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Outcomes of intensification of induction chemotherapy for children with high-risk acute myeloid leukemia: A report from the Children's Oncology Group

Caitlin W. Elgarten[1,2], **Andrew C. Wood**[3], **Yimei Li**[4], **Todd A. Alonzo**[5], **Lisa Eidenschink Brodersen**[6], **Robert B. Gerbing**[7], **Kelly D. Getz**[2,4], **Y-S Vera Huang**[8], **Michael Loken**[6], **Soheil Meshinchi**[9], **Jessica A. Pollard**[10,11], **Lillian Sung**[12], **William G. Woods**[13], **E. Anders Kolb**[14], **Alan S. Gamis**[15], **Richard Aplenc**[1,2,4]

[1]Division of Oncology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

[2]Center for Pediatric Clinical Effectiveness, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

[3]University of Auckland, Auckland, New Zealand

[4]Department of Biostatistics, Epidemiology, and Informatics, Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA

[5]University of Southern California, Los Angeles, California, USA

[6]Hematologics, Inc., Seattle, Washington, USA

[7]Children's Oncology Group, Monrovia, California, USA

[8]Department of Biomedical Health Informatics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

[9]Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

[10]Dana-Farber Cancer Institute, Boston, Massachusetts, USA

[11]Boston Children's Hospital, Boston, Massachusetts, USA

[12]The Hospital for Sick Children, Toronto, Ontario, Canada

[13]Aflac Cancer and Blood Disorders Center, Emory University/Children's Healthcare of Atlanta, Atlanta, Georgia, USA

[14]Alfred I.duPont Hospital for Children, Wilmington, Delaware, USA

Correspondence Richard Aplenc, Children's Hospital of Philadelphia, Division of Oncology, Philadelphia, PA, USA. Aplenc@chop.edu.

Caitlin W. Elgarten and Andrew C. Wood contributed equally to this work.

CONFLICT OF INTEREST

Michael Loken and Lisa Eidenschink Brodersen are employees of Hematologics Inc, which performed the MRD-based flow cytometry assays used in this clinical trial.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Prior presentations: Findings presented in part as an oral presentation at the annual meeting of the American Society of Clinical Oncology June 2019 (https://doi.org/10.1200/JCO.2019.37.15_suppl.10002; Journal of Clinical Oncology (May 20, 2019) 37(15_suppl):10002).

[15]Children's Mercy Hospital and Clinics, Kansas City, Missouri, USA

Abstract

Background: High-risk pediatric acute myeloid leukemia confers a poor prognosis, and alternative strategies are needed to improve outcomes. We hypothesized that intensifying induction on the AAML1031 clinical trial would improve outcomes compared to the predecessor trial AAML0531.

Methods: Patients on AAML0531 received cytarabine (1600 mg/m^2)/daunorubicin (150 mg/m^2)/etoposide (ADE) for induction II and patients on AAML1031 received mitoxantrone (48 mg/m^2)/cytarabine (8000 mg/m^2) (MA). Stem cell transplant (SCT) conditioning included busulfan/cyclophosphamide on AAML0531, whereas AAML1031 used busulfan/fludarabine and liberalized donor eligibility. Patients were included in this analysis if they met high-risk criteria common to the two trials by cytogenics or poor disease response after induction I ADE.

Results: MA provided no benefit over ADE at: induction II response (complete response [CR]: 64% vs. 62%, $p = .87$; measurable residual disease [MRD]+: 57% vs. 46%, $p = .34$); or intensification I response (CR: 79% vs. 94%, $p = .27$; MRD+: 27% vs. 20%, $p = 1.0$). When considered with altered SCT approach, MA did not improve 5-year disease-free survival (24% ± 9% vs. 18% ± 15%, $p = .63$) or 5-year overall survival (35% ± 10% vs. 38% ± 18%, $p = .66$). MA was associated with slower neutrophil recovery (median 34 vs. 27 days, $p = .007$) and platelet recovery (median 29 vs. 24.5 days, $p = .04$) and longer hospital stay (32 vs. 28 days, $p = .01$) during induction II.

Conclusion: Intensification of induction II did not improve treatment response or survival, but did increase toxicity and resource utilization. Alternative strategies are urgently needed to improve outcomes for pediatric patients with high-risk acute myeloid leukemia (trials registered at clinicaltrials.gov NCT01371981, NCT00372593).

