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ORIGINAL ARTICLE

Intermediate-dose cytarabine plus mitoxantrone versus standard-dose cytarabine plus daunorubicin for acute myeloid leukemia in elderly patients

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Background: The combination of intermediate-dose cytarabine plus mitoxantrone (IMA) can induce high complete remission rates with acceptable toxicity in elderly patients with acute myeloid leukemia (AML). We present the final results of a randomized-controlled trial comparing IMA with the standard 7 + 3 induction regimen consisting of continuous infusion cytarabine plus daunorubicin (DA).

Patients and methods: Patients with newly diagnosed AML >60 years were randomized to receive either intermediate-dose cytarabine (1000 mg/m^2 twice daily on days 1, 3, 5, 7) plus mitoxantrone (10 mg/m^2 days 1–3) (IMA) or standard induction therapy with cytarabine (100 mg/m^2 continuously days 1–7) plus daunorubicin (45 mg/m^2 days 3–5) (DA). Patients in complete remission after DA received intermediate-dose cytarabine plus amsacrine as consolidation treatment, whereas patients after IMA were consolidated with standard-dose cytarabine plus mitoxantrone.

Results: Between February 2005 and October 2009, 485 patients were randomized; 241 for treatment arm DA and 244 for IMA; 76% of patients were >65 years. The complete response rate after DA was 39% [95% confidence interval (95% CI): 33–45] versus 55% (95% CI: 49–61) after IMA (odds ratio 1.89, $P = 0.001$). The 6-week early-death rate was 14% in both arms. Relapse-free survival curves were superimposable in the first year, but separated afterwards, resulting in 3-year relapse-free survival rates of 29% versus 14% in the DA versus IMA arms, respectively ($P = 0.042$). The median overall survival was 10 months in both arms ($P = 0.513$).

Conclusion: The dose escalation of cytarabine in induction therapy lead to improved remission rates in the elderly AML patients. This did not translate into a survival advantage, most likely due to differences in consolidation treatment. Thus, effective consolidation strategies need to be further explored. In combination with an effective consolidation strategy, the use of intermediate-dose cytarabine in induction may improve curative treatment for elderly AML patients.

Key words: acute myeloid leukemia, cytarabine dose, elderly

Introduction

Most patients diagnosed with acute myeloid leukemia (AML) are above the age of 60 (Surveillance, Epidemiology, and End Results Database [SEER]) and this majority of AML patients has considerably lower chances to respond to even intensive induction chemotherapy [1, 2]. A range of complete response (CR) rates from 43% to 64% has been reported with different regimens in nonrandomized trials [3, 4]. In 2002, Niederwieser et al. published results on elderly AML patients treated with induction chemotherapy consisting of intermediate-dose cytarabine plus mitoxantrone (IMA) [5]. Their intention was to increase induction efficacy by applying higher doses of cytarabine than in standard induction regimens such as 7 + 3. On the basis of observations by Mantovani et al., it was hypothesized that this would lead to a lower toxicity in comparison with high-dose cytarabine regimens such as high-dose cytarabine plus mitoxantrone (HAM) due to (i) lower levels of extracellular cytarabine and (ii) recovery intervals every other day during chemotherapy [6]. In a cohort of AML patients older than 60 years, a CR rate of 74% was described in 117 patients with *de novo* AML while in secondary AML patients, 59% achieved a CR. The reported early death rate of 12%–19% with the IMA regimen was comparable with standard induction regimens.

Since remission rates highly depend on patient selection, particularly in elderly AML, we planned to compare the IMA regimen with the 7 + 3 induction regimen using standard-dose cytarabine. For this purpose, we set up an open-label randomized-controlled phase-III trial powered to detect an increase in CR rates by 13% after IMA treatment.

Patients and methods

Patient characteristics

Patients > 60 years of age with newly diagnosed AML according to WHO criteria were eligible for study inclusion. Patients with acute promyelocytic leukemia (FAB M3) were treated in a separate protocol and excluded from study treatment. Sufficient cardiac, renal and hepatic function and a clinical performance status of Eastern Cooperative Oncology Group (ECOG) ≤2 were required for eligibility. The study was approved by the institutional review boards of the 33 participating centers. Informed consent was obtained from all patients according to the Declaration of Helsinki. The AML 60+ trial was registered at the NCI website www.clinicaltrials.gov (NCT 00180167).

