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ORIGINAL REPORT

Optimization of Chemotherapy for Younger Patients With Acute Myeloid Leukemia: Results of the Medical Research Council AML15 Trial

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ABSTRACT

Purpose
Treatment outcomes in younger patients with acute myeloid leukemia (AML) have improved, but optimization and new combinations are needed. We assess three combinations in induction and consolidation.

Patients and Methods
Younger untreated patients with AML (median age, 49 years; range, 0 to 73 years) were randomly allocated to two induction courses of daunorubicin and cytarabine (DA) with or without etoposide (ADE; n = 1983) or ADE versus fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-Ida; n = 1268), and to amsacrine, cytarabine, etoposide, and then mitoxantrone/cytarabine (MACE-MidAC) or high-dose cytarabine (n = 1,445) 3 g/m^2 or 1.5 g/m^2 (n = 657) in consolidation, and finally to a fifth course (cytarabine) or not (n = 227).

Results
Overall remission rates were similar for DA versus ADE (84% *v* 86%; *P* = .14) and ADE versus FLAG-Ida (86% *v* 85%; *P* = .7), with more course 1 remissions after FLAG-Ida (77%) reducing relapse (38% *v* 55%; *P* < .001) and improving relapse-free survival (45% *v* 34%; *P* = .01), overall and in subgroups, but with increased myelosuppression, reducing participation in the consolidation randomization. Overall outcomes were similar between MACE/MidAc and high-dose cytarabine (1.5/3.0 g/m^2), but cytarabine required less supportive care. MACE/MidAc was superior for high-risk patients. A fifth course provided no benefit. The outcome for recipients of only two FLAG-Ida courses were not different from that with DA/ADE with consolidation.

Conclusion
FLAG-Ida is an effective remission induction treatment, with a high complete remission rate after course 1 and reduced relapse. Consolidation with MACE/MidAc is similar overall to high-dose cytarabine, but superior in high-risk patients. Cytarabine at 1.5 g/m^2 is equivalent to a 3 g/m^2 dose. A fifth course is unnecessary. In patients receiving FLAG-Ida (two courses) and cytarabine (two courses), 8-year survival was 63% for patients with intermediate-risk and 95% for those with favorable-risk disease.

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INTRODUCTION

Although we, and others, frequently report that outcomes for younger patients with acute myeloid leukemia (AML) have improved in the last two decades,[1-5] much of this could be explained by optimization of supportive care. Several schedules deliver broadly similar outcomes, albeit with differences in the details and duration of therapy and supportive care requirements. Standard of care in induction is the combination of an anthracycline with cytarabine. We have adopted for induction daunorubicin 50 mg/m^2 for 3 days and cytarabine 100 mg/m^2 administered via intravenous (IV) bolus twice daily for 10 days and an identical second course except with cytarabine given for 8 days, to which a third drug may be added. All combinations deliver remission rates in excess of 80%, so any superior combination would require a better quality of remission, reflected in a reduced relapse rate. The aim in AML15 was to compare cytarabine, daunorubicin, and etoposide (ADE) with daunorubicin and cytarabine (DA) and fludarabine, cytarabine, granulocyte colony-stimulating factor (G-CSF), and idarubicin (FLAG-Ida), each of which could be combined with the immunoconjugate, gemtuzumab ozogamicin (GO). FLAG-Ida is effective when used in relapse,[6,7] and a single unrandomized report in

untreated patients showed an encouraging remission rate,[8] but there has been no randomized assessment in untreated patients.

Previous Medical Research Council (MRC) trials used amsacrine, cytarabine, and etoposide (MACE) followed by mitoxantrone and cytarabine (MidAC) as consolidation. Here we compared it with high-dose cytarabine (3 g/m^2), which represents the international standard. There has been little exploration of cytarabine dose for consolidation, so we compared the 3 g/m^2 dose with 1.5 g/m^2. Finally,

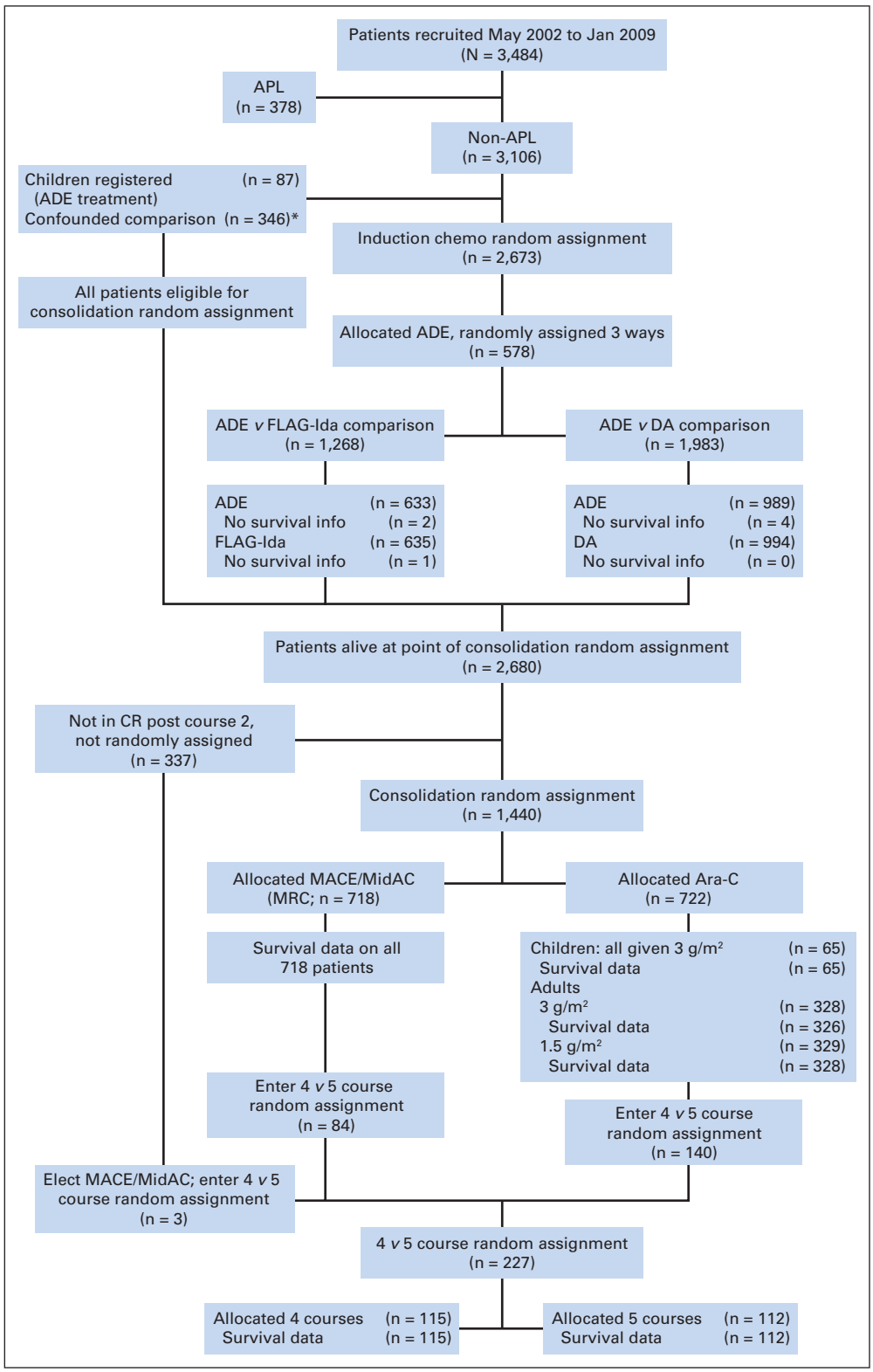

Fig 1. CONSORT diagram. (*) Patients allocated to daunorubicin and cytarabine (Ara-C; DA) plus gemtuzumab ozogamicin (GO) or fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-Ida) plus GO before the opening of the daunorubicin, cytarabine, and etoposide (ADE) plus GO arm in 2005 are excluded because the comparison with ADE would be confounded by GO. APL, acute promyelocytic leukemia; chemo, chemotherapy; CR, complete remission; MACE, amsacrine, cytarabine, and etoposide; MidAC, mitoxantrone and cytarabine; MRC, Medical Research Council.

