

Intensified double induction therapy with high dose mitoxantrone, etoposide, m-amsacrine and high dose ara-C for patients aged 61-65 years with acute myeloid leukemia

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Background and Objectives. Treatment outcome in elderly patients with acute myeloid leukemia (AML) is still disappointing. However, some trials showed that increasing the dosage of anthracyclines within induction therapy improved treatment outcome substantially. We, therefore, tried to escalate induction therapy further in a group of *young elderly* AML patients.

Design and Methods. In a multicenter trial 33 patients aged 61-65 years with *de novo* or secondary AML were treated with double induction therapy including high dose mitoxantrone, etoposide and ara-C (MAV) in the first course and m-amsacrine together with high dose ara-C (MAMAC) in the second course. Treatment results were compared to those in 39 AML patients older than 65 years receiving conventional double induction therapy including daunorubicin and ara-C (DA I and DA II) within the same time period.

Results. Compared to results achieved with conventional induction therapy, intensified double induction therapy did not significantly improve CR rates, overall or disease-free survival. Hematologic toxicity was not different between the two groups, but non-hematologic toxicity was significantly higher with MAV/MAMAC. This was mainly due to gastro-intestinal or liver toxicity. The rate of early mortality (death within the first 12 weeks) was 42% in the group receiving intensified therapy and 18% in that given conventional induction therapy ($p=0.04$).

Interpretation and Conclusion. Intensification of double induction therapy using high dose mitoxantrone and high dose ara-C in AML patients aged 61-65 years did not lead to improved treatment outcome and conferred an unacceptable early death rate due to high non-hematologic toxicity. Risk-adapted or alternative treatment strategies are needed to improve treatment outcome in these *young elderly* AML patients.

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Key words: AML, elderly patients, induction therapy, intensification, treatment outcome.

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The incidence of acute myeloid leukemia (AML) increases with age and most patients with this disease are elderly.¹ However, elderly patients are generally underrepresented in clinical trials.² This might reflect the reluctance of physicians to expose such patients to anti-leukemic therapy due to poor performance status or a generally poor treatment outcome in older AML patients. Indeed AML in the elderly seems to be a biologically different and often therapy-resistant disease. Compared to AML occurring at a younger age AML in the elderly more often emerges from an antecedent myelodysplastic syndrome,³ has higher levels of *mdr1* expression⁴ and more often displays karyotype changes leading to aneuploidy. Complete or partial losses of chromosomes, most often chromosome 5 or 7, and multiple aberrations have been found.⁵

Nevertheless, it was clearly shown in a prospective, randomized trial a decade ago that remission induction chemotherapy results in a significantly longer median survival of elderly AML patients than a watch-and-wait strategy combined with palliative care.⁶

Although since then chemotherapy has been the treatment of choice for the elderly AML patient, there is still controversy about the value of the intensity of induction treatment. Several approaches to intensify the standard ara-C and anthracycline (e.g. daunorubicin or doxorubicin)-containing induction therapy have been taken so far. In the first attempts addition of etoposide⁷ or variations in the ara-C dose⁸ did not further improve overall survival. However, more recent trials have produced growing evidence that higher doses of daunorubicin might prolong survival^{2,9} giving a rationale for more intensified induction treatment strategies in elderly AML patients. Furthermore, it is difficult to define *elderly* patients because this is not simply a matter of chronological age but must include biological considerations. Thus, the cut-off

age varies between 55 and 65 years in different treatment trials.¹⁰ It is not known whether *young-elderly* AML patients aged 61-65 years might benefit particularly from intensified induction treatment strategies. We, therefore, started a multicenter treatment trial giving AML patients aged 61-65 years the same intensified double induction therapy containing high dose mitoxantrone, etoposide, m-amsacrine and high dose ara-C as AML patients ≤ 60 years treated within the SHG AML96 trial¹¹ and compared them with AML patients older than 65 years receiving standard induction therapy with daunorubicin and ara-C.

