# Arsenic trioxide and all-*trans* retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomised, controlled, phase 3 trial

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**Background** Acute promyelocytic leukaemia is a chemotherapy-sensitive subgroup of acute myeloid leukaemia characterised by the presence of the *PML–RARA* fusion transcript. The present standard of care, chemotherapy and all-*trans* retinoic acid (ATRA), results in a high proportion of patients being cured. In this study, we compare a chemotherapy-free ATRA and arsenic trioxide treatment regimen with the standard chemotherapy-based regimen (ATRA and idarubicin) in both high-risk and low-risk patients with acute promyelocytic leukaemia.

**Methods** In the randomised, controlled, multicentre, AML17 trial, eligible patients (aged ≥16 years) with acute promyelocytic leukaemia, confirmed by the presence of the *PML–RARA* transcript and without significant cardiac or pulmonary comorbidities or active malignancy, and who were not pregnant or breastfeeding, were enrolled from 81 UK hospitals and randomised 1:1 to receive treatment with ATRA and arsenic trioxide or ATRA and idarubicin. ATRA was given to participants in both groups in a daily divided oral dose of 45 mg/m$^2$ until remission, or until day 60, and then in a 2 weeks on–2 weeks off schedule. In the ATRA and idarubicin group, idarubicin was given intravenously at 12 mg/m$^2$ on days 2, 4, 6, and 8 of course 1, and then at 5 mg/m$^2$ on days 1–4 of course 2; mitoxantrone at 10 mg/m$^2$ on days 1–4 of course 3, and idarubicin at 12 mg/m$^2$ on day 1 of the final (fourth) course. In the ATRA and arsenic trioxide group, arsenic trioxide was given intravenously at 0·3 mg/kg on days 1–5 of each course, and at 0·25 mg/kg twice weekly in weeks 2–8 of course 1 and weeks 2–4 of courses 2–5. High-risk patients (those presenting with a white blood cell count >10×10$^9$ cells per L) could receive an initial dose of the immunoconjugate gemtuzumab ozogamicin (6 mg/m$^2$ intravenously). Neither maintenance treatment nor CNS prophylaxis was given to patients in either group. All patients were monitored by real-time quantitative PCR. Allocation was by central computer minimisation, stratified by age, performance status, and de-novo versus secondary disease. The primary endpoint was quality of life on the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 global health status. All analyses are by intention to treat. This trial is registered with the ISRCTN registry, number ISRCTN55675535.

**Findings** Between May 8, 2009, and Oct 3, 2013, 235 patients were enrolled and randomly assigned to ATRA and idarubicin (n=119) or ATRA and arsenic trioxide (n=116). Participants had a median age of 47 years (range 16–77; IQR 33–58) and included 57 high-risk patients. Quality of life did not differ significantly between the treatment groups (EORTC QLQ-C30 global functioning effect size 2·17 [95% CI −2·79 to 7·12; p=0·39]). Overall, 57 patients in the ATRA and idarubicin group and 40 patients in the ATRA and arsenic trioxide group reported grade 3–4 toxicities. After course 1 of treatment, grade 3–4 alopecia was reported in 23 (23%) of 98 patients in the ATRA and idarubicin group versus 5 (5%) of 95 in the ATRA and arsenic trioxide group, raised liver alanine transaminase in 11 (10%) of 108 versus 27 (25%) of 109, oral toxicity in 22 (19%) of 115 versus one (1%) of 109. After course 2 of treatment, grade 3–4 alopecia was reported in 25 (28%) of 89 patients in the ATRA and idarubicin group versus 2 (3%) of 77 in the ATRA and arsenic trioxide group; no other toxicities reached the 10% level. Patients in the ATRA and arsenic trioxide group had significantly less requirement for most aspects of supportive care than did those in the ATRA and idarubicin group.

**Interpretation** ATRA and arsenic trioxide is a feasible treatment in low-risk and high-risk patients with acute promyelocytic leukaemia, with a high cure rate and less relapse than, and survival not different to, ATRA and idarubicin, with a low incidence of liver toxicity. However, no improvement in quality of life was seen.

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## Introduction

Progress in the treatment of acute promyelocytic leukaemia has been one of the few clear successes in acute myeloid leukaemia therapy in the past two decades. As a genetically defined subgroup, characterised by the *PML–RARA* fusion gene generated by the t(15;17)(q22;q21) chromosomal translocation, it has been shown to be especially sensitive to anthracycline-based chemotherapy. However, it was not until the use of all-*trans* retinoic acid (ATRA), which induces degradation of the PML–RARA oncoprotein, combined with chemotherapy, that most patients with acute promyelocytic leukaemia became

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## Research in context

### Evidence before this study

We did not do a formal literature search, but instead contacted other collaborative groups working on acute promyelocytic leukaemia, and based the trial design on the results of the UK national trials run by the group since 1988. In the acute promyelocytic leukaemia subgroup of acute myeloid leukaemia, all-*trans* retinoic acid (ATRA), although not able to durably control the disease as monotherapy, has been shown to greatly improve cure when added to conventional chemotherapy in several studies. Arsenic trioxide was also shown to be effective as monotherapy, and in due course received regulatory approval for treatment of relapsed disease (in September, 2000, in the USA and in October, 2001, in the European Union). Initial non-randomised studies suggested that the combination of ATRA and arsenic trioxide resulted in a high cure rate. The Italian and German collaboration (GIMEMA-AMLSG-SAL) did the first randomised comparison of this combination against the standard of care (ATRA and idarubicin) and showed that ATRA and arsenic trioxide resulted in superior survival compared with the chemotherapy-based standard of care. However, this study was restricted to low-risk patients and excluded the 25% of patients who presented with a white blood count of $10 \times 10^9$ cells per L or higher. It involved an intensive schedule of up to 140 doses of arsenic trioxide given by infusion daily over a period of 6 months, and was associated with a high proportion of patients having grade 3–4 liver toxicity.

### Added value of this study

The randomised National Cancer Research Institute AML17 trial, reported here, also compared ATRA and arsenic trioxide with ATRA plus chemotherapy, but included high-risk patients (who were given a single injection of the CD33 targeted immunoconjugate, gemtuzumab ozogamicin, at diagnosis to control the initial high white blood cell count). A less frequent dosing schedule of arsenic trioxide was used (63 doses within 6 months) and showed a high cure rate with low toxicity and substantially less supportive care requirements than the standard of care (ATRA and chemotherapy). Once patients on ATRA and arsenic trioxide had achieved molecular remission, none relapsed. The results are consistent with those of the GIMEMA-AMLSG-SAL trial.

### Implications of all the available evidence

The combination of ATRA and arsenic trioxide is highly effective in patients with acute promyelocytic leukaemia, irrespective of risk group, with the use of a modified administration schedule. This finding suggests that a de-escalation of therapy in this disease can be implemented, with an associated high cure rate above 90%, without affecting quality of life.

curable.[1–4] Sequential studies have investigated therapy de-intensification, showing that in combination with ATRA, traditional cytotoxic chemotherapy can be limited to anthracyclines alone excluding cytarabine[5] and arguably chemotherapy-based maintenance therapy[6] (6-mercaptopurine plus methotrexate), to provide the present standard of care. However, other treatments have been shown to be effective in acute promyelocytic leukaemia, namely arsenic trioxide, which also induces degradation of PML–RARA,[7–10] and the immunoconjugate gemtuzumab ozogamicin that targets CD33 (a receptor that is highly expressed in acute promyelocytic leukaemia). Several phase 2 studies[7–9] of arsenic trioxide led to its regulatory approval for the treatment of relapsed acute promyelocytic leukaemia. Encouraging non-randomised data have also been reported with gemtuzumab ozogamicin in this setting.[11,12] A further step in treatment de-escalation was the exploration of arsenic trioxide plus ATRA in non-randomised trials,[13,14] with investigators from the MD Anderson Cancer Center (TX, USA) reporting excellent results in low-risk patients (presenting with a white blood cell count $<10 \times 10^9$ cells per L). High-risk patients (those with a white blood cell count $\geq 10 \times 10^9$ cells per L) were more difficult to treat, with differentiation syndrome emerging as a limitation to a completely chemotherapy-free approach. However, following the addition of gemtuzumab ozogamicin, treatment of high-risk patients became feasible.[15] It was subsequently necessary to establish that this standard cytotoxic chemotherapy-free approach was not inferior to the anthracycline and ATRA standard of care.

The pivotal randomised GIMEMA-AMLSG-SAL trial[16] compared arsenic trioxide and ATRA versus idarubicin and ATRA treatment in low-risk patients, with the primary aim of showing that the chemotherapy-free approach was at least equivalent to the chemotherapy-based standard of care. Results showed that patients treated with arsenic trioxide and ATRA had significantly better event-free survival than those treated with standard of care and after extended follow-up of more patients, overall survival was also significantly improved.[17] However, this study excluded the roughly 25% of patients who are high risk (ie, those who have a white blood cell count $\geq 10 \times 10^9$ cells per L), who are known to have an increased rate of early mortality. Here, we report on the AML17 trial, where we adopted an alternative dosing schedule for arsenic trioxide based on previous experience in a trial for myelodysplastic syndrome, giving 63 doses of arsenic trioxide within 6 months.[18] This new dosing schedule was expected to be more convenient for patients and improve compliance. Importantly, this study assessed all patients, including those with high-risk disease, who had the option of receiving gemtuzumab ozogamicin within the first 4 days of the first course of treatment. When the trial was designed, it was already known that the standard of care resulted in most patients being cured, so this trial was designed to investigate potential improvements in quality of life while at the same time not compromising survival outcomes.

## Methods

### Study design and participants

The AML17 trial is a randomised, controlled, phase 3, open-label multicentre trial for patients with acute myeloid leukaemia and high-risk myelodysplastic syndrome (MDS) including acute promyelocytic leukaemia; only the results of patients with acute promyelocytic leukaemia are reported here. Patients with clinically suspected acute promyelocytic leukaemia aged 16 years and older were enrolled from 81 hospitals in the UK, Denmark, and New Zealand (appendix p 1). For patients to be eligible for the study, the presence of the *PML–RARA* transcript had to be confirmed molecularly by a reference laboratory (Molecular Oncology Unit, Guy's Hospital, London, UK). Patients could not have received previous treatment for acute promyelocytic leukaemia, and those with a concurrent active malignancy, substantial cardiac arrhythmia, ECG abnormalities or neuropathy, left ventricular ejection fraction lower than 50%, uncontrolled life-threatening disease, or severe uncontrolled pulmonary or cardiac disease, and pregnant or breastfeeding women, were excluded. Expected survival in this group of patients on the basis of our AML15 trial was roughly 90% at 4 years. Ethics approval was provided by Wales REC 3, and all participants provided signed informed consent.

### Randomisation and masking

In this open-label trial, eligible participants were randomly assigned 1:1 between arsenic trioxide and ATRA therapy or ATRA and idarubicin (the standard of care). Treatment allocation was done by web-based computer minimisation hosted by Cardiff University (Cardiff, UK). Minimisation parameters were age (0–15, 16–29, 30–39, 40–49, 50–59, or 60 years and older), WHO performance status (0, 1, 2, 3, or 4), and de-novo versus secondary disease.

### Procedures

Treatments are shown in the appendix pp 2,3. Patients allocated to the ATRA and idarubicin group received four courses of treatment. ATRA 45 mg/m² daily was given in an oral divided dose (in two equal doses per day) for up to 60 days as part of their first course, and then at the same dose (45 mg/m² as an oral divided dose) on days 1–15 of subsequent courses. Chemotherapy was idarubicin 12 mg/m² intravenously on days 2, 4, 6, and 8 of course 1 and 5 mg/m² on days 1–4 of course 2; mitoxantrone 10 mg/m² on days 1–4 of course 3; and idarubicin 12 mg/m² on day 1 of course 4. In the ATRA and arsenic trioxide group, patients received five courses of treatment: ATRA was given at the same dose as in the other group (45 mg/m² daily in an oral divided dose) on days 1–60 of course 1 or until remission, and at the same dose on days 1–14 and 29–42 in courses 2–4, and days 1–14 of course 5. Arsenic trioxide was given intravenously at a dose of 0·3 mg/kg on days 1–5 of each course, and then in weeks 2–8 of course 1 and weeks 2–4 of courses 2–5 at 0·25 mg/kg twice weekly. High-risk patients (those with a white blood cell count ≥$10\times10^9$ cells per L at diagnosis), if randomly assigned to the arsenic trioxide and ATRA group, could receive gemtuzumab ozogamicin (6 mg/m²) as a single infusion within the first 4 days of the first course, but clinicians were advised to give them this drug on day 1 if possible and on day 4 if necessary, of the first course. Neither maintenance treatment nor CNS prophylaxis was given to patients in either group.

During induction treatment, ATRA could be discontinued temporarily in either treatment group if differentiation syndrome, pseudotumour cerebri, or hepatotoxicity occurred. Arsenic trioxide could be discontinued temporarily in the presence of differentiation syndrome, QT prolongation on ECG, or hepatotoxicity; the drug would be discontinued permanently in the event of cardiac arrhythmias or severe neurological toxicity. Although provision was made for clinicians to discuss treatment or dosing modification with clinical coordinators (ie, with no formal guidance being part of the protocol), no treatment modifications were actually needed. If prolongation of the corrected QT interval (QTc prolongation) was recorded, clinicians were advised to ensure that electrolyte levels, including that of magnesium, were corrected.

See Online for appendix

Molecular confirmation of the presence of a *PML–RARA* rearrangement by a reference laboratory enabled each patient to be monitored by real-time quantitative PCR (RT-qPCR) assays for *PML–RARA* (and reciprocal *RARA–PML* transcripts, if applicable) exclusively in bone marrow after each course of treatment and at 3-monthly intervals for 3 years, as previously described.[19] Patients with confirmed RT-qPCR positivity at the end of treatment were defined as having molecularly persistent disease. For patients who achieved a molecular complete remission, a diagnosis of molecular relapse was defined by RT-qPCR positivity in two successive bone marrow samples at least 2 weeks apart. Guidance was provided for blood product and platelet support and intervention for suspected differentiation syndrome as set out in the British Committee for Standards in Haematology guidelines.[20] No prophylaxis for differentiation syndrome was recommended, but prompt use of dexamethasone was suggested on clinical suspicion of emergent differentiation syndrome. Recommended salvage treatment for patients who relapsed was treatment with arsenic trioxide, with the option of a subsequent stem cell transplant if judged appropriate.

### Outcomes

The primary outcome was quality of life, assessed with the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire and the Hospital Anxiety and Depression Scale. Questionnaires were completed at baseline and at 3, 6, 12, and 24 months post randomisation. Toxicity was recorded using the National Cancer Insistute Common Terminology Criteria for Adverse Events (NCI-CTC) version 3.0.

Secondary outcomes were overall survival, relapse-free survival and event-free survival, and the incidence of

relapse (both morphological and molecular), death without relapse, and treatment-related myelodysplastic syndrome or acute myeloid leukaemia.

### Statistical analysis

All analyses are by intention-to-treat on the population with confirmed acute promyelocytic leukaemia. All randomly assigned patients were followed up for all outcomes. We calculated that if we were able to enrol 300 patients, the trial would have more than 80% power to detect a difference of a third of a standard deviation (SD) on the primary outcome (quality of life), equating to 6–7 points (out of 100) on the global health scale of the EORTC QLQ-C30 on the basis of data from our previous Medical Research Council AML15 trial (ISRCTN17161961). The trial closed after 235 eligible patients had been recruited because no further drug supply was available (because ownership of the company changed). Thus, as recruited, our trial had 72% power to detect a difference of a third of an SD or 80% power to detect three-eighths of an SD difference in quality of life (7·5 points out of 100 on the global health scale of the EORTC QLQ-C30).

We analysed quality of life using a multilevel models repeated measures analysis. The EORTC QLQ-C30 questionnaire, the Leukaemia Specific Module, and the Hospital Anxiety and Depression Scale (HADS) were used. We calculated effect sizes so that in all cases a positive value represents a benefit for ATRA and arsenic trioxide treatment. We compared categorical secondary endpoints (eg, complete remission) using Mantel-Haenszel tests, to yield Peto odds ratios and 95% CIs. To analyse continuous or scale variables we used Wilcoxon rank-sum tests, and for time-to-event outcomes (including 30-day and 60-day mortality) we used log-rank tests and Kaplan-Meier or cumulative incidence curves. Odds ratios (ORs) or hazard ratios (HRs) smaller than 1 indicate a benefit for ATRA and arsenic trioxide versus ATRA and idarubicin. All percentages are at 4 years (unless otherwise stated) with 95% CIs, and all p values are two-sided.

Endpoint definitions used revised International Working Group criteria,[21] but the cumulative incidence of molecular relapse was defined only for patients with confirmed molecular negativity as time to any relapse (haematological or molecular), with death or

| | ATRA and idarubicin (n=119) | ATRA and arsenic trioxide (n=116) |
|---|---|---|
| Age, years | 47 (16–77; 32–58) | 47 (16–75; 33–57) |
| Age group | | |
| 16–29 | 22 (18%) | 22 (19%) |
| 30–39 | 18 (15%) | 17 (15%) |
| 40–49 | 28 (24%) | 27 (23%) |
| 50–59 | 27 (23%) | 25 (22%) |
| ≥60 | 24 (20%) | 25 (22%) |
| Sex | | |
| Male | 60 (50%) | 60 (52%) |
| Female | 59 (50%) | 56 (48%) |
| Median white blood cell count (×10$^9$ cells per L) | 2·2 (0·4–78·2; 1·2–7·9) | 3·0 (0·4–100·9; 1·2–10·7) |
| 0–9·9 | 92 (77%) | 86 (74%) |
| 10–49·9* | 20 (17%) | 21 (18%) |
| 50–99·9* | 7 (6%) | 8 (7%) |
| ≥100* | 0 | 1 (1%) |
| Diagnosis | | |
| De novo | 117 (98%) | 113 (97%) |
| Secondary | 2 (2%) | 3 (3%) |
| WHO performance status | | |
| 0 | 80 (67%) | 82 (71%) |
| 1 | 32 (27%) | 29 (25%) |
| 2 | 5 (4%) | 4 (3%) |
| 3 | 1 (1%) | 1 (1%) |
| 4 | 1 (1%) | 0 |
| *RARA–PML* | | |
| Positive | 82 (69%) | 89 (77%) |
| Negative | 37 (31%) | 27 (23%) |
| *PML* breakpoint | | |
| Intron 4 | 4 (3%) | 4 (3%) |
| BCR1 | 64 (54%) | 63 (54%) |
| BCR2 | 6 (5%) | 7 (6%) |
| BCR3 | 45 (38%) | 42 (36%) |

Data are median (range; IQR) or n (%). ATRA=all-*trans* retinoic acid. *Patients in these three categories of white blood cell count were high risk.

***Table 1:*** **Baseline characteristics**

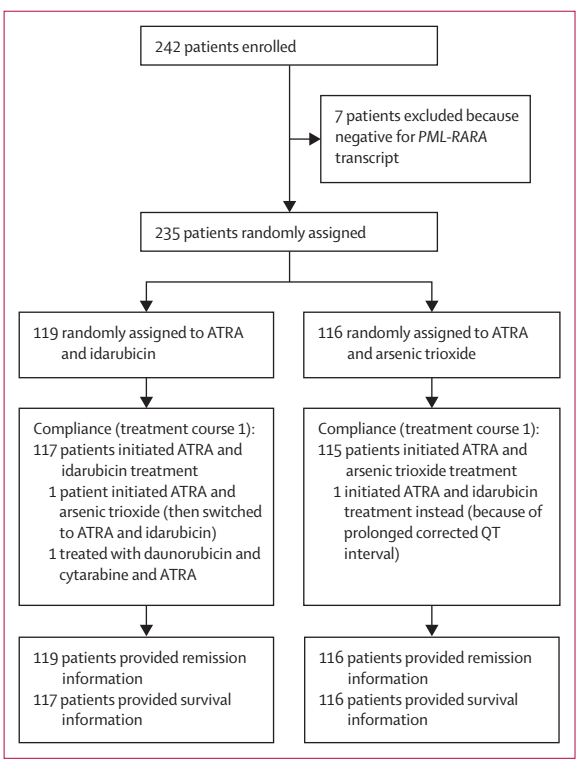


***Figure 1:*** **Trial profile**
ATRA=all-*trans* retinoic acid.

treatment-related myelodysplastic syndrome or acute myeloid leukaemia as competing risks. The cumulative incidence of treatment-related myelodysplastic syndrome or acute myeloid leukaemia has competing risks of death or relapse; whereas for the cumulative incidence of haematological relapse, treatment-related myelodysplastic syndrome, acute myeloid leukaemia, and death are competing risks. Event-free survival is defined as time from randomisation to death, treatment-related myelodysplastic syndrome or acute myeloid leukaemia, or morphological relapse for patients entering remission; patients who do not achieve a complete remission are defined as experiencing an event on day 1.

In addition to overall analyses, we did prespecified exploratory analyses stratified for age, sex, white blood cell count (including high-risk and low-risk patients), diagnosis, performance status, reverse transcript (*RARA–PML*) status, and *PML* breakpoint, with appropriate tests for interaction.

SAS version 9.4 was used for all analyses. The trial is registered with the ISRCTN registry, number ISRCTN55675535. Follow-up is complete until Jan 1, 2014.

### Role of the funding source

The funder of the study had no role in the design or analysis of the trial, data collection or interpretation, or in drafting of the report. AKB and RKH had access to all the raw data, and DG also had access to all raw monitoring data. The corresponding author (AKB) had full access to all the data and had final responsibility for the decision to submit for publication.

## Results

Between May 8, 2009, and Oct 3, 2013, 242 patients with suspected acute promyelocytic leukaemia were enrolled. Seven patients were excluded because they tested negative for the *PML–RARA* fusion transcript and 235 eligible patients were randomly assigned to receive either ATRA and arsenic trioxide (n=116) or ATRA and idarubicin (n=119). Of these 235 participants, 57 were high-risk patients (30 in the ATRA and arsenic trioxide group and 27 in the ATRA and idarubicin group). The median age of the participants was 47 years (range 16–77; IQR 33–58) and 49 were aged older than 60 years. Table 1 provides the patient characteristics and figure 1 shows the trial profile. 28 (93%) of 30 high-risk patients in the ATRA and arsenic trioxide group received gemtuzumab ozogamicin (the other two high-risk patients did not because there was no gemtuzumab ozogamicin available at their site pharmacy so they were given an anthracycline instead), with a further seven low-risk patients given gemtuzumab ozogamicin for a rising white blood cell count. 117 (98%) of 119 patients allocated to ATRA and idarubicin received their allocated treatment in course 1, compared with 115 (99%) of 116 allocated to ATRA and arsenic trioxide (figure 1). Median overall follow-up for the trial was 30·5 months (IQR 22·3–41·2). The rate of compliance with molecular monitoring to at least 12 months post treatment exceeded 90% in both groups.

Arsenic levels in plasma were monitored in 41 patients who were given arsenic trioxide upfront (n=33) or in relapse (n=8). All levels were within the therapeutic range, but numbers of patients were too small to correlate dosing with demographics, toxicity, or outcome.

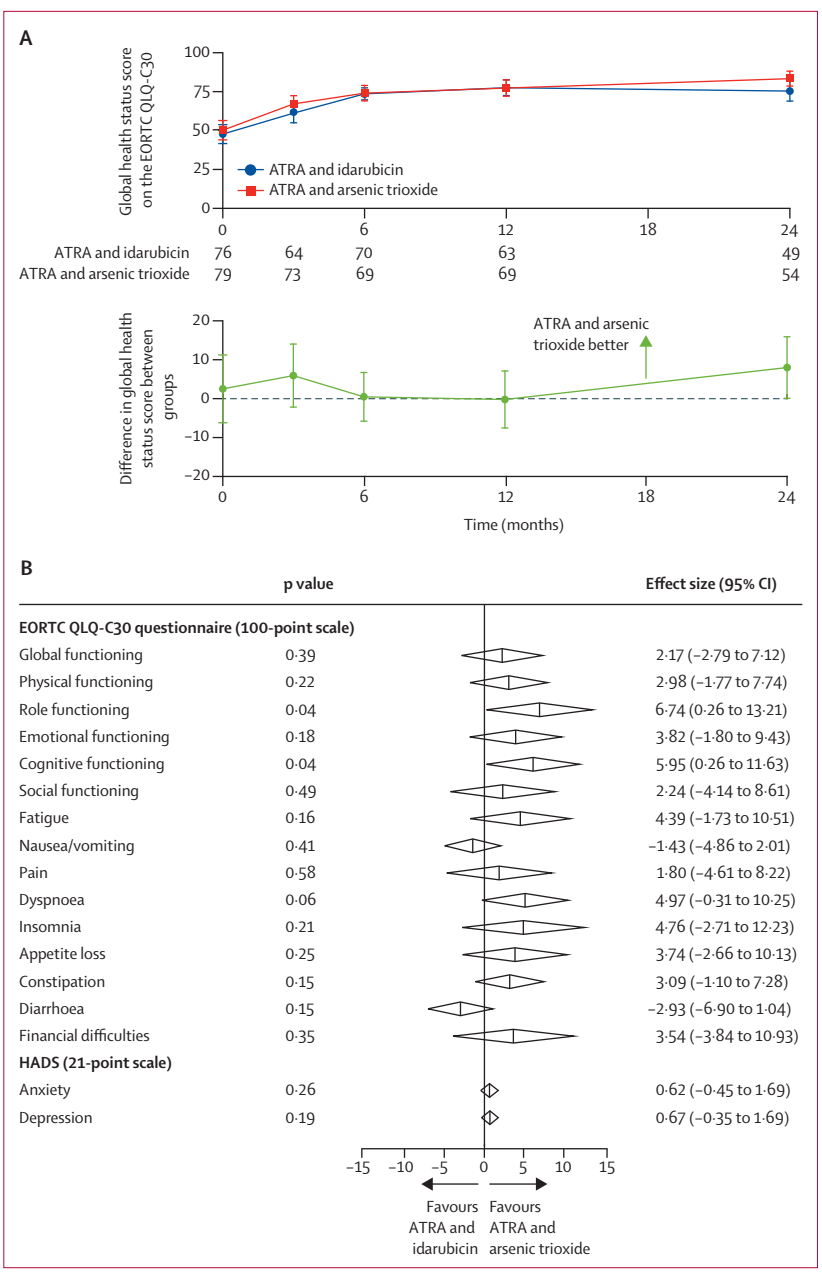


***Figure 2:*** **Quality-of-life outcomes**
(A) Global health status on the EORTC QLQ-C30 over time. Numbers at baseline are forms on which global health status was evaluable. (B) Results of all subscales of the EORTC QLQ-C30 and the HADS. Effect sizes were calculated so that in all cases a positive value represents a benefit for ATRA and arsenic trioxide treatment. ATRA=all-*trans* retinoic acid. EORTC=European Organisation for Research and Treatment of Cancer. HADS=Hospital Anxiety and Depression Scale.

A total of 671 completed quality-of-life forms were received (156 at baseline, 137 at 3 months, 139 at 6 months, 136 at 12 months, and 103 at 24 months). In each treatment group, the numbers of completed quality-of-life forms at each timepoint were: ATRA and idarubicin 76 at baseline versus ATRA and arsenic trioxide 80 at baseline; 64 versus 73 at 3 months; 70 versus 69 at 6 months; 64 versus 72 at 12 months; and 49 versus 54 at 24 months. The results showed no statistically significant difference on the primary outcome of global functioning (effect size 2·17 [95% CI −2·79 to 7·12], p=0·39; figure 2), and, based on the power calculation, the confidence intervals rule out a minimally clinically important disadvantage of six points for ATRA and arsenic trioxide versus ATRA and idarubicin. On other measures, point estimates tended to favour ATRA and arsenic trioxide over ATRA and idarubicin, with significant benefits recorded for cognitive and role functioning, although the size of any benefit was modest (figure 2B).

Of the 235 patients, 215 (91%) achieved morphological remission, which was confirmed molecularly in 211 patients, with four cases of molecularly persistent disease (one in the ATRA and idarubicin group and three in the ATRA and arsenic trioxide group). The proportion of patients achieving complete remission were higher in the ATRA and arsenic trioxide group than in the ATRA and idarubicin group (table 2). At 30 days, five deaths had occurred in the ATRA and arsenic trioxide group compared with seven in the ATRA and idarubicin group; 30-day mortality did not differ significantly between the two groups (table 2). At 60 days, six patients had died in the ATRA and arsenic trioxide group compared with 11 in the ATRA and idarubicin group; the 60-day mortality did not differ between the groups (table 2).

The causes of death at 60 days in the six patients who died in the ATRA and arsenic trioxide group were: three cardiac events, one infection, one renal failure, and one from several causes. In the 11 patients who died in the ATRA and idarubicin group after 60 days, the causes of death were: three haemorrhages, three infections, two pulmonary causes, one renal cause, and two cases of progressive disease. Complete molecular remission was achieved by patients in the ATRA and idarubicin group at a median time of 83 days (IQR 65–124) and by patients in the ATRA and arsenic trioxide group at a median time of 111 days (61–140); this difference was not significant (p=0·055). More patients had confirmed molecular negativity at 60 days in the ATRA and idarubicin group (54 [73%] of 74 patients) than in the ATRA and arsenic trioxide group (46 [56%] of 82 patients; p=0·03). Differentiation syndrome was reported in 38 (21%) of 178 low-risk patients (23 in the ATRA and arsenic trioxide group, and 15 in the ATRA and idarubicin group) and in 17 (30%) of 57 high-risk patients (seven in the ATRA and arsenic trioxide group and ten patients in the ATRA and idarubicin group; overall p value for comparison=0·38). Only four patients (two in each treatment group, three of whom were low risk and one high risk) survived beyond day 60 without morphological remission.

One case of treatment-related acute myeloid leukaemia was reported (trisomy 11, in a patient in the ATRA and idarubicin group who was confirmed as *PML–RARA* negative 39·5 months after diagnosis), and 23 patients in both treatment groups combined exhibited either disease persistence or recurrence (four molecularly persistent disease [including one subsequent CNS relapse], six molecular relapse alone, eight haematological relapse, two haematological and CNS relapse, and three cases of isolated extramedullary disease). In all cases, extramedullary disease involving the skin (n=1, in the ATRA and idarubicin group) or CNS (n=4, one in the ATRA and arsenic trioxide group and three in the ATRA and idarubicin group) was accompanied by detection of acute promyelocytic leukaemia fusion transcripts in the bone marrow. Three patients in

| | ATRA and idarubicin (n=119) | ATRA and arsenic trioxide (n=116) | OR/HR (95% CI) | p value |
|---|---|---|---|---|
| Complete remission | 106 (89%) | 109 (94%) | OR 0·54 (0·21–1·34) | 0·18 |
| Confirmed molecular negativity | 105 (88%) | 106 (91%) | OR 0·71 (0·31–1·65) | 0·43 |
| 30-day mortality | 6% (3–12) | 4% (2–10) | HR 0·72 (0·23–2·31) | 0·56 |
| 60-day mortality | 9% (5–16) | 5% (2–11) | HR 0·55 (0·21–1·43) | 0·22 |
| 4-year survival | 89% (81–93) | 93% (86–96) | HR 0·60 (0·26–1·42) | 0·25 |
| 4-year event-free survival | 70% (56–80) | 91% (84–95) | HR 0·35 (0·18–0·68) | 0·002 |
| 4-year morphological recurrence-free survival | 78% (63–88) | 97% (90–99) | HR 0·24 (0·09–0·60) | 0·004 |
| 4-year molecular recurrence-free survival* | 70% (62–83) | 98% (91–99) | HR 0·17 (0·08–0·39) | <0·0001 |
| 4-year cumulative incidence of death in remission | 1% (0·2–8) | 2% (1–9) | HR 1·72 (0·18–16·6) | 0·64 |
| 4-year cumulative incidence of morphological relapse | 18% (10–34) | 1% (0·1–7) | HR 0·16 (0·06–0·46) | 0·0007 |
| 4-year cumulative incidence of molecular relapse* | 27% (18–45) | 0% | HR 0·12 (0·05–0·30) | <0·0001 |
| 4-year cumulative incidence of treatment-related myelodysplastic syndrome or acute myeloid leukaemia | 3% (0·4–17) | 0% | HR 0·15 (0·003–7·48) | 0·34 |

Data are n (%) or % (95% CI), unless otherwise indicated. ATRA=all-*trans* retinoic acid. OR=odds ratio. HR=hazard ratio. *In patients achieving molecular negativity.

***Table 2:*** **Clinical outcomes**

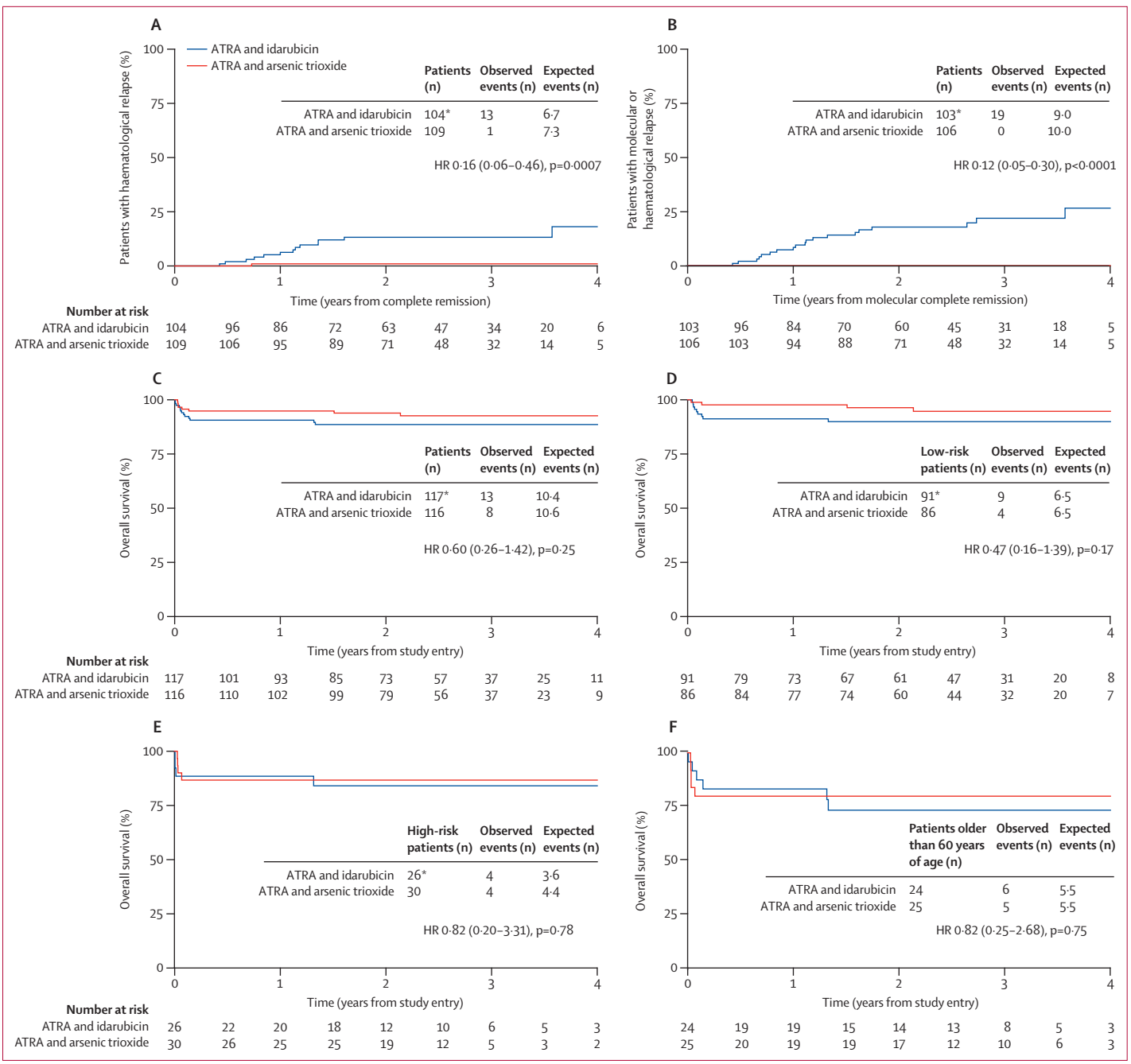


***Figure 3:*** **Clinical outcomes**

(A) Cumulative incidence of haematological relapse. (B) Cumulative incidence of molecular or haematological relapse. (C) Overall survival in the intention-to-treat population. (D) Overall survival in low-risk patients (white blood cell count 0–9·9 × $10^9$ cells per L). (E) Overall survival in high-risk patients (white blood cell count ≥10 × $10^9$ cells per L). (F) Overall survival in patients older than 60 years of age. ATRA=all-*trans* retinoic acid. *Two patients in the ATRA and idarubicin group (one high risk and one low risk) had no follow-up data available for survival or relapse.

the ATRA and arsenic trioxide group had molecularly persistent disease (associated with CNS involvement in one case) compared with one patient in the ATRA and idarubicin group. The number of patients who relapsed in the latter group was significantly higher (20 relapses across both groups [19 in the ATRA and idarubicin group *vs* one in the ATRA and arsenic trioxide group]), of which 13 were haematological and seven were molecular alone, giving a cumulative incidence of haematological relapse of 18% (95% CI 10–34) in the ATRA and idarubicin group versus 1% (0·1–7) in the ATRA and arsenic trioxide group (figure 3A). The one patient who relapsed in the ATRA and arsenic group did not become molecularly negative, thus the cumulative incidence of molecular relapse at 4 years

was 27% (95% CI 18–45) in the ATRA and idarubicin group versus 0% in the ATRA and arsenic trioxide group (figure 3B).

19 (95%) of the 20 patients who relapsed received arsenic trioxide salvage therapy; the other died before salvage treatment could be given. Of nine patients in either group treated pre-emptively for molecularly persistent disease or molecular relapse with arsenic trioxide, all achieved complete molecular remission and eight remain alive at final follow-up. Overall, nine patients in the ATRA and idarubicin group that relapsed received a transplant (six post-morphological relapse [three autografts and three allografts], five of whom were in second complete remission; and three post-molecular relapse only [two allografts and one autograft]) and the patient in the ATRA and arsenic trioxide group also received an allograft transplant but died afterwards. Eight of the nine patients in the ATRA and idarubicin group who received a transplant remain alive with median post-transplant follow-up of 7·6 months (IQR 6·2–9·7). Of the 20 patients in both groups who relapsed, two died (including the only patient in the ATRA and arsenic trioxide who relapsed, who died from an infection 78 days after receiving a sibling allograft transplant in their second remission); eight relapses occurred in 49 high-risk patients and 12 in 166 low-risk patients.

The cumulative incidence of death in remission was low overall and did not differ significantly between the groups (table 2). Event-free survival for all patients was 80% at 4 years (82% in low-risk patients and 76% in high-risk patients), and was significantly better in the ATRA and arsenic trioxide group than in the ATRA and idarubicin group (table 2). This significant benefit was apparent in low-risk patients (4-year event-free survival 92% [95% CI 84–97] in the ATRA and arsenic trioxide group *vs* 71% [55–83] in the ATRA and idarubicin group; HR 0·34 [0·15–0·75], p=0·008), but was not significant in the 57 high-risk patients (87% [68–95] *vs* 64% [42–79]; HR 0·34 [0·11–1·08], p=0·07), despite near-identical hazard ratios and no interaction with risk (p=1·0).

Overall survival at 4 years did not differ significantly between the groups (table 2, figure 3C). In low-risk patients, 4-year survival was 95% (95% CI 86–98) in the ATRA and arsenic trioxide group versus 90% (81–95) in the ATRA and idarubicin group (figure 3D) compared with 87% (68–95) versus 84% (63–94) in high-risk patients (figure 3E) with no evidence of interaction between treatment and risk group (p=0·5). Excluding early mortality in a landmark analysis of survival post day 30, overall 4-year survival was 97% (95% CI 90–99) for ATRA and arsenic trioxide (96% [87–99] in low-risk patients, 100% in high-risk patients) compared with 94% (88–97) with ATRA plus idarubicin (94% [86–97] in low-risk patients, 95% [70–99] in high-risk patients). Survival at 4 years in the 28 of 30 high-risk patients who were allocated to ATRA and arsenic trioxide and given gemtuzumab ozogamicin was 89% (95% CI 70–96). The trial included 49 patients aged older than 60 years (37 low-risk and 12 high-risk patients) whose 4-year survival did not differ significantly between the treatment groups: 80% (58–91) in the ATRA and arsenic trioxide group, compared with 74% (50–87) in the ATRA and idarubicin group (figure 3F).

Exploratory analyses showed no significant interaction between treatment and baseline features, with the exception of a suggestion of heterogeneity by *PML* breakpoint (appendix p 4).

146 serious adverse events (64 in the ATRA and arsenic trioxide group *vs* 82 in the ATRA and idarubicin group), including death (not routinely assessed for relatedness to study drug), were recorded in 99 patients (46 *vs* 53 in the two groups, respectively). During treatment courses 1–2, grade 3–4 toxicities were reported in 40 patients randomly assigned to ATRA and arsenic trioxide and in 57 randomly assigned to ATRA and idarubicin (tables 3 and 4). For treatment course 1, alopecia, gastrointestinal events, hyperbilirubinaemia, and cardiac events were more common with ATRA and idarubicin, and there was no difference in high liver alanine transaminase (ALT) levels between the two groups. Apart from alopecia, few grade 3–4 toxicities were reported in course 2 or in subsequent courses of treatment in either treatment group (table 4). After course 1 of treatment, liver grade 3–4 toxicities of ALT were more frequent in the ATRA and arsenic trioxide group than in the ATRA and idarubicin group (table 3), whereas liver grade 3–4 toxicities of aspartate aminotransferase (AST) did not differ between the groups, and grade 3–4 hyperbilirubinaemia, although rare, was significantly more frequent with idarubicin than with arsenic trioxide (table 3). Liver toxicities did not differ between the groups after treatment course 2, and they were not increased in either course in the recipients of gemtuzumab ozogamicin (grade 3–4 liver toxicity for gemtuzumab ozogamicin *vs* no gemtuzumab ozogamicin after course 1: raised ALT 26% *vs* 24%, raised AST 9% *vs* 20%, raised bilirubin 0% *vs* 1%; after course 2 raised ALT 3% *vs* 2%, and no grade 3–4 AST or bilirubin toxicities) with no evidence of additional myelosuppression. After course 2, cardiac toxicity was more common in the ATRA and arsenic trioxide group than in the ATRA and idarubicin group (p=0·001; table 4).

Dose modifications or delays to ATRA occurred in 13 patients in the ATRA and idarubicin group and in 30 patients in the ATRA and arsenic trioxide group during course 1; idarubicin was modified in six patients and arsenic trioxide in nine patients, three of whom had a prolonged QTc. In the ATRA and arsenic trioxide group, two additional patients interrupted all treatment, and one withdrew from the trial during course 1 of treatment because of fungal chest complications. During course 2, nine patients on ATRA and idarubicin had treatment modifications or delays, including one who switched to ATRA and arsenic trioxide (clinician's decision), whereas 18 patients in the ATRA and arsenic trioxide group had dose modifications or delays, including six who switched to idarubicin (clinician's decision). Two patients in the ATRA

| | ATRA and idarubicin | | | | ATRA and arsenic trioxide | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Nausea | 36/115 (31%) | 20/115 (17%) | 5/115 (4%) | 0/115 | 38/110 (35%) | 19/110 (17%) | 0/110 | 0/110 |
| Alopecia | 16/98 (16%) | 24/98 (24%) | 13/98 (13%) | 10/98 (10%) | 10/95 (11%) | 2/95 (2%) | 3/95 (3%) | 2/95 (2%) |
| Diarrhoea | 27/115 (23%) | 39/115 (34%) | 7/115 (6%) | 0/115 | 25/109 (23%) | 9/109 (8%) | 1/109 (1%) | 0/109 |
| Oral | 24/115 (21%) | 27/115 (23%) | 17/115 (15%) | 5/115 (4%) | 18/109 (17%) | 10/109 (9%) | 1/109 (1%) | 0/109 |
| Cardiac | 3/110 (3%) | 1/110 (1%) | 5/110 (5%) | 1/110 (1%) | 13/107 (12%) | 7/107 (7%) | 1/107 (1%) | 1/107 (1%) |
| Raised liver ALT | 33/108 (31%) | 17/108 (16%) | 9/108 (8%) | 2/108 (2%) | 25/109 (23%) | 25/109 (23%) | 22/109 (20%) | 5/109 (5%) |
| Raised liver AST | 5/51 (10%) | 2/51 (4%) | 2/51 (4%) | 0/51 | 8/46 (17%) | 6/46 (13%) | 2/46 (4%) | 0/46 |
| Hyperbilirubinaemia | 24/114 (21%) | 11/114 (10%) | 6/114 (5%) | 2/114 (2%) | 15/110 (14%) | 6/110 (5%) | 1/110 (1%) | 0/110 |
| Raised creatinine | 20/114 (18%) | 10/114 (9%) | 0/114 | 1/114 (1%) | 21/110 (19%) | 3/110 (3%) | 1/110 (1%) | 0/110 |
| Proteinuria | 1/87 (1%) | 3/87 (3%) | 0/87 | 1/87 (1%) | 3/82 (4%) | 1/82 (1%) | 0/82 | 0/82 |
| Haematuria | 4/90 (4%) | 4/90 (4%) | 0/90 | 1/90 (1%) | 5/82 (6%) | 2/82 (2%) | 0/82 | 0/82 |

ATRA=all-*trans* retinoic acid. ALT=alanine transaminase. AST=aspartate aminotransferase. The denominators differ for the various toxic effects because of variations in the total numbers of patients returning data for each effect.

***Table 3:*** **Incidence of non-haematological toxic effects following the first course of treatment**

| | ATRA and idarubicin | | | | ATRA and arsenic trioxide | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Nausea | 11/101 (11%) | 7/101 (7%) | 1/101 (1%) | 0/101 | 26/93 (28%) | 8/93 (9%) | 0/93 | 0/93 |
| Alopecia | 6/89 (7%) | 28/89 (31%) | 11/89 (12%) | 14/89 (16%) | 12/77 (16%) | 0/77 | 0/77 | 2/77 (3%) |
| Diarrhoea | 5/101 (5%) | 3/101 (3%) | 1/101 (1%) | 0/101 | 10/93 (11%) | 3/93 (3%) | 1/93 (1%) | 0/93 |
| Oral | 9/101 (9%) | 5/101 (5%) | 0/101 | 0/101 | 10/94 (11%) | 0/94 | 0/94 | 0/94 |
| Cardiac | 0/99 | 0/99 | 0/99 | 0/99 | 5/92 (5%) | 2/92 (2%) | 3/92 (3%) | 0/92 |
| Raised liver ALT | 5/48 (10%) | 0/48 | 0/48 | 0/48 | 6/38 (16%) | 0/38 | 0/38 | 0/38 |
| Raised liver AST | 23/98 (23%) | 10/98 (10%) | 2/98 (2%) | 0/98 | 26/93 (28%) | 9/93 (10%) | 2/93 (2%) | 0/93 |
| Hyperbilirubinaemia | 4/101 (4%) | 1/101 (1%) | 0/101 | 0/101 | 6/93 (6%) | 0/93 | 0/93 | 0/93 |
| Raised creatinine | 8/101 (8%) | 2/101 (2%) | 0/101 | 0/101 | 9/93 (10%) | 0/93 | 0/93 | 0/93 |
| Proteinuria | 0/73 | 0/73 | 0/73 | 0/73 | 3/82 (4%) | 1/82 (1%) | 0/82 | 0/82 |
| Haematuria | 0/76 | 0/76 | 0/76 | 0/76 | 1/67 (1%) | 0/67 | 0/67 | 0/67 |

ATRA=all-*trans* retinoic acid. ALT=alanine transaminase. AST=aspartate aminotransferase. The denominators differ for the various toxic effects because of variations in the total numbers of patients returning data for each effect.

***Table 4:*** **Incidence of non-haematological toxic effects following two courses of treatment**

and arsenic trioxide group were not given arsenic trioxide because of QTc prolongation. At day 60, 17 patients had died; deaths were not assessed for relatedness to treatment.

Supportive care requirements were significantly lower during the first two courses of treatment for ATRA and arsenic trioxide than for ATRA and idarubicin on all measures except for antibiotic use in course 2 (table 5). During the first two courses of treatment, compared with ATRA and idarubicin, ATRA and arsenic trioxide treatment was associated with an average of 7·4 fewer days in hospital, 4·5 fewer units of blood, 4·3 fewer units of platelets, and 10·7 fewer days of intravenous antibiotics.

## Discussion

This study found that the quality of life did not differ significantly in patients with acute promyelocytic leukaemia treated with either ATRA and arsenic trioxide or ATRA and idarubicin. This study also confirms the feasibility and benefit of ATRA and arsenic trioxide

| | ATRA and idarubicin | ATRA and arsenic trioxide | p value |
|---|---|---|---|
| **Blood, units** | | | |
| Course 1 | 9·5 (5·1) | 5·9 (5·5) | <0·0001 |
| Course 2 | 1·0 (1·7) | 0·1 (0·5) | <0·0001 |
| **Platelets, units** | | | |
| Course 1 | 12·8 (9·1) | 8·8 (10·8) | <0·0001 |
| Course 2 | 0·3 (1·0) | 0 (0) | 0·0001 |
| **Antibiotics, days** | | | |
| Course 1 | 19·2 (9·7) | 9·3 (9·4) | <0·0001 |
| Course 2 | 1·7 (4·2) | 0·9 (2·5) | 0·40 |
| **Hospital stay, days** | | | |
| Course 1 | 33·3 (9·6); 34 (29–37) | 27·3 (16·5); 25 (15–34) | <0·0001 |
| Course 2 | 7·9 (8·7); 5 (2–10) | 6·5 (9·8); 1 (0–10) | 0·01 |

Data are mean (SD) or mean (SD); median (IQR). Differences between the groups were assessed by the Wilcoxon rank-sum test. ATRA=all-*trans* retinoic acid.

***Table 5:*** **Supportive care for patients with acute promyelocytic leukaemia in the two groups during treatment courses 1 and 2**

treatment as the next stage in treatment de-escalation in low-risk patients with acute promyelocytic leukaemia, with excellent outcomes. This experience from the present AML17 study and the GIMEMA-AMLSG-SAL trial[16] emerges from 81 National Cancer Research Institute and 67 GIMEMA-AMLSG-SAL centres, and thereby endorses the widespread applicability of this approach. Here, we suggest that a similar approach is also feasible in high-risk patients, if provision is made for at least one dose of a chemotherapeutic agent during induction therapy, such as gemtuzumab ozogamicin as used in this trial, but an anthracycline might have been just as effective. Although known to be an effective agent in acute promyelocytic leukaemia, and not associated with hepatotoxicity or additional myelosuppression in this study, we cannot definitively say whether or not the single dose of gemtuzumab ozogamicin used here contributed to the notable low risk of relapse. 49 older patients entered, with encouraging 83% 4-year survival—a promising finding in view of the fact that older patients are usually more difficult to treat and have poorer survival than younger patients.

As was the case in GIMEMA-AMLSG-SAL,[16,22] we recorded little significant difference in quality of life between the groups in this trial. However, a reduced requirement for infusions would be expected to be beneficial, and the quality-of-life surveys used do not directly capture this parameter. Apart from the inclusion of high-risk patients, the AML17 trial differs in several important ways to the GIMEMA-AMLSG-SAL study. In particular, in patients in the AML17 trial, the alternative dosing schedule used meant that fewer days, and a correspondingly lower cumulative dose, of arsenic trioxide treatment were scheduled (63/168 days, compared with 140/180 days in the GIMEMA-AMLSG-SAL protocol). In AML17, treatment with ATRA and arsenic trioxide resulted in a lower incidence of hyperbilirubinaemia than treatment with ATRA and idarubicin, with little incidence and no significant differences between the treatment groups in subsequent treatment courses. Conversely, higher liver AST levels were observed in patients treated with ATRA and arsenic trioxide than in those treated with ATRA and idarubicin. Liver toxicity was not associated with gemtuzumab ozogamicin treatment. In the GIMEMA-AMLSG-SAL trial, grade 3–4 liver toxicity was recorded in 63% of patients treated with ATRA and arsenic trioxide, sometimes necessitating dose modification. Our results suggest that similarly excellent survival can be achieved with less frequent dosing, with concomitantly less liver toxicity. Cardiac toxicity during courses 1–2 of treatment was reported in 25 (22%) of 114 patients in the ATRA and arsenic trioxide group and was more frequent (11% *vs* 0%) than for ATRA and idarubicin post course 2. However, the incidence of cardiac toxicity was still less frequent than the 16% QTc prolongation reported with the more frequent arsenic trioxide dosing in GIMEMA-AMLSG-SAL. Supportive care, as measured by days in hospital and use of antibiotics, was significantly less in the ATRA and arsenic trioxide group than in the ATRA and idarubicin group for the first course of therapy. A further difference from GIMEMA-AMLSG-SAL was the elimination of maintenance therapy in AML17, because of previous concerns that it might contribute to treatment-related acute myeloid leukaemia or myelodysplastic syndrome, which has been reported as a cause of treatment failure in 1–2% of cases of acute promyelocytic leukaemia.[5] Encouragingly, we recorded only one case of treatment-related acute myeloid leukaemia in AML17 (in the idarubicin group), compared with nine cases in 285 chemotherapy-treated patients in the previous AML15 trial that included maintenance treatment.[5]

The attenuated dosing schedule used in this trial offers the obvious advantage of convenience for the patients compared with ATRA and idarubicin, but also reduces administration and acquisition costs of arsenic trioxide.

In our view, the main limitation of ATRA and idarubicin treatment has been its inability to completely eliminate early deaths, which will not appear in standard quality-of-life measures because patients will have died before their first assessment point. Although this treatment regimen showed some improvement in quality of life over the course of treatment in this trial (with quality of life in survivors improving during treatment, reaching a median of 75 points out of 100 on the global functioning scale), its inability to eliminate early deaths remains the main reason for treatment failure. Few deaths occurred beyond 30 days in either group and the landmark Kaplan-Meier survival analysis post day 30, 4-year survival was higher in the ATRA and arsenic trioxide group than in the ATRA and idarubicin group, especially in high-risk patients. The rationale to initiate arsenic trioxide at diagnosis was to reduce early fatality. Mortality at day 30 was reduced in low-risk patients from our historical rate of 5% (in AML15) to 1% for ATRA and arsenic trioxide in AML17 and seems to endorse the strategy of giving patients arsenic trioxide from the time of diagnosis rather than in consolidation, by which time the period of greatest risk has passed.[23] Although 30-day mortality was reduced in the ATRA and arsenic trioxide group compared with previous studies, this was also the case in the ATRA and idarubicin group. This finding suggests that the clear guidance given to investigators within the protocol and national and international guidelines[20,24] about early supportive care for patients with acute promyelocytic leukaemia has had an effect in recent years. However, death within 30 days remains a challenge.

These data raise some questions as to next steps that should be taken in this now highly curable disease. Acquisition costs, even for the attenuated schedule of arsenic trioxide, are clearly important, and are compounded by an absence of licensing approval for first-line treatment. The schedule for front-line therapy could possibly be attenuated further (ie, reduced treatment and reduced toxicity, which could be especially relevant in children), but attention will now move to substitution with oral

formulations, the experience of which suggests equivalence of effect[25,26] and arguably a better pharmacokinetic profile[27] with consequent potential for reduced toxicity.[28] The risk of relapse on the arsenic trioxide and ATRA schedule is low (1% in AML17 and 2·6% in GIMEMA-AMLSG-SAL) which questions whether routine molecular monitoring is needed if arsenic trioxide and ATRA is adopted as the standard of care. However, patients monitored on ATRA and idarubicin benefited from early detection and intervention to give 89% 4-year survival. A further issue is the consequences of delay in implementation of treatment,[29] which mandates prompt referral and, crucially, that relevant medication is immediately available in each treating institution.

#### Contributors

AKB designed the trial, interpreted the data, wrote the report, and coordinated the study. NHR and DB recruited patients and coordinated the study. RKH collected and analysed data and wrote the report. JK recruited patients and did the safety review. SK recruited patients and arranged analysis of arsenic trioxide levels in patient samples. YGM and JL did the molecular analyses. AG gathered data and administered the trial. GJ, AK, LF, MFMcM, AH, and REC recruited patients. DG supervised the molecular analyses. All authors reviewed the final version of the report.

#### Declaration of interests

AKB received funding from Cancer Research UK, and free drug and grants from Cephalon/Teva during the course of the study. RKH received honoraria for speaking from Teva. DG received research funding from Cephalon/Teva during the course of the study. The other authors declare no competing interests.

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