Table 1. Treatment Schedules for AML15 and Protocol Amendments

Treatment	Details	Changes/Comments
DA 3 + 10	Daunorubicin 50 mg/m^2 days 1, 3, 5; cytarabine 100 mg/m^2 days 1-10 every 12 hours	DA regimen in adults only; pediatric patients from June 2004 (ADE *v* FLAG-Ida)
DA 3 + 8	Daunorubicin 50 mg/m^2 days 1, 3, 5; cytarabine 100 mg/m^2 days 1-8 every 12 hours	
ADE 10 + 3 + 5	Daunorubicin 50 mg/m^2 days 1, 3, 5; cytarabine 100 mg/m^2 days 1-10 every 12 hours; etoposide 100 mg/m^2 days 1-5	
ADE 8 + 3 + 5	Daunorubicin 50 mg/m^2 days 1, 3, 5; cytarabine 100 mg/m^2 days 1-8 every 12 hours; etoposide 100 mg/m^2 days 1-5	
Mylotarg	Gemtuzumab ozogamicin 3 mg/m^2 day 1	Mylotarg + ADE opened June 2005; Mylotarg randomization closed June 2006
MACE	Amsacrine 100 mg/m^2 days 1-5; cytarabine 200 mg/m^2 continuous days 1-5; etoposide 100 mg/m^2 days 1-5	
MidAC	Mitoxantrone 10 mg/m^2 daily by slow IV push on days 1-5 inclusive (5 doses), cytarabine 1.0 g/m^2 12-hourly by 2-hour IV infusion on days 1-3 inclusive (6 doses)	
FLAG-Ida	Fludarabine 30 mg/m^2 IV days 2-6 inclusive, cytarabine 2 g/m^2 over 4 hours starting 4 hours after fludarabine on days 2-6, G-CSF (lenograstim 263 μg [1 vial]) SC daily days 1-7; idarubicin 8 mg/m^2 IV daily on days 4-6	FLAG-Ida randomization closed May 2007
Cytarabine (1.5 g/m^2)	Cytarabine 1.5 g/m^2 given IV over 4 hours 12 hourly on days 1, 3, 5 (6 doses)	C3,4: not in children (MACE-MidAC *v* cytarabine 3 g/m^2) 5 courses not recommended over age 45 years January 2005
Cytarabine (3.0 g/m^2)	Cytarabine 3.0 g/m^2 given IV over 4 hours 12 hourly on days 1, 3, 5 (6 doses)	

Abbreviations: G-CSF, granulocyte colony-stimulating factor; IV, intravenous; SC, subcutaneous.

we have continuously tried to establish the optimum total number of courses required, so we compared the value of adding, or not, a fifth course (high-dose cytarabine).

PATIENTS AND METHODS

The trial recruited from May 2002 to January 2009. The idarubicin dose was initially 10 mg/m^2 but was reduced to 8 mg/m^2 after 20 patients as a result of prolonged thrombocytopenia after course 2, which to some extent ameliorated the problem, which was unrelated to GO. A CONSORT diagram is shown in Figure 1, and Table 1 and Figure 2 show treatment schedules and protocol amendments. All randomizations were in a one-to-one ratio. Those allocated to cytarabine were further randomly assigned one to one to 3 g/m^2 versus 1.5 g/m^2. The trial was open to any patient with de novo or secondary AML (defined as secondary to previous chemotherapy/radiotherapy or a prior hematologic disorder, including myelodysplastic syndrome [MDS]). Patients in blast transformation of chronic myeloid leukemia, pregnant or lactating, or who had other concurrent active malignancy or received prior cytotoxic therapy for leukemia were excluded. Hydroxycarbamide was permitted for up to 7 days before treatment initiation. Written consent was required for each randomization. Patients treated at pediatric centers entered a limited number of randomizations (from June 2004, ADE *v* FLAG-Ida in induction and MACE-MidAC *v* cytarabine 3 g/m^2 and four *v* five courses in consolidation). Patients in the DA or FLAG-Ida arms could be randomly assigned to a single dose of GO (3 mg/m^2) in induction course 1. In June 2005 this was extended to the ADE arm. The GO randomization was completed in June 2006, and the results have been published.[9] The four versus five courses randomization was modified in January 2005, limiting it to patients younger than 45 years because data from our previous AML12 trial indicated that a fifth course was detrimental in older patients. Stem-cell transplantation was permitted for patients with intermediate- or poor-risk disease with a recommendation that myeloablative conditioning was used for patients younger than 35 years and reduced intensity conditioning in patients more than 45 years with investigator/patient choice in the intermediate age group. The trial was approved by the Wales Multicentre Research Ethics Committee and each institution's ethical committee in accordance with the Declaration of Helsinki.

Cytogenetics were carried out in accredited regional laboratories and reports reviewed centrally; molecular analysis was carried out in two reference labs. Patients were designated as having favorable, intermediate, or

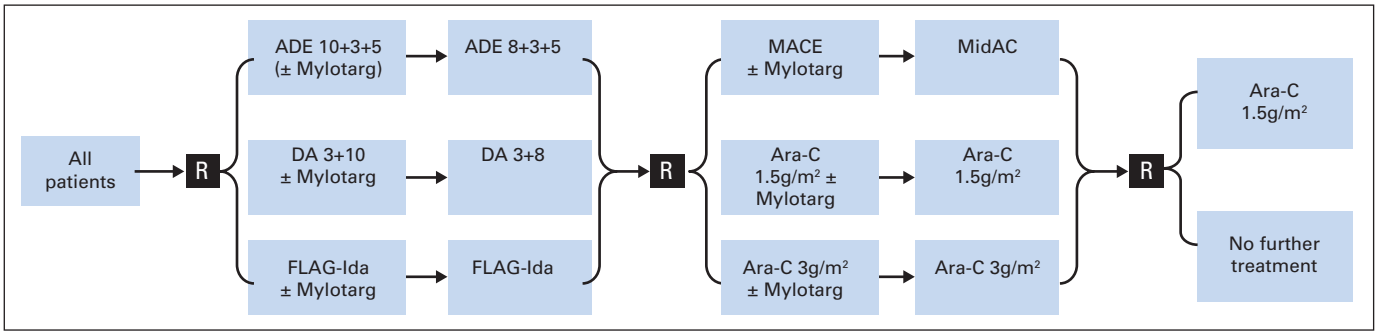

Fig 2. Trial schema for AML15. ADE, daunorubicin, cytarabine, etoposide; Ara-C, cytarabine; DA, daunorubicin and cytarabine; FLAG-Ida, fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin; MACE, amsacrine, cytarabine, and etoposide; MidAC, mitoxantrone and cytarabine.

adverse risk on the basis of cytogenetic criteria previously published.[10] In addition, patients with more than 15% residual blasts in a marrow sample taken at least 18 to 21 days from the end of course 1 were defined as high risk irrespective of cytogenetics.