Design and Methods

Patients

Between February 1996 and September 1997, 72 adult patients older than 60 years with *de novo* or secondary AML were included in the German multi-center treatment trial of the SHG AML96 study group. In September 1997 the intensified therapy arm for patients aged 61-65 years had to be closed. Thereafter all patients older than 60 years received conventional induction therapy as recently published.¹¹ Patients were eligible if they had had no prior treatment for AML and had AML with French-American-British (FAB) subtypes M0-M2 and M4-M7 as defined by standard morphologic and immunophenotypic criteria. Patients with acute promyelocytic leukemia (FAB-M3) were not eligible and were treated within ATRA-based European trials. Performance status score was defined according to the performance status scale of the Eastern Cooperative Oncology Group (ECOG).¹²

Therapy and remission criteria

Double induction therapy was stratified according to age. Thirty-three patients aged 61-65 years received one course of MAV (mitoxantrone 10 mg/m² days 4-8, ara-C 100 mg/m² continuous infusion days 1-8, VP-16 100 mg/m² days 4-8) and a second course of MAMAC (ara-C 1,000 mg/m² every 12h days 1-5 (total dose 10 g/m²), m-amsacrine 100 mg/m² days 1-5) starting three weeks after the first course according to protocol.

Thirty-nine patients older than 65 years were treated with two consecutive courses of DA induction therapy (daunorubicin 45 mg/m² days 3-5, ara-C 100 mg/m² continuous infusion days 1-7). Again the proposed time-interval between the two courses was three weeks. From day four after each course of chemotherapy 5 μ g/kg granulocyte colony-stimulating factor (G-CSF) were given until the neutrophil count was higher than 500/ μ L. An

early bone marrow puncture was scheduled for day 15 to evaluate response to the first induction course. A blast cell count of <5% was regarded as good, <25% as moderate and $\geq 25\%$ as no response. Complete remission (CR) was defined as the presence of <5% of blast cells in the bone marrow with no profound hypoplasia after the second course of induction therapy.

Patients of both induction therapy groups who achieved a CR and were in good clinical condition were eligible to receive a cycle of MAMAC post-remission chemotherapy with an interval of 6-8 weeks after double induction therapy. Supportive therapy including adequate blood and platelet support, prophylactic and in the case of fever early empirical anti-microbial and -fungal therapy as well as treatment of proven infections was standardized. The study was approved by the ethics committee of the University of Dresden. Each patient gave written informed consent.

Toxicity

Treatment-related toxicity was documented for every cycle of chemotherapy according to WHO criteria. Early death was defined as death in or before week 12 after beginning the first cycle of induction therapy.

Flow cytometry

For the discrimination of CD34⁺ cells CD34 monoclonal antibody QBE10 (Coulter-Immunotech Diagnostics, Hamburg, Germany) was used according to previously published protocols.¹³ CD34 positivity was defined as $\geq 20\%$ CD34⁺ blast cells within the examined blast samples.

Cytogenetics

Chromosome analyses were performed on metaphases from direct preparations, as well as on 24h and 48h cultures of bone marrow and/or peripheral blood samples as described previously.¹⁴

MDR1 gene expression

RNA extraction, cDNA synthesis and reverse transcription polymerase chain reaction (RT-PCR) analysis were performed as previously described.¹¹

Statistical analysis

Basic statistical data such as median values, standard deviations and frequencies were obtained using the SPSS software package. Differences in clinical parameters, toxicities, CR and early death rate between the analyzed induction therapy groups were evaluated by a two-tailed Fisher's exact test. Overall and disease-free survival analyses were performed using the Kaplan-Meier method and survival curves were compared using

the log-rank test. The significance level of median survival was obtained using Wilcoxon's test.

Results

Patients' characteristics

The pre-treatment characteristics of the 33 AML patients receiving intensified induction therapy (MAV/MAMAC) and the 39 receiving conventional induction therapy (DA/DA) are summarized in Table 1. The median age was 63 years for patients in the intensified induction group, in which the age for enrolment was 61-65 years. Patients enrolled in the conventional induction group were older than 65 years and had a median age of 70 years.

Patients who were 61-65 years old tended to have a better performance status at diagnosis than the patients older than 65 years (15% vs. 28% ECOG 3 or 4).

No significant differences between both groups were found for sex, disease status, white cell count, bone marrow-blast counts, CD34, lactate dehydrogenase, FAB classification or *MDR1* gene expression. Trilineage dysplastic abnormalities were found in the bone marrow of five (15%) MAV/MAMAC and two (5%) DA/DA patients at diagnosis. This difference was not significant ($p=0.24$).

Cytogenetic data were available for 86% of patients and aberrant karyotypes were found in 48% of both groups. Cytogenetic risk groups were defined according to the revised MRC criteria for older AML patients.¹⁵ In both induction therapy groups only one patient displayed a favorable karyotype, whereas five MAV/MAMAC patients compared to three DA/DA ones had an adverse karyotype (Table 2). This difference was not statistically significant ($p=0.45$). Thus, the results of the study were not influenced by an imbalance of adverse karyotypes between the two treatment groups.