Keywords

acute leukemia; Children's Oncology Group; induction; mitoxantrone; myeloid leukemia; pediatric oncology

1 | INTRODUCTION

Outcomes for children with acute myeloid leukemia (AML) have improved primarily because of intensification of therapy[1-3] and progress in supportive care,[4,5] but relapse rates remain high. For patients with high-risk disease based on cytogenetics or poor response to initial therapy, 3-year disease-free survival (DFS) is as low as 20%–30%, even with the inclusion of stem cell transplant (SCT) in first remission.[6-9] For these patients, intensification of remission induction through prolonging chemotherapy exposure and increasing drug dose may improve initial leukemia response and long-term postremission disease control.[1,2] However, intensified induction approaches may also increase treatment-related morbidity and mortality.

The inclusion of high-dose cytarabine to intensify consolidation has been shown to reduce relapse and prolong survival.[10-16] However, intensification of induction courses of therapy with high-dose cytarabine has yielded mixed results relative to treatment outcomes.[17-19] Alternatively, prior studies have suggested there may be benefit from alternative anthracycline or anthracenediones in induction for pediatric patients.[5,15,16]

In an effort to improve outcomes for high-risk AML, the Children's Oncology Group (COG) AAML1031 trial intensified induction II chemotherapy by switching from daunorubicin to mitoxantrone, and escalating cytarabine exposure compared to the predecessor trial.[20,21] This provided an opportunity to evaluate the impact of induction intensification using the predecessor trial, AAML0531, as a comparator. In a protocol described aim, high-risk patients who received cytarabine/mitoxantrone (MA) as induction II on AAML1031 were compared to a similar cohort who received cytarabine/daunorubicin/etoposide (ADE) as induction II on AAML0531. AAML1031 also modified SCT by liberalizing donor source and utilizing a different conditioning regimen. Here, we describe the impact of these two changes on survival. We also examine the impact of induction II intensification on disease response pretransplant and induction II toxicities, costs, and resource utilization. We hypothesized that these changes would be associated with improved survival but would also confer increased toxicity.

2 | METHODS

2.1 | Study population

The source population was patients treated on either COGAAML0531 or AAML1031 who survived and remained on study to the beginning of the second cycle of chemotherapy (termed Induction II). The entry criteria for these trials included newly diagnosed de novo AML patients aged 0–30 years old. Patients with secondary AML, acute promyelocytic leukemia, and bone marrow failure syndromes were excluded. The National Cancer Institute central institutional review board (IRB) and IRB at each enrolling institution approved both studies with patients and families providing consent and assent as appropriate. The trials were conducted in accordance with the Declaration of Helsinki. Both trials were registered at clinicaltrials.gov NCT01371981, NCT00372593.

These studies had identical backbones for cycles 1 and 3, and then diverged in their approach (Figure 1,Table S1). On AAML0531, patients were randomized to receive or not receive gemtuzumab ozogamicin (GO) during cycle 1. Patients were allocated to high-risk therapy based on cytogenetics or >15% blasts by morphology after induction I chemotherapy. Multidimensional flow cytometry measurable residual disease (MRD) was analyzed, but investigators were blinded to the result. High-risk patients then received two more cycles of chemotherapy, and then proceeded to related or unrelated allogeneic SCT with busulfan/cyclophosphamide, or two additional cycles of chemotherapy if there was no suitable donor.[20] On AAML1031, patients were randomized to receive or not receive bortezomib on days 1, 4, and 8 of each cycle of chemotherapy. Risk stratification occurred after cycle 1, and poor response to therapy was defined as MRD ≥0.1%. On AAML1031, after two additional cycles of chemotherapy, high-risk patients underwent SCT with busulfan/fludarabine and haploidentical donors were also permitted in addition to

matched related and unrelated donors. Those without an appropriate donor received a single additional cycle of chemotherapy.

The definition of "high risk" was discrepant between trials. To create a uniform population for this analysis, high risk was defined based on criteria common to the two trials: (a) adverse cytogenetics (monosomy 7, monosomy 5, or deletion 5q); or (b) poor disease response to Induction 1 ADE. The inclusion criteria for poor disease response required patients to satisfy both studies' criteria: residual blasts >15% by morphology, the definition used on AAML0531[20]; and ≥0.1% MRD, the definition used on the AAML1031 trial.[21,22]