Definitions of End Points

End point definitions follow the criteria of the International Working Group,[11] with remission failures classified as induction death (ID; related to treatment/hypoplasia within 30 days) or resistant disease (RD; failure to eliminate disease). Where evaluation was not available, deaths within 30 days were deemed ID and other failures RD. For consolidation questions, relapse-free survival (RFS), relapse, and death in complete remission (CR) are measured from that randomization. All percentages are quoted at 8 years.

Statistical Methods

Primary analyses are by intention to treat. Surviving patients were censored at first January 2012; follow-up is 96% complete. Patients lost to

Table 2. Demographics of Patients by Induction Comparison

Characteristic	ADE (n = 989)		DA (n = 994)		ADE (n = 633)		FLAG-Ida (n = 635)	
	No.	%	No.	%	No.	%	No.	%
Age, years								
0-14	0		0		52	8	52	8
15-29	120	12	119	12	73	12	73	12
30-39	136	14	141	14	83	13	85	13
40-49	231	23	229	23	132	21	132	21
50-59	370	37	372	37	214	34	213	34
60+	132	13	133	13	79	12	80	13
Median	50		50		48		48	
Range	16-68		16-73		0-67		0-71	
Sex								
Female	459	46	463	47	294	46	300	47
Male	530	54	531	53	339	54	335	53
Diagnosis								
De novo	905	92	906	91	584	92	586	92
Secondary	84	8	88	9	49	8	49	8
Performance status (adults)*								
WHO 0	670	68	671	68	402	67	401	67
WHO 1	260	26	260	26	161	27	158	26
WHO 2	32	3	35	4	20	3	20	20
WHO 3	24	2	25	3	15	3	16	3
WHO 4	3	< 0.5	3	< 0.5	2	< 0.5	3	1
Cytogenetic group								
Favorable	113	13	125	15	79	15	91	17
Intermediate	613	72	599	70	393	72	361	69
Adverse	120	14	127	15	71	13	69	13
Unknown	143		153		90		114	
WBC $\times 10^9$/L								
0-9.9	452	46	470	48	278	44	311	50
10-49.9	285	29	301	31	175	28	173	28
50-99.9	122	12	102	10	78	12	81	13
100+	120	12	111	11	95	15	62	10
Unknown	10		10		7		8	
Median	11.8		11.0		13.3		10.0	
Range	0.2-467		0.2-456		0.3-477.9		0.2-497.0	
FLT3 ITD status								
Wild type	226	76	221	78	99	73	84	71
Mutant	72	24	63	22	37	27	34	29
Unknown	691		710		499		517	
NPM1 status								
Wild type	185	71	191	73	69	68	72	74
Mutant	74	29	69	27	32	32	25	26
Unknown	730		734		532		538	
GO in induction								
Allocated GO	76	8	76	8	78	12	80	13
No GO/not randomly assigned	913	92	918	92	555	88	555	87

NOTE. Percentages are based on those patients with known data.
Abbreviations: ADE, cytarabine, daunorubicin, and etoposide; DA, daunorubicin and cytarabine; FLAG-Ida, fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin; GO, gemtuzumab ozogamicin.
*Younger children were not included, as they complete the WHO Play Performance Score.

follow-up are censored at the date last known to be alive. Median follow-up is 5.6 years (range, 0.2 to 9.5 years).

Categorical end points were compared using Mantel-Haenszel tests, giving Peto odds ratios and CIs, continuous variables by Wilcoxon rank-sum tests, and time-to-event outcomes by log-rank tests, with Kaplan-Meier curves. Odds ratios (ORs) and hazard ratios (HRs) less than 1 indicate benefit for investigational therapy. The protocol required at least 1,000 patients to be randomly assigned to each induction question to give 90% power to detect a 10% survival difference at $P < .05$ and 800 patients in consolidation to give 80% power to detect a 10% difference in overall survival (OS). In addition to overall analyses, exploratory subgroup analyses were performed by randomization stratification parameters and other important variables, with suitable tests for interaction.

RESULTS

Patient Random Assignment

Induction. Between May 2002 and January 2009, 3,106 patients with AML (excluding acute promyelocytic leukemia), median age 49 years (range, 0 to 73 years), were recruited, including 87 children who received ADE after the closure of the FLAG-Ida arm in May 2007; 424 patients older than 60 years were recruited. Patient characteristics are shown in Table 2. Twelve hundred sixty-eight patients entered the ADE versus FLAG-Ida and 1,983 entered the ADE versus DA induction comparisons.

Consolidation. Of the remitters, 1,440 entered the randomization between MRC consolidation and high-dose cytarabine, and of 722 allocated to cytarabine, 657 adults were further randomly assigned to a dose level of 3 g/m^2 or 1.5 g/m^2 (demographics in Appendix Table A1, online only). The 65 children randomly assigned to cytarabine received 3 g/m^2. Patients could also be randomly assigned to receive, or not, GO on day 1 of the first consolidation course. Finally, of 1,709 patients who received both induction and both consolidation courses, 227 were randomly assigned to an additional (fifth) course or not: in January 2005, after analysis of the four course versus five course randomization in AML12, this randomization was restricted to patients younger than 45 years, thus excluding 550 older patients.

Induction Response

In the comparison of ADE and DA, the CR rate was nonsignificantly better with ADE (82% *v* 78%: HR, 1.24; 95% CI, 0.99 to 1.54; $P = .06$; Table 3). Complete remission with incomplete peripheral count recovery (CRi) rates were respectively 4% and 6%, giving an overall complete marrow response of 86% versus 84%. The proportion of patients achieving CR or CRi after course 1 was 70% for ADE and 63% for DA, which comprised 81% and 75%, respectively, of those who achieved remission ($P = .002$). There were no significant differences in induction deaths or 30- or 60-day mortalities.

In the comparison of ADE and FLAG-Ida, there was no significant difference in the rate of CR (81% *v* 84%), or CRi (4% *v* 2%) or overall marrow response (85% *v* 86%). The proportion achieving CR/CRi with one course was 67% for ADE (78% of those who achieved remission) but was significantly better for FLAG-Ida at 77% (90% of all patients achieving remission; $P < .001$). The rates of induction death and 30- and 60-day mortality were not different.

Toxicity. Grade 3 or 4 GI toxicity was greater in ADE compared with DA, but any differences in other toxicities, blood count recovery, and supportive care, even if statistically different, were of modest clinical significance (Appendix Table A2, online only). When comparing FLAG-Ida with ADE, the most important differences were seen after course 2, when recovery of neutrophils and platelets were significantly delayed for FLAG-Ida patients (32 *v* 19 days for neutrophils to 1.0×10^9/L: $P < .001$, and 48 *v* 21 days for platelets to 100×10^9/L: $P < .001$). This resulted in a significantly greater transfusion requirement (11.6 *v* 6.5 red cell units: $P < .001$, and 14.0 *v* 6.9 platelet units: $P = .001$), mean days on antibiotics (19.1 *v* 10.9: $P < .001$), and days in hospital (34.6 *v* 25.6 days: $P < .001$) after course 2. It should be noted that the idarubicin dose used here in the FLAG-Ida combination was 8 mg/m^2, rather than the conventional 10 or 12 mg/m^2 used when combined with cytarabine alone.

Long-term outcomes. ADE was equivalent to DA with respect to relapse risk, deaths in remission, RFS, and OS (Data Supplement). FLAG-Ida significantly reduced relapse (38% *v* 55%: $P < .001$; Fig 3), but there was an excess of deaths in remission in the recipients of FLAG-Ida (17% *v* 11%; $P = .02$). RFS was significantly better with FLAG-Ida (45% *v* 34%; HR, 0.82; 95% CI, 0.70 to 0.96; $P = .01$), but there was no OS benefit (44% *v* 37%; HR, 0.92; 95% CI, 0.79 to 1.06; $P = .2$).