Study design and treatment

Patients eligible for study inclusion were randomly assigned to treatment arms A containing the standard control treatment and B as experimental intervention. Randomization was carried out centrally after registration of patients in the Study Alliance Leukemia (SAL) study office. Treatment allocation was concealed by using sealed randomization envelopes containing either the assignment A or B; the randomization result was open to investigators and patients. Patients randomized into arm A were planned to receive two cycles of induction treatment containing continuous infusion with standard-dose cytarabine 100 mg/m^2 on days 1–7 plus daunorubicin bolus infusion 45 mg/m^2 on days 3–5 (DA). First response assessment was planned after two cycles of DA. Patients in CR were scheduled for one cycle of consolidation treatment containing intermediate-dose cytarabine infusion of 1000 mg/m^2 over 2 h twice daily on days 1–5 plus m-amsacrine 100 mg/m^2 2 h after cytarabine over 1 h on days 1–5 (MAMAC). In case of treatment complications or low tolerability of induction treatment, patients could receive one induction cycle of DA only and proceed to consolidation if a CR was achieved. Patients with primary refractory disease were treated outside the trial at the discretion of the treating physician. Patients randomized into treatment arm B were assigned to receive one cycle of induction treatment with intermediate-dose cytarabine infusion 1000 mg/m^2 over 3 h twice daily on days 1, 3, 5, 7 plus mitoxantrone bolus 10 mg/m^2 on days 1–3 (IMA). If patients achieved a CR after one cycle of IMA, they were to receive two cycles of consolidation treatment containing standard-dose cytarabine bolus of 120 mg/m^2 twice daily on days 1–5 plus mitoxantrone bolus infusion of 10 mg/m^2 on days 1 and 2 (2 + 5). If patients showed a blast reduction to 5%–25% in the bone marrow after one cycle of IMA, they were planned for a second cycle of IMA followed by 2 + 5 in case of CR. Patients who did not achieve a CR after two cycles of induction or who had a primary refractory or progressive disease were treated outside the trial at the discretion of the treating physician. Patients who received at least one dose of protocol-conform treatment formed the intent-to-treat (ITT) population. If patients were eligible for autologous or allogeneic stem cell transplantation in first CR, this strategy was considered the preferable consolidation treatment.

End points and response criteria

The primary end point of the trial according to the protocol was the CR rate after induction treatment. Secondary end points were early-death rate, relapse-free survival (RFS), overall survival (OS), toxicity and tolerability as defined by number of adverse events (AEs) and serious adverse events.

Statistical analyses

Descriptive analyses were carried out for patient characteristics. CR rates were compared using logistic regression models to allow for cytogenetic risk stratification; the log-rank test was used for the evaluation of RFS and OS. Cumulative incidences of relapse and nonrelapse mortality were analyzed with competing risk methodology according to Gray. The possible heterogeneity of the treatment effects in subgroups was explored *post hoc* by estimation of the hazard ratios (HRs) for survival end points using multivariable Cox proportional hazard models and by estimation of odds ratios (ORs) for CR, early death and induction death in multivariable logistic regression models. Tests for interaction were carried out and 95% confidence intervals (95% CIs) calculated for each HR and OR, respectively. The *post hoc* analyses were carried out for a limited number of subgroups defined by age, lactate dehydrogenase (LDH), white blood cell count (WBC), platelet count, secondary AML, ECOG, cytogenetic risk group, *NPM1* and *FLT3-ITD*. Significance testing in multivariable analyses was done using likelihood ratio tests. All reported *P* values are two sided. Multiple imputations with chained equations were used to substitute missing values for multivariable analyses. Statistical analyses were carried out with SPSS software, version 16.0 and R software, version 2.15.1 with the 'survival' package (2.38-1), the 'mice' package (2.22) and the 'cmprsk' package (2.2-7).

Results

Patients, treatment course and response

Between 2005 and 2009, 852 newly diagnosed AML patients >60 years of age were screened for study inclusion and 485 patients fulfilling the eligibility criteria were randomized, 241 patients for treatment arm A (DA) and 244 for treatment arm B (IMA) (for screening failures, see supplementary Table S1, available at *Annals of Oncology* online). Their median age was 69 years (range, 61–84) with 76% of patients older than 65 years, 50% of patients were female and 70% of all AMLs were categorized as *de*

novo AML. Further patient characteristics were equally distributed between the two arms as presented in Table 1 (for patient flow, see Figure S1, available at *Annals of Oncology* online).

Of all 485 patients of the ITT population, 47% achieved a CR with 39% (95% CI: 33–45) after DA versus 55% (95% CI: 49–61) after IMA (OR 1.89, $P = 0.001$). In the protocol group, the total CR rate was 52% with 43% (95% CI: 37% to 50%) after DA versus 61% (95% CI: 55% to 68%) after IMA (OR 2.08, $P < 0.001$). If all first CRs were taken into account including those achieved after premature trial discontinuation and salvage treatment outside the trial, the CR rates after DA versus IMA induction were 55% versus 64% ($P = 0.043$).

The separate evaluation of treatment response in the subgroups of *de novo* AML revealed a significantly higher CR rate after induction with IMA (62%) compared with DA (41%; $P < 0.001$), whereas no significant difference between the study arms was observed in secondary AML (40% versus 32%; $P = 0.302$).

In multivariable analyses, induction treatment with IMA maintained its significant association with higher CR rates with an OR of 2 (95% CI: 1.38–3.00; $P < 0.001$). Apart from induction treatment, the following characteristics also showed a significant association with CR achievement: cytogenetic risk, *de novo* versus secondary AML and $NPM1_{mut}$. Results on response in different subgroups are shown in supplementary Figure S2, available at *Annals of Oncology* online and multivariable analyses for CR achievement are presented in supplementary Table S2, available at *Annals of Oncology* online.

Of 18 patients (4%) who died early during the first 14 days of induction, 8 (3%) had received DA and 10 (4%) received IMA. A total of 67 patients died within the first 6 weeks of induction, i.e. 33 (14%) in arm DA and 34 (14%) in arm IMA.

Of all 228 patients who achieved a CR in the trial, 188 received postremission treatment. In arm DA, 63 patients received intermediate-dose cytarabine and m-amsacrine (MAMAC); in arm IMA, 103 patients received standard-dose cytarabine and mitoxantrone (2 + 5). In the course of treatment, 11 patients in each arm received an allogeneic stem cell transplantation (allo SCT) (5% of all patients in each arm and in 8%–12% of CRs). The median number of administered treatment cycles was two in the entire trial and also in arms DA and IMA. Almost half of all patients received only one induction cycle and discontinued study treatment afterwards.

The median administered cumulative cytarabine dose for DA induction was 715 mg/m^2 [interquartile range (IQR), 697–1394] and 7984 mg/m^2 (IQR, 7636–8098) for IMA induction. The cumulative cytarabine dose for MAMAC consolidation in arm DA was 9973 mg/m^2 (IQR, 9500–10 400) and for 2 + 5 consolidation in the IMA arm was 1185 mg/m^2 (IQR, 1161–1200).

Table 1. Patient characteristics

	DA ($n = 241$)	IMA ($n = 244$)
Age, years		
Median	69	69
Range	61–84	61–84
>65 years	178 (74)	192 (79%)
Gender, *n* (%)		
Female	126 (52)	116 (48)
Male	115 (48)	128 (53)
RAEB-2	6 (2)	5 (2)
Disease status, *n* (%)		
De novo AML	172 (71)	168 (69)
Therapy related AML	16 (7)	9 (4)
AML with preceding MDS	50 (21)	63 (26)
Missing	3 (1)	4 (2)
ECOG status, *n* (%)		
0	52 (22)	39 (16)
1	125 (52)	142 (58)
2	28 (12)	32 (13)
3	5 (2)	0 (0)
Missing	31 (13)	31 (13)
White blood count (10^9/l)		
Median	6.7	8.7
Range	0.4–209.6	0.4–308.6
Missing, *n* (%)	0 (0)	1 (0)
Platelet count (10^9/l)		
Median	52	49
Range	0.2–630	4–597
Missing, *n* (%)	0 (0)	1 (0)
Lactate dehydrogenase (U/l)		
Median	368	429.5
Range	128–4219	46–4088
Missing, *n* (%)	9 (4)	6 (3)
Cytogenetic risk groups according to ELN 2017, *n* (%)		
Favorable	8 (3)	8 (3)
Intermediate	122 (51)	129 (53)
Unfavorable	62 (26)	47 (19)
Missing, *n* (%)	49 (20)	62 (25)
Normal karyotype, *n* (%)	85 (35)	87 (36)
NPM1 mutation, *n* (%)		
Positive	46 (19)	53 (22)
Negative	150 (62)	148 (61)
Missing	45 (19)	43 (18)
FLT3-ITD, *n* (%)		
Positive	30 (12)	38 (16)
Negative	168 (70)	168 (69)
Missing	43 (18)	38 (16)

Cytogenetic risk classification was done according to the ELN 2017 criteria.

Remission duration and survival

Of all 228 patients who achieved a CR in the study, the cumulative incidence of relapse after 1 and 3 years was 47% (95% CI: 40–53) and 70% (95% CI: 64–76) for all patients. The corresponding values were 47% (95% CI: 37–58) and 61% (95% CI: 51–71) for arm DA versus 46% (95% CI: 37–54) and 76% (95% CI: 68–83) for arm IMA. This resulted in a median CR duration of 13 months in all patients and 13 months versus 14 months after DA and IMA, respectively ($P = 0.104$). Nonrelapse mortality was similar in both arms with 10% (95% CI: 4–16) in arm DA versus 11% (95% CI: 5–16) in arm IMA after 3 years ($P = 0.545$, Figure 1A).

The group of CR patients had a median RFS of 11 months (95% CI: 8–13) and a RFS at 1 and 3 years of 46% (95% CI: 39–52) and

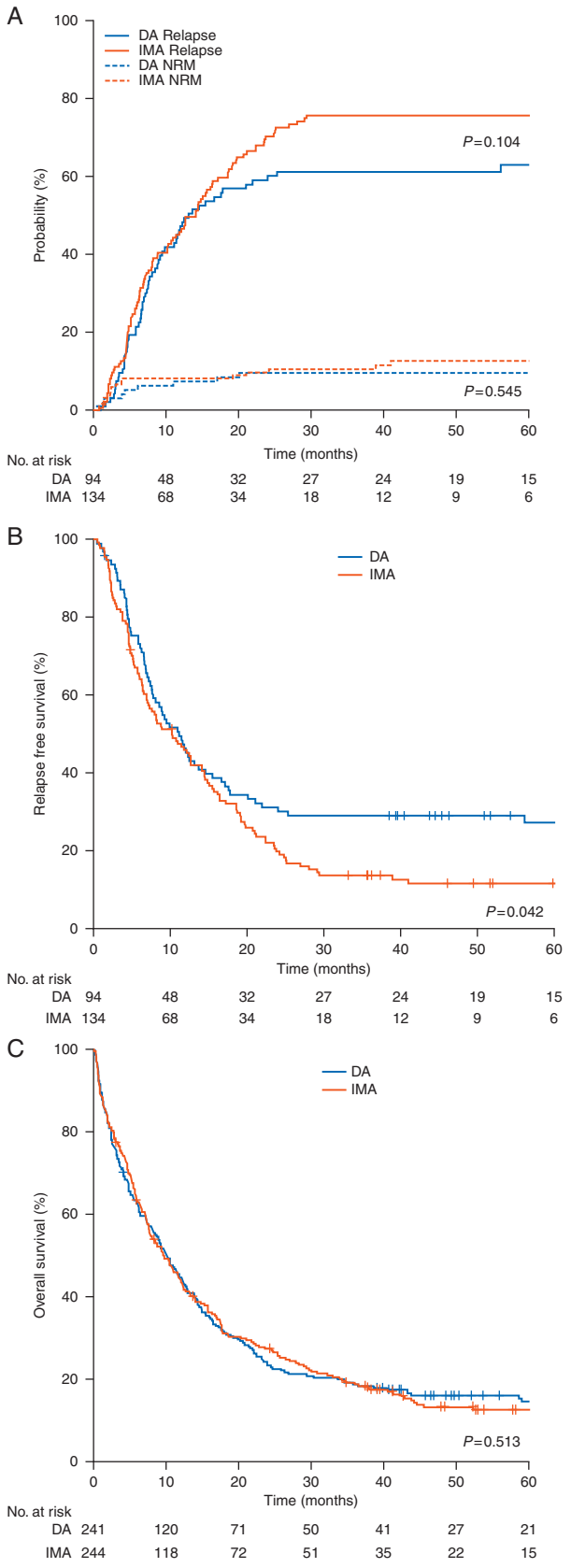

Figure 1. Kaplan–Meier plots displaying (A) cumulative incidence of relapse and nonrelapse mortality (NRM), (B) relapse-free survival and (C) overall survival in the DA and IMA study arms. *P* values from significance testing using log-rank tests.

20% (95% CI: 15–25). Survival curves show a superimposable pattern for the first year with a similar median RFS of 11 and 10 months after DA and IMA, respectively. However, a separation of RFS curves developed with longer follow-up, with a higher proportion of patients being relapse free and alive after treatment in the DA arm in comparison with IMA. Corresponding 1- and 3-year RFS rates are 45% and 29% in the DA arm and 46% and 14% in the IMA arm, respectively (Figure 1B). This difference is significant in the univariate Cox regression model stratified for cytogenetic risk with an HR of 1.37 (95% CI: 1.01–1.85) for the risk of relapse or death in the IMA arm compared with DA ($P = 0.042$).

We assessed the HR for RFS in a multivariable Cox regression model including age, clinical performance (ECOG), cytogenetic risk according to ELN 2017 criteria [7], secondary versus *de novo* AML, LDH, WBC and the mutational status of *NPM1* and *FLT3-ITD* at initial diagnosis. The assigned treatment arm had a significant influence on RFS with an HR for IMA of 1.50 (95% CI: 1.09–2.07; $P = 0.014$). Additionally, cytogenetic risk, *NPM1* status, age and LDH had a significant impact on the outcome.

After a median follow-up time of 66 months (IQR, 48–77), the median OS for all patients was 10 months (95% CI: 8–11). The median OS in arms DA and IMA was 10 months (95% CI: 8–12 and 7–12, respectively; $P = 0.513$) with almost superimposable curves as shown in Figure 1C. In the multivariable regression model accounting for well-known prognostic factors, the HR for death after DA versus IMA was 1.08 (95% CI: 0.89–1.32; $P = 0.424$). Other factors with a significant impact on OS were cytogenetic risk, secondary AML, *NPM1*, age and LDH at initial diagnosis (supplementary Table S2 and Figure S3, available at *Annals of Oncology* online).

Tolerability and toxicity

Nearly all patients in both arms were severely cytopenic (CTC-AE $\geq$ grade 3). The median duration of neutropenia $\geq$ grade 3 was 23 days after DA I and 25 days after IMA I ($P = 0.031$). No clear differences were observed in neutropenia after consolidation with MAMAC in arm A and 2 + 5 in arm B. The median duration of thrombocytopenia $\geq$ grade 3 was 16 days versus 20 days after DA I and IMA I, respectively ($P < 0.001$).

The most frequent nonhematologic grade-3/4 AE was febrile neutropenia, followed by infections, liver toxicity and gastrointestinal symptoms in both treatment arms (supplementary Table S3, available at *Annals of Oncology* online). The incidences were slightly higher with DA; however, a significant difference was only observed for a higher incidence of liver toxicity (OR IMA/DA = 0.52; $P = 0.001$) and gastrointestinal symptoms (OR IMA/DA = 0.62; $P = 0.041$) after DA.

Discussion

We investigated the potential of an alternative induction regimen with intermediate-dose cytarabine applied on alternating days in comparison with the standard 7 + 3 protocol containing continuously infused cytarabine in a standard dose.