Treatment outcome

The bone marrow was evaluated early after the first induction course, i.e. at day 15, in 23/33 MAV patients and in 31/39 DA ones. Fifteen patients had a good response to MAV, seven a moderate response and one no response, whereas twelve patients had a good response to DA, ten a moderate response and nine no response. Five patients of each group died within these first fifteen days. Finally, five MAV and three DA patients had no early bone marrow puncture results for unknown reasons.

Complete remission rates after second induction therapy were comparable with 11/33 (33%) AML patients aged 61-65 years receiving MAV/MAMAC and 15/39 (39%) patients aged >65 years receiving

Table 1. Characteristics of AML patients 61-65 years treated with intensified induction therapy and AML patients older than 65 years treated with conventional induction therapy.

	Intensified induction therapy (n=33)	Conventional induction therapy (n=39)	p-value ^a
Sex [n]			
Female	18	18	0.48
Male	15	21	
Age [years]			
Median	63	70	<0.001
Range	61-65	66-81	
Performance status [n]			
0	5	1	0.34 ^b
1	7	8	
2	10	12	
3	4	6	
4	0	2	
Unknown	7	10	
Disease status [n]			
De novo	25	32	0.57
Secondary	8	7	
WBC [$\times 10^9/L$]			
Median	7.7	19	0.10
Range	0.7 - 322.0	1.1 - 453.0	
Blast Count in BM [%]			
Median	57	70	0.26
Range	30-94	30-93	
CD34⁺ blasts [%]			
Median	28	37	0.90
Range	0-88	0-96	
LDH [mmol/sL]			
Median	13.5	13.0	0.94
Range	3.8-63.7	4.3-69.7	
FAB class [n]			
M0	2	3	0.73
M1	7	7	
M2	14	15	
M4	2	8	
M5	5	5	
M6	2	0	
M7	1	1	
Mdr1 positivity [%]	29%	40%	0.36

^ap values of non-parametric variables were obtained by two-tailed Mann-Whitney-U-test, of parametric variables by two-tailed Fisher's exact test except FAB class, for which a linear regression analysis was performed.

^bfor significance analysis patients were grouped into performance status 0-2 vs. 3+4.

ing DA I/DA II ($p=0.42$).

Consolidation therapy with MAMAC in accordance with the protocol could be given to 6 out of 11 patients in CR after induction therapy with MAV/MAMAC. Therapy was discontinued in 2 patients because of severe side effects of treatment, one patient relapsed after induction therapy, one got consolidation therapy not in accordance with the protocol and one patient refused to receive consolidation therapy.

Four out of 15 patients in CR after induction therapy with DA I/DA II received consolidation with

Table 2. Cytogenetics of AML patients 61-65 years treated with intensified induction therapy and those older than 65 years treated with conventional induction therapy. Cytogenetic data were available for 29/33 patients (88%) in the intensified induction and for 33/39 (85%) in the conventional induction therapy group.

	Intensified induction therapy (n=29)	Conventional induction therapy (n=33)
Cytogenetics		
Normal karyotype	15 (52%)	17 (52%)
Aberrant karyotype	14 (48%)	16 (48%)
Risk groups [#]		
Favorable	1 (4%)	1 (3%)
Intermediate	23 (79%)	29 (88%)
Adverse	5 (17%)	3 (9%)

[#]Cytogenetic risk classification was done according to the revised MRC criteria for older AML patients:¹⁵ favorable: t(15;17), t(8;21) or inv(16) irrespective of the presence of additional cytogenetic aberrations; adverse: complex karyotype; intermediate: all other cases including normal karyotypes. Differences between the two treatment groups are not statistically significant.

MAMAC. One patient had an early relapse. Treatment was discontinued in 2 patients because of severe toxicity of induction therapy, in another 2 because of severe infectious complications and in 6 because of a poor general condition.

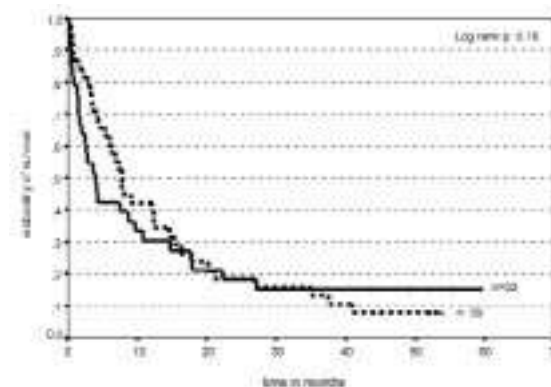
The median overall survