Defining the dose of gemtuzumab ozogamicin in combination with induction chemotherapy in acute myeloid leukemia: a comparison of 3 mg/m² with 6 mg/m² in the NCRI AML17 Trial

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ABSTRACT

A recent source data meta-analysis of randomized trials in adults assessing the immunoconjugate gemtuzumab ozogamicin combined with standard chemotherapy in acute myeloid leukemia showed a significant survival benefit in patients without an adverse karyotype. It is not clear whether the optimal dose should be 3 mg/m² or 6 mg/m². In this study, we randomized 788 patients to a single dose of gemtuzumab ozogamicin 3 mg/m² or 6 mg/m² with the first course of induction therapy. We found that the rate of complete remission was higher with 3 mg/m² [82% *vs.* 76%; odds ratio 1.46 (1.04-2.06); *P*=0.03], but this was balanced by a higher rate of complete remission with incomplete peripheral blood count recovery in the 6 mg/m² treatment (10% *vs.* 7%) resulting in similar overall response rate [89% *vs.* 86%; hazard ratio 1.34 (0.88-2.04); *P*=0.17]. There was no overall difference in relapse or survival at four years between the arms: 46% *vs.* 54%; hazard ratio 1.17 (0.94-1.45), *P*=0.5, and 50% *versus* 47%; hazard ratio 1.10 (0.90-1.34), *P*=0.3, respectively. The 30- and 60-day mortality was significantly higher in the 6 mg/m² recipients: 7% *versus* 3%; hazard ratio 2.07 (1.11-3.87), *P*=0.02, and 9% *versus* 5%; hazard ratio 1.99 (1.17-3.39), *P*=0.01, respectively, which in addition was associated with a higher rate of veno-occlusive disease (5.6% *vs.* 0.5%; *P*<0.0001). Our conclusion from this trial is that there is no advantage in using a single dose of 6 mg/m² of gemtuzumab ozogamicin in combination with induction chemotherapy when compared with a 3 mg/m² dose, with respect to response, disease-free and overall survival, either overall, or in any disease subgroup. (AML17 was registered as ISRCTN55675535.)

Introduction

Gemtuzumab ozogamicin (GO) was the first antibody directed chemotherapy in cancer, but has had a chequered development in acute myeloid leukemia (AML) where it has had clinical exposure in a number of settings. None of the five randomized trials in adults (involving 3325 patients) or the trial in children (n=1022)[1-6] has shown that GO improves the rate of remission. In all but one there was no excess in induction mortality, and even in the trial where this was seen, the explanation was not that the mortality in the combination arm was high, but that mortality in

the control arm was unusually low.[3] Five of the six trials showed a significant reduction in relapse risk. No trial showed a benefit for patients with adverse cytogenetics. An up-dated individual patient data-based meta-analysis of the adult patients confirmed that there was an overall survival benefit due to the reduction in relapse risk.[7] Similar data have since emerged in children.[6] In these trials, the dose and schedule of GO differed, being 6 mg/m^2 on day 4 in two trials,[3,5] 3 mg/m^2 on day 1 in two trials,[1,4] and a fractionated schedule of 3 mg/m^2 (to a maximum dose of 5 mg per dose) on days 1, 4 and 7.[2] The latter schedule was derived from an encouraging study in relapsed disease.[8] The meta-analysis further suggested that a single dose of 3 mg/m^2 was as effective at preventing relapse as a 6 mg/m^2 dose, while having less toxicity, and, therefore, may be the optimal dose, with the question of dose frequency remaining to be confirmed.

The majority of patients in these studies received 3 mg/m^2 as a single dose which was given on day 1 of course 1. This was based on a pilot study which suggested that toxicity was minimal and efficacy was encouraging at this dose,[9] in contrast to the experience of combining the licensed dose of 9 mg/m^2 with chemotherapy.[10] This assumption turned out to be the case in our large multicenter setting trial.[1] Since the toxicity found in the 3 mg/m^2 single dose experience was modest, we postulated that there was a rationale to compare the higher dose (6 mg/m^2) with the 3 mg/m^2 dose in the hope that efficacy could be increased, particularly in patients with adverse risk cytogenetics. Therefore, as part of the UK NCRI AML17 trial, we prospectively compared two doses of GO, 3 mg/m^2 *versus* 6 mg/m^2, to be given on day 1 of the first course of induction treatment.

