines, so ATRA-based therapy can lead to complete remission in APL (Shen 2004). ATRA in APL is administered orally (45 mg/m² per day), divided into two daily doses and maintained until CR, then according to risk status assigned as low, intermediate or high (Ades 2008). It is generally well tolerated but can induce a severe, life-threatening complication called differentiation syndrome (DS), formerly known as retinoic acid syndrome (RAS). The most common manifestations include respiratory distress and fever, and the diagnosis is difficult because no definitive diagnostic criteria are known. Mortality has been reported in about 2% of patients treated with ATRA and suffering from DS (Larson 2003; Patatani 2008).

ATRA has been reported to increase the sensitivity of AML cell lines to drugs such as cytosine-arabinoside (AraC) by down regulating the oncoprotein bcl-2 (Andreeff 1999; Hu 1995; Zheng 2000). High expression of bcl-2 protein is associated with poor response to chemotherapy and therefore is a determinant of poor prognosis in AML (Karakas 1998; Karakas 2002; Tothova 2002). These in vitro data have led to the assumption that ATRA added to chemotherapy may improve outcomes. The literature provides contradictory data showing results of in vivo studies.

One prospective randomised controlled treatment trial with more than 1000 patients with AML showed significantly improved response to induction therapy and event-free survival (EFS) in *NPM1*-mutated AML, as well as overall survival (OS) in younger adult patients with AML, regardless of whether they had a mutation (Schlenk 2011). The *NPM1* mutation thereby was confirmed as a predictive factor of response for the addition of ATRA. In contrast, in some studies, benefit derived from the addition of ATRA has not been shown, irrespective of a genetic mutation (Gale 2009; Nazha 2013). Rates and severity of adverse effects were similar.

Why it is important to do this review

Most patients diagnosed with AML are at advanced age and present with co-morbidities, meaning that an intensive therapy such as SCT is impossible to provide or is accompanied by a high risk for serious adverse events and treatment-related mortality. Especially for these patients, it is necessary to find out whether ATRA added to chemotherapy confers increased benefit or harm when compared with the same chemotherapy only.

OBJECTIVES

This review aims to determine benefits and harms of all-trans retinoic acid (ATRA) in addition to chemotherapy compared with chemotherapy alone for adults with acute myeloid leukaemia (AML) (not those with acute promyelocytic leukaemia (non-APL)).

METHODS

Criteria for considering studies for this review

Types of studies

We considered only randomised controlled trials (RCTs). We included both full-text and abstract publications if sufficient information was available on study design, characteristics of participants and interventions provided.

Types of participants

We included trials on adult (≥ 18 years) participants with a confirmed diagnosis of AML. We applied no gender or ethnicity restrictions. We considered individuals at all stages of AML, including newly diagnosed patients and those with relapsed or drug-resistant disease. We excluded trials if less than 80% of participants were adults, and if no subgroup data were available. Patients with myelodysplastic syndrome (MDS) were included, if they had a refractory anaemia and more than 20% of blasts, so called refractory anaemia with excess blasts in transformation (RAEB-T). Patients with MDS and less than 20 % myeloblasts were excluded.

Types of interventions

The intervention consisted of ATRA added to chemotherapy versus chemotherapy only. Participants in both study arms should have received the same therapy, such as the same chemotherapeutics, the same number of cycles and additional allogeneic or autologous SCT.

Types of outcome measures

Primary outcomes

- Overall survival (OS) defined as time from random treatment assignment to death from any cause or to last follow-up

Secondary outcomes

We analysed the following as secondary outcomes.

- Quality of life
- Disease or relapse-free survival instead of the pre-planned event-free survival, as event-free survival has not been reported
- Complete response rate
- On-study mortality

- Adverse events (haematological toxicity, infection, diarrhoea, cardiac and pulmonary failure, nausea, differentiation syndrome (DS))

Search methods for identification of studies

Electronic searches

We adapted search strategies as suggested in Chapter Six of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). We applied no language restrictions to reduce language bias.

We searched the following databases and sources.

- Databases of medical literature
 - The Cochrane Central Register of Controlled Trials (CENTRAL) the Cochrane Library, 2018, Issue 07) ([Appendix 1](#))
 - MEDLINE (Ovid) (1950 to 13 July 2018) ([Appendix 2](#))
- Databases of ongoing trials
 - EU clinical trials register: <https://www.clinicaltrialsregister.eu/ctr-search/search>
 - World health organisation: <http://apps.who.int/trialsearch/>
 - Clinicaltrials.gov: <https://clinicaltrials.gov/>
 - ISRCTN: <http://www.isrctn.com/>
- Conference proceedings of annual meetings of the following societies for abstracts, if not included in CENTRAL (2010 to 2017)
 - American Society of Hematology (until 2017)
 - American Society of Clinical Oncology (until 2017)
 - European Hematology Association (until 2017)

Searching other resources

- Handsearching of references
 - References of all identified trials and relevant review articles; current treatment guidelines as further literature

Data collection and analysis

Selection of studies

Two review authors (YK-B, NS) independently screened results of search strategies for eligibility for this review by reading all abstracts and titles. In cases of disagreement, we obtained the full-text publication. If no consensus had been reached, we would have asked a third review author to adjudicate ([Higgins 2011](#)).

We documented the process of study selection in a flow chart, as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement ([Moher 2009](#)), showing total numbers of retrieved references and numbers of included and excluded studies.

Data extraction and management

Two review authors (YK-B, NS) independently extracted data according to Chapter Seven of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We contacted authors of individual studies to ask for additional information, if required. We used a standardised data extraction form containing the following items.

- General information
 - Author, title, source, publication date, country, language, duplicate publications

- Quality assessment
 - Allocation concealment, blinding (participants, personnel, outcome assessors), incomplete outcome data, selective outcome reporting, other sources of bias
- Study characteristics
 - Trial design, aims, setting and dates, source of participants, inclusion/exclusion criteria, subgroup analysis, treatment cross-overs, compliance with assigned treatment, length of follow-up
- Participant characteristics
 - Newly diagnosed/relapsed patients, histological subtype, additional diagnoses, age, gender, ethnicity, number of participants recruited/allocated/evaluated, participants lost to follow-up, type of treatment (multi-agent chemotherapy (intensity of regimen, number of cycles), allogeneic/autologous SCT)
- Interventions
 - Dose and cycles of ATRA; type, dose and cycles of chemotherapy; duration of follow-up
- Outcomes
 - Overall survival, quality of life, disease-free survival (instead of the pre-planned event-free survival), complete response rates, on-study mortality, adverse events

Assessment of risk of bias in included studies

Two review authors (YK-B, NS) independently assessed risk of bias for each study using the following criteria, as outlined in Chapter Eight of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

- Sequence generation
- Allocation concealment.
- Blinding (participants, personnel, outcome assessors)
- Incomplete outcome data
- Selective outcome reporting
- Other sources of bias

We made a judgement for each criterion, using one of the following categories.

- 'Low risk': if the criterion is adequately fulfilled in the study (i.e. the study is at low risk of bias for the given criterion).
- 'High risk': if the criterion is not fulfilled in the study (i.e. the study is at high risk of bias for the given criterion).
- 'Unclear': if the study report does not provide sufficient information to allow a clear judgement, or if risk of bias is unknown for one of the criteria listed above.

Measures of treatment effect

We used intention-to-treat data. For binary outcomes, we calculated risk ratios (RRs) with 95% confidence intervals (CIs) for each trial. For time-to-event outcomes, we extracted hazard ratios (HRs) from published data according to Parmar 1998 and Tierney 2007. We would have calculated continuous outcomes as mean differences (MDs) when assessed with the same instruments; otherwise we would have used standardised mean differences (SMDs). However, as none of the included trials reported quality of life data, we did not analyse continuous data.

Dealing with missing data

As suggested in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b), many potential sources of missing data must be taken into account: at study level, at outcome level and at summary data level. First, it is important to distinguish between 'missing at random' and 'not missing at random'. We contacted the original investigators to request missing data. If data were still missing, we made explicit assumptions regarding any methods used, for example, that the data were assumed to be missing at random, or that missing values were assumed to have a particular value, such as a poor outcome. We imputed missing data for participants lost to follow-up after randomisation (dichotomous data) by assuming poor outcomes (worse case scenario) for missing individuals. We performed sensitivity analysis to assess how sensitive results were to reasonable changes in assumptions made. We addressed in the Discussion the potential impact of missing data on the findings of the review.

Assessment of heterogeneity

We assessed heterogeneity of treatment effects between trials using the χ^2 test with a significance level of P value < 0.1 . We used the I^2 statistic to quantify possible heterogeneity ($I^2 > 30\%$ moderate heterogeneity, $I^2 > 75\%$ considerable heterogeneity) (Deeks 2011). We explored potential causes of heterogeneity by performing sensitivity and subgroup analyses.

Assessment of reporting biases

In meta-analyses with 10 or more trials, we would have investigated potential publication bias by generating a funnel plot, and would have tested statistics by using a linear regression test (Sterne 2011). A P value less than 0.1 would be considered significant for this test. However, as we included eight trials only, this analysis was not possible.

Data synthesis

When the data were considered sufficiently similar to be combined, we pooled results by applying meta-analyses while using the fixed-effect model, and we used the random-effects model as a sensitivity analysis for the primary outcome. Had we considered trials to be clinically too heterogeneous to be combined, we would only have performed subgroup analyses without calculating an overall estimate.

We performed analyses according to recommendations provided in Chapter Nine of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011), and we used the statistical software of Cochrane - Review Manager (RevMan) 2014 - for analysis. We created a 'Summary of findings' table on absolute risks in each group according to the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system (GRADEpro 2014; Schuenemann 2011), and in this table, we summarised the evidence on overall survival, quality of life, disease-free survival (instead of event-free survival), on-study mortality and adverse events.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses using the following characteristics, but data were too sparse to perform these analyses.

- Subgroups of AML (genetic mutations)

We performed the following sensitivity analyses.

- Participant disease status (newly diagnosed, relapsed, resistant)
- Background treatment (chemotherapy, allogenic or autologous transplantation)
- Age (< 60 years versus $\geq$ 60 years)

Sensitivity analysis

We performed the following sensitivity analyses.

- Quality components with regard to low and high risk of bias
- Random-effects modelling for the primary outcome

RESULTS

Description of studies

Results of the search

The initial screening of literature via databases led to 2192 potentially relevant references. Of these, we excluded 2156 at the initial stage after screening the titles and abstracts, due to a lack of conformity with our predefined inclusion criteria or because they were duplicates. We further evaluated the remaining 36 publications as full-text publications and, if not possible, as abstract publications. Of these, we excluded a further eight publications. Finally, we included 28 publications of eight trials with 3998 patients in this systematic review.

The overall number of references screened, identified, selected, excluded and included are documented in the PRISMA flow diagram [Figure 1 \(Moher 2009\)](#).

Figure 1. Study flow diagram.

Included studies

Eight trials published in 28 publications with 3998 patients (range 95 to 1144) fulfilled our inclusion criteria (see [Characteristics of included studies](#) for further details) ([AML-SG 14-09](#); [AMLSG 07-04](#); [AMLSG HD 98-B](#); [Belhabri 2002](#); [MRC AML 16](#); [MRC AML HR](#); [MRC AML12](#); [NCRI LRF AML 14](#)).

The earliest trial recruited from 1995 to 1998 ([Belhabri 2002](#)), and the latest from 2011 to 2015 ([AML-SG 14-09](#)).

Design

Sample sizes

The smallest trial from [Belhabri 2002](#) involved 95 randomised participants. [AML-SG 14-09](#) included 204 participants, but excluded four participants because no treatment was administered. [NCRI LRF AML 14](#) randomised 217 participants, of these about 15 % with high-risk myelodysplastic syndrome (MDS). Finally, only 207 were randomised to all-trans retinoic acid (ATRA) or to no additional ATRA. [AMLSG HD 98-B](#) randomised 242 participants, of these, three did not receive ATRA, although they were randomised to receive ATRA. [MRC AML HR](#) included 405 participants, 362 were randomised to ATRA or to no additional ATRA. [MRC AML 16](#) randomised 616 participants, [MRC AML12](#) evaluated 1075 participants, and the largest trial [AMLSG 07-04](#), involved 1144 patients, of whom only 1000 were analysed.

Location

The studies [MRC AML HR](#), [MRC AML12](#), [MRC AML 16](#) and [NCRI LRF AML 14](#) were conducted in the UK. [AMLSG 07-04](#), [AML-SG 14-09](#) and [AMLSG HD 98-B](#) were conducted in Germany and [Belhabri 2002](#) was conducted in France.

Participants

In total, the trials included 3998 male and female participants with acute myeloid leukaemia (AML) or high-grade MDS. Of these, we evaluated 3794 randomised patients who received different chemotherapy regimens, with or without ATRA.

Patients in the [AMLSG 07-04](#) trial were 18 to 60 years old; a median age and the gender distribution was not mentioned. The [AML-SG 14-09](#) trial included patients with a median age of 76 years (range 61 to 92), the gender distribution was not reported. In the [AMLSG HD 98-B](#) trial, patients had a median age of 66.6 years (range 61 to 84) with 53% males. [Belhabri 2002](#) included patients with a median age of 58 years (range 20 to 80), 43% were males. Patients in the [MRC AML 16](#) trial had a median age of 67 years (range 53 to 82); no information about the gender distribution was given. Participants in the [MRC AML HR](#) trial were 15 to 70 years, the mean group was 50 to 59 years old and 52% were males. In the [MRC AML12](#) trial, participants had a median age of 48 years (range 14 to 68) with 49% males. The [NCRI LRF AML 14](#) trial included patients with a median age of 74 years (range 51 to 90), of these 51% were males. About 15% of the patients had high-risk MDS.

Interventions

In two trials the induction therapy with ifosfamide, carboplatin, etoposide (Idarubicin, cytarabine and etoposide) and ATRA was followed by consolidation therapy (high-dose cytarabine and ATRA or hematopoietic stem cell transplantation (HSCT)) ([AMLSG 07-04](#); cytarabine, mitoxantrone, idarubicin and etoposide ([AMLSG HD 98-](#)

[B](#))) was compared with ifosfamide, carboplatin, etoposide alone during induction.

[Belhabri 2002](#) compared the induction therapy with idarubicin and cytarabine with and without ATRA followed by HSCT.

The [AML-SG 14-09](#) trial compared decitabine with and without ATRA, both arms in combination or without valproic acid (VPA).

In one trial two induction schedules DA (daunorubicin, cytarabine) and ADE (DA and etoposide) were compared, each in combination with and without ATRA followed by HSCT ([MRC AML 16](#)).

In the [MRC AML HR](#) trial, the two induction regimens ADE (cytarabine, daunorubicin, etoposide) and FLA (fludarabine, cytarabine) in combination with or without G-CSF and ATRA followed by consolidation (HSCT or high-dose cytarabine or other) were compared.

The [MRC AML12](#) trial evaluated two courses of DAT (daunorubicin, cytarabine, thioguanine), without or with ATRA followed by MACE (amsacrine, cytarabine, etoposide) and then SCT or ifosfamide, carboplatin, etoposide or MidAC (mitoxantrone, cytarabine).

In the [NCRI LRF AML 14](#) trial, low-dose cytarabine or hydroxyurea was given, each with or without ATRA.

Outcomes

Primary outcome measure

Overall survival (OS) was reported in each of the included trials. However, [Belhabri 2002](#) did not report data in a way to meta-analyse data.

Secondary outcome measures

Complete response rates were analysed in all trials ([AMLSG 07-04](#); [AML-SG 14-09](#); [AMLSG HD 98-B](#); [Belhabri 2002](#); [MRC AML 16](#); [MRC AML HR](#); [MRC AML12](#); [NCRI LRF AML 14](#)).

Adverse events were analysed in six trials ([AMLSG 07-04](#); [Belhabri 2002](#); [MRC AML 16](#); [MRC AML HR](#); [MRC AML12](#); [NCRI LRF AML 14](#)). However, [Belhabri 2002](#) reported adverse events only after one induction therapy.

Five studies reported death in complete remission ([AMLSG 07-04](#); [Belhabri 2002](#); [MRC AML 16](#); [MRC AML12](#); [MRC AML HR](#)), which we defined as 'on-study mortality'.

Two trials analysed event-free survival ([AMLSG 07-04](#); [AMLSG HD 98-B](#)). Five trials reported disease-free survival ([AMLSG 07-04](#); [AMLSG HD 98-B](#); [MRC AML 16](#); [MRC AML HR](#); [MRC AML12](#)). As disease-free survival is similar to event-free survival, we combined these endpoints. However, as several of the included trials randomised participants in a multifactorial study to receive various types of chemotherapy, with or without ATRA, results for the arms ATRA versus no ATRA have not always been published.

Quality of life was not reported in any trial.

Conflicts of interest

[MRC AML12](#) reported no relevant conflicts of interest. [MRC AML HR](#) was funded by the Medical Research Council of the UK. [MRC AML 16](#) researched support from Cancer Research UK and the Cardiff Experimental Cardiff Medicine Centre. [Belhabri 2002](#) did not

mention any conflicts of interest. [NCRI LRF AML 14](#) was supported by research grants from the Leukemia Research Fund of the UK. Two trials mentioned a financial relationship of the authors with pharmaceutical industry ([AMLSG 07-04](#): Roche GmbH, Amgen GmbH, Pfizer GmbH, Novartis, Celgene; [AML-SG 14-09](#): Celgene, Janssen-Cilag, Ratiopharm, Pfizer, Amgen, Tetralogic, BerGenBio, Karyopharm Therapeutics Inc, Bayer Pharma AG, Novartis, Astellas, Nord Medica, AstraZeneca). [AMLSG HD 98-B](#) was supported by grants from the Federal Ministry of Education and Research, Germany.

Excluded studies

After a detailed evaluation of the retrieved full-text publications, we excluded four trials, of which one was not a RCT ([Di Febo 2007](#)), two trials involved less than 80% of patients with AML (28% of patients with MDS; not RAEB-T) and we did not get subgroup analyses after request ([Estey 1997](#); [Nazha 2013](#)), and one trial had no comparison group ([Stone 2000](#)) (see [Characteristics of excluded studies](#) table).

Risk of bias in included studies

For a summary of risk of bias see also [Figure 2](#) and [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 participants and personnel (performance bias)	Blinding of outcome detection (OS)	Blinding of outcome detection (other outcomes)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
AMLSG 07-04	?	?	-	+	-	-	-	?
AML-SG 14-09	+	+	-	+	+	+	?	?
AMLSG HD 98-B	?	+	-	+	-	+	?	?
Belhabri 2002	?	?	-	+	-	+	?	+
MRC AML12	+	+	-	+	-	+	+	+
MRC AML 16	+	+	-	+	-	+	+	?
MRC AML HR	+	+	-	+	-	+	-	+
NCRI LRF AML 14	+	+	-	+	-	+	?	+

Allocation

The methods of random sequence generation and allocation concealment were adequate in the [AML-SG 14-09](#), [MRC AML HR](#) and [NCRI LRF AML 14](#) trials and we considered these trials to be at low

risk of potential bias. There was no information about the methods of random sequence generation and allocation concealment in the [MRC AML 16](#) and [MRC AML12](#) trials, so we contacted study authors, both are also low risk of bias due to centralised randomisation

process. The information was insufficient in the [AMLSG 07-04](#) and [Belhabri 2002](#) trials, so here we judged unclear risk for both criteria.

Insufficient information about random sequence generation was also given in [AMLSG HD 98-B](#), but as patients were randomised via telephone call, we considered allocation concealment as low risk of potential bias. Random sequence generation was also adequate for [AML-SG 14-09](#), [MRC AML HR](#), [MRC AML 16](#), [MRC AML12](#) and [NCRI LRF AML 14](#) trials and we considered these to be at low risk of potential bias.

Blinding

Blinding was not reported in any of the included studies. However, given the study design it is likely that there was no blinding of either participants or physicians, we judged these studies to be at high risk of performance bias.

For the primary outcome of OS we judged detection bias to be at low risk, as death is an endpoint not susceptible to bias from the outcome assessor.

For all of the secondary outcomes in the remaining included studies, blinding was relevant as the absence of blinding could have influenced the evaluation of these outcomes. Only one study shows a low risk of bias for detection bias for secondary outcomes ([AML-SG 14-09](#)), as outcome assessors were blinded. For the other seven studies no information was provided, so we judged the risk of detection bias for secondary outcomes to be high.

Incomplete outcome data

The largest trial [AMLSG 07-04](#) randomised 1144 participants, but only 1100 were analysed. Forty-four patients were excluded due to violation of inclusion/exclusion criteria, no informed consent or other reasons. We judged high risk for attrition bias.

[NCRI LRF AML 14](#) randomised 217 participants for non-intensive therapy, but only 207 out of these were randomised between ATRA and no ATRA. There is no information why 10 people were not randomised between these two options and what happened to them. Because the outcome data of the finally 207 randomised people are complete, we judged low risk for attrition bias. [AML-SG 14-09](#) randomised 204 patients, but four patients were excluded from the analysis because no treatment was administered. There is no information why these four patients did not receive treatment, but because the number of these is low, we judged low risk for attrition bias. [MRC AML HR](#) had 405 participant, only 362 were randomised between ATRA and no ATRA. The remaining patients elected not to receive ATRA before randomisation, therefore we judged low risk for attrition bias. For all the other included trials, there are no obvious data missing, therefore we judge also low risk of attrition bias for [AMLSG HD 98-B](#), [Belhabri 2002](#), [MRC AML 16](#) and [MRC AML12](#).

Selective reporting

We found two different study protocols of the [MRC AML12](#) trial, but both protocols did not match exactly with the trial (different inclusion criteria, different therapy). Thus we contacted study authors and judged risk as low risk of bias as all pre-planned outcomes are reported. We also contacted study authors for the [MRC AML 16](#) trial and also judge this as low risk of bias.

The study protocols of [MRC AML HR](#) and [AMLSG 07-04](#) were available, but not all pre-planned outcomes such as toxicity, quality of life, supportive care requirements ([MRC AML HR](#)) and haematological and non-hematological toxicity after consolidation therapy, days in hospital after each consolidation cycle ([AMLSG 07-04](#)) were reported adequately. Therefore, we judged high risk for selective reporting.

As [AML-SG 14-09](#) was reported as abstract only, we were not able to assess risk of selective reporting and judged as unclear. Due to this publication form, we did not have all the data, especially no data for each intervention arm.

Due to insufficient information and the unavailability of the study protocols, we judged the risk of reporting bias for [AMLSG HD 98-B](#), [Belhabri 2002](#) and [NCRI LRF AML 14](#) as unclear.

Other potential sources of bias

Due to their publications in abstract form, [MRC AML 16](#) and [AML-SG 14-09](#) did not provide sufficient information on this subject, so we assessed the risk of other potential sources of bias to be unclear in these studies.

A financial relationship of the authors from [AMLSG 07-04](#) and [AML-SG 14-09](#) with pharmaceutical industry ([AMLSG 07-04](#): Roche GmbH, Amgen GmbH, Pfizer GmbH, Novartis, Celgene; [AML-SG 14-09](#) (funded by the Federal Ministry of Education and Research): Celgene, Janssen-Cilag, Ratiopharm, Pfizer, Amgen, Tetralogic, BerGenBio, Karypharm Therapeutics Inc, Bayer Pharma AG, Novartis, Astellas, Nord Medica, Astrazeneca) was mentioned in the abstracts. It is unclear, if that relationship influenced the studies, so we judged unclear risk for other potential sources of bias.

All other studies seemed to be free of any other potential sources of bias. Although we cannot rule out other bias, we judged them to be at low risk of other sources of bias.

[AMLSG HD 98-B](#) randomised 242 participants. Three out of 242 patients did not receive ATRA, although they were randomised to receive it, there is no information why. Because the number of missing patients is low, we judged low risk for other potential bias.

Effects of interventions

See: [Summary of findings for the main comparison ATRA in addition to chemotherapy compared to chemotherapy only for adults with acute myeloid leukaemia \(AML\) \(non-acute promyelocytic leukaemia \(APL\)\)](#)

Primary outcome: Overall survival (OS)

Results

Seven trials with 2985 participants reported overall survival ([AMLSG 07-04](#); [AML-SG 14-09](#); [AMLSG HD 98-B](#); [MRC AML 16](#); [MRC AML HR](#); [MRC AML12](#); [NCRI LRF AML 14](#)).

The addition of ATRA to chemotherapy probably resulted in no or little difference in OS (hazard ratio (HR) 0.94, 95% CI 0.87 to 1.02; moderate-certainty evidence, see [Analysis 1.1](#))

Subgroup and sensitivity analyses

The analysis of the subgroup stage of disease showed a benefit for the ATRA-group ($P = 0.01$) when ATRA was given after the first remission for consolidation therapy (HR 0.71, 95% CI 0.55 to 0.92, see [Analysis 1.2](#)). There is no evidence for a difference for the subgroups newly diagnosed (HR 0.95, 95% CI 0.87 to 1.03) and relapsed AML (HR 1.23, 95% CI 0.96 to 1.59).

The analysis showed no evidence for a difference whether chemotherapy was combined with stem cell transplantation (SCT) or not (HR 0.94, 95% CI 0.87 to 1.02, see [Analysis 1.3](#)).

The subgroup analysis by type of chemotherapy (decitabine versus all other combinations given in the trials (ifosfamide, carboplatin, etoposide, Idarubicin+ cytarabine, DA, ADE, FLA, DAT, MACE, MidAC) ($P = 0.010$) showed a potential benefit for the combination ATRA plus decitabine (HR 0.65, 95% CI 0.48 to 0.87, see [Analysis 1.4](#)). However, this analysis includes one trial in the decitabine subgroup only and should be taken with caution.

The age may influence the outcome ($P = 0.003$) of patients receiving ATRA, because the analysis showed a benefit for patients older than 60 years (HR 0.76, 95% CI 0.65 to 0.89, see [Analysis 1.5](#)). The subgroup analysis of groups with mixed age (HR 1.05, 95% CI 0.95 to 1.17), and patients younger than 60 years (HR 0.91, 95% CI 0.77 to 1.09) did not show evidence for a difference.

The subgroup analyses showed no statistically difference between the subgroups chemotherapy only versus chemotherapy plus SCT ($P = 0.37$, see [Analysis 1.3](#)).

Because the type of bias (high risk or low risk) may affect the results, we conducted a sensitivity analysis. However, we did not identify hints for differences between both groups ($P = 0.30$, see [Analysis 1.7](#)).

The random-effect model did not show significant difference to the fixed-effect model (HR 0.93, 95% CI 0.80 to 1.07, see [Analysis 1.6](#)).

Secondary outcomes

Disease-free survival

Results

Three trials with 1258 patients reported disease-free survival (DFS) ([MRC AML 16](#); [MRC AML HR](#); [MRC AML12](#)).

The addition of ATRA to chemotherapy may have no evidence for a difference in DFS (HR 0.99, 95% CI 0.87 to 1.12; moderate-certainty evidence, see [Analysis 1.8](#)).

Subgroup and sensitivity analyses

The subgroup analyses showed no statistically differences between the subgroups stage of disease [Analysis 1.9](#) and chemotherapy only versus chemotherapy plus SCT [Analysis 1.10](#)).

The other pre-planned subgroups could not be investigated due to lack of data.

There is no statistically significant subgroup differences in the sensitivity analysis (low risk of bias versus high risk of bias) as well ($P = 0.41$), see [Analysis 1.11](#).

Complete response rate (CRR)

Results

Six trials with 3081 patients reported the complete response rate ([AMLSG 07-04](#); [AMLSG HD 98-B](#); [Belhabri 2002](#); [MRC AML HR](#); [MRC AML12](#); [NCRI LRF AML 14](#)).

We found no evidence of an improvement in CRR in favour of chemotherapy with the ATRA group (risk ratio (RR) 1.02, 95% CI 0.96 to 1.09, see [Analysis 1.12](#)), with no evidence of heterogeneity across the trials in the meta-analysis (P value of the homogeneity test = 0.43; $I^2 = 0\%$).

Subgroup and sensitivity analyses

The subgroup analyses showed no statistically differences ($P = 0.34$) between the subgroups examined (stage of disease [Analysis 1.13](#), chemotherapy only versus chemotherapy plus SCT [Analysis 1.14](#), age [Analysis 1.15](#)).

There is no statistically significant subgroup differences in the sensitivity analysis (low risk of bias versus high risk of bias) as well ($P = 0.34$), see [Analysis 1.16](#).

The other pre-planned subgroups were not evaluated, due to lack of data.

On-study mortality

Results

Five trials including 2839 patients reported on-study mortality ([AMLSG 07-04](#); [Belhabri 2002](#); [MRC AML HR](#); [MRC AML12](#); [NCRI LRF AML 14](#)).

The addition of ATRA to chemotherapy did not improve on-study mortality (RR 1.02, 95% CI 0.81 to 1.30; moderate-certainty evidence, see [Analysis 1.17](#)) with no evidence of heterogeneity between trials ($I^2 = 0\%$).

Subgroup and sensitivity analyses

The subgroup analyses showed no statistically differences ($P = 0.91$) between the subgroups examined (stage of disease [Analysis 1.18](#), chemotherapy only versus chemotherapy plus SCT [Analysis 1.19](#), age [Analysis 1.20](#)).

There is no statistically significant subgroup differences in the sensitivity analysis (low risk of bias versus high risk of bias) as well ($P = 0.56$), see [Analysis 1.21](#).

The other pre-planned subgroups could not be investigated, due to lack of data.

Infection grade III/IV

Results

Three trials with 1428 patients reported infection rate ([AMLSG 07-04](#); [AMLSG HD 98-B](#); [Belhabri 2002](#)).

Regarding the infection grade there are no statistically significant differences between the use of ATRA alone or in addition to chemotherapy (RR 1.05, 95% CI 0.96 to 1.15; participants = 1428; moderate-certainty evidence, see [Analysis 1.22](#)) with no evidence of heterogeneity between trials ($I^2 = 0\%$).

Subgroup and sensitivity analyses

The subgroup analyses showed no statistically differences ($P = 0.80$) between the subgroups examined (stage of disease [Analysis 1.23](#), chemotherapy only versus chemotherapy plus SCT [Analysis 1.24](#), age [Analysis 1.25](#)).

There is no statistically significant subgroup differences in the sensitivity analysis (low risk of bias versus high risk of bias) as well ($P = 0.61$), see [Analysis 1.26](#).

The other pre-planned subgroups have not been evaluated, due to lack of data.

Diarrhoea grade III/IV

Results

Two trials including 337 patients reported diarrhoea grade III/IV ([AMLSG HD 98-B](#); [Belhabri 2002](#)).

The addition of ATRA to chemotherapy may lead to more severe diarrhoea for patients in the ATRA-group (RR 2.19, 95% CI 1.07 to 4.47; very low-certainty evidence, see [Analysis 1.27](#)) with no evidence of heterogeneity between both trials ($I^2 = 0\%$).

Subgroup and sensitivity analyses

No subgroup analyses and sensitivity analyses could be performed, due to lack of studies.

Nausea/vomiting grade III/IV

Results

Two trials with 337 patients reported nausea/vomiting grade III/IV ([AMLSG HD 98-B](#); [Belhabri 2002](#)).

Regarding the adverse affect nausea/vomiting grade III/IV there are no significant differences between both groups ATRA and no-ATRA (RR 1.46, 95% CI 0.75 to 2.85; very low-certainty evidence, see Analysis 1.28). There is no evidence of heterogeneity between both trials ($I^2 = 0\%$).

Subgroup and sensitivity analyses

Subgroup analyses and sensitivity analyses could not be performed, due to lack of studies.

Cardiac toxicity grade III/IV

Results

Three trials including 1428 patients reported cardiac toxicity grade III/IV ([AMLSG 07-04](#); [AMLSG HD 98-B](#); [Belhabri 2002](#)).

The addition of ATRA may lead to less cardiac side effects (RR 0.46, 95% CI 0.24 to 0.90; very low-certainty evidence, see [Analysis 1.29](#)) with no evidence of heterogeneity between both trials ($I^2 = 0\%$).

Subgroup and sensitivity analyses

Subgroup analyses and sensitivity analyses could not be performed, due to lack of studies.

Quality of life

Quality of life was not reported by any trial.

DISCUSSION

Summary of main results

The following findings emerge from this Cochrane Review and meta-analysis evaluating the effect of all-trans retinoic acid (ATRA) in addition to chemotherapy for adults with acute myeloid leukaemia (AML) (eight randomised controlled trials (RCTs), 3998 (3794 randomised) patients).

- The addition of ATRA to chemotherapy probably makes little or no difference to overall survival (OS), but subgroup analysis showed there is possibly a benefit for patients given ATRA after the first remission for consolidation therapy (results for this subgroup from one trial only), for patients older than 60 years and patients receiving the combined therapy ATRA plus decitabine (results for this subgroup from one trial only). The analysis showed no evidence for a difference for patients younger than 60 years and patients with newly diagnosed or relapsed AML. There is no subgroup difference in the outcome for patients receiving stem cell transplantation (SCT) or not.
- Regarding disease-free survival (DFS), complete response rate (CRR) and on-study mortality, there are probably no differences between chemotherapy in combination with ATRA and chemotherapy alone.
- Regarding the adverse effects infection grade III/IV and nausea/vomiting grade III/IV, there are probably no differences between chemotherapy alone or chemotherapy in combination with ATRA.
- We are uncertain whether ATRA decreases cardiac toxicity, however, cardiac toxicity did not occur often in general. As the certainty of the evidence has been assessed as very low for diarrhoea, we are uncertain whether there is a difference between treatment arms.
- Quality of life was not reported by any trial.

Overall completeness and applicability of evidence

There were eight published RCTs with 3998 (3794 randomised) patients dealing with a comparison of chemotherapy plus ATRA and chemotherapy without ATRA in patients with AML.

Six of the included studies were published as full-text articles, providing sufficient information about the design, participants, methods and outcomes ([AMLSG 07-04](#); [AMLSG HD 98-B](#); [Belhabri 2002](#); [MRC AML HR](#); [MRC AML12](#); [NCRI LRF AML 14](#)). The remaining two trials were published as abstracts and therefore lacked information on relevant data, especially for each intervention arm ([AML-SG 14-09](#); [MRC AML 16](#)).

None of these trials evaluated the same chemotherapy schedules, but in contrast to all other trials only one trial evaluated the effect of a hypomethylating agent (HMA, decitabine) in combination with ATRA ([AML-SG 14-09](#)).

The primary endpoint of this review was OS, a commonly accepted direct measure of the benefit of cancer treatment. All trials reported OS and the meta-analysis showed no evidence for a difference in OS for the addition of ATRA to chemotherapy. Only the subgroup analysis showed a benefit for ATRA in combination with HMA, for older patients (> 60 years) and for consolidation therapy after first remission.

Quality of the evidence

Overall, we judged the potential risk of bias of the eight included trials as moderate. All trials were reported as randomised and open-label studies, but only five of the trials reported the sequence generation process. The treatment allocation was reported adequately in six trials. Blinding was not reported in any of the included studies. However, given the study design it is likely that there was no blinding of either participants or physicians, therefore we judged the studies to be at high risk of performance bias, except for the primary endpoint OS. As death is an endpoint not susceptible to bias from the outcome assessor, we judged detection bias to be at low risk for all eight trials. Only one trial reported that outcomes assessors were blinded, we judged this as low risk of bias for detection bias for the other evaluated outcomes. For the remaining seven trials no information was provided and we judged them as being high risk of bias. The Study protocols were not available for two trials and two trials were reported as abstract only, therefore, we judged selective reporting as unclear for four trials. Two trials were judged as low risk of bias after contacting study authors which provided study protocols. All pre-planned outcomes are reported for these two trials. The remaining two trials were judged high risk for selective reporting, as study protocols were available, but not all pre-planned outcomes were reported adequately. Because the authors of two studies mentioned a financial relationship with the pharmaceutical industry and due to the publication in abstract form of two other studies we assessed the risk of other potential sources of bias to be unclear in these four studies.

The quality of evidence was moderate for OS, with enough events and precise results allowing meaningful statements. However, there was significant heterogeneity, therefore we downgraded by one point. Heterogeneity can be explained to some extent by subgroup analyses by type of accompanying chemotherapy, age of patients and stage of disease. Quality of life was not reported, although one study protocol says it had been evaluated. The quality of evidence is moderate for progression-free survival, as the open-label design of the included trials and unblinded outcome assessors could lead to performance or detection biases. We downgraded by one level for this outcome. Due to the small number of events, we downgraded the quality of evidence for the outcome on-study mortality by one point (imprecision). The quality of evidence was moderate for the adverse event infection grade III/IV, due to the unblinded study decision. We downgraded by one point for risk of bias. The quality of evidence was very low for the adverse events diarrhoea, nausea and cardiac toxicity. The very small number of events leading to highly imprecise results (downgraded by two points), the unblinded trial design leads to potential risk of bias (downgraded by one point).

We did not identify risk of publication bias, as all registered trials were published or still ongoing and we are not aware of further completed studies that have not been published.

Potential biases in the review process

To prevent bias within the review, only RCTs were considered. In addition, all important conference proceedings were searched up

to their latest issues. We tried to avoid bias by performing all relevant processes in duplicate. We are not aware of any obvious deficiencies in our review process. However, the small number of trials included in this analysis could lead to publication bias, as we could not generate a funnel plot. However, as mentioned before, we did not identify risk of publication bias, as all registered trials are published and we are not aware of further ongoing studies or completed studies that have not been published.

In summary, there is maximum likelihood that all relevant studies were identified, all relevant data could be obtained and the review process (searching, data collection, analysis) did not introduce bias into the review.

Agreements and disagreements with other studies or reviews

To our knowledge, this is the first comprehensive review with meta-analysis focusing on patients with AML in adults that compared ATRA in addition to chemotherapy with chemotherapy alone.

The literature provides contradictory data showing results of individual studies about the question whether a benefit of ATRA in combination with chemotherapy exists. The meta-analyses and the subgroup analyses of this review give hints which patients might benefit and which accompanying regimen should be preferred.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review focused on clinically relevant outcomes such as survival, quality of life and adverse events. There was no evidence from our review that the addition of all-trans retinoic acid (ATRA) made a difference to survival overall. However, the subgroup analysis showed that there is possibly a benefit for ATRA in combination with decitabine (subgroup included one trial only), for older patients and for consolidation therapy after first remission (one trial only). Regarding disease-free survival (DFS), complete response rate (CRR) and on-study mortality, there is no evidence for a difference between treatment groups. Rates and severity of toxicities are comparatively low, but the quality of evidence is very low to low for these outcomes. Currently, it seems that ATRA can administered safely to patients with acute myeloid leukaemia (AML), especially with regard to cardiac toxicity. Thus, the addition of ATRA to chemotherapy seems to be safe and might be effective for some groups of patients.

Implications for research

Further research is needed to clarify the effect of ATRA on quality of life and side effects and for the potential beneficial subgroups.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

AML-SG 14-09

Methods	Randomised multicentre phase II study, 2 x 2 factorial design Therapy: <ul style="list-style-type: none"> Decitabine without and with VPA or Decitabine + ATRA without and with VPA Recruitment period <ul style="list-style-type: none"> December 2011 to February 2015 Median follow-up time <ul style="list-style-type: none"> Not mentioned
Participants	Eligibility criteria <ul style="list-style-type: none"> Patients 60 years and older Primary or secondary AML ECOG performance status score ≤ 2 Not previously treated for AML Written informed consent Excluded: <ul style="list-style-type: none"> AML subtype M3 (APL) Not previously treated for AML except with hydroxyurea or cytarabine Severe liver, kidney or heart disease Participants randomised (N = 204) <ul style="list-style-type: none"> Induction therapy without ATRA <ul style="list-style-type: none"> N = no information Induction therapy with ATRA <ul style="list-style-type: none"> N = no information Age: <ul style="list-style-type: none"> ≥ 60 years

AML-SG 14-09 (Continued)

- Mean age: 76 years (61 to 92 years)

Gender:

- Both

Country:

- Germany

Interventions	Decitabine <ul style="list-style-type: none"> • 20 mg/m² intravenous over 1 hour, days 1 to 5 (total dose 100 mg/m²), repeated every 4 weeks VPA <ul style="list-style-type: none"> • By mouth starting on day 6 of first cycle continuously throughout all treatment cycles ATRA <ul style="list-style-type: none"> • 45 mg/m² by mouth days 6 to 28 of each treatment cycle
Outcomes	Primary <ul style="list-style-type: none"> • Complete remission Secondary <ul style="list-style-type: none"> • Progression-free survival • Quality of life • Safety and toxicity
Notes	Funded by the Federal Ministry of Education and Research A financial relationship of the authors with pharmaceutical industry (Celgene, Janssen-Cilag, Ratio-pharm, Pfizer, Amgen, Tetralogic, BerGenBio, Karypharm Therapeutics Inc, Bayer Pjarma AG, Novartis, Astellas, Nord Medica, Astracenece) was mentioned.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Center-stratified block randomization with randomly varying block size is performed based on computer generate lists."
Allocation concealment (selection bias)	Low risk	Quote: "Block sizes are documented separately from the study protocol in an document not accessible to investigators."
Blinding of participants and personnel (performance bias) All outcomes	High risk	This is an open-label study, so there was no blinding.
Blinding of outcome detection (OS)	Low risk	Death is an endpoint not susceptible to bias from the outcome assessor.
Blinding of outcome detection (other outcomes)	Low risk	Quote: "...reviewers of response will be blinded with regard to the patient's treatment arm."
Incomplete outcome data (attrition bias)	Low risk	Four out of 204 patients did not receive treatment, although they were randomised to. There is no information why.