Our results show an improved CR rate after induction with intermediate-dose cytarabine that is statistically significant and across subgroups except for the small favorable cytogenetic

group. However, in patients with secondary AML, intermediate-dose cytarabine did not increase CR rates. Recently, the use of the liposomal formulation CPX-351 was shown to result in significant improvement in responses and survival in elderly sAML/tAML in a randomized trial [8].

In general, CR rates in our trial appear low in comparison with other trials in elderly AML patients. In the nonrandomized AML97 trial of the East German Hematology and Oncology Study Group (OSHO), IMA produced a CR rate of 67% [9]. The main reason for the lower CR rate in our trial is the higher age of the enrolled patient population. The median age in the OSHO trial was 66 years, whereas it was 69 years in our trial with 76% of patients being older than 65 years.

In the SWOG S1203 trial comparing a 7 + 3 regimen with intermediate-dose cytarabine plus idarubicin (IA), the CR rates were similar between treatment arms, but significantly more patients required two cycles of 7 + 3 for CR achievement [10].

The general tolerability of both regimens was similar. Early mortality did not differ and was within limits previously reported from other patient cohorts [1, 2, 4, 11]. The results of the present trial show a more favorable tolerability of intermediate versus high doses of cytarabine in this patient population.

Once patients were in CR, the probability for relapse or death in CR was similar during the first 12 months after CR achievement, but then significantly more patients in the IMA arm relapsed, resulting in a drop in the RFS curve. The most likely explanation for this observation is the lower consolidation dose of cytarabine in the IMA arm that was less effective for relapse prevention. Considering the fact that the cumulative cytarabine doses in both arms were equal, but differently distributed, our results suggest that not the cumulative dose over all treatment phases of a complete treatment period is important, but that high-dose or at least intermediate-dose cytarabine is essential for an effective consolidation. This finding is supported by the results of the SWOG S1203 trial, in which patients with favorable risk were not scheduled for primary allo SCT but for consolidation with either high-dose (3 g/m^2) or standard-dose (0.75 g/m^2) cytarabine. Survival outcomes were significantly better in the high-dose consolidation group [10]. While the need for dose-intensive cytarabine in consolidation has been proven in a randomized trial in younger AML patients, it could not be shown to be beneficial for postremission treatment of patients beyond 60 years [12]. Our data confirm that also in elderly AML, intermediate-dose cytarabine in consolidation significantly reduces relapse risk and leukemia associated death compared with standard-dose cytarabine.

When interpreting the results, it should be noted that a daunorubicin dose of 45 mg/m^2 was used in the standard arm. At least for patients between 60 and 65 years, a higher dose seems to be more beneficial. However, the fact the equivalent daily dose of 10 mg/m^2 mitoxantrone in the IMA arm equals 40 mg/m^2 daunorubicin [13] and the fact that 76% of patients were older than 65 years, still allows a valid comparison.

As fewer patients in the DA arm achieved a CR but more patients in the IMA arm suffered from a disease relapse, OS in both treatment groups was almost identical since CR is a prerequisite for long-term survival and relapse in the older AML population is associated with very short survival. With a median OS of 10 months and a 5-year OS of 14%, the long-term outcomes are in line with data from other intensively treated cohorts [9, 14, 15]. Apart from cytogenetics and age, adverse molecular factors beyond *FLT3-ITD* such as *TP53*, *RUNX1* or *ASXL1* could have contributed to the unfavorable outcome. Only about half of all patients received more than one cycle of cytostatic treatment in the trial as an indirect indicator for toxicity and moderate tolerability of induction treatment. For the time being, our goal must be to optimize the selection of eligible patients, induce remission with one treatment cycle followed by an effective postremission strategy.

Conclusion

In conclusion, the results of the AML 60+ trial indicate that elderly AML patients benefit from a dose escalation of cytarabine in induction therapy by significantly higher CR rates and similar tolerability compared with a standard 7 + 3 approach. In our trial, this did not translate into a survival advantage, most likely due to differences in consolidation treatment of the respective treatment arms. In combination with an effective consolidation strategy such as high-dose cytarabine or allogeneic transplantation, our current results favor the use of intermediate dose cytarabine in induction for patients with a curative AML treatment approach.

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Disclosure

The authors have declared no conflicts of interest.

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