Patients with high allelic ratio FLT3/ITD+ were excluded. In addition, patients randomized to the experimental arm of AAML0531 (standard therapy + GO) were excluded to mitigate confounding as GO was found to improve EFS and GO was not included in AAML1031.[9] AAML1031 randomization of bortezomib receipt did not modify survival so all patients were included in the primary analysis.[21]

2.2 | Exposure

On COG AAML1031, induction II consisted of cytarabine 1000 mg/m^2/dose every 12 hours on days 1–4 (cumulative dose 8000 mg/m^2) and mitoxantrone 12 mg/m^2/dose on days 3–6. Induction II on AAML0531 included cytarabine 100 mg/m^2/dose every 12 hours on days 1–8 (cumulative dose 1600 mg/m^2), daunorubicin 50 mg/m^2/dose on days 1, 3, and 5, and etoposide 100 mg/m^2/dose on days 1–5. The AAML1031 approach equated to 50% more cytarabine exposure (20 vs. 13.6 g/m^2) and 15%–78% more anthracycline exposure (342–534 vs. 300 mg/m^2 doxorubicin equivalents) over the first three cycles of chemotherapy.

2.3 | Outcomes

Patients were observed from the start of induction II through last available follow-up. The primary protocol-described outcomes were DFS and OS. DFS was defined as the time from end of induction I to induction failure, relapse, secondary malignancy, or death. OS was defined as time from end of induction I to death. We anticipated that DFS and OS would be confounded due to differences in approach to SCT between the two trials. Therefore, we included secondary outcomes proximal to transplant to evaluate treatment response: complete remission (CR)/CR incomplete recovery (CRi) rate and MRD at the end of induction II and intensification I; and median change in MRD between end of induction I and end of induction II chemotherapy. Secondary outcomes to evaluate toxicity included hematologic toxicity, infections, course length, hospital stay, and intensive care unit (ICU) days. Additional resource utilization and cost outcomes were examined in a subset of patients treated at hospitals contributing to the Pediatric Health Information System (PHIS), as described previously.[23]

2.4 | Covariates

Demographic information including sex, age at diagnosis, race, Hispanic ethnicity, central nervous system disease, end induction marrow response, and cytogenetics were obtained from the COG study databases for AAML0531 and AAML1031.

2.5 | Analysis

Patient characteristics and treatment responses were compared by study using chi-square test, or, in the event of sparse data, Fisher's exact test. Medians for continuous characteristics were compared using the Mann–Whitney test. The Kaplan–Meier method was used to compare DFS and OS from end of induction I for patients who continued on protocol; patients were censored at date of last known contact. Multivariable cox models were constructed to adjust for baseline variables that were unbalanced between the two trials. Inpatient treatment costs were summarized as means, and crude cost ratios were estimated from a general linear model with gamma distribution to compare costs between studies. Poisson regression was used to compare resource utilization rates with resource days as the outcome, inpatient days as the offset, and Pearson scale adjustment for overdispersion. These methodologies have been described in detail previously.[24,25] Sensitivity analyses were performed to compare survival and toxicities between the standard and experimental arms of AAML1031 to determine if the inclusion of bortezomib as an experimental agent was associated with differential outcomes. Data from AAML0531 and AAML1031 were current as of December 31, 2019. All analyses were performed using SAS (version 9.4, SAS Institute, Inc., Cary, NC).

3 | RESULTS

A total of 124 patients were treated on AAML0531 ($n = 29$) or AAML1031 ($n = 95$) and met criteria for inclusion in the current analyses (Figure 1). Patient characteristics are shown in Table 1 and the distribution of high-risk features differed between trials. Patients on AAML1031 had a higher disease burden at the end of induction I by MRD (25% vs. 16%, $p = .027$) and morphology (median blast percentage 30% vs. 16.5%, $p = .097$). More patients on AAML0531 had monosomy 5/del5q compared to AAML1031 (34.5% vs. 10.6%, $p = .002$). Following intensification I, 13 of 29 (44.8%) patients on AAML0531 continued on protocol-directed therapy, including nine of 13 who proceeded to SCT. On AAML1031, 24 of 95 (25.3%) patients continued on protocol-directed therapy and 19 of 24 underwent SCT.

3.1 | Comparison of survival and disease response

Figure 2 presents the Kaplan–Meier estimates for DFS and OS from end of induction I. High-risk patients treated on AAML1031 did not have different 5-year DFS (24.2% ± 8.8% vs. 18.3% ± 14.7%, $p = .632$) or OS (34.6% ± 10.1% vs. 37.9% ± 18.0%, $p = .658$) compared to AAML0531. In the sensitivity analysis that considered the two arms of AAML1031 separately, Kaplan–Meier estimates of DFS and OS were similar in all three groups. In this group, 5-year DFS on AAML1031 arm A was 28.7% ± 13.5% and on arm B was 20.0% ± 11.3%, and 5-year OS on AAML1031 was 36.6% ± 15.2% and 32.3% ± 13.5% on arms A and B, respectively. The corresponding survival curves are shown in Figure S1.

Similarly, there was no improvement in treatment response at end of induction II as a result of inclusion of MA (Table 2). On AAML1031, 63.7% of patients who received MA as induction II achieved a CR/CRi compared to 62.1% of patients who received ADE as induction II on AAML053 ($p = .871$). At the end of induction II, there were no statistically significant differences in the proportion with positive MRD ≥0.1% or median MRD between

the two trials. Intensification I treatment was identical between the two trials, and end-intensification I disease evaluation also did not reveal any statistically significant differences between the studies. While patients in the AAML1031 cohort had higher mean MRD at the start of induction II, there was no significant difference in the median percentage change of MRD from induction I to either end induction II (−12.7 vs. −18.0, $p = .788$), or end intensification I (−22.4 vs. −15.8, $p = .676$).

As the proportion of patients who met the high-risk definition by cytogenetics or end induction I disease response differed between the two trials (Table 1), we performed a post hoc multivariable Cox analysis to evaluate if survival was confounded by these variables. This analysis did not identify a difference between DFS and OS on the two trials: DFS-adjusted HR 0.67, 95% CI 0.41–1.10 and OS-adjusted HR 0.95, 95% CI 0.56–1.64. The full multivariable model is shown in Table 3. To further explore this, we performed stratified analyses in subgroups of patients who were high risk by cytogenetics ($n = 49$) and by disease response ($n = 86$). The end induction I disease response or OS estimates were similar to the overall estimates and did not demonstrate a difference by induction II regimen in either strata (Table S2). The point estimates did suggest a potential benefit of MA compared to ADE relative to DFS for patients who were high risk by disease response (DFS 0% vs. 16.7%, $p = .154$).

3.2 | Comparison of toxicity

Patients on AAML1031 who received MA had a significantly lower probability of neutrophil and platelet recovery and significantly longer median time to recovery of both cell lines in induction II (Table 4). In addition, patients on AAML1031 had more median hospital days during induction II (32 [range 5–72] vs. 28 [range 1–49] days, $p = .013$). Hematologic toxicity, course length, and hospital days in intensification I were not statistically significantly different between the two trials (Table 4). The proportion of patients requiring ICU care was similar in both courses. In addition, the proportion of patients who experienced microbiologically documented infectious toxicity in induction II and intensification I did not differ between the two trials (Table 4). Importantly, there was no evidence of increased hematological toxicity or course length among AAML1031 patients allocated to bortezomib versus not (Table S3) nor was it differential by end induction I disease status (Table S4).

3.3 | Comparisons of resource utilization and cost

There were 9 and 27 patients from AAML0531 and AAML1031, respectively, identified in PHIS. These patients were representative of the larger cohorts of patients included in these analyses (Table S5). The induction II costs did not differ significantly between trials when total course cost was compared (cost ratio 1.41 [95% CI 0.86–2.29], $p = .17$) or cost per day was compared (cost ratio 1.26 [95% CI 0.92–1.74], $p = .15$) (Table S6). Rates of specific resource utilization did not differ between trials after accounting for inpatient days (Table S7).

4 | DISCUSSION

The COG trial AAML1031 modified therapy for patients with high-risk AML by intensifying induction II chemotherapy with MA (mitoxantrone and cytarabine 8000 mg/m^2), using busulfan/fludarabine as SCT conditioning and liberalizing donor eligibility. The data comparing AAML0531 and AAML1031 outcomes do not demonstrate a survival benefit for pediatric patients with high-risk AML as a result of those changes, although the relative contribution of each change cannot be parsed. These two trials demonstrated equivalent rates of remission induction after induction II, an outcome that was not confounded by changes in the SCT approach between the two trials. As remission induction is highly correlated with survival in AML,[22,26-28] together these data suggest that there is no short- or long-term benefit especially as a result of intensified induction II chemotherapy. Although the chemotherapy intensification did not improve outcomes, it was associated with additional hematologic toxicity and longer time to course completion.

Compared to a backbone of cytarabine and daunorubicin, attempts have been made to intensify induction in order to more effectively induce or maintain remissions, including increasing cytarabine exposure, using alternative anthracycline agents, or incorporating additional chemotherapeutic agents. To date, the evidence supporting any of these approaches has been limited.

Prior studies have compared low-dose cytarabine (100–200 mg/m^2) to intermediate and high-dose cytarabine (1000–3000 mg/m^2 BID) on backbones that vary the number of induction cycles, additional agents, and methods to evaluate treatment response. A comparison of successive AML Berlin–Frankfurt–Münster (BFM) group studies reported that an additional cycle containing cytarabine (3000 mg/m^2) and mitoxantrone in induction was associated with improved survival in high-risk[16] and cytogenetically favorable *RUNX1-RUNX1T1*[29] AMLs compared to patients treated on the predecessor trial. In addition, the AML-12 study performed by the European Organization for Research and Treatment of Cancer and Research and Gruppo Italiano Malattie Ematologiche dell' Adulto randomized young adults to induction with high- (total 24,000 mg/m^2) or low-dose cytarabine (total 1000 mg/m^2). Intensified cytarabine was associated with superior CR rate and 6-year OS for patients younger than 46 years.[19] The authors hypothesized that the survival benefit was due to improvements in supportive care and the availability of more intensive postremission strategies. In contrast, three analyses, Pediatric Oncology Group 9421, St. Jude AML02, and Medical Research Council (MRC) AML-12, did not show a benefit to intensified induction, with similar CR rates, EFS, and OS between treatment approaches.[17,18,30]

Prior pediatric studies have also examined the utility of incorporating alternative anthracycline or anthracenediones in induction.[5,15,16] As above, the use of mitoxantrone in combination with an extra cycle of high-dose cytarabine improved outcomes on the BFM 93 trial.[16] Similarly, results of the MRC AML12 trial suggested that substituting mitoxantrone for daunorubin during induction improved DFS. However, this survival benefit was offset by increased treatment-related mortality.[5] Importantly, in adults, dose intensification of anthracyclines during induction has not consistently improved response rates and overall survival.[31-34]

These analyses do suggest that MA is associated with increased hematologic toxicity as evidenced by longer time to both neutrophil and platelet recovery in induction II. This effect may persist even beyond induction II, as our analyses suggest increased hematologic toxicity after identical consolidation I chemotherapy as well. The increase in hospital days for patients treated with MA, likely as a result of delayed count recovery, has important implications for health services delivery.[25,35] In addition, these analyses did not capture late effects of treatment, but the use of mitoxantrone on AAML1031 may confer an increased risk of long-term cardiotoxicity compared to daunorubicin.[36-38]

This observational study is limited by its use of historic controls, leading to potential misclassification and confounding.[39,40] Figure 1 highlights the limitations of such a study, demonstrating the small proportion of patients that met inclusion criteria for these analyses and imbalance in patient and disease charateristics between studies. Risk of misclassification in this analysis was mitigated through the stringent inclusion criteria employed for inclusion on these analyses and the requirement that patients meet high-risk criteria common to both trials. With regards to confounding, unobserved differences in supportive care and SCT strategies would be expected to bias in favor of AAML1031, the more recent clinical cohort,[4,6,7,39,40] so an absence of improved outcomes on the later trial further reinforces that intensified induction may not confer a survival advantage. Furthermore, the post hoc analysis that controlled for important unbalanced clinical criteria between the trials did not substantially change the response rate or survial estimates. Finally, this study was limited by its modest sample size, particularly among patients who continued on protocol-defined SCT, which may have limited our ability to detect a true association in either direction.

In conclusion, data from AAML0531 and AAML1031 do not suggest a disease response or overall survival benefit from higher dose cytarabine and mitoxantrone in induction II in pediatric high-risk AML in the context of COG chemotherapy, even in the modern era of supportive care and broader transplant criteria. Despite the acknowledged limitations to this study, these are the best data available to guide selection of COG backbone chemotherapy for future high-risk clinical trials, and importantly these data provide a clear signal of increased hematologic toxicity associated with MA. In the context of increased toxicity and an absent signal of efficacy, the next-generation COG Phase III trial, AAML1831, has reverted to the prior backbone and now uses low-dose cytarabine with daunorubicin as induction II for high-risk AML patients. Unfortunately, these analyses underscore that despite intensified therapy in both the induction and postremission phases, survival for children with high-risk AML remains unacceptably poor. Alternative approaches that incorporate rationally designed targeted therapies are urgently needed to achieve cure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ADE	cytarabine/daunorubicin/etoposide
AML	acute myeloid leukemia
BFM	Berlin–Frankfurt–Münster
COG	Children's Oncology Group
CR	complete remission
DFS	disease-free survival
GO	gemtuzumab ozogamicin
ICU	intensive care unit
IRB	institutional review board
MA	mitoxantrone/cytarabine
MRC	Medical Research Council
MRD	measurable residual disease
PHIS	Pediatric Health Information System
SCT	stem cell transplant

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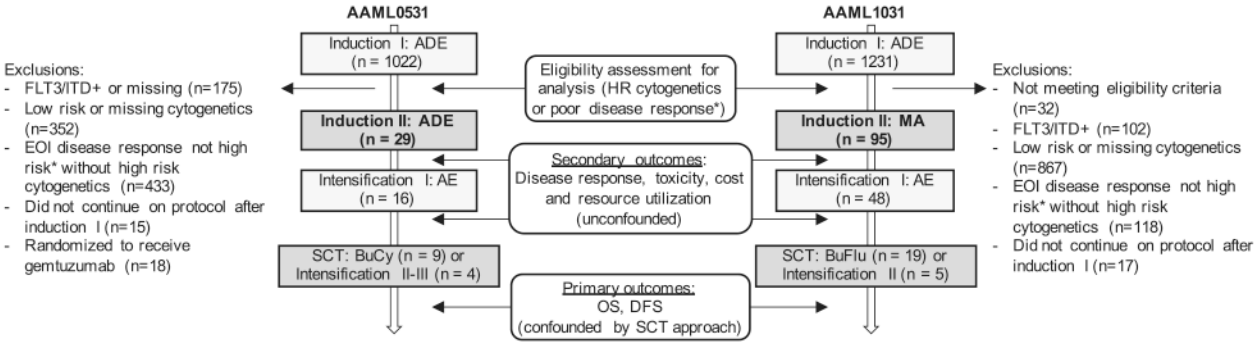

*By criteria common to two trials: HR cytogenetics - Monosomy 7, Monosomy 5, or deletion 5q; Disease response - residual blasts > 15% by morphology *and* MRD ≥ 0.1%
ADE: Cytarabine, Daunorubicin, Etoposide; MA: Cytarabine, Mitoxantrone; AE: Cytarabine, Etoposide; BuCy: Busulfan, Cyclophosphamide; BuFlu: Busulfan, Fludarabine; OS Overall survival; DFS Disease Free Survival; EMD Extramedullary Disease; HR High Risk; EOI End of Induction; MRD Measurable Residual Disease; EMD Extramedullary Disease

FIGURE 1.

Schematic of therapy for high-risk patients on AAML0531 and AAML1031. Patients were included for analysis if they met high-risk criteria common to both trials: cytogenetics (7-, 5-, del5q), or poor disease response requiring morphological blasts >15%, and measurable residual disease (MRD) ≥0.1%. Exclusions and timing of outcome ascertainment are shown

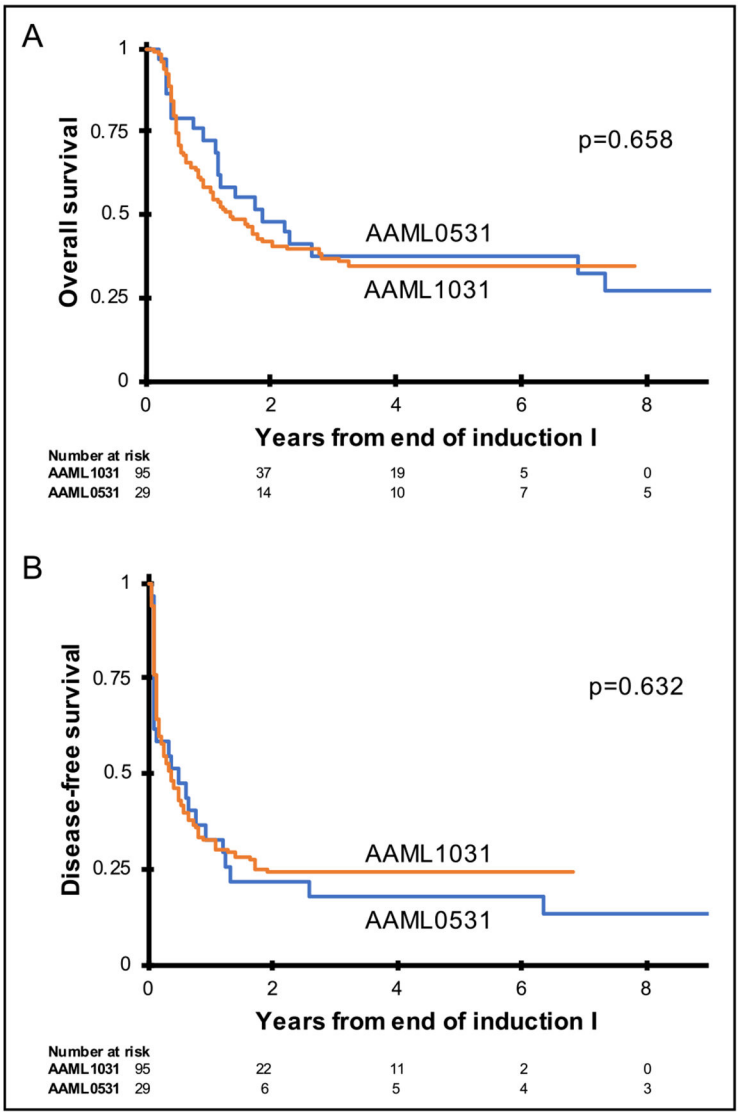

FIGURE 2.

Kaplan–Meier curves for overall survival (A) and disease-free survival (B) comparing high-risk patients treated on AAML0531 arm A and AAML1031

TABLE 1

Characteristics of high-risk[a] AML study population

	AAML0531 (arm A)	AAML1031	*p*-Value
Total, *N*	29	95	
Sex			
Male	16 (55.2%)	55 (57.9%)	.795
Female	13 (44.8%)	40 (42.1%)	
Age at diagnosis, years			
Median (range)	9.95 (0.88–29.8)	9.03 (1.08–24.7)	.549
0–1	6 (20.7%)	14 (14.7%)	.564
2–10	11 (37.9%)	45 (47.4%)	.371
11–20	11 (37.9%)	32 (33.7%)	.674
≥21	1 (3.4%)	4 (4.2%)	1.000
Race			
American Indian or Alaskan Native	0 (0.0%)	2 (2.5%)	1.000
Asian	1 (3.7%)	3 (3.8%)	1.000
Black or African American	8 (29.6%)	15 (18.8%)	.234
White	18 (66.7%)	60 (75%)	.400
Unknown	2 (6.9%)	15 (15.8%)	
Ethnicity			
Hispanic or Latino	6 (21.4%)	20 (22.0%)	.951
Not Hispanic or Latino	22 (78.6%)	71 (78.0%)	
Unknown	1 (3.4%)	4 (4.3%)	
CNS disease classification at study entry			
CNS1	25 (86.2%)	71 (75.5%)	.258
CNS2	3 (10.3%)	16 (17.0%)	.559
CNS3	1 (3.4%)	6 (6.4%)	1.000
Unknown	0 (0.0%)	2 (2.1%)	
Adverse cytogenetics[b]			
Monosomy 7	9 (31.0%)	19 (20.2%)	.224
Monosomy 5/del5q	10 (34.5%)	10 (10.6%)	.002

	AAML0531 (arm A)	AAML1031	*p*-Value
End induction I marrow response			
Median MRD% (range)	16 (0–73)	25 (0–92)	.027
Median blast percentage by morphology (range)	16.5 (0–89)	30 (0–89)	.097
Criteria for high-risk definition			
Cytogenetics	15 (51.7%)	23 (24.2%)	.005
Disease response	11 (37.9%)	64 (67.4%)	.005
Both	3 (10.3%)	8 (8.4%)	.718
Patients proceeding to transplant, *n*	9	19	
Matched sibling	1(11.1%)	3 (15.8%)	
Unrelated	8 (88.9%)	16 (84.2%)	1.000

Note: Data presented as *n* (%) unless otherwise noted.

Abbreviations: AML, acute myeloid leukemia; CNS, central nervous system; MRD, measurable residual disease.

[a] High risk based on criteria mutual to both studies.

[b] Specific cytogenetics unknown for two patients.

TABLE 2

Disease response

	AAML0531 (arm A)	AAML1031	*p*-Value
Induction II			
Total, *N*	29	95	
Response			
Clinical remission	18 (62.1%)	58 (63.7%)	
Refractory/relapse	11 (37.9%)	33 (36.3%)	0.871
Death	0 (0.0%)	0 (0.0%)	
Not evaluable	0	4	
MRD evaluation			
Median MRD (range)	0.01 (0.0–46.0)	0.4 (0.0–75.0)	.426
MRD positive (>0.1)	10 (45.5%)	41 (56.9%)	.344
Unknown MRD	7 (24.1%)	23 (24.2%)	
Median MRD change from end induction I (range)	−18.0 (−39.2, −3.02)	−12.7 (−78.9,32)	.788
Intensification I			
Total, *N*	16	48	
Response			
Clinical remission	15 (93.8%)	38 (79.2%)	.265
Relapse	1 (6.3%)	9 (18.8%)	.429
Death	0 (0.0%)	1 (2.1%)	1.000
MRD evaluation			
Median MRD (range)	0.0 (0.0–4.4)	0.0 (0.0–15.0)	.523
MRD positive (>0.1)	1 (20.0%)	8 (26.7%)	1.000
Unknown MRD	11 (68.8%)	18 (37.5%)	
Median MRD change from end induction I (range)	−15.8 (−18.0, −13.6)	−22.4 (−68.0, 0.2)	.676

Note: Data presented as *N* (%) unless otherwise noted.

Abbreviation: MRD, measurable residual disease.

TABLE 3

Multivariable Cox analyses for disease-free survival and overall survival from end of induction 1

		Disease-free survival			Overall survival		
	N	**HR**	**95% CI**	***p*-Value**	**HR**	**95% CI**	***p*-Value**
Study							
AAML0531 arm A	29	1			1		
AAML1031	95	0.67	0.41–1.10	.112	0.95	0.56–1.64	.873
High-risk cytogenetics							
None	75	1			1		
Present	49	1.51	0.77–2.98	.235	2.64	1.32–5.28	.006
End induction MRD							
Negative	38	1			1		
Positive	86	3.69	1.70–7.99	.009	3.59	1.63–7.94	.002

Abbreviations: HR, hazard ratio; MRD, measurable residual disease.

TABLE 4

Hematologic and infectious toxicity, hospital days, and course length

	AAML0531 (arm A)	AAML1031	*p*-Value
Induction II			
Total, *N*	29	95	
Neutrophil recovery (ANC >500 cells/ml)			
Patients recovered	23 (79.3%)	50 (52.6%)	.011
Days to recovery, median (range)	27 (22–58)	34 (19–73)	.007
Platelet recovery (platelets >50,000/ml)			
Patients recovered	24 (82.8%)	57 (60.0%)	.024
Days to recovery, median (range)	24.5 (11–62)	29 (14–63)	.040
Days in course, median (range)	35 (21–69)	40 (16–115)	.007
Hospital days, median (range)	28 (1–49)	32 (5–72)	.013
ICU days, median (range)	4 (1–28)	4 (1–54)	.859
Bacterial infection	8 (27.6%)	27 (28.4%)	.930
Viridans group streptococcus	3 (10.3%)	14 (14.7%)	.760
Gram negative bacilli	4 (13.8%)	6 (6.3%)	.241
Fungal infection	0 (0.0%)	3 (3.2%)	1.000
Intensification I			
Total, *N*	16	48	
Neutrophil recovery (ANC >500 cells/ml)			
Patients recovered	12 (75.0%)	37 (77.1%)	1.000
Days to recovery, median (range)	25 (19–33)	28 (21–49)	.052
Platelet recovery (platelets >50,000/ml)			
Patients recovered	10 (62.5%)	35 (72.9%)	.530
Days to recovery, median (range)	23 (15–30)	28(19–55)	.011
Days in course, median (range)	38.5 (1–73)	45.5 (25–66)	.121
Hospital days, median (range)	23 (1–38)	48 (5–66)	.067
ICU days, median (range)	2 (1–3)	11.5 (2–20)	.088
Bacterial infection	5 (31.3%)	20 (41.7%)	.460
Viridans group streptococcus	1 (6.3%)	8 (16.7%)	.430
Gram-negative bacilli	1 (6.3%)	10 (20.8%)	.265

	AAML0531 (arm A)	AAML1031	*p*-Value
Fungal infection	0 (0.0%)	0 (0.0%)	

Note: Data presented as *n* (%) unless otherwise noted.

Abbreviation: ANC, absolute neutrophil count.