Consolidation

Of the 2,860 patients who were alive at day 60, 1,445 were randomly assigned between MRC consolidation and high-dose cytarabine, and the 657 adults allocated to high-dose cytarabine were

Table 3. Patient Outcomes: Induction (%)

	CR	CRi	ORR (CR + CRi)	ORR post C1	Res Dis	Ind Death	30-Day Mortality	60-Day Mortality
DA	78	6	84	63	10	6	6	8
ADE	82	4	86	70	8	5	5	7
OR/HR	1.24		1.20	1.35	1.25	1.09		
95% CI	0.99 to 1.54		0.94 to 1.54	1.12 to 1.63	0.93 to 1.70	0.93 to 1.70		
P	.06		.14	.002	.14	.7		
FLAG-Ida	84	2	86	77	7	7	6	9
ADE	81	4	85	67	8	7	6	7
OR	0.84		0.94	0.60	0.82	1.09		
95% CI	0.63 to 1.13		0.69 to 1.29	0.47 to 0.76	0.54 to 1.26	0.71 to 1.68		
P	.2		.7	< .001	.4	.7		

Abbreviations: ADE, cytarabine, daunorubicin, and etoposide; CR, complete remission; CRi, complete remission with incomplete count recovery; DA, daunorubicin and cytarabine; FLAG-Ida, fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin; HR, hazard ratio; Ind, induction; OR, odds ratio; ORR, overall response rate; Res Dis, residual disease.

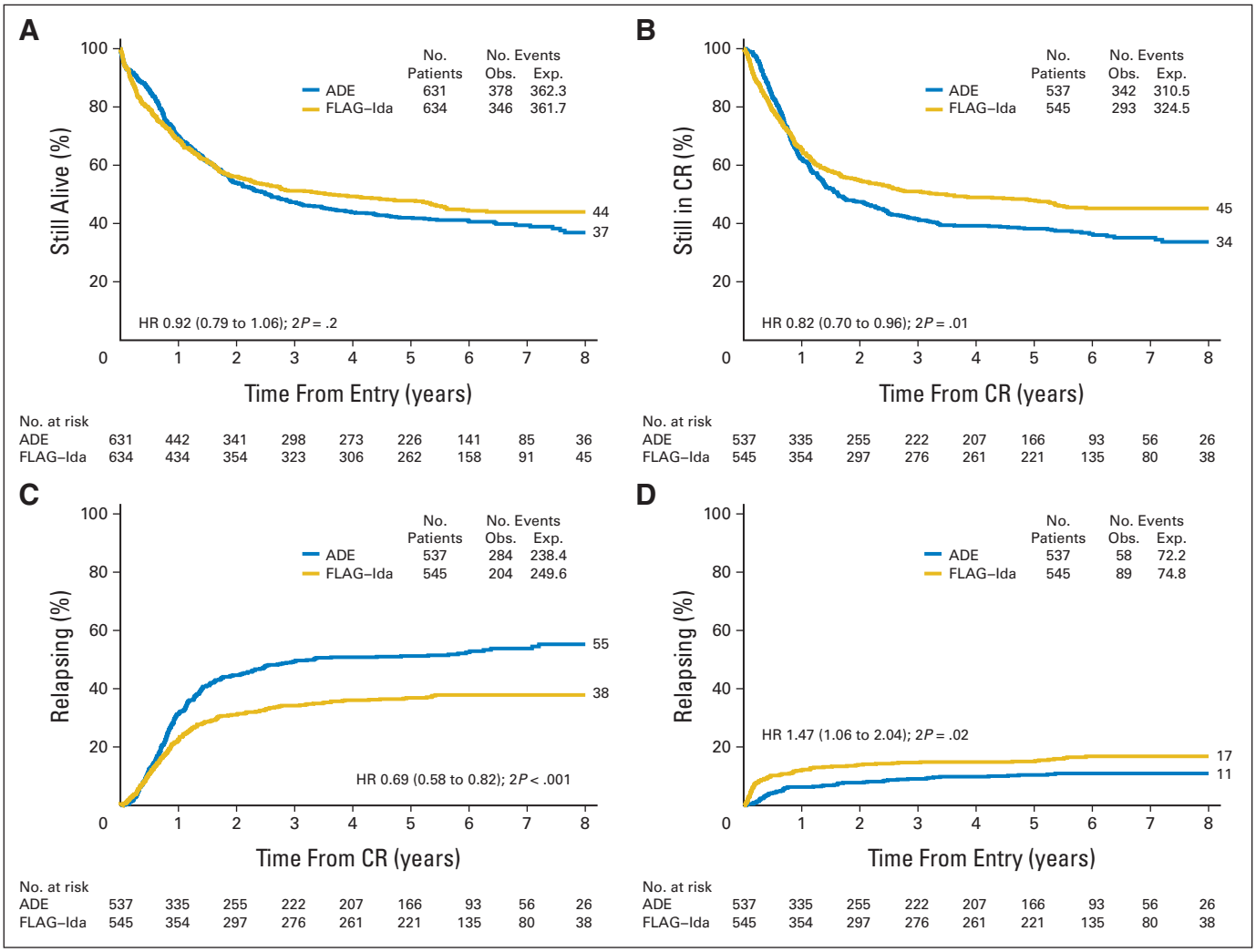

Fig 3. Outcomes for induction fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-Ida) versus daunorubicin, cytarabine, etoposide (ADE) randomization. (A) Overall survival; (B) relapse-free survival; (C) cumulative incidence of relapse; (D) cumulative incidence of death in complete remission (CR). Exp, expected; HR, hazard ratio; Obs, observed.

simultaneously randomly assigned to a 3 g/m^2 or 1.5 g/m^2 dose level. This randomization took place at a median of 77 days from diagnosis (range, 36 to 236 days), and the demographics of patients randomly assigned in consolidation were balanced (Appendix Table A1). There was no significant difference between the arms in cumulative incidence of relapse, cumulative incidence of death in CR, RFS, or OS (Data Supplement). When divided by cytogenetic risk group (Fig 4A), the cumulative incidence of relapse, cumulative incidence of death in CR, RFS, and OS did not differ in the favorable or intermediate-risk group, but OS in the MRC consolidation was significantly better in patients with adverse risk cytogenetics (39% *v* 0%; $P = .0004$: $P = .003$ for interaction). The MRC consolidation was associated with more toxicity and myelosuppression, particularly after the second course, during which the slower neutrophil (31 *v* 23 days: $P < .001$) and platelet recoveries (50 *v* 31 days: $P < .001$) required significantly more blood product and antibiotic support and resulted in more hospitalization (Appendix Table A4, online only).

Within the cytarabine dose comparison, there was a trend for a higher relapse risk in the 1.5g/m^2 arm, but the OS was not different (Fig 4B; Data Supplement); numbers were generally too small for reliable inference by cytogenetics. Although there were modest differences in hematologic toxicity, significantly more supportive care and hospitalization was deployed in the 3g/m^2 arm (Appendix Table A4).

Of the 1,779 patients who completed course 4, 227 were randomly assigned to receive a fifth course of cytarabine or not. The fifth course provided no advantage overall or for any subgroup (Data Supplement).

Compliance with consolidation. Overall, 1,440 (50%) of the 2,860 patients alive at day 60 entered the consolidation randomization. Of the patients not randomly assigned, 575 received an allogeneic transplant in first CR, the results of which will be discussed elsewhere. The results presented here do not change if the patients who underwent transplantation are censored at transplant. Significantly fewer patients who received FLAG-Ida in induction entered the randomization compared with the other two induction combinations: FLAG-Ida (43%) versus ADE (56%; $P < .001$), and DA (48%) versus ADE (53%; $P = .07$), reflecting the delayed hematopoietic recovery seen with

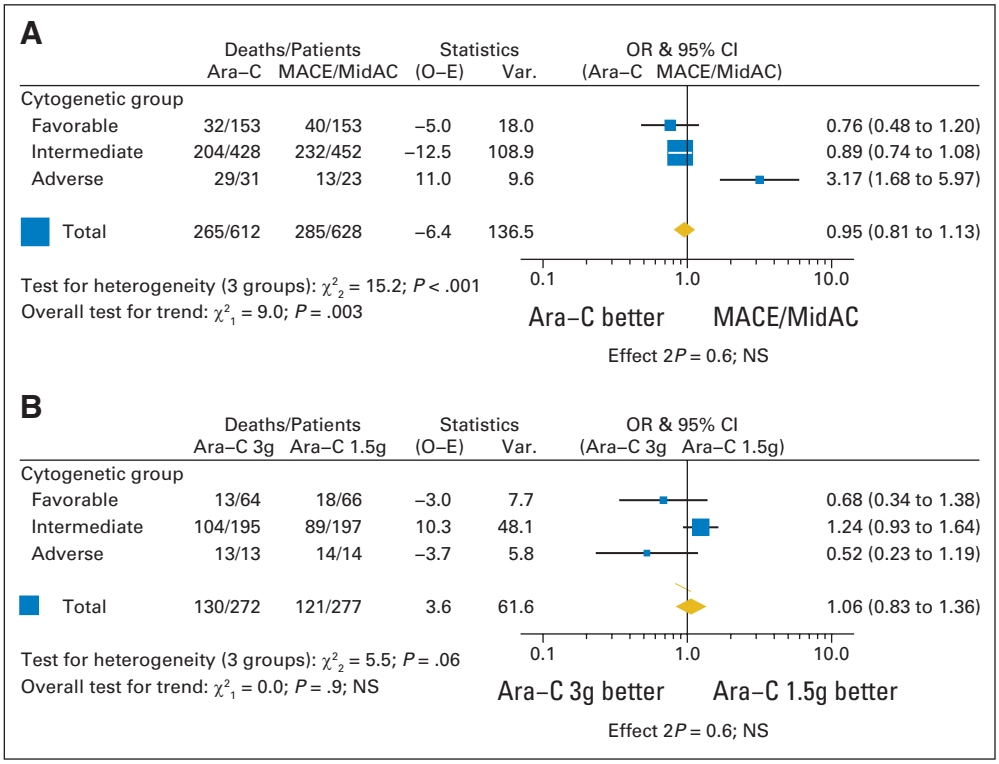

Fig 4. Outcomes for consolidation randomization stratified by cytogenetics. (A) Comparison of Medical Research Council consolidation versus cytarabine; (B) comparison of cytarabine dose. Ara-C, cytarabine; MACE, amsacrine, cytarabine, and etoposide; MidAC, mitoxantrone and cytarabine; NS, not significant; O-E, observed-expected; OR, odds ratio.

FLAG-Ida. There was no effect on compliance of GO given in induction on the subsequent consolidation treatment.

Fifty-four patients received only two induction courses of FLAG-Ida and are known not to have received any consolidation therapy primarily because of delayed hematopoietic recovery. However, in a landmark analysis of patients surviving 60 days from CR (to allow for zero time-shift bias), the survival from CR was not significantly different from that of patients who received all four courses of ADE or DA induction and consolidation (57% *v* 54%; $P = .5$; Fig 5A). The result was unaffected if the recipients of transplant were censored at transplant. However, there were 101 patients given ADE or DA induction who were known to not receive consolidation, but they had a worse survival than those who in addition received both courses of consolidation (35% *v* 54%, $P < .001$; Fig 5B). Among the 230 FLAG-Ida patients who were fully compliant with induction and consolidation (four courses), the survival was significantly superior to the that of 979 ADE/DA patients who were fully compliant (70% *v* 54%; $P < .001$; Fig 5C). After adjustment for age, WBC, cytogenetics, and secondary disease, significant benefit remains ($P = .002$). We observed that patients with favorable and intermediate-risk disease who received FLAG-Ida as induction (two courses) and high-dose cytarabine (two courses) as consolidation had an 8-year survival rate of 72% (favorable 95%: intermediate 63%; Fig 5D). If the recipients of transplant are censored at transplant, the respective survivals are 100% and 77%. This suggests that this is the optimal treatment plan that emerges from this study. Numbers are too small to investigate the effect of GO, although the overall results of the GO randomization suggest that for these patients, GO is beneficial.[9]

Allogeneic transplantation from a matched sibling or unrelated donor was recommended for patients with high-risk disease. The outcome for these patients will be reported in detail elsewhere, but the survival from transplant in first remission for recipients of reduced intensity conditioning (n = 316) and myeloablative (n = 321) transplants was 52% and 48%, respectively. The results of the primary comparisons are robust to censoring at any transplant (Data Supplement), although the benefit of cytarabine consolidation in favorable/intermediate risk and the benefit of MRC consolidation in patients with adverse-risk disease may be more pronounced in these analyses (Data Supplement).

DISCUSSION

Although the molecular diversity of AML provides potential targets for future therapeutic development, there is still interest in optimizing chemotherapy via the introduction of new therapeutic agents or combinations. In younger patients in whom remission rates are already high, an expectation to improve rates of remission may be overly optimistic. The recent evidence that intensification of daunorubicin[3,12-14] or the inclusion of an alternative nucleoside, cladribine,[15] can improve remission rate and/or survival in the context of the classic "3+7" induction illustrates that further refinements can be made. In this AML15 trial, several questions were posed with respect to the core chemotherapy. We have previously reported that the addition of the immunoconjugate, GO,[9] to induction in this trial was beneficial only when given to patients with more favorable features, irrespective of the chemotherapy it was combined with. This has been corroborated by others[16] and in our trial in older patients.[17] The comparison of the addition of etoposide is not new), but was chosen to assess whether the addition of GO is beneficial as a fourth drug in induction. Apart from improving the rate of remission, a more effective treatment might deliver more remissions with course 1 and/or a