Methods

The NCRI AML17 trial (ISRCTN55675535) was open to patients (the majority under 60 years of age, and also including children) who had any form of *de novo* or secondary AML and high-risk MDS (defined as marrow blasts >10%). Acute promyelocytic leukemia was excluded. As induction treatment, 759 adult patients were randomized between DA (3+10) (n=380) or ADE (10+3+5) (n=379) (Figures 1 and 2); 29 children (patients <16 years) received only ADE. GO was administered on day 1 of the induction chemotherapy except when the white blood cell (WBC) count was more than 30x10^9/L when cyto-reduction treatment with hydroxyurea could be given to reduce the count to less than 30x10^9/L, or the GO delayed until day 4 of chemotherapy. Liver function biochemistry was required to be less than 2 x ULN (upper limit of normal). Toxicity was defined as in NCI CTCAE v.3.0. Veno-occlusive disease (VOD) of the liver was defined by published criteria.[11] After the first induction course, patients with a FLT-3 mutation were eligible to enter a randomization to receive the experimental *FLT3* inhibitor lestaurtinib or placebo in a 2:1 ratio after each course of chemotherapy. For other patients who completed the first induction course, a previously reported validated score was used to assess the risk of relapse.[12] Factors used were age, presenting WBC count, secondary disease, cytogenetics and the morphological response of the bone marrow (% blasts) after the first course. Patients with good or standard risk disease received the second daunorubicin/cytosine arabinoside course (with or without etoposide), and were then randomized to receive either one or two courses of high-dose cytosine arabinoside or MACE/MidAC as consolidation (Figure 1). High-risk patients were allocated to a randomization between FLAG-Ida (fludarabine/ara-C/G-CSF/idarubicin) or daunorubicin/clofarabine for up to three courses with the intention to undergo allogeneic trans-

Table 1. Patients' characteristics.

Characteristic	GO 6 mg/m^2 (n=395)	GO 3 mg/m^2 (n=393)
Chemotherapy		
ADE	205	203
DA	190	190
Age		
0-15	15	14
16-29	50	51
30-39	40	41
40-49	86	86
50-59	149	148
60+	55	53
Median	50	50
Range	0-81	0-81
Sex		
Female	190	178
Male	205	215
Diagnosis		
De novo	336	337
Secondary	37	36
MDS	22	20
WHO PS		
0	279	280
1	91	91
2	11	8
3	4	4
4	0	1
Not reported*	10	9
WBC		
0-9.9	215	196
10-49.9	126	126
50-99.9	25	39
100+	29	32
Median	8.8	10.0
Range	0.4-386.5	0.5-291.8
Cytogenetics		
Favorable	44	52
Intermediate	272	249
Adverse	60	73
Unknown	19	19
FLT3 ITD		
WT	304	321
Mutant	77	57
Unknown	14	15
NPM1c		
WT	267	271
Mutant	107	102
Unknown	21	20
ITD/NPM1c		
ITD WT, NPM1c WT	233	244
ITD WT, NPM1c Mutant	66	73
ITD Mutant, NPM1c WT	34	27
ITD Mutant, NPM1c Mutant	41	29
Unknown	21	20
Post course 1 risk score		
Good risk	62	77
Standard risk	180	165
Poor risk	115	132
Not assessable**	38	19

*Children under the age of 10 completed the WHO play performance score. **Post course 1 validated risk score[12] is not available for patients who suffer induction death, have missing cytogenetics or in whom a response to course 1 is not available.*

plantation. Patients who were not good risk, not FLT3 positive or adverse risk progressed with the core chemotherapy, but could be randomized or not to the mTOR inhibitor, everolimus, which was given between chemotherapy courses. The results of these randomizations will be reported elsewhere, but are taken into account when assessing the GO dose question in this trial.

Diagnosis was confirmed locally and immunophenotyping and cytogenetics (20 metaphases) were performed in regional accredited laboratories and classified as previously published.[13] Molecular characterization was undertaken in two reference labs. Supportive care was determined by the policy of each center. Stem cell transplantation was undertaken in regional transplant centers.

The trial was sponsored by Cardiff University and approved by Wales Research Ethics Committee 3 on behalf of all UK investigators, by the Danish Medicines Agency for sites in Denmark, and by MEDSAFE for sites in New Zealand. The trial was conducted in accordance with the Declaration of Helsinki, and received research funding from Cancer Research UK. GO was provided by Pfizer Inc. who had no role in the design or management of the trial.

Statistical analysis

Response end point definitions are as described by Cheson.[14] All analyses are by intention-to-treat. Categorical end points [e.g. complete remission (CR) rates] were compared using Mantel-Haenszel tests, to give Peto odds ratios and confidence intervals. Continuous/scale variables were analyzed by non-parametric (Wilcoxon rank sum) tests. Time-to-event outcomes were analyzed using the log rank test, with Kaplan-Meier survival curves. Odds/hazard ratios (OR/HR) less than 1 indicate benefit for the investigational therapy GO 6 mg/m^2 *versus* GO 3 mg/m^2. All survival percentages are at four years unless otherwise stated.

In addition to overall analyses, exploratory analyses were performed stratified by the randomization stratification parameters and other important variables, with suitable tests for interaction. Because of the well-known dangers of subgroup analysis, these were interpreted with caution.

The randomization was originally planned to run over the course of the entire AML17 trial (5 years recruitment); however, the supply of GO enabled 788 patients to be randomized. This gave 80% power to detect a 10% absolute improvement in survival at five years from 45% to 55%, requiring 382 events.

Follow up is complete as at 1st March 2015, with a median follow up for survival of 50 months (range 26.8-67.8 months) and 386 events.

Results

Between June 2009 and October 2011 788 patients were randomized: their median age was 50 years (range 0-81 years, with 29 aged <16 years). Eighty-five percent had *de novo* AML, 9% secondary AML and 5% high-risk MDS; 53% were male. Thirteen percent were favorable, 69% intermediate, and 18% adverse cytogenetic risk; the median presenting WBC was 9.2 (0.4-386.5); 18% had a *FLT3 ITD* and 28% had an NPM1c mutation (Table 1). Four hundred and eight patients received ADE (including all 29 children recruited who were allocated ADE therapy) and 380 received DA (Figure 2) as induction treatment.

Remission induction

Eighty-seven percent of all patients entered CR/CRi (79% CR, 8% complete remission with incomplete blood count (CRi)]. CR rates were higher in the GO 3 mg/m^2 arm [82% *vs.* 76%, OR 1.46 (1.04-2.06); *P*=0.03], but this was balanced by more CRi with 6 mg/m^2 (7% *vs.* 10%), leading to no significant difference in overall response rate (ORR) [9% *vs.* 86%; OR 1.34 (0.88-2.04); *P*=0.17] (Table 2).

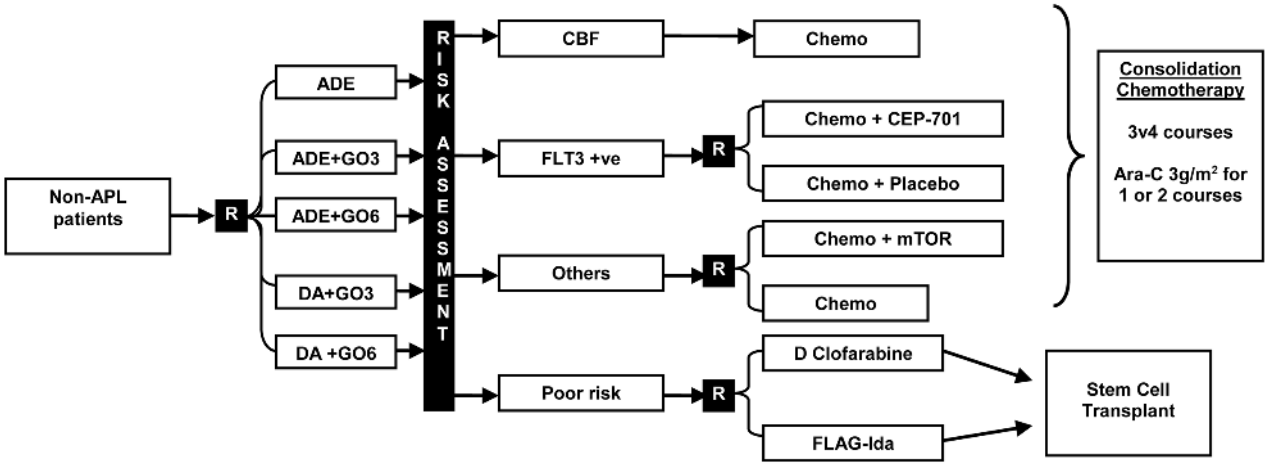

Figure 1. Trial design of AML17. ADE: course 1, daunorubicin 50 mg/m^2 d 1,3,5; ara-C 100 mg/m^2 every 12 hours d 1-10, etoposide 100 mg/m^2 d1-5; course 2, daunorubicin 50 mg/m^2 d 1,3,5; ara-C 100 mg/m^2 every 12 hours d 1-8, etoposide 100 mg/m^2 d1-5; DA (no children): course 1 daunorubicin 50 mg/m^2 d 1,3,5; ara-C 100 mg/m^2 every 12 hours d 1-10, course 2 daunorubicin 50 mg/m^2 d 1,3,5; ara-C 100 mg/m^2 every 12 hours d 1-8; GO3: gemtuzumab ozogamicin 3 mg/m^2 given on day 1 of course 1 of chemotherapy; GO6: gemtuzumab ozogamicin 6 mg/m^2 given on day 1 of course 1 of chemotherapy; Lestaurtinib: lestaurtinib (CEP-701) 40-80 mg bd (depending on azole antifungals) from 2 days post chemo to 2 days pre subsequent course, up to a maximum of 28 days; mTOR (everolimus, available post October 2009): everolimus 5-10 mg/day, from 2 days post chemo to 2 days pre subsequent course, up to a maximum of 28 days; D Clofarabine (available post November 2009): daunorubicin 50 mg/m^2 d 1,3,5; clofarabine 20 mg/m^2 d 1-5; FLAG-Ida: fludarabine 30 mg/m^2 (d 2-6); ara-C 2 g/m^2 (4 h post fludarabine), d 2-6; G-CSF 263 g s.c. d 1-7; ara-C (post July 2010): ara-C 3 g/m^2 12-hourly, d 1, 3, 5. Patients allocated either CEP-701 or everolimus post course 1 carried this allocation forward into subsequent courses. * Prior to July 2010 patients in the 3 *versus* 4 course randomization were randomized between MACE (amsacrine 100 mg/m^2 d 1-5, ara-C 200 mg/m^2 d 1-5, etoposide 100mg/m^2 d 1-5) and MACE/MidAC (course 3 as above, MidAC: mitoxantrone 10 mg/m^2 d1-5; ara-C 1 g/m^2 twice daily d 1-3).

There was no significant difference in remission rates achieved with the first induction course between the arms.

Toxicity and supportive care

The 30-day mortality [3% *vs.* 7%; OR 2.07 (1.11-3.87); *P*=0.02] and 60-day mortality [5% *vs.* 9%; OR 1.99 (1.17-3.39); *P*=0.01] were both significantly increased in the 6 mg/m^2 arm (Table 2). There were 18 *versus* 36 deaths within 60 days: the causes of which were infection (10 *vs.* 11); infection+hemorrhage (0 *vs.* 1); hemorrhage (3 *vs.* 4); resistant disease (2 *vs.* 6); veno-occlusive disease (0 *vs.* 5); cardiac (1 *vs.* 3); pulmonary (2 *vs.* 1); renal (0 *vs.* 3); or multiple causes (0 *vs.* 2). Survival beyond 60 days was the same in both arms [53% *vs.* 52%, HR 1.00 (0.81-1.24); *P*=1.0]. When grade 3 or 4 toxicities were compared

Table 2. Trial outcomes and results of dose comparisons.

	GO 6 mg/m^2	GO 3 mg/m^2	OR/HR & CI	*P*
CR	76%	82%	1.46 (1.04-2.06)	0.03
CRi	10%	7%		
CR/CRi	86%	89%	1.34 (0.88-2.04)	0.17
Induction death	7%	3%		
Resistant disease	7%	8%		
CR/CRi post course 1	73%	78%	1.29 (0.93-1.78)	0.13
30-day mortality	7%	3%	2.07 (1.11-3.87)	0.02
60-day mortality	9%	5%	1.99 (1.17-3.39)	0.01
4 year OS	47%	50%	1.10 (0.90-1.34)	0.3
4 year RFS	38%	44%	1.11 (0.91-1.35)	0.3
4 year cumulative incidence of relapse	54%	46%	1.17 (0.94-1.45)	0.15
4 year cumulative incidence of death in CR	9%	10%	0.83 (0.51-1.36)	0.5
4 year OS from CR	53%	56%	1.07 (0.85-1.35)	0.6
4 year OS censored at SCT	53%	60%	1.20 (0.93-1.54)	0.16

OR: odds ratio; HR: hazard ratio; CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete blood count; OS: overall survival; RFS: relapse-free survival; SCT: stem cell transplantation.

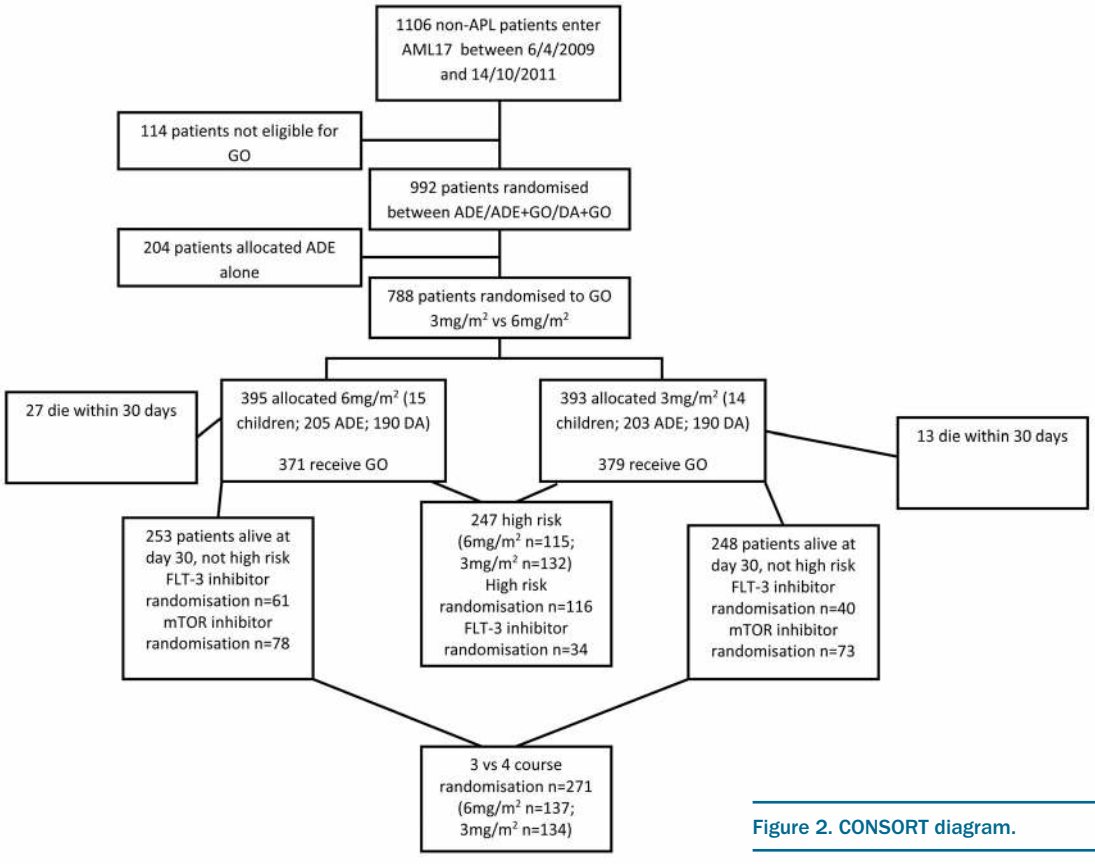

Figure 2. CONSORT diagram.

between the 3 mg/m^2 and 6 mg/m^2 doses, alanine transaminase (ALT), creatinine and hematuria in course 1 (7% *vs.* 17%; 1% *vs.* 2%; 1% *vs.* 2%, respectively) were the only significant differences during courses 1 and 2 (Figure 3). Although the kinetics of peripheral blood recovery were similar, with the exception of slower platelet recovery, there was increased platelet transfusion requirement and increased days on antibiotics during course 1 in the 6 mg/m^2 arm, but there were no differences after course 2 (*Online Supplementary Table S1*). Central assessment of VOD was confirmed as definite (n=17) or possible (n=5) in 22 of 395 (5.6%) patients on 6 mg/m^2 compared with 2 definite and 0 possible in 2 of 393 on the 3 mg/m^2 arm (0.5%) (P<0.0001).

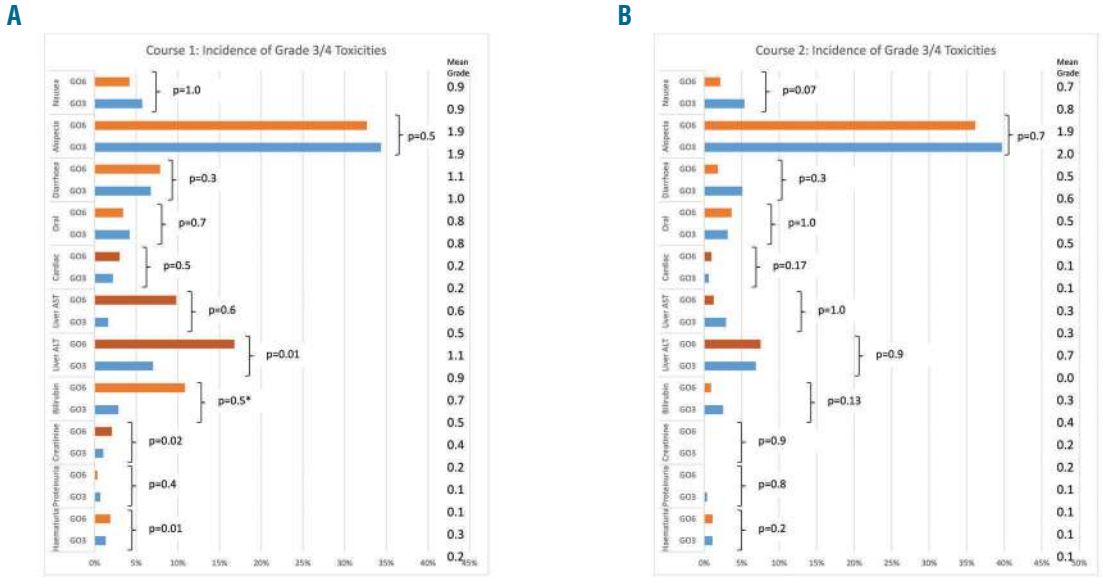

Figure 3. Grade 3-4 toxicities following (A) **course 1,** (B) **course 2.**

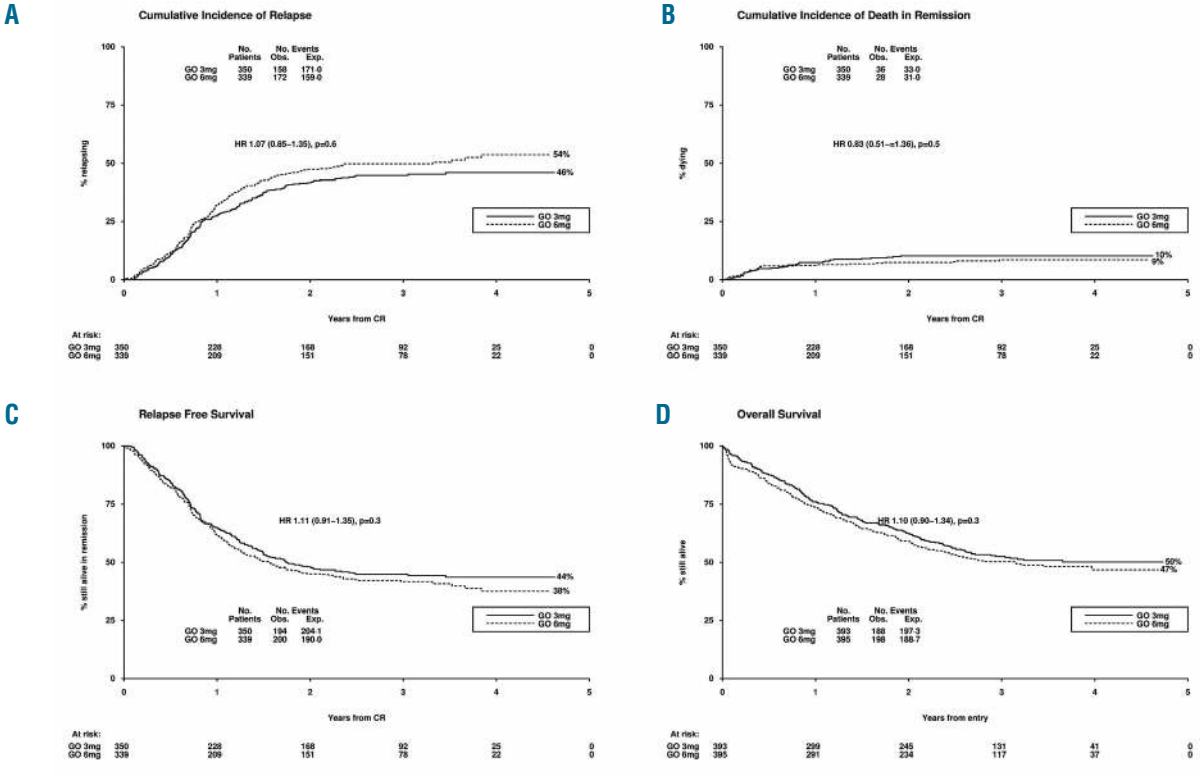

Figure 4. Outcomes for gemtuzumab ozogamicin dose randomization: (A) cumulative incidence of relapse; (B) cumulative incidence of death in remission; (C) relapse-free survival; (D) overall survival.

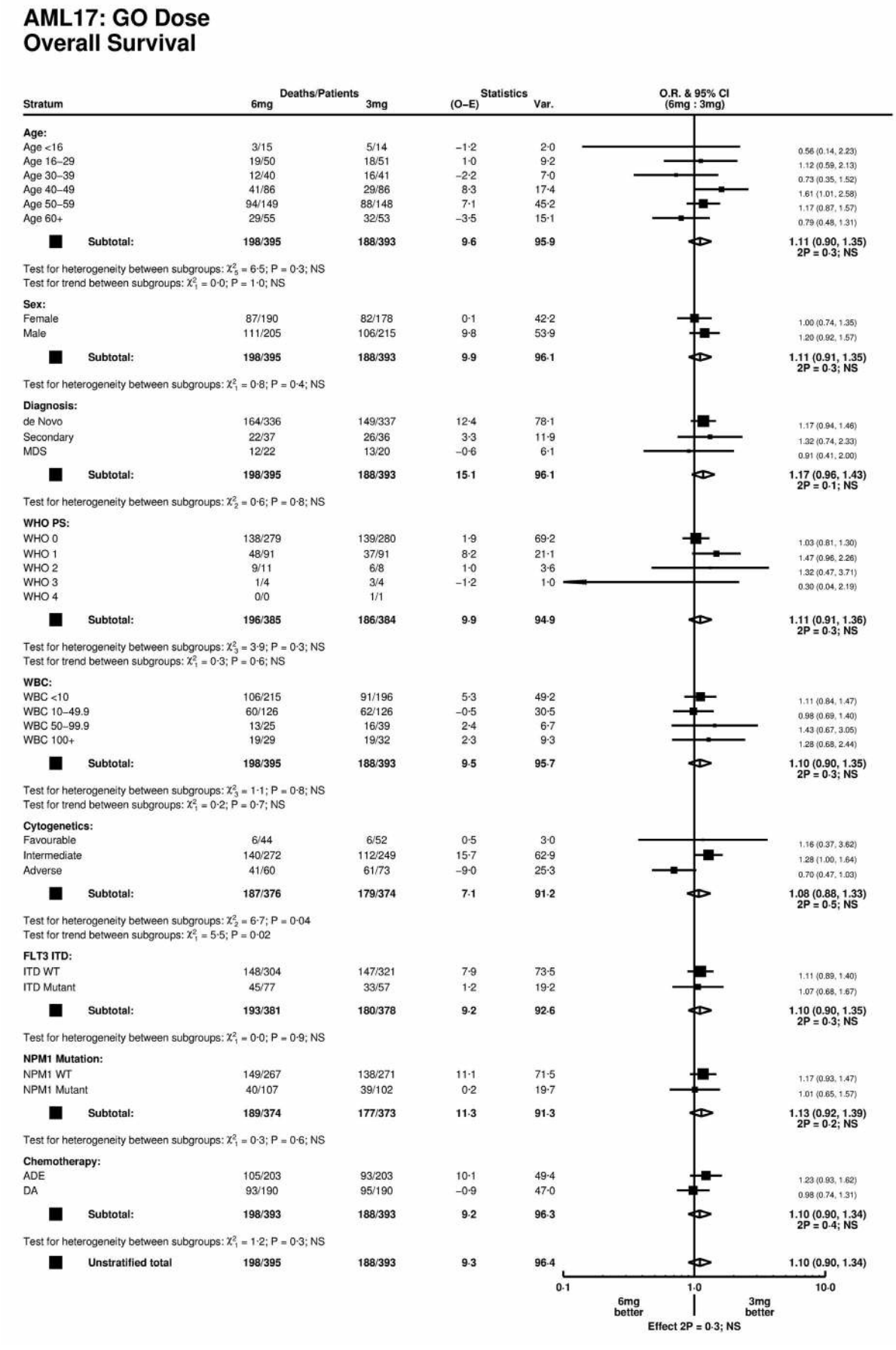

Figure 5. Stratified analysis of survival.

Relapse and survival

There was no significant difference in relapse [46% *vs.* 54%, HR 1.17 (0.94-1.45), *P*=0.15] or death in remission [(10% *vs.* 9%, HR 0.83 (0.51-1.36) *P*=0.5)] leading to no significant differences in relapse-free survival which was 41% overall [44% *vs.* 38%; HR 1.11 (0.91-1.35); *P*=0.3] (Table 2 and Figure 4). Four-year overall survival was 49% [50% *vs.* 47%; HR 1.10 (0.90-1.34); *P*=0.3] (Table 2 and Figure 4D). There was no difference in mortality after day 60. A total of 329 patients received transplant; of the 273 allografts, 158 were performed in first remission. The distribution of transplants was similar between the arms, and censoring survival at stem cell transplant did not alter the overall treatment effect. Neither the 3 mg/m^2 or the 6 mg/m^2 dose caused excessive post-transplant toxicity; in particular no liver toxicity was observed.

Exploration of subgroups

No subgroup showed any suggestion of a significant response or survival benefit from the 6 mg/m^2 dose, but there was a trend for benefit for both response rate (test for heterogeneity *P*=0.02) (*Online Supplementary Figure S1*) and overall survival (test for heterogeneity *P*=0.04) (Figure 5) in the adverse cytogenetics patients (n=133).

Discussion

In the early studies of GO, it was observed that there was an association with the then licensed dose (9 mg/m^2) and liver toxicity if combined with chemotherapy or stem cell transplant.[15] The risk was related to the time interval to or from transplant.[16] The pathological diagnosis was referred to as sinusoidal obstructive syndrome (SOS) and thought likely to be caused by cytotoxicity to leukemia cells which had accumulated in the liver sinusoids.[11] However, the concept of augmenting treatment with targeted chemotherapy remained attractive, but establishing the dose which could safely be combined with standard intensive chemotherapy required a dose-finding trial. To do this, we tested the DAT chemotherapy schedule (daunorubicin, Ara-C, thioguanine). It emerged that the observed liver toxicity was associated with the use of thioguanine, which, somewhat fortunately, became unavailable.[9] Since the efficacy in that pilot study was encouraging at the 3 mg/m^2 dose, this was adopted as the study dose for the subsequent large trials conducted by our group.

Since minimal toxicity was seen, the question remained as to whether we were under-dosing at this level, even although the dose was effective in patients who did not have adverse risk disease. Subsequently a 6 mg/m^2 was adopted by others,[3,5] so we thought it relevant to examine this dose to better define the dose level required. In this large randomized study we saw no significant benefit of using GO at the 6 mg/m^2 dose, although there was a possible trend for benefit in the adverse risk patients who have not been shown to benefit from GO irrespective of dose or schedule in other trials. The 6 mg/m^2 dose did have a detrimental effect with respect to liver toxicity and platelet count recovery, and significantly increased the day 30 and 60 mortality; this suggests that in cases in which a single dose schedule is used, the 3 mg/m^2 dose is adequate.

The remaining issue is whether a single dose is inferior to the fractionated dosing schedule developed by the French group. The rationale for this approach is that, following exposure to antibody, there is re-expression of CD33 within hours, and, therefore, it is logical to expect a repeated challenge.[17] This was endorsed by the initial study in relapsed disease[8] where 57 patients were treated with the 1-, 4- and 7-day schedule and achieved an overall response rate of 33% [26% CR and 7% complete remission with incomplete platelet recovery (CRp)] with minimal toxicity.

The French ALFA group took this forward to front-line treatment in a randomized study involving 280 non-favorable risk patients who were randomized to receive the addition of GO in a dose of 3 mg/m^2 in a day 1, 4 and 7 schedule with the first induction course, followed by a single dose each of two post induction courses. This produced a very encouraging initial report with a significant survival benefit,[2] but one that longer follow up has shown to be a little less clear.[18] However, in that study, each dose was capped at 5 mg and the schedule given was on day 1, 4 and 7, and also as a single dose in consolidation. It is plausible that at least some of the benefit was due to dosing in consolidation. There was some hematologic toxicity, particularly to platelets. So while a 3 mg/m^2 dose appears adequate, an optimal schedule still has to be defined. However, the MRC AML15 trial did not show any additional benefit of adding GO to consolidation irrespective of whether it had been given with the first induction course,[1] so the pressing issue to be resolved is whether the single or fractionated schedule is to become the standard approach. To resolve this, we have initiated a direct comparison of a 3 mg/m^2 dose on day 1 *versus* days 1 and 4 in our ongoing trials (registered as ISRCTN31682779 and ISRCTN78449203).

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References

1. Burnett AK, Hills RK, Milligan D, et al. Identification of patients with Acute Myeloblastic Leukemia who benefit from the addition of Gemtuzumab Ozogamicin: Results of the MRC AML15 Trial. J Clin Oncol. 2011;29(4):369-377.
2. Castaigne S, Pautas C, Terre C, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. Lancet. 2012; 379(9825):1508-1516.
3. Petersdorf SH, Kopecky KJ, Slovak M, et al. A phase 3 study of gemtuzumab ozogamicin during induction and postconsolidation therapy in younger patients with acute myeloid leukemia. Blood. 2013; 121(24):4854-4860.
4. Burnett AK, Russell NH, Hills RK, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy improves survival in older patients with acute myeloid leukemia. J Clin Oncol. 2012;30(32):3924-3931.
5. Delaunay J, Recher C, Pigneux A, et al. Addition of Gentuzumab ozogamycin to chemotherapy improves event-free surivval

but not overall survival of AML patients with intermediate cytogenetics not eligible for allogeneic transplantation. Results of the GOELAMS AML2006 IR study. Blood. 2011;118:79(Abstract).
6. Gamis AS, Alonzo TA, Meshinchi S, st al. Gemtuzumab ozogamicin in children and adolescents with de novo acute myeloid leukemia improves event-free survival by reducing relapse risk: results from the randomized phase III Children's Oncology Group trial AAML0531. J Clin Oncol 2014: 32(27):3021-3032.
7. Hills RK, Castaigne S, Appelbaum FR, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. Lancet Oncol. 2014;15(9):986-996.
8. Taskin AL, Legrand O, Raffoux E, et al. High efficacy and safety profile of fractionated doses of Mylotarg as induction therapy in patients with relapsed acute myeloblastic leukemia: a prospective study of the alfa group. Leukemia. 2007;21(1):66-71.
9. Kell WJ, Burnett AK, Chopra R, et al. A feasibility study of simultaneous administration of gemtuzumab ozogamicin with intensive chemotherapy in induction and consolidation in younger patients with acute myeloid leukemia. Blood. 2003; 102:4277-4283.
10. Giles FJ, Kantarjian HM, Kornblau SM, et al. Mylotarg (gemtuzumab ozogamicin) therapy is associated with hepatic venoocclusive disease in patients who have not received stem cell transplantation. Cancer. 2001;92(2):406-413.
11. Rajvanshi P, Schulman HM, Sievers EL, McDonald GB. Hepatic sinusoidal Obstruction after Gemtuzumab Ozogamicin (mylotatg) therapy. Blood. 2002;99(7):2310-2314.
12. Burnett AK, Hills RK, Wheatley K, et al. A sensitive risk score for directing treatment in younger patients with AML. Blood. 2006;108(11):10a.
13. Grimwade D, Hills RK, Moorman AV, et al. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. Blood. 2010;116(3):354-365.
14. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendation of the International Working Group for diagnosis standardisation, of response criteria treatment outcomes and reporting standards for therapeutic trials in acute myeloid leukaemia. J Clin Oncol. 2003;21(24):4642-4649.
15. Larson RA, Sievers EL, Stadtmauer EA, et al. Final report of the efficacy and safety of gemtuzumab ozogamicin (Mylotarg) in patients with CD33-positive acute myeloid leukemia in first recurrence. Cancer. 2001; 104(7):1442-1452.
16. Wadleigh M, Richardson PG, Zahrieh D, et al. Prior gemtuzamab ozogamicin exposure significantly increases the risk of veno-occlusive disease in patients who undergo myeloablative allogeneic stem cell transplantation. Blood. 2003;102(5):1578-1582.
17. van Der Velden VH, te Marvelde JG, Hoogeveen PG, et al. Targeting of the CD33-calicheamicin immunoconjugate Mylotarg (CMA-676) in acute myeloid leukemia: in vivo and in vitro saturation and internalization by leukemic and normal myeloid cells. Blood. 2001; 97(10):3197-3204.