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Clofarabine plus low-dose cytarabine is as effective as and less toxic than intensive chemotherapy in elderly AML patients

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Abstract

Most patient with acute myeloid leukemia (AML) age ≥60 are not offered intensive induction because of high mortality. Phase 2 studies of clofarabine plus low-dose cytarabine (CLDA) as frontline therapy for elderly AML patients demonstrated high response and acceptable toxicity. We hypothesized that induction therapy with CLDA provides equivalent outcomes to but is less toxic than intensive induction in these patients. To test this hypothesis, we conducted a propensity score-matched comparison of AML patients age ≥60 given induction CLDA versus idarubicin and cytarabine (IA). Ninety-five patients in both groups were matched according to their propensity score. We did not observe statistically significant differences in response, overall survival, or mortality rate between the two induction regimens. However, CLDA produced significantly fewer grade 3 or worse toxicities (46% for CLDA versus 62% for IA; $P = .03$). Furthermore, among responders, the median response duration was significantly longer with CLDA when we censored patients who underwent stem cell transplantation (15.9 months for CLDA versus 7.0 months for IA; $P = .033$). Compared with intensive induction, CLDA offers equivalent responses and survival but less toxicity in clinically well-matched cohorts of elderly AML patients. Prospective randomized trials to confirm these findings are warranted.

Introduction

Survival of acute myeloid leukemia (AML) in young patients has improved over the past few decades. However, outcomes of AML in elderly patients remain dismal.[1] One of the

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Authorship

Contribution: K.T. designed the study, collected and analyzed data, and wrote the manuscript. H.K., F.R., G.G.M., G.B., C.D., E.J., M.K., and M.A. treated the patients, managed the clinical trials, and reviewed the manuscript. S.P. collected data and reviewed the manuscript. J.C. designed the study, analyzed data, organized the project, and wrote the manuscript.

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challenges in treating AML in elderly patients is that patient and disease characteristics affect the treatment choices and decrease the probability of success. Many measurable and unmeasurable confounding factors influence decision-making for induction therapy in elderly patients, such as comorbidities, patient wishes, performance status, and physician preference. As a result, only a minority of elderly AML patients undergo intensive induction chemotherapy, with the majority of them offered low-intensity therapy such as low-dose cytarabine, 5-azacitidine, and decitabine, mostly with palliative intent.[2,3] Although these low-intensity therapies are well tolerated and provide a survival benefit over best supportive care, complete remission (CR) is achieved at the best in 25% of the patients, and prolongation of survival is marginal.[4–6]

We previously reported the results of two phase 2 clinical trials investigating the efficacy of frontline therapy with clofarabine plus low-dose cytarabine (CLDA) in elderly patients with newly diagnosed AML.[7–9] In these trials, 50–60% of the treated patients achieved CR, median overall survival was 11–13 months and the treatment-related mortality rate was 7–20%; these findings were comparable with those previously reported with intensive induction chemotherapy in similar patients. We therefore investigated whether patients treated with CLDA, a regimen that is generally better tolerated among older patients, might result in at least equivalent outcomes compared to intensive induction chemotherapy, but perhaps better tolerated. To test this hypothesis, we compared the efficacy, toxicity, and outcomes of patients with newly diagnosed AML who were at least 60 years old treated with CLDA to historical similar patients treated with intensive induction chemotherapy with idarubicin and high-dose cytarabine (IA). Given the intrinsic nature of patient selection bias with the two regimens, we controlled for known pretreatment confounding factors by using propensity score (PS) matching.

Methods

Patients

Seven hundred eighty-eight patients with previously untreated AML who were at least 60 years old and received frontline therapy at The University of Texas MD Anderson Cancer Center from 2002 to 2012 were identified. Of these patients, 192 received induction therapy with CLDA in one of two clinical trials: NCT00088218 (n = 78) and NCT00778375 (n = 114). In comparison, 133 patients received induction therapy with the IA regimen: 45 patients as part of the NCT00422591 trial, and 88 patients outside of the trial. Patients received CLDA treatment between 2004 and 2011 whereas IA treatment was given between 2002 and 2012. Patients who had received prior therapy for antecedent hematological disorders (AHDs), such as hypomethylating agents (HMA) for myelodysplastic syndromes and had progressed to AML were included in the analysis, provided that CLDA or IA was the first therapy for AML. This research protocol was approved by the MD Anderson Institutional Review Board, and the study was conducted in accordance with the Declaration of Helsinki.