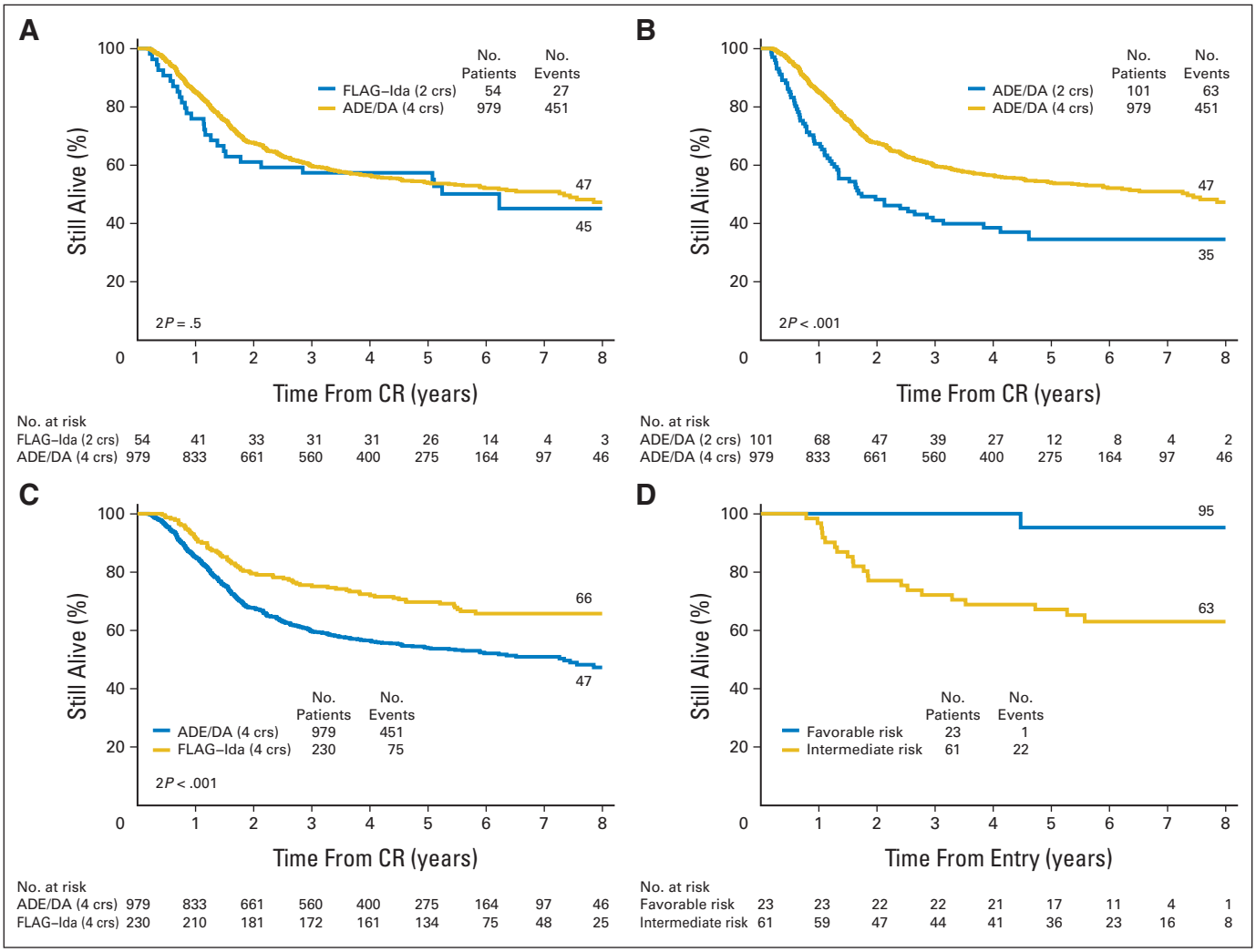

Fig 5. Survival from complete remission (CR) for patients by number of courses given and induction chemotherapy. (A) Two courses of fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-Ida) versus daunorubicin and cytarabine (DA)/daunorubicin, cytarabine, and etoposide (ADE) plus consolidation; (B) ADE/DA with and without consolidation; (C) FLAG-Ida versus DA/ADE, both with consolidation; (D) FLAG-Ida plus cytarabine consolidation by cytogenetics. crs, courses.

better quality of remission, which is reflected in a reduced relapse rate and improved OS. The Eastern Cooperative Oncology Group 1900 trial demonstrated that the 90-mg/m^2 daunorubicin dose produced more remissions than a 45-mg/m^2 dose, more with course 1 and an improvement in survival overall, but not in all subgroups (eg, adverse cytogenetics, age $>$ 50 years, *FLT3 ITD*). The remission rate overall was 64%, with 83% achieving remission after course 1.[3] Here, when the daunorubicin dose was 50 mg/m^2, all induction schedules produced a higher CR rate, which reflects our experience over the last 10 years, and the FLAG-Ida arm had an 84% remission rate with 92% of remissions after course 1. In AML15, the inclusion of etoposide provided no benefit in rate or durability of response. FLAG-Ida has been a popular regimen for the treatment of relapse, but this is the first randomized comparison of its efficacy as a first-line approach. Although the remission rate was not statistically superior to that of ADE, there was an impressive rate of overall remission of 86%, with significantly more (77%) entering CR with the first course (ie, 92% of all patients achieving remission), the benefit of which is reflected in the significant reduction in relapse risk and improved RFS. However, there was greater hematologic toxicity, most obviously after course 2, which resulted in significantly fewer FLAG-Ida patients entering the consolidation randomization. However, it is of interest that the OS in the recipients of two courses of FLAG-Ida was the same as that of the patients receiving DA or ADE plus consolidation, which was not the case for patients who received only two courses of DA or ADE induction, when there was benefit from the addition of consolidation. For the 230 patients who received FLAG-Ida and consolidation, their 8-year survival rate from CR, at 66%, was significantly superior to that of the other inductions. This suggests that two courses of FLAG-Ida may be able to deliver similar outcomes to a total of four courses of so-called standard therapy, but survival will be further improved if consolidation can also be given. However, this issue requires prospective evaluation. The favorable effect of FLAG-Ida on relapse was apparent over all ages and demographic subgroups, including poor risk, patients older than 50 years, and those with *FLT3 ITD*, subgroups who did not benefit in the 90-mg daunorubicin arm of the Eastern Cooperative Oncology Group trial (Data Supplement).

Our standard consolidation has been MACE/MidAc, which was here compared with the international standard of high-dose cytarabine. It was equivalent to cytarabine for favorable and intermediate risk but superior in patients with high-risk disease, although it resulted in more hematologic toxicity requiring more supportive care, particularly after the second course. There was no important difference between cytarabine given at the 3 or 1.5 g/m^2 dose level. In the context of this treatment, a fifth course is not required. Approximately 20% of patients achieving remission received a transplant in first CR, with either myeloablative or reduced intensity conditioning with a matched sibling or volunteer donor. These data will be reported in full elsewhere, but the findings reported here did not change when transplant recipients were censored at the date of transplant.

In summary, this study demonstrates that FLAG-Ida, with the idarubicin given on days 4, 5, and 6 even at the modest dose of 8 mg/m^2, gives a superior remission rate and reduced risk of relapse and compares favorably with recent studies of intensified daunorubicin. Even a total of two courses seems similar to four courses of more conventional therapy, but there is nevertheless an incentive to deliver consolidation. For patients with favorable or intermediate-risk disease, high-dose cytarabine at either of the chosen doses is equivalent to our traditional consolidation and requires less supportive therapy. For poor-risk patients who did not undergo transplantation, MACE/MidAc is a superior consolidation. In this trial, patients with favorable and intermediate-risk disease who received two induction courses of FLAG-Ida with GO in course 1, followed by two courses of high-dose cytarabine, had an 8-year survival rate from remission of 72% (favorable 95%, intermediate 63%) or 84% (favorable 100%, intermediate 77%), if censored at SCT.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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REFERENCES