AML-SG 14-09 (Continued)

All outcomes

Selective reporting (reporting bias)	Unclear risk	Protocol available at clinicaltrials.gov/show/NCT00867672 Only an interim report and an abstract with final results are available and not all of the pre-assigned outcome measures are mentioned in the abstract.
Other bias	Unclear risk	A financial relationship of the authors with pharmaceutical industry. Insufficient information to assess whether another important risk of bias exists.

AMLSG 07-04

Methods	<p>Randomised controlled trial</p> <p>Induction therapy: 2 cycles of ifosfamide, carboplatin, etoposide without or with ATRA</p> <p>Consolidation therapy:</p> <ul style="list-style-type: none"> Haematopoietic stem cell transplantation for high-risk AML <ul style="list-style-type: none"> High-risk cytogenetics (from November 2006 on) Or induction failure High-dose cytarabine 3 cycles with ATRA <p>Recruitment period</p> <ul style="list-style-type: none"> August 2004 to January 2006 <p>Median follow-up time</p> <ul style="list-style-type: none"> 39 months (3.3 years)
Participants	<p>Eligibility criteria</p> <ul style="list-style-type: none"> Newly diagnosed AML Age 18 to 60 years Written informed consent Molecular and cytogenetical diagnostic <p>Excluded:</p> <ul style="list-style-type: none"> APL Bleeding independent of the AML Uncontrollable infection Participation in a concurrent clinical study Insufficiency of the kidneys (creatinine >1.5 x upper the normal level or the liver (2 x upper normal level) Pregnancy <p>Participants randomised (N = 1144)</p> <p>excluded 44 due to violation of in-/exclusion criteria, no informed consent or other reasons</p> <ul style="list-style-type: none"> Induction therapy without ATRA <ul style="list-style-type: none"> Ifosfamide, carboplatin, etoposide: N = 544, per protocol N = 538 Death before start of treatment N = 6 Induction therapy with ATRA <ul style="list-style-type: none"> ATRA, ifosfamide, carboplatin, etoposide: N = 556, per protocol N = 553 Death before start of treatment N = 3

AMLSG 07-04 (Continued)

- Consolidation therapy without ATRA
 - High-dose cytarabine: N = 272
 - Allogeneic HCT: N = 45
- Consolidation therapy with ATRA
 - high-dose cytarabine: N = 256
 - Allogeneic HCT: N = 54

Age:

- 18 to 60 years
- Mean age: no information

Country:

- Germany

Interventions	<p>Chemotherapy:</p> <ul style="list-style-type: none"> • Ifosfamide, carboplatin, etoposide: <p>idarubicin 12 mg/m², days 1, 3, 5 (in induction II reduced to day 1 ,day 3)</p> <p>cytarabine 100 mg/m² continuous intravenous days 1 to 7</p> <p>etoposide 100 mg/m², days 1 to 3</p> <ul style="list-style-type: none"> • HiDAC: <p>high-dose cytarabine 18 g/m² per cycle(3 cycle, different temporal sequences</p> <p>ATRA :</p> <ul style="list-style-type: none"> • During induction: 45 mg/m² days 6 to 8, and 15 mg/m² days 9 to 21 • During HiDAC: 15 mg/m² days 6 to 28 <p>Allogeneic hematopoietic stem cell transplantation</p> <ul style="list-style-type: none"> • From a matched related or unrelated donor
Outcomes	<p>Primary outcomes after induction therapy</p> <ul style="list-style-type: none"> • Event-free survival • Complete remission <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Relapse-free survival • Overall survival • Side-effects
Notes	<p>A financial relationship of the authors with pharmaceutical industry(Roche GmbH, Amgen GmbH, Pfizer GmbH, Novartis,Celgene) was mentioned.</p>
Risk of bias	
Bias	<p>Authors' judgement</p> <p>Support for judgement</p>
Random sequence generation (selection bias)	<p>Unclear risk</p> <p>Insufficient information about the sequence generation process.</p> <p>Quote: "They were randomized up-front for open-label treatment with ATRA."</p>

AMLSG 07-04 (Continued)

Allocation concealment (selection bias)	Unclear risk	Insufficient information of the method of concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	This is an open-label study, so there was no blinding.
Blinding of outcome detection (OS)	Low risk	Death is an endpoint not susceptible to bias from the outcome assessor.
Blinding of outcome detection (other outcomes)	High risk	This is an open-label study, so there was no blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	Data of 44 patients missing.
Selective reporting (reporting bias)	High risk	Protocol available at clinicaltrials.gov/ct/show/NCT00151242 . Not all of the pre-assigned outcome measures are analysed: haematologic and non-hematologic toxicity after consolidation therapy, days in hospital after each consolidation cycle.
Other bias	Unclear risk	A financial relationship of the authors with pharmaceutical industry (Roche GmbH, Amgen GmbH, Pfizer GmbH, Novartis, Celgene) was mentioned.

AMLSG HD 98-B

Methods	<p>Randomised controlled phase III trial</p> <p>Induction therapy: 2 cycles of ifosfamide, carboplatin, etoposide without or with ATRA</p> <p>- patients with refractory disease after first induction therapy were assigned to a second induction therapy</p> <p>First consolidation therapy: 1 cycle of high-dose cytosine arabinoside and mitoxantrone with or without ATRA</p> <p>Recruitment period</p> <ul style="list-style-type: none"> February 1998 to September 2001 <p>Median follow-up time</p> <ul style="list-style-type: none"> 34 months (2.10 years)
Participants	<p>Eligibility criteria</p> <ul style="list-style-type: none"> De novo AML or refractory anaemia RAEB-T Secondary AML with a preceding history of MDS at least 3 months before the diagnosis of AML or therapy-related AML Patients over 60 years old WHO performance status of 0 to 2 Written informed consent Chromosome banding analysis performed centrally for all patients <p>Excluded:</p>

AMLSG HD 98-B (Continued)

- Patients with concomitant liver, renal or cardiac disease

Participants randomised (N = 242)

- Standard arm induction therapy
 - ifosfamide, carboplatin, etoposide-1: N = 120
- Experimental arm induction therapy with ATRA
 - ATRA, ifosfamide, carboplatin, etoposide: N = 122
 - Receiving ATRA, ifosfamide, carboplatin, etoposide: N = 119
 - Not receiving ATRA: N = 3

Age:

- 61 to 84 years
- Mean age: 66.6 years

Gender:

- 128 men, 114 women

Country:

- Germany

Interventions

Chemotherapy:

- Ifosfamide, carboplatin, etoposide:
 - idarubicin 12 mg/m², days 1 and 3
 - cytarabine 100 mg/m² continuous intravenous days 1 to 5
 - etoposide 100 mg/m², days 1 to 3
- HAM
 - cytarabine 0.5 g/m²/12 hours intravenous days 1 to 3
 - mitoxantrone 10 mg/m² intravenous days 2 and 3
- IE
 - intravenous:
 - idarubicin 12 mg/m² intravenous days 1 and 3
 - etoposide 100 mg/m², intravenous days 1 to 5
 - oral:
 - idarubicin 5 mg by mouth days 1, 4, 7, 10, 13
 - etoposide 100 mg by mouth days 1 and 13
 - 1-year oral maintenance therapy, repeated on day 29 for 12 courses

ATRA :

- During induction: 45 mg/m² from days 3 to 5 and 15 mg/m² days 6 to 28
- During consolidation: 15 mg/m² from days 3 to day 28

Allogeneic hematopoietic stem cell transplantation

- From a matched related donor

Outcomes

- Complete remission
- Event-free survival
- Overall survival

Notes

AMLSG HD 98-B (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process. Quote: "...were randomly assigned to ATRA.."
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomised via telephone call.."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Regarding the study design, it is likely that there was no blinding.
Blinding of outcome detection (OS)	Low risk	Death is an endpoint not susceptible to bias from the outcome assessor.
Blinding of outcome detection (other outcomes)	High risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No study protocol available, therefore insufficient information to judge
Other bias	Unclear risk	Three out of 122 patients did not receive ATRA, although they were randomised to. There is no information why.

Belhabri 2002

Methods	<p>Randomised controlled phase II trial</p> <p>Induction therapy : idarubicin + cytarabine without and with ATRA</p> <p>after complete remission:</p> <ul style="list-style-type: none"> • Maintenance therapy with idarubicin + cytarabine or • Stem cell transplantation <p>Recruitment period</p> <ul style="list-style-type: none"> • June 1995 to May 1998 <p>Median follow-up time</p> <ul style="list-style-type: none"> • 34 months (2.10 years)
Participants	<p>Eligibility criteria</p> <ul style="list-style-type: none"> • De novo high-risk AML • Secondary AML with a history of MDS or therapy-related AML • AML resistant to primary chemotherapy or relapsing AML • Patients over 18 years old • WHO performance status of 0 to 2

Belhabri 2002 (Continued)

- Written informed consent
- Chromosome banding analysis performed centrally for 55 of 95 patients (58%)

Excluded:

- Blast transformation of chronic myeloid leukaemia

Chromosome banding analysis N = 55

- favourable-risk karyotypes with abnormalities of chromosome 16 and t(8;21) N = 1
- Intermediate-risk karyotypes with normal karyotypes N=22
- Unfavourable-risk karyotypes with all other chromosomal abnormalities

N = 32

Participants randomised (N = 95)

- Induction therapy without ATRA
 - N = 48
- Induction therapy with ATRA
 - N = 47

Age:

- 20 to 80 years
- Mean age: 58

Gender:

- 41 men, 54 women

Country:

- France

Interventions
Chemotherapy:

- idarubicin 12 mg/m², days 1 to 3
- cytarabine 1 g/m²/12 hours from days 1 to 6

ATRA :

- During induction: 45 mg/m² orally from day 1 until haematological recovery or day 28 if resistant disease
- During HiDAC: 15 mg/m² days 6 to 28

Allogeneic hematopoietic stem cell transplantation

- From a matched related or unrelated donor

Autologous peripheral stem cell transplantation
Outcomes
Primary outcomes

- Complete remission after one induction therapy and maintenance therapy
- Disease-free survival
- Overall survival

Secondary outcomes

- Relapse-free
- Adverse side effects after one induction therapy

Belhabri 2002 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process. Quotes: "All patients received Ida... without (group A) or with (group B) oral ATRA...according to randomization." "There were no statistical difference, regarding initial characteristics...."
Allocation concealment (selection bias)	Unclear risk	Insufficient information of the method of concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Regarding the study design, it is likely that there was no blinding.
Blinding of outcome detection (OS)	Low risk	Death is an endpoint not susceptible to bias from the outcome assessor.
Blinding of outcome detection (other outcomes)	High risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No study protocol available, therefore insufficient information to judge
Other bias	Low risk	The trial seems free of other biases

MRC AML 16

Methods	<p>Randomised controlled trial, 2 x2 factorial design</p> <p>Therapy:</p> <ul style="list-style-type: none"> • Induction: DA vs ADE, ATRA vs no ATRA • Consolidation: allogeneic stem cell transplantation; <p>Azacytidine or not</p> <p>Recruitment period</p> <ul style="list-style-type: none"> • August 2010 to May 2012 <p>Median follow-up time</p> <ul style="list-style-type: none"> • 18.7 months
Participants	<p>Eligibility criteria</p> <ul style="list-style-type: none"> • De novo high-risk AML • Secondary AML

MRC AML 16 (Continued)

- High-risk MDS (RAEB-2)
- Patients over 60 years old or not considered fit for MRC AML 15 trial
- Written informed consent

Excluded:

- Patients have previously received cytotoxic chemotherapy for AML
- Concurrent active malignancy
- Patients are pregnant or lactating
- Abnormal liver function exceeding twice the local upper limit of normal

Participants randomised (N = 616)

- Induction therapy without ATRA
 - N = no information
- Induction therapy with ATRA
 - N = no information

Age:

- 53 to 82 years
- Mean age: 67

Gender:

- No information

Country:

- United Kingdom

Interventions	<p>Chemotherapy:</p> <ul style="list-style-type: none"> • DA: daunorubicin 50 mg/m² days 1 to 3 + cytarabine 100 mg/m² days 1 to 10 or days 1 to 8 • ADE: DA+ etoposide 100 mg/m²/day on days 1 to 5 of courses 1+2 <p>ATRA:</p> <ul style="list-style-type: none"> • 45 mg/m²/day for 60 days <p>Allogeneic hematopoietic stem cell transplantation</p> <ul style="list-style-type: none"> • From a matched related or unrelated donor
Outcomes	<p>Primary outcomes:</p> <ul style="list-style-type: none"> • Overall survival • Complete remission • Duration of remission • Relapse rates • Death in 1st CR <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Toxicity
Notes	The study researched support from Cancer Research UK and the Cardiff Experimental Cardiff Medicine Centre.

Risk of bias

MRC AML 16 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Personal communication: Quote: "Centralised randomisation process".
Allocation concealment (selection bias)	Low risk	Personal communication: Quote: "Centralised randomisation process".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Regarding the study design, it is likely that there was no blinding.
Blinding of outcome detection (OS)	Low risk	Death is an endpoint not susceptible to bias from the outcome assessor.
Blinding of outcome detection (other outcomes)	High risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data.
Selective reporting (reporting bias)	Low risk	Personal communication, study protocol provided by Ian Thomas. All of the pre-planned outcome measures are analysed and reported.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

MRC AML HR

Methods	<p>Randomised controlled trial, 2 x 2 x 2 factorial design</p> <p>Induction (2 courses):</p> <ul style="list-style-type: none"> • FLA vs ADE • G-CSF vs no G-CSF • ATRA vs no ATRA <p>Patients could undergo all 3 randomisations, any combination of 2, or just one</p> <p>Consolidation:</p> <ul style="list-style-type: none"> • Stem-cell transplantation • High-dose cytarabine • Other therapy at the discretion of the patient's clinician <p>Recruitment period</p> <ul style="list-style-type: none"> • December 1998 to December 2003 <p>Median follow-up time</p> <ul style="list-style-type: none"> • All point estimates quoted are at 4 years.
Participants	<p>Eligibility criteria</p> <ul style="list-style-type: none"> • De novo or secondary AML and relapsed from first CR

MRC AML HR (Continued)

- Poor risk cytogenetics at initial diagnosis (-5, -7, del 5q, abnormal 3q or complex karyotype defined as >4 abnormalities) after one course of chemotherapy
- Resistant disease defines as greater than 15% marrow blasts after one course
- Written informed consent

Excluded:

- APL
- Concurrent active malignancy
- Blast transformation of CML
- Relapse from second or greater CR
- Severe renal impairment
- Pregnant, lactating or potentially fertile and no adequate contraceptive

Participants randomised (N = 405)
Participants randomised to ATRA vs no ATRA: N = 362

- Induction therapy without ATRA
 - N = 182
 - FLA= 57
 - ADE=55
 - G-CSF=80
- Induction therapy with ATRA
 - N = 180
 - FLA + ATRA= 56
 - ADE + ATRA= 57
 - G-CSF + ATRA =79

Age:

- 15 to 70 years and older
- Mean age: 50 to 59 years

Gender:

- 189 men, 173 women

Country:

- UK

Interventions
Chemotherapy:
• ADE
Course 1

cytarabine 100 mg/m² every 12 hours day 1 to 10

daunorubicin 50 mg/m² days 1 + 3 + 5

etoposide 100 mg/m² days 1 to 5

Course 2

cytarabine 100 mg/m² every 12 hours days 1 to 8

daunorubicin 50 mg/m² days 1 + 3 + 5

etoposide 100 mg/m² days 1 to 5

MRC AML HR (Continued)

- **FLA**

fludarabine 30 mg/m² days 1 to 5

cytarabine 2 g/m² days 1 to 5

Patients over 60 years old received 1 g/m²

G-CSF

0,5 MU/kg per day subcutaneous or intravenous, starting on first day of each course of induction until the neutrophil count is greater than 0,5 x 10⁹/L for 2 days

ATRA

45 mg/m² per day orally, starting on first day of chemotherapy course 1 and continuing daily during and after courses 1 and 2 to a maximum of 90 days

Outcomes	<ul style="list-style-type: none"> • Overall survival • Complete remission • Relapse rate • Disease-free survival • Toxicity • Supportive care requirements • Death in complete remission
Notes	Study was funded by the Medical Research Council of the U.K.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Allocation was computer generated using minimization to ensure balance overall..."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed by telephone call..."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Regarding the study design, it is likely that there was no blinding.
Blinding of outcome detection (OS)	Low risk	Death is an endpoint not susceptible to bias from the outcome assessor.
Blinding of outcome detection (other outcomes)	High risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No data missing.
Selective reporting (reporting bias)	High risk	Protocol available at isrctn.com/ISRCTN88373119 Not all outcome measures are reported: toxicity, quality of life, supportive care requirements.
Other bias	Low risk	The trial seems free of other biases

MRC AML12

Methods	<p>Randomised controlled trial</p> <p>Induction therapy: 2 courses of DAT without or with ATRA</p> <p>Consolidation therapy:</p> <ul style="list-style-type: none"> • 1 course MACE • SCT or ifosfamide, carboplatin, etoposide or MidAC <p>Recruitment period</p> <ul style="list-style-type: none"> • November 1998 to May 2002 <p>Median follow-up time</p> <ul style="list-style-type: none"> • Median follow-up was 8.4 years (longest survival was 13.0 years).
Participants	<p>Eligibility criteria</p> <ul style="list-style-type: none"> • De novo or secondary AML • High-risk MDS with marrow blasts > 10% • Patients are normally under 60 years old, but can be older as long as intensive therapy is considered suitable • Written informed consent <p>Excluded:</p> <ul style="list-style-type: none"> • CML • APL for ATRA randomisation • Pregnant or lactating patients • Other concurrent malignancy • Prior cytotoxic therapy for leukaemia other than hydroxycarbamide <p>Participants randomised (N = 1075)</p> <ul style="list-style-type: none"> • Induction therapy with ATRA <ul style="list-style-type: none"> ◦ N = 540 • Induction therapy without ATRA <ul style="list-style-type: none"> • N = 535 <p>Age:</p> <ul style="list-style-type: none"> • 14 to 68 years • Mean age: 48 years <p>Gender:</p> <ul style="list-style-type: none"> • 535 men, 540 women <p>Country:</p> <ul style="list-style-type: none"> • UK
Interventions	<p>Chemotherapy</p> <ul style="list-style-type: none"> • DAT <ul style="list-style-type: none"> • H-DAT 3+10 (course 1): <ul style="list-style-type: none"> • daunorubicin 50 mg/m² days 1 + 3 + 5 • cytarabine 200 mg/m² every 12 hours days 1 to 10

MRC AML12 (Continued)

- thioguanine 100 mg/m² every 12 hours days 1 to 10
- HDAT 3+8 (course 2):
- daunorubicin 50 mg/m² day 1 + 3 + 5
- cytarabine 200 mg/m² every 12 hours days 1 to 8
- thioguanine 100 mg/m² every 12 hours days 1 to 8
- S-DAT 3+10 (course 1):
- daunorubicin 50 mg/m² d 1+3+5
- cytarabine 100 mg/m² every 12 hours days 1 to 10
- thioguanine 100 mg/m² every 12 hours days 1 to 10
- S-DAT 3+8 (course 2):
- daunorubicin 50 mg/m² days 1 + 3 + 5
- cytarabine 100 mg/m² every 12 hours days 1 to 8
- thioguanine 100 mg/m² every 12 hours days 1 to 8
- **MACE**
 - amsacrine
 - cytarabine
 - etoposide
- **MidAC**
 - mitozantrone
 - cytarabine
- **Ifosfamide, carboplatin, etoposide**
 - idarubicin
 - cytarabine
 - etoposide

ATRA:

45 mg/m² days 1 to 60

Stem cell transplantation

Outcomes	<ul style="list-style-type: none">• Overall survival• Relapse-free survival• Complete remission• Cumulative incidence of death in complete remission• Duration of remission• Toxicity• Quality of life• Supportive care requirements	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Personal communication: Quote: "Centralised randomisation process".
Allocation concealment (selection bias)	Low risk	Personal communication: Quote: "Centralised randomisation process".

MRC AML12 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Regarding the study design, it is likely that there was no blinding.
Blinding of outcome detection (OS)	Low risk	Death is an endpoint not susceptible to bias from the outcome assessor.
Blinding of outcome detection (other outcomes)	High risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data.
Selective reporting (reporting bias)	Low risk	Personal communication, study protocol provided by Ian Thomas. All of the pre-planned outcome measures are analysed and reported.
Other bias	Low risk	The trial seems free of other biases

NCRI LRF AML 14

Methods	<p>Randomised controlled trial</p> <p>Therapy: low-dose cytarabine or hydroxyurea without or with ATRA</p> <p>Recruitment period</p> <ul style="list-style-type: none"> December 1998 to November 2003 <p>Median follow-up time</p> <ul style="list-style-type: none"> Not reported
Participants	<p>Eligibility criteria</p> <ul style="list-style-type: none"> Any type of AML (de novo or secondary) High-risk MDS Patients aged < 70 years should have a documented comorbidity that precluded chemotherapy <p>Excluded:</p> <ul style="list-style-type: none"> APL and blast transformation of chronic myeloid leukaemia <p>Participants randomised (N = 207)</p> <ul style="list-style-type: none"> Induction therapy without ATRA <ul style="list-style-type: none"> N = 100 Induction therapy with ATRA <ul style="list-style-type: none"> N = 107 <p>Age:</p> <ul style="list-style-type: none"> 51 to 90 years Mean age: 74 <p>Gender:</p> <ul style="list-style-type: none"> 105 men, 92 women

NCRI LRF AML 14 (Continued)

Country:

- United Kingdom

Interventions	Chemotherapy: <ul style="list-style-type: none"> • LD cytarabine 20 mg 2/day subcutaneously for 10 days Hydroxyurea: <ul style="list-style-type: none"> • Sufficient to keep the white blood cell count below $10 \times 10^9/L$ ATRA : <ul style="list-style-type: none"> • 45 mg/m² per day for 60 days
Outcomes	<ul style="list-style-type: none"> • Complete remission • Overall survival • Disease-free survival • Toxicities
Notes	The study was supported by research grants from the Leukemia Research Fund of the U.K.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Allocation was computer generated using minimization to ensure balance overall..."
Allocation concealment (selection bias)	Low risk	Quote: "...was performed by telephone call to the central trial..."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Regarding the study design it is likely that there was no blinding.
Blinding of outcome detection (OS)	Low risk	Death is an endpoint not susceptible to bias from the outcome assessor.
Blinding of outcome detection (other outcomes)	High risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 217 patients were randomised for non-intensive therapy, but only 207 at least were randomised between ATRA and No-ATRA. It is unclear why ten patients were not randomised between the two arms.
Selective reporting (reporting bias)	Unclear risk	No study protocol available, therefore insufficient information to judge
Other bias	Low risk	The trial seems free of other biases

Abbreviations: **AML**: acute myeloid leukaemia; **APL**: acute promyelocytic leukaemia; **ATRA**: all-trans retinoic acid; **CR**: complete remission; **CML**: chronic myeloid leukaemia; **ECOG**: Eastern Cooperative Oncology Group; **G-CSF**: granulocyte-colony stimulating factor; **MDS**: myelodysplastic syndrome; **N**: number; **RAEB-T**: refractory anaemia with excess blasts in transformation; **SCT**: stem-cell transplantation; **VPA**: valproic acid; **WHO**: World Health Organization

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

Study	Reason for exclusion
Di Febo 2007	Not a randomised trial
Estey 1997	Less than 80% of patients with AML (28% MDS)
Nazha 2013	Less than 80% of patients with AML (28% MDS)
Stone 2000	Single-arm trial, all patients received ATRA

AML: acute myeloid leukaemia; **ATRA:** all-trans retinoic acid; **MDS:** myelodysplastic syndrome;

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

AMLSG 15-10

Trial name or title	Randomized phase III study of low-dose cytarabine and etoposide with or without all-trans retinoic acid in older patients not eligible for intensive chemotherapy with acute myeloid leukaemia and NPM1 mutation
Methods	Randomised multicentre phase III study, no more information given
Participants	<p>Eligibility criteria</p> <ul style="list-style-type: none"> • Patients 60 years old and older • De novo AML • Not previously treated for AML except with hydroxyurea • Written informed consent • WHO performance status ≤ 3 <p>Excluded</p> <ul style="list-style-type: none"> • All other AML subtypes • Severe liver, kidney or heart disease <p>Age:</p> <ul style="list-style-type: none"> • ≥ 60 years <p>Gender:</p> <ul style="list-style-type: none"> • Both <p>Country:</p> <ul style="list-style-type: none"> • Germany
Interventions	<p>Low-dose cytarabine and etoposide with or without all-trans retinoic acid</p> <p>No more information given</p>
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • Overall survival <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Complete remission

AMLSG 15-10 (Continued)

- Cumulative incidence of relapse and death in CR
- Event-free survival

Starting date	December 2010 (record was first entered in the EudraCT)
Contact information	University hospital Ulm, AMLSG Clinical Trials Offfiosfamide, carboplatin, etoposide, richard.schlenk@uniklinik-ulm.de
Notes	Ongoing, but not recruiting patients

Abbreviations: **AML:** acute myeloid leukaemia; **CR:** complete remission; **WHO:** World Health Organization

DATA AND ANALYSES

Comparison 1. ATRA in addition to chemotherapy versus chemotherapy only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	7	2985	Hazard Ratio (Fixed, 95% CI)	0.94 [0.87, 1.02]
2 Overall survival: subgroup: stage of disease	7		Hazard Ratio (Fixed, 95% CI)	0.94 [0.87, 1.02]
2.1 newly diagnosed	5		Hazard Ratio (Fixed, 95% CI)	0.95 [0.87, 1.03]
2.2 relapsed AML	1		Hazard Ratio (Fixed, 95% CI)	1.23 [0.96, 1.59]
2.3 first remission: consolidation therapy	1		Hazard Ratio (Fixed, 95% CI)	0.71 [0.55, 0.92]
3 Overall survival: subgroup: chemotherapy only versus chemotherapy plus SCT	7		Hazard Ratio (Fixed, 95% CI)	0.94 [0.87, 1.02]
3.1 chemotherapy only	5		Hazard Ratio (Fixed, 95% CI)	0.92 [0.84, 1.01]
3.2 chemotherapy plus SCT	2		Hazard Ratio (Fixed, 95% CI)	0.99 [0.87, 1.14]
4 Overall survival: subgroup: decitabine included in chemotherapy?	7		Hazard Ratio (Fixed, 95% CI)	0.94 [0.87, 1.02]
4.1 chemotherapy without decitabine	6		Hazard Ratio (Fixed, 95% CI)	0.97 [0.90, 1.05]
4.2 decitabine containing chemotherapy	1		Hazard Ratio (Fixed, 95% CI)	0.65 [0.48, 0.87]
5 Overall survival: subgroup: age	7		Hazard Ratio (Fixed, 95% CI)	0.94 [0.87, 1.02]
5.1 < 60 years	1		Hazard Ratio (Fixed, 95% CI)	0.91 [0.77, 1.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 ≥ 60 years	3		Hazard Ratio (Fixed, 95% CI)	0.76 [0.65, 0.89]
5.3 mixed	3		Hazard Ratio (Fixed, 95% CI)	1.05 [0.95, 1.17]
6 Overall survival: sensitivity analysis: random-effects model	7		Hazard Ratio (Random, 95% CI)	0.93 [0.80, 1.07]
7 Overall survival: sensitivity analysis: high risk versus low risk of bias	7		Hazard Ratio (Fixed, 95% CI)	0.94 [0.87, 1.02]
7.1 high risk of bias	2		Hazard Ratio (Fixed, 95% CI)	1.01 [0.87, 1.16]
7.2 low risk of bias	5		Hazard Ratio (Fixed, 95% CI)	0.92 [0.84, 1.01]
8 Disease or relapse-free survival	3	1258	Hazard Ratio (Fixed, 95% CI)	0.99 [0.87, 1.12]
9 Disease or relapse-free survival: subgroup: stage of disease	3		Hazard Ratio (Fixed, 95% CI)	0.99 [0.87, 1.12]
9.1 newly diagnosed	2		Hazard Ratio (Fixed, 95% CI)	0.97 [0.85, 1.10]
9.2 relapsed AML	1		Hazard Ratio (Fixed, 95% CI)	1.12 [0.82, 1.53]
10 Disease or relapse-free survival: subgroup: chemotherapy only versus chemotherapy plus SCT	3		Hazard Ratio (Fixed, 95% CI)	0.99 [0.87, 1.12]
10.1 chemotherapy only	2		Hazard Ratio (Fixed, 95% CI)	1.01 [0.87, 1.16]
10.2 chemotherapy plus SCT	1		Hazard Ratio (Fixed, 95% CI)	0.93 [0.72, 1.20]
11 Disease or relapse-free survival: sensitivity analysis: high risk versus low risks	3		Hazard Ratio (Fixed, 95% CI)	0.99 [0.87, 1.12]
11.1 high risk of bias	1		Hazard Ratio (Fixed, 95% CI)	1.12 [0.82, 1.53]
11.2 low risk of bias	2		Hazard Ratio (Fixed, 95% CI)	0.97 [0.85, 1.10]
12 Complete response rate	6	3081	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.96, 1.09]
13 Complete response rate: subgroup: stage of disease	6	3176	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.96, 1.09]
13.1 newly diagnosed	4	2477	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.95, 1.09]
13.2 relapsed AML	1	362	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.81, 1.12]
13.3 first remission: consolidation	1	242	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.95, 1.98]
13.4 mixed	1	95	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.67, 1.35]
14 Complete response rate: subgroup chemotherapy only versus chemotherapy plus SCT	6	3081	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.96, 1.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 chemotherapy only	5	1981	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.94, 1.09]
14.2 chemotherapy plus SCT	1	1100	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.93, 1.18]
15 Complete response rate: subgroup: age	6	3081	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.96, 1.09]
15.1 < 60 years	1	1100	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.93, 1.18]
15.2 ≥60 years	2	449	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.00, 1.97]
15.3 mixed	3	1532	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.91, 1.05]
16 Complete response rate: sensitivity analysis: high risk versus low risk of bias	6	3081	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.96, 1.09]
16.1 high risk of bias	2	1462	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.92, 1.12]
16.2 low risk of bias	4	1619	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.95, 1.12]
17 On-study mortality	5	2839	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.81, 1.30]
18 On-study mortality: subgroup: stage of disease	5	2839	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.81, 1.30]
18.1 newly diagnosed	3	2382	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.81, 1.36]
18.2 relapsed AML	1	362	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.47, 1.90]
18.3 mixed	1	95	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.28, 2.60]
19 On-study mortality: subgroup chemotherapy only versus chemotherapy plus SCT	5	2839	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.81, 1.30]
19.1 chemotherapy only	4	1739	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.80, 1.40]
19.2 chemotherapy plus SCT	1	1100	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.58, 1.49]
20 On-study mortality: subgroup: age	5	2839	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.81, 1.30]
20.1 < 60 years	1	1100	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.58, 1.49]
20.2 ≥60 years	1	207	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.79, 2.06]
20.3 mixed	3	1532	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.70, 1.37]
21 On-study mortality: sensitivity analysis: high risk versus low risk of bias	5	2839	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.81, 1.30]
21.1 high risk of bias	2	1462	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.63, 1.38]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.2 low risk of bias	3	1377	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.80, 1.46]
22 Infection grade III/IV	3	1428	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.96, 1.15]
23 Infection: subgroup: stage of disease	3	1523	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.96, 1.15]
23.1 newly diagnosed	1	1091	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.97, 1.17]
23.2 first remission: consolidation	1	242	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.63, 1.38]
23.3 mixed	1	190	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.62, 1.68]
24 Infection: subgroup chemotherapy only versus chemotherapy plus SCTI	3	1428	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.96, 1.15]
24.1 chemotherapy only	2	337	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.71, 1.35]
24.2 chemotherapy plus SCT	1	1091	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.97, 1.17]
25 Infection: subgroup: age	3	1428	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.96, 1.15]
25.1 < 60 years	1	1091	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.97, 1.17]
25.2 ≥60 years	1	242	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.63, 1.38]
25.3 mixed	1	95	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.63, 1.88]
26 Infection: sensitivity analysis: high risk versus low risk of bias	3	1428	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.96, 1.15]
26.1 high risk of bias	1	1091	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.97, 1.17]
26.2 low risk of bias	2	337	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.71, 1.35]
27 Diarrhoea grade III/IV	2	337	Risk Ratio (M-H, Fixed, 95% CI)	2.19 [1.07, 4.47]
28 Nausea/vomiting grade III/IV	2	337	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.75, 2.85]
29 Cardiac toxicity grade III/IV	3	1428	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.24, 0.90]

Analysis 1.1. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 1 Overall survival.

Study or subgroup	ATRA	no additional ATRA	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
	N	N				
AML-SG 14-09	0	0	-0.4 (0.15)		7.12%	0.65[0.48,0.87]
AMLSG 07-04	544	556	-0.1 (0.09)		19.79%	0.91[0.77,1.09]
<div> <div>Favours ATRA</div> <div>0.010.1110100</div> <div>Favours no ATRA</div> </div>

Analysis 1.2. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 2 Overall survival: subgroup: stage of disease.

**Analysis 1.3. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only,
Outcome 3 Overall survival: subgroup: chemotherapy only versus chemotherapy plus SCT.** **Analysis 1.4. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy
only, Outcome 4 Overall survival: subgroup: decitabine included in chemotherapy?.**

Analysis 1.5. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 5 Overall survival: subgroup: age.

Analysis 1.6. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 6 Overall survival: sensitivity analysis: random-effects model. **Analysis 1.7. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 7 Overall survival: sensitivity analysis: high risk versus low risk of bias.**

Analysis 1.8. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 8 Disease or relapse-free survival.

Analysis 1.9. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 9 Disease or relapse-free survival: subgroup: stage of disease.

Analysis 1.10. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 10 Disease or relapse-free survival: subgroup: chemotherapy only versus chemotherapy plus SCT.

Analysis 1.11. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 11 Disease or relapse-free survival: sensitivity analysis: high risk versus low risks.

Analysis 1.12. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 12 Complete response rate.

Analysis 1.13. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 13 Complete response rate: subgroup: stage of disease.

Analysis 1.14. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 14 Complete response rate: subgroup chemotherapy only versus chemotherapy plus SCT.

Analysis 1.15. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 15 Complete response rate: subgroup: age.

Analysis 1.16. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 16 Complete response rate: sensitivity analysis: high risk versus low risk of bias.

Analysis 1.17. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 17 On-study mortality.

Analysis 1.18. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 18 On-study mortality: subgroup: stage of disease.

Analysis 1.19. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 19 On-study mortality: subgroup chemotherapy only versus chemotherapy plus SCT.

Analysis 1.20. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 20 On-study mortality: subgroup: age.

Analysis 1.21. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 21 On-study mortality: sensitivity analysis: high risk versus low risk of bias.

Analysis 1.22. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 22 Infection grade III/IV.

Analysis 1.23. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 23 Infection: subgroup: stage of disease.

Analysis 1.24. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 24 Infection: subgroup chemotherapy only versus chemotherapy plus SCTL.

Analysis 1.25. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 25 Infection: subgroup: age.

Analysis 1.26. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 26 Infection: sensitivity analysis: high risk versus low risk of bias.

Analysis 1.27. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 27 Diarrhoea grade III/IV.

Analysis 1.28. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 28 Nausea/vomiting grade III/IV.

Analysis 1.29. Comparison 1 ATRA in addition to chemotherapy versus chemotherapy only, Outcome 29 Cardiac toxicity grade III/IV.

APPENDICES

Appendix 1. CENTRAL search strategy

ID	Search
#1	MeSH descriptor: [Leukemia, Myeloid, Acute] explode all trees
#2	MeSH descriptor: [Leukemia, Myeloid] explode all trees
#3	MeSH descriptor: [Acute Disease] explode all trees
#4	#2 and #3
#5	(acut* or akut*)
#6	((myelo* or nonlympho* or granulocytic* or mielo*) and (leuk*em* or leuc*))
#7	#5 and #6
#8	aml

(Continued)

#9	#1 or #4 or #7 or #8
#10	MeSH descriptor: [Retinoids] explode all trees
#11	MeSH descriptor: [Vitamin A] explode all trees
#12	MeSH descriptor: [Tretinoin] explode all trees
#13	(retino* and acid*)
#14	((all-trans* or all trans*) and retino*)
#15	((retin* or vitamin*) near/2 a)
#16	((vitamin* or retino*) near/2 acid*)
#17	atra
#18	(abrel* or aknoten* or avita* or renova* or vesanoid*)
#19	(airol* or dermairol* or epiabere* or eudyna* or retisol* or stieva* or vitinoin*)
#20	tretinoin*
#21	MeSH descriptor: [Receptors, Retinoic Acid] explode all trees
#22	receptors near/2 retinoic acid
#23	(ro 5488 or ro5488)
#24	aquasol a
#25	#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
#26	#9 and #25 in Trials

Appendix 2. MEDLINE search strategy

#	Searches	Results
1	exp LEUKEMIA, MYELOID, ACUTE/	43902
2	Leukemia, Myeloid/	21948
3	ACUTE DISEASE/	183257
4	2 and 3	6216
5	(acut\$ or akut\$).tw,kf,ot.	835830
6	((myelo\$ or nonlympho\$ or granulocytic\$ or mielo\$) and (leuk?em\$ or leuc \$)).tw,kf,ot.	74373

(Continued)

7	5 and 6	40980
8	aml.tw,kf,ot.	19694
9	1 or 4 or 7 or 8	68174
10	exp RETINOIDS/	46468
11	VITAMIN A/	19614
12	TRETINOIN/	19570
13	(retino\$ and acid\$).tw,kf,ot.	30893
14	((all-trans\$ or all trans\$) and retino\$).tw,kf,ot.	8389
15	((retin\$ or vitamin\$) adj3 a).tw,kf,ot.	64976
16	((vitamin\$ or retino\$) and acid\$).tw,kf,ot.	58699
17	atra.tw,kf,ot.	3966
18	(abrel\$ or aknoten\$ or avita\$ or renova\$ or vesanoid\$).tw,kf,ot.	8979
19	(airol\$ or dermairol\$ or epiabrel\$ or eudyna\$ or retisol\$ or stieva\$ or viti- noin\$).tw,kf,ot.	27
20	tretinoin\$.tw,kf,ot,nm.	19829
21	Receptors, Retinoic Acid/	7398
22	receptors, retinoic acid.tw,kf,ot,nm.	7449
23	(ro 5488 or ro5488).tw,kf,ot,nm.	0
24	aquasol a.tw,kf,ot.	5
25	or/10-24	137492
26	randomized controlled trial.pt.	379042
27	controlled clinical trial.pt.	88839
28	randomi?ed.ab.	331494
29	placebo.ab.	147769
30	drug therapy.fs.	1718772
31	randomly.ab.	196133
32	trial.ab.	287204
33	groups.ab.	1258953
34	or/26-33	3236730

(Continued)

35	humans.sh.	13582558
36	34 and 35	2650638
37	9 and 25	4061
38	37 and 36	2098

CONTRIBUTIONS OF AUTHORS

Yasemin Küley-Bagheri (YK): conception and writing of the review

Prof. Karl-Anton Kreuzer (KK): clinical expertise

Prof. Michael Lübbert (ML): clinical expertise

Ina Monsef: developing and running search strategies

Dr. Nicole Skoetz (NS): methodological and clinical expertise

All review authors have read and accepted the final version of this review

DECLARATIONS OF INTEREST

Yasemin Küley-Bagheri (YK): none known

Prof. Karl-Anton Kreuzer (KK): Grants and honoraria from the following companies: Aexion, Amgen, Ariad, Baxter, Bayer, Biotest, Boehringer Ingelheim, Bristol-Meyers Squibb, Celgene, EUSA Pharma, Gilead, GSK, Grifols, Hexal, Janssen, LEO, MSD, Novartis, Pfizer, Roche, TEVA do not lead to a conflict related to interventions evaluated in this systematic review

Ina Monsef: none known

Prof. Michael Lübbert (ML): Investigator for the DECIDER phase III trial; advisory board honoraria from Janssen-Cilag, Janssen-Cilag provided study drug (decitabine), TEVA provided study drug (valproic acid); Relevant financial activities outside the submitted work: Janssen-Cilag: research support, travel support, Celplapharm: ATRA study drug (TRANSATRA investigator-initiated trial, sponsor: German Cancer Consortium (DKTK)), Celgene: travel support, Astex: advisory board honoraria.

Dr. Nicole Skoetz (NS): none known.

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- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol, we specified that we would analyse event-free survival. As this outcome was not reported in the included trials we evaluated relapse-free/disease-free survival instead.

In meta-analyses with 10 or more trials, we would have investigated potential publication bias by generating a funnel plot and would test statistics by using a linear regression test (Sterne 2011). A P value less than 0.1 would be considered significant for this test. However, as we included eight trials only, this analysis was not possible.

In accordance with Methodological Expectations of Cochrane Intervention Reviews (MECIR), we additionally searched the following clinical trials registers.

- EU clinical trials register: <https://www.clinicaltrialsregister.eu/ctr-search/search>
- World health organisation: <http://apps.who.int/trialsearch/>
- Clinicaltrials.gov: <https://clinicaltrials.gov/>
- ISRCTN: <http://www.isrctn.com/>

NOTES

We used standard wording from the CHMG template for the methods section.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [adverse effects] [*therapeutic use]; Decitabine [adverse effects] [therapeutic use]; Diarrhea [chemically induced]; Disease Progression; Heart [drug effects]; Infections [chemically induced]; Leukemia, Myeloid, Acute [*drug therapy] [mortality]; Nausea [chemically induced]; Recurrence; Tretinoin [adverse effects] [*therapeutic use]; Vomiting [chemically induced]

MeSH check words

Adult; Humans