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Induction regimens

Details of the two clinical trials of the CLDA regimen as frontline therapy for AML in elderly patients were described previously.[7,8] Briefly, patients in the NCT00088218 trial received daily intravenous injections of 30 mg/m^2 clofarabine on days 1–5 and once-daily subcutaneous injections of 20 mg/m^2 cytarabine on days 1–14. Patients in the NCT00778375 trial received daily intravenous injections of 20 mg/m^2 clofarabine on days 1–5 and twice-daily subcutaneous injections of 20 mg cytarabine on days 1–10.

All of the patients undergoing the IA regimen received idarubicin 12 mg/m^2 daily on days 1–3 and cytarabine 1.5 g/m^2 daily on days 1–3.

At least for the first course of induction therapy, all patients were admitted to the hospital and given treatment in a laminar airflow-protected environment. Additionally, all patients received prophylactic antibiotics, antifungals, and antivirals during induction therapy.

Postremission therapy

The details on the postremission therapy in the two CLDA trials were described previously.[7,8] Briefly, in the NCT00088218 trial, patients who had CR alone or CR with insufficient platelet recovery (CRp) received up to 12 cycles of consolidation therapy with attenuated doses of clofarabine and cytarabine (clofarabine 30 mg/m^2 intravenous injection daily on days 1–3 and cytarabine 20 mg/m^2 subcutaneous injections daily on days 1–7). In the NCT00778375 trial, responders received up to 17 cycles of consolidation therapy alternating with attenuated doses of CLDA (clofarabine 20 mg/m^2 intravenous injection daily on days 1–3 and cytarabine 20 mg subcutaneous injections twice-daily on days 1–7) and daily intravenous injections of 20 mg/m^2 decitabine for 5 days in blocks of three cycles. Patients whose AML responded to induction IA received up to six additional cycles of consolidation therapy with attenuated doses of idarubicin (8 mg/m^2 daily for 2 days) and cytarabine (0.75 g/m^2 daily for 3 days).

Term definitions

Response to treatment was defined according to the recommendations of the International Working Group[10]. Overall survival (OS) duration was defined as the time from the date of first therapy to that of death or last follow-up, whichever came first. For patients who experienced either CR or CRp, the CR duration was calculated as the time from the beginning of response to therapy to loss of response or death, whichever occurred first.

Statistical methods

The chi-square or Fisher exact test was used to assess differences in categorical variables, and the Mann-Whitney *U* test was used to analyze continuous variables. Also, the log-rank test was used to examine between-group differences in OS. The propensity score (PS) for each patient was calculated by conducting multilogistic regression analysis against the type of induction treatment (CLDA versus IA)[11]. Seven dichotomized variables were entered into the multilogistic regression: age (≥70 years versus <70 years), serum creatinine level (>1.3 versus ≤1.3 mg/dL), serum total bilirubin level (>1.5 versus ≤1.5) BM blast count (≥30% versus <30%), cardiac ejection fraction (EF; >40% versus ≤40%), Eastern Cooperative

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Oncology Group (ECOG) performance status (2–4 versus 0–1), and Medical Research Council cytogenetic risk (high risk versus low and intermediate risk).[12]. These clinical factors were selected because they likely influence physician's decision-making regarding induction therapy and have been shown to impact treatment outcome of elderly AML patients[13]. We used 70 years as a cut-off for age because previous studies have shown that intensive chemotherapy may not benefit to most of the patients with at least age 70[14]. Cut-off for creatinine and bilirubin followed the normal upper limit of lab value in our institution. We used 40% as an EF cut-off following the definition of systolic dysfunction in European Society of Cardiology Guidelines[15]. PS matching of the patient cohorts was then conducted using a caliper of 0.25 standard deviation[16,17]. More stringent caliper was tried but 0.25 gave the best matching model. Statistical analyses were performed using the R statistical programming language (version 3.1.3) and the SPSS software program (version 22; IBM Corporation, Armonk NY).

Results

Clinical characteristics of the prematching cohorts

The pretreatment patient characteristics before PS matching are listed in Supplemental Table 1. Several clinical parameters differed significantly between the two groups. For instance, the CLDA group had a better pretreatment serum creatinine level, lower white blood cell (WBC) count, lower serum lactate dehydrogenase (LDH) level, lower BM blast count, and better ECOG performance status. Although the median EF was not different between the two groups, the CLDA group had 5 patients whose EF was less than 40%, while none of the patient in the IA group had it. These differences were likely secondary to differences in the enrollment criteria between the two groups. For example, the CLDA protocols specifically excluded patients with renal dysfunction while 88 patients were treated with IA off protocol, thus with no strict eligibility criteria. Also, patients with systolic dysfunction were less likely to be treated with IA. Furthermore, the WBC count and LDH level differed because patients who had proliferative disease at presentation were more likely to undergo intensive induction chemotherapy outside a clinical trial such as IA.

PS matching

The PS distributions in the two patient groups are shown in Supplemental Figure 1. Caliper matching resulted in matching of 95 patients in both cohorts according to their pretreatment characteristics (Table 1). After PS matching, the pretreatment clinical characteristics in the two groups were well balanced except for less pronounced but still detectable differences in WBC count and LDH level.

Response to treatment and response duration in matched cohort

Table 2 lists the response rates for the two cohorts. Although the CLDA group had a higher cumulative CR rate, there was no statistically significant difference between the two groups regarding the occurrence of CR within the first two courses of induction therapy (57% in the CLDA group versus 46% in the IA group; $P = .09$). Among responders, 96% of those treated with CLDA achieved CR within two cycles of induction therapy (one achieved CR after 3 courses and one after 6 courses), whereas 100% of the ones treated with IA did so. In

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analysis sub-grouped by patient characteristics, there was a higher response rate with CLDA than with IA in patients with low WBC counts and no history of AHDs (Supplemental Table 2).

The median CR duration was 12.0 months (95% confidence interval [CI], 7.3–16.8 months) in the CLDA cohort and 10.6 months (95% CI, 7.4–13.9 months) in the IA cohort ($P = .82$) (Figure 1A). After censoring patients who underwent stem cell transplantation (SCT) in first CR, responders in the CLDA group had a significantly longer median CR duration (15.9 months [95% CI, 7.4–23.4 months]) than did those in the IA group (7.0 months [95% CI, 3.2–10.8 months]; $P = .033$) (Figure 1B).

Postremission therapy and bridging to SCT in matched cohort

Among responders, the median numbers of consolidation courses was 3 (range, 0–17) in the CLDA group and 2 (range, 0–6) in the IA group ($P = .06$). There was no statistically significant difference in the number of patients bridged to SCT in first CR between the two groups (6% in the CLDA group versus 5% in the IA group; $P = .99$).

Treatment-related toxic effects and early mortality rate in matched cohort

Table 3 compares the treatment-related toxicities and early mortality rates for the two groups. The proportion of patients who experienced grade 3 or worse treatment-related adverse effects during induction was significantly lower in the CLDA group (46% versus 62% in the IA group; $P = .03$). However, the induction-related mortality rates at 4 and 8 weeks in the two groups were similar (6% in the CLDA group versus 10% in the IA group at 4 weeks and 14% versus 15% at 8 weeks; $P = .42$ and .84, respectively). The median hospital stays during the first induction course was similar in the two groups (27 days in the CLDA group versus 26 days in the IA group; $P = .85$) (data not shown).

Overall Survival in matched cohort

The difference in median OS duration between the CLDA (11.4 months [95% CI, 7.3–15.5 months]) and the IA groups (9.3 months [95% CI, 6.9–11.7 months]) was not statistically significant ($P = .34$) (Figure 2). In an analysis of the patients subgrouped according to their characteristics, there was no difference in OS between the two groups according to age ($\geq$70 years versus <70 years), adverse risk cytogenetics versus favorable or intermediate risk cytogenetics, *FLT3* internal tandem duplication (*FLT3*-ITD) versus wild-type *FLT3*, BM blast count (>30% versus $\leq$30%), WBC count (>20×10^9/L versus $\leq 20 \times 10^9$/L), history of AHD, therapy-related AML, and ECOG performance status ($\geq$2 versus <2). Multivariate Cox proportional hazard regression analysis of OS demonstrated that adverse risk cytogenetics, age of at least 70 years, and a performance status of at least 2 adversely affected OS but that the induction regimens did not affect it (Supplemental Table 3).

Discussion

Several studies have evaluated the benefit of intensive induction chemotherapy in older patients with AML.[13,14,18–20] Although there is considerable controversy regarding what patients in this category should be treated with intensive chemotherapy, a subset of elderly

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AML patients clearly does benefit from this induction therapy.[14,21,22] Hence, for older AML patients, it is regular practice to first evaluate for fitness and desire for intensive induction therapy.[23,24] Those who are not deemed to be adequate candidates are usually offered low-intensity therapy, such as low-dose cytarabine or demethylating agents. Several factors can influence this decision-making process. An analysis of the Swedish Acute Leukemia Registry suggested that the propensity to choose more intensive therapy differs significantly according to the location of where patients are treated.[2,3] Also, the AML 14 trial in the United Kingdom suggested that the treating physician's preference was one of the key components of treatment selection.[25] These results underscore that not all older patients have equal chances to receive CR-targeting therapy because of the fear of high morbidity and mortality rates regarding intensive induction chemotherapy. In that context, our group as well as others have attempted to build prognostic models for elderly AML patients to better define the subset of patients who would tolerate and benefit from intensive induction[13,14,26–30].

In the present study, we sought to determine whether an intermediate-intensity approach, such as the CLDA regimen, may be useful to treat this patient population. Intermediate-intensity induction therapy may have fewer treatment-associated toxicity than intensive induction regimens but may still offer the possibility of achieving CR, possibly durable in at least some patients. Such an approach would provide wider access to CR-targeting treatments to a significant percentage of older AML patients who are traditionally offered low-intensity therapy because of the concern of high treatment-related morbidity and mortality rates with intensive therapy. We first sought to retrospectively compare the efficacy, toxicity, and outcomes of the CLDA and IA regimens. We chose the CLDA regimen for intermediate-intensity induction therapy because previous phase 2 studies demonstrated it to have promising results in terms of response rate and toxicity in elderly AML patients. However, no randomized trial exists of this regimen compared to a more intensive approach making the true impact of these results less clear. Because of the intrinsic nature of patient selection bias, we used PS matching to balance pretreatment confounding factors in the two cohorts. Although matching made the cohorts smaller, it allowed for head-to-head comparison of the two regimens in a clinically well-balanced population that minimized intergroup heterogeneity. The data presented herein demonstrate that the two regimens had equivalent response rates and outcomes but that the CLDA regimen had significantly fewer treatment-associated toxic effects than the IA regimen. An interesting finding was that the median CR duration in responders in the CLDA group was significantly longer than that in the IA group after censoring patients who underwent SCT at the time of transplantation. This can be explained by well-tolerated prolonged consolidation therapy offered in CLDA trials. Although the median numbers of consolidation courses of the two regimens were not statistically significantly different, 18 (19%) patients in the CLDA group received more than six courses of consolidation therapy, which is more than the maximum number of consolidation courses the patients in the IA group could receive.

Although we tried to carefully balance the pretreatment confounding factors, interpretation of these data still requires some caution. First, PS matching can only control for measurable pretreatment characteristics, so biasing of the results by unmeasurable or latent pretreatment characteristics is possible. Second, the dosing and schedules of the CLDA regimens were