1. Burnett AK, Hills RK, Milligan DW, et al: Attempts to optimize induction and consolidation treatment in acute myeloid leukemia: Results of the MRC AML12 trial. J Clin Oncol 28:586-595, 2010
2. Mandelli F, Vignetti M, Suciu S, et al: Daunorubicin versus mitoxantrone versus idarubicin as induction and consolidation chemotherapy for adults with acute myeloid leukemia: The EORTC and GIMEMA Groups Study AML-10. J Clin Oncol 27: 5397-5403, 2009
3. Fernandez HF, Sun Z, Yao X, et al: Anthracycline dose intensification in acute myeloid leukemia. N Engl J Med 361:1249-1259, 2009
4. Hann IM, Stevens RF, Goldstone AH, et al: Randomized comparison of DAT versus ADE as induction chemotherapy in children and younger adults with acute myeloid leukaemia: Results of the Medical Research Council's 10th AML Trial (MRC AML 10)—Adult and Childhood Leukaemia Working Parties of the Medical Research Council. Blood 89:2311-2318, 1997
5. Büchner T, Schlenk RF, Schaich M, et al: Acute myeloid leukemia (AML): Different treatment strategies versus a common standard arm—Combined prospective analysis by the German AML Intergroup. J Clin Oncol 30:3604-3610, 2012
6. Estey E, Thall P, Andreeff M, et al: Use of granulocyte colony-stimulating factor before, during, and after fludarabine plus cytarabine induction therapy of newly diagnosed acute myelogenous leukemia or myelodysplastic syndromes: Comparison with fludarabine plus cytarabine without granulocyte colony-stimulating factor. J Clin Oncol 12:671-678, 1994
7. Parker JE, Pagliuca A, Mijovic A, et al: Fludarabine, cytarabine, G-CSF and idarubicin (FLAG-IDA) for the treatment of poor-risk myelodysplastic syndromes and acute myeloid leukemia. Br J Haematol 99:939-944, 1997
8. Clavio M, Gatto S, Beltrami G, et al: Fludarabine, ARA-C, idarubicin and G-CSF (FLAG-Ida), high dose ARA-C and early stem cell transplant: A feasable and effective therapeutic strategy for de novo AML patients. J Exp Clin Cancer Res 21:481-487, 2002
9. 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 29:369-377, 2011
10. Grimwade D, Walker H, Oliver F, et al: The importance of diagnostic cytogenetics on outcome in AML: Analysis of 1,612 patients entered into the MRC AML 10 trial. Blood 92:2322-2333, 1998
11. Cheson BD, Bennett JM, Kopecky KJ, et al: Revised recommendation of the International Working Group for diagnosis standardization, of response criteria treatment outcomes and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol 21:4642-4649, 2003
12. Löwenberg B, Ossenkoppele GJ, van Putten W, et al: High-dose daunorubicin in older patients with acute myeloid leukemia. N Engl J Med 361: 1235-1248, 2009
13. Lee JH, Joo YD, Kim H, et al: A randomized trial comparing standard versus high-dose daunorubicin induction in patients with acute myeloid leukemia. Blood 118:3832-3841, 2011
14. Ohtake S, Miyawaki S, Fujita H, et al: Randomized study of induction therapy comparing standard-dose idarubicin with high-dose daunorubicin in adult patients with previously untreated acute myeloid leukemia: The JALSG AML201 Study. Blood 117:2358-2365, 2011
15. Holowiecki J, Grosicki S, Giebel S, et al: Cladribine, but not fludarabine, added to daunorubicin and cytarabine during induction prolongs survival of patients with acute myeloid leukemia: A multicenter, randomized phase III Study. J Clin Oncol 30:2441-2448, 2012
16. Castaigne S, Pautas C, Terré 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 379:1508-1516, 2012
17. 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 30:3924-3931, 2012

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Appendix

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Table A1. Demographics of Patients in Consolidation Randomizations

	MACE/MidAC (n = 718)		Cytarabine (any dose) (n = 722)†		Cytarabine 3 g (adults) (n = 328)		Cytarabine 1.5 g (adults) (n = 329)		4 Courses (n = 115)		5 Courses (n = 112)	
Total	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age, years												
0-14	58	8	61	8	0		0		27	23	24	21
15-29	104	14	106	15	51	16	51	16	26	23	29	26
30-39	103	14	105	15	52	16	53	16	29	25	24	21
40-49	159	22	163	23	82	25	81	25	21	18	19	17
50-59	224	31	221	31	109	33	112	34	10	9	14	13
60+	70	10	66	9	34	10	32	10	2	2	2	2
Median	45		45		47		48		31		31	
Range	0-69		0-69		16-67		15-69		0-63		0-61	
Sex												
Female	346	48	346	48	169	52	168	51	51	44	57	51
Male	372	52	372	52	159	48	161	49	64	56	55	49
Diagnosis												
De novo	685	95	690	96	313	95	312	95	113	98	111	99
Secondary	33	5	32	4	15	5	17	5	2	2	1	1
Performance status (adults)*												
WHO 0	474	70	474	69	229	70	228	69	70	72	73	77
WHO 1	170	25	177	26	85	26	82	25	19	20	18	19
WHO 2	20	3	26	3	9	3	15	5	4	4	3	3
WHO 3	12	2	8	1	5	2	3	1	4	4	0	
WHO 4	1	< 0.5	2	< 0.5	0		1	< 0.5	0		1	1
Cytogenetic group												
Favorable	153	24	153	25	66	24	64	23	30	31	25	26
Intermediate	452	72	431	70	199	71	196	72	65	66	66	68
Adverse	23	4	31	5	14	5	13	5	3	3	6	6
Unknown	90		107		49		56		17		15	
WBCs $\times 10^9$/L												
0-9.9	320	45	313	43	145	44	143	44	41	36	42	38
10-49.9	244	34	243	34	108	33	115	35	47	41	36	32
50-99.9	80	11	94	13	36	11	48	15	12	10	16	14
100+	72	10	70	10	38	12	22	7	15	13	18	16
Unknown	2		2		1		1		0		0	
Median	13.0		13.9		13.5		13.9		19.1		23.3	
Range	0.3-497.0		0.2-467.0		0.5-298.0		0.4-467.0		0.2-402.0		0.9-497.0	
FLT3 ITD status												
Wild type	169	82	141	76	71	74	70	77	18	67	18	78
Mutant	37	18	45	24	24	26	21	23	9	33	5	22
Unknown	512		536		236		238		88		89	
NPM1 status												
Wild type	112	70	102	69	52	76	50	63	10	77	8	50
Mutant	49	30	45	31	16	24	29	37	3	23	8	50
Unknown	557		575		260		250		102		96	
Induction chemo (± GO)‡												
ADE	281	39	295	41	123	38	125	38	50	43	39	35
DA	273	38	271	38	135	41	136	41	38	33	37	33
FLAG-Ida	164	23	156	22	70	21	68	21	27	23	36	32
GO in induction												
Allocated GO	137	19	130	18	63	19	65	20	25	22	24	21
No GO/not randomly assigned	581	81	592	82	265	81	264	80	90	78	88	79
Consolidation												
MACE/MidAC									45	39	39	35
HD cytarabine									68	59	72	64
NR									2	2	1	1
Cytarabine dose, g†												
3									35	51	38	53
1.5									33	49	34	47

(continued on following page)

Table A1. Demographics of Patients in Consolidation Randomizations (continued)

	MACE/MidAC (n = 718)		Cytarabine (any dose) (n = 722)†		Cytarabine 3 g (adults) (n = 328)		Cytarabine 1.5 g (adults) (n = 329)		4 Courses (n = 115)		5 Courses (n = 112)	
Total	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
GO in consolidation												
Allocated GO	220	31	219	30	109	33	110	33	29	25	29	26
No GO	220	31	220	30	110	34	110	33	30	26	29	26
Not randomized	278	39	283	39	109	33	109	33	56	49	54	48

NOTE. Percentages are of those patients with data.
Abbreviations: ADE, cytarabine, daunorubicin, and etoposide; DA, daunorubicin and cytarabine; FLAG-Ida, fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin; GO, gemtuzumab ozogamicin; HD, high dose; MACE, amsacrine, cytarabine, and etoposide; MidAC, mitoxantrone and cytarabine; NR, not randomly assigned.
*Younger children are not included, as they complete the WHO Play Performance Score.
†Includes 65 patients treated at pediatric centers who were given cytarabine 3 g/m^2 as per protocol.
‡Includes children who were registered and treated with ADE outside the randomization.

Table A2. Toxicity and Resource Usage for Induction Randomizations

	DA		ADE			FLAG-Ida		ADE		
Toxicity	No.	%	No.	%	*P*	No.	%	No.	%	*P*
Course 1 toxicities, mean grade (% grade 3-4)										
Nausea/vomiting	1.0	11	1.1	13	.11	1.4	21	1.2	16	.003
Alopecia	2.2	45	2.6	57	< .001	2.5	53	2.7	61	.03
Oral	0.9	6	1.1	10	< .001	0.8	6	1.1	11	< .001
Diarrhea	1.0	11	1.4	16	< .001	1.4	18	1.4	17	.4
Cardiac	0.3	5	0.3	5	.7	0.2	4	0.3	6	.3
Liver AST	0.4	4	0.5	5	.4	0.6	6	0.6	5	.4
Liver ALT	0.8	8	0.8	8	.10	0.8	8	0.9	10	.2
Bilirubin	0.7	7	0.7	8	.7	0.8	8	0.7	8	.04
Median recovery time from end of course 10										
Neutrophils (to 1.0 × 10^9/L)	20		18		.001	20		18		.18
Platelets (to 100 × 10^9/L)	18		18		.09	19		18		.03
Course 1 resource usage										
Mean units of blood	11.3		11.8		.19	12.0		12.0		.8
Mean units of platelets	12.9		13.1		.7	14.4		14.1		.9
Mean days of IV antibiotics	19.0		19.5		.06	19.0		19.8		.06
Mean nights in hospital	32.1		32.1		.6	30.4		32.3		< .001
Course 2 toxicities, mean grade (% grade 3-4)										
Nausea/vomiting	0.9	8	0.9	8	.9	1.2	17	1.0	11	< .001
Alopecia	2.6	59	2.8	68	.0002	2.9	72	3.0	73	.3
Oral	0.5	3	0.7	3	.0004	0.8	6	0.7	3	.3
Diarrhea	0.6	5	0.9	9	< .001	1.0	13	0.9	9	.2
Cardiac	0.2	3	0.1	2	.3	0.2	5	0.1	3	.02
Liver AST	0.3	2	0.3	2	.08	0.5	3	0.4	3	.02
Liver ALT	0.6	5	0.7	6	.4	0.8	8	0.7	7	.02
Bilirubin	0.4	3	0.4	5	1.0	0.7	6	0.4	3	< .001
Median recovery time from end of course 2										
Neutrophils (to 1.0 × 10^9/L)	20		19		.9	32		19		< .001
Platelets (to 100 × 10^9/L)	18		21		.002	48		21		< .001
Course 2 resource usage										
Mean units of blood	6.2		6.6		.01	11.6		6.5		< .001
Mean units of platelets	6.3		6.6		.006	14.0		6.9		< .001
Mean days of IV antibiotics	9.5		10.6		.0003	19.1		10.9		< .001
Mean nights in hospital	24.0		25.4		.003	34.7		25.6		< .001

NOTE. Percentages are of patients with data for the course. All *P* values are by Wilcoxon rank-sum test.
Abbreviations: ADE, cytarabine, daunorubicin, and etoposide; DA, daunorubicin and cytarabine; FLAG-Ida, fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin; IV, intravenous.

Table A3. Causes of Death

	DA	ADE	FLAG-Ida	ADE	MACE/MidAC	Cytarabine
No. of patients with follow-up	994	985	634	631	718	719
No. of deaths	585	588	346	378	332	312
Infection	189	188	115	121	111	88
Hemorrhage	20	31	16	18	11	12
Infection + hemorrhage	10	7	10	5	3	4
Recurrent disease	168	168	106	120	127	136
Cardiac	9	7	7	7	7	2
Renal	2	7	5	2	0	1
Hepatic	0	1	4	0	1	2
Respiratory	6	11	8	9	4	8
Resistant disease	67	47	22	33	1	1
VOD	2	1	2	1	1	1
Second cancer	6	6	7	5	5	5
GVHD	7	9	6	7	7	3
Graft failure	1	2	0	2	1	0
Sudden death	1	0	1	0	0	1
Multiple	35	41	12	23	17	13
Other/unknown	62	62	25	25	33	35

Abbreviations: ADE, cytarabine, daunorubicin, and etoposide; DA, daunorubicin and cytarabine; FLAG-Ida, fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin; GVHD, graft-versus-host disease; MACE, amsacrine, cytarabine, and etoposide; MidAC, mitoxantrone and cytarabine; VOD, veno-occlusive disease.

Table A4. Toxicity (course 3 and 4) and Resource Usage for Consolidation Randomizations

Toxicity	Cytarabine		MACE/MidAC			Cytarabine 1.5 g		Cytarabine 3 g		
	No.	%	No.	%	*P*	No.	%	No.	%	*P*
Course 3 toxicities, mean grade (% grade 3-4)										
Nausea/vomiting	0.9	12	1.3	17	< .001	0.8	9	0.9	11	.09
Alopecia	2.6	59	3.0	73	< .001	2.6	60	2.5	57	.19
Oral	0.5	3	1.1	12	< .001	0.5	2	0.5	3	.5
Diarrhea	0.6	5	1.2	17	< .001	0.5	3	0.6	4	.03
Cardiac	0.1	1	0.2	3	.005	0.1	2	0.1	1	.4
Liver AST	0.4	2	0.5	6	.02	0.3	2	0.3	1	.4
Liver ALT	0.7	6	0.8	9	.3	0.6	5	0.7	6	.11
Bilirubin	0.4	2	0.6	5	.006	0.4	2	0.4	2	.3
Median recovery time from end of course 3										
Neutrophils (to 1.0×10^9/L)	23		24		.0002	22		23		.8
Platelets (to 100×10^9/L)	29		34		< .001	28		31		.16
Course 3 resource usage										
Mean units of blood	6.0		6.9		.001	5.6		6.9		< .001
Mean units of platelets	7.1		9.5		.0002	6.0		8.7		.0004
Mean days of IV antibiotics	10.7		14.3		< .001	9.8		11.6		.002
Mean nights in hospital	22.9		25.7		< .001	22.2		23.3		.13
Course 4 toxicities, mean grade (% grade 3-4)										
Nausea/vomiting	0.8	7	1.0	10	.0002	0.6	4	0.8	7	.09
Alopecia	2.5	57	3.0	77	< .001	2.5	57	2.3	54	.19
Oral	0.4	2	0.7	6	< .001	0.4	1	0.5	2	.3
Diarrhea	0.5	3	0.7	6	.0004	0.4	2	0.5	2	.03
Cardiac	0.1	1	0.1	2	.12	0.1	< 0.5	0.1	2	.07
Liver AST	0.3	2	0.3	3	.4	0.2	1	0.3	2	1.0
Liver ALT	0.7	7	0.6	4	.01	0.6	5	0.8	8	.02
Bilirubin	0.3	2	0.5	5	.0007	0.3	1	0.4	2	.05
Median recovery time from end of course 4										
Neutrophils (to 1.0×10^9/L)	23		31		< .001	23		23		.3
Platelets (to 100×10^9/L)	31		50		< .001	30		34		.08
Course 4 resource usage										
Mean units of blood	5.5		7.8		< .001	5.3			6.2	.007
Mean units of platelets	5.5		10.6		< .001	4.8			6.7	.0003
Mean days of IV antibiotics	9.2		14.4		< .001	7.9			10.2	< .001
Mean nights in hospital	21.2		26.5		< .001	19.7			22.0	.006

NOTE. Percentages are of patients with data for course in question. *P* values are by Wilcoxon rank-sum test.
Abbreviations: IV, intravenous; MACE, amsacrine, cytarabine, and etoposide; MidAC, mitoxantrone and cytarabine.