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somewhat heterogeneous. Specifically, the NCT00088218 trial used 30 mg/m^2 clofarabine, whereas the NCT00778375 trial used 20 mg/m^2 clofarabine. The frequency and duration of treatment with cytarabine also differed in the two trials (10 days for NCT00778375 versus 14 days for NCT00088218). Third, the postremission therapy in the two trials also was heterogeneous. Although the numbers of patients who underwent SCT in the two groups were comparable, patients receiving one of the CLDA regimens also received decitabine as part of postremission therapy. These heterogeneities may have biased outcome. Fourth, matched patients in our study were highly selected. Most of the matched patients had good performance status and normal organ function. This may not be a direct reflection of the elderly AML population of the majority. In fact, the early mortality rates at 4 and 8 weeks of intensive induction therapy were much lower than those reported previously.[31] Finally, the "control" group was treated with an IA regimen that is more intensive and not exactly akin to the more widely used "3+7" regimen. However, results similar to those achieved with IA in our series have been reported with 3+7 in older patients with AML (CR 43%, early mortality 19%)[22]. With all of these caveats in mind, we believe that the CLDA regimen, at minimum, is equally effective as the IA regimen in selected patients with elderly AML. This result warrants further validation in prospective randomized trials.

In summary, our analysis suggests that treatment with CLDA results in responses and outcomes equivalent to those for achieved with a more intensive induction therapy but is associated with fewer treatment-related toxic effects in clinically well-matched cohorts of elderly patients with newly diagnosed AML. It also allows for use of prolonged courses of consolidation therapy because of low toxicity, which may translate into improved CR durations. Introducing the use of intermediate-intensity induction therapy may expand access to CR-targeting therapy for patients traditionally considered to be unfit for intensive induction therapy. Prospective randomized trials to confirm these findings are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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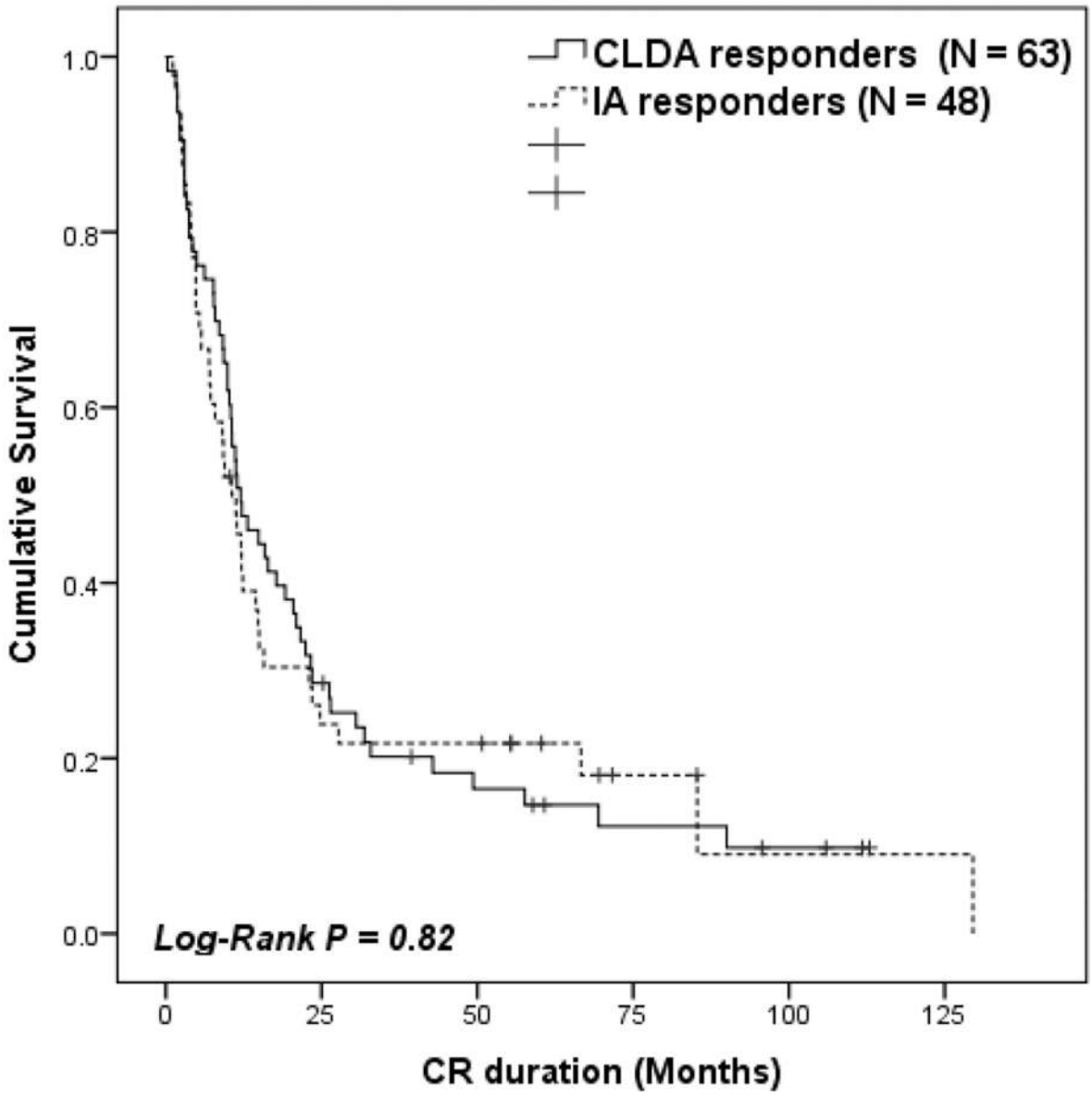

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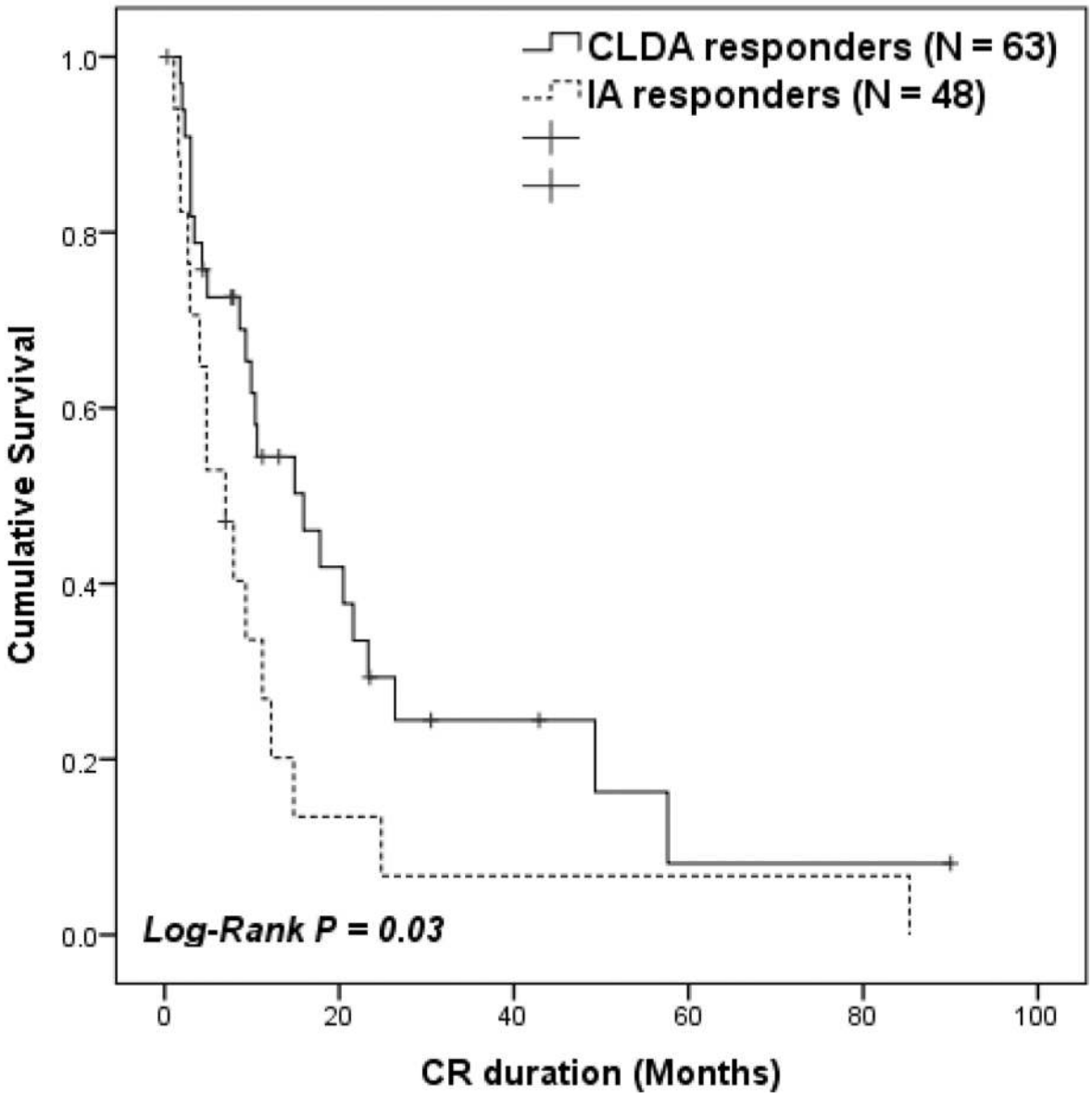

Figure 1.
Comparison of CR duration in (A) patients whose AML responded to induction CLDA versus induction IA. (B) CR durations after censoring of patients who underwent SCT at the time of transplantation.

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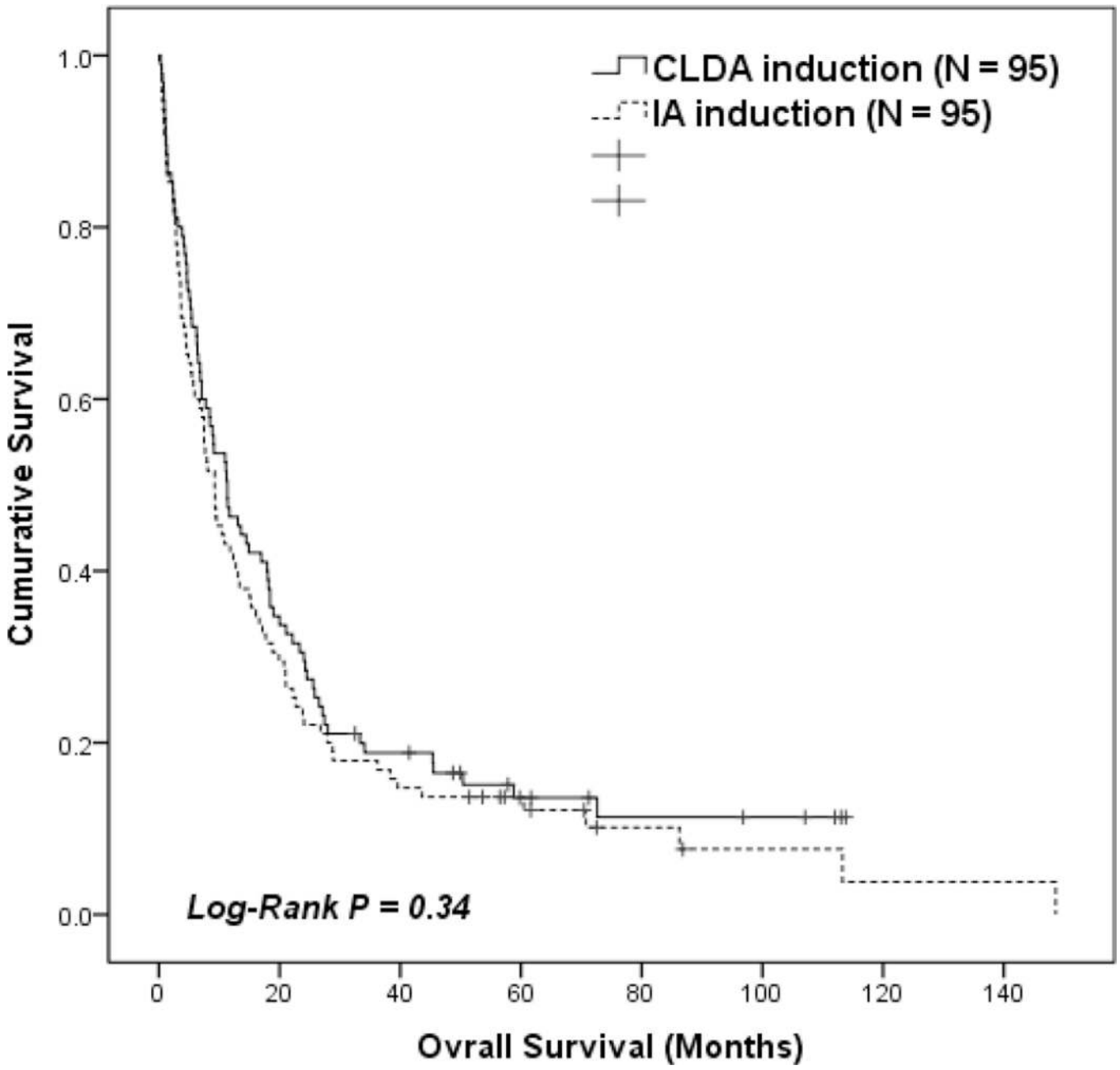

Figure 2.
Comparison of OS in PS-matched cohorts given either CLDA or IA using the log-rank test.

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Table 1

Pretreatment patient characteristics according to induction therapy for AML after PS matching

Characteristic	No. (%) CLDA (n = 95)	No. (%) IA (n = 95)	*P*
Median age, range, y	68 (60–80)	67 (60–85)	.140
Age ≥70 y	38 (40)	38 (40)	.990
Female	37 (39)	28 (29)	.170
ECOG performance status			.070
0–1	85 (89)	76 (80)	
2–3	10 (11)	19 (20)	
Therapy-related AML	21 (22)	18 (19)	.590
History of AHDs	44 (46)	36 (38)	.240
Prior HMA therapy for AHDs	16 (17)	14 (15)	.620
Median cardiac EF, range, %	60.0 (35.0–75.0)	64.5 (45.0–76.0)	.070
Cardiac EF >40%	94 (99)	95 (100)	.980
Median WBC count, range, $\times 10^9$/L	2.2 (0.4–433.0)	5.5 (0.3–211.5)	.003
Median HGB count, range, g/dL	9.2 (4.0–13.5)	9.0 (4.0–13.2)	.560
Median PLT count, range, $\times 10^9$/L	52 (6–416)	45 (2–376)	.270
Median BM blast count, range, %	43 (20–94)	46 (20–95)	.870
BM blast count ≥30%	75 (79)	75 (79)	.990
Median LDH level, range, IU/L	639 (226–8887)	830 (267–15507)	.009
Median CRE level, range, mg/dL	1.0 (0.6–1.8)	1.0 (0.5–4.0)	.400
Median TBIL level, range, mg/dL	0.5 (0.1–2.0)	0.5 (0.2–2.7)	.390
Median ALB level, range, mg/dL	3.5 (2.0–4.8)	3.5 (1.4–5.0)	.570
MRC cytogenetic risk category			.190
Favorable	0 (0)	2 (2)	
Intermediate	59 (62)	50 (53)	
Adverse	35 (37)	42 (44)	
Not evaluable	1 (1)	1 (1)	
Molecular analysis			
FLT3-ITD	8 (8)	7 (7)	.890
NPM1 mutation	10 (11)	6 (6)	.890
RAS-activating mutation	7 (7)	9 (9)	.270

HGB, hemoglobin; PLT, platelet; CRE, creatinine; TBIL, total bilirubin; ALB, albumin; HMA; hypomethylating agents, MRC, Medical Research Council.

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Table 2

Responses to induction therapy for AML in the matched cohorts

Response	No. (%) CLDA (n = 95)	No. (%) IA (n = 95)	*P*
Cumulative CR	56 (59)	44 (46)	.07
Cumulative CRp	7 (7)	4 (4)	.34
Cumulative OR	63 (66)	48 (51)	.02
CR within two cycles of induction	54 (57)	44 (46)	.09
CR after one cycle of induction	48 (53)	42 (44)	.38

OR, overall response.

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Table 3

Toxic effects and treatment-related mortality in the matched cohorts receiving induction therapy for AML

Variable	CLDA (n = 95)	IA (n = 95)	*P*
Any grade <3 toxicity, no. (%)	51 (54)	36 (38)	.03
Any grade ≥3 toxicity, no. (%)	44 (46)	59 (62)	
TRM rate at 4 weeks	5%	11%	.42
TRM rate at 8 weeks	14%	15%	.84

TRM, treatment-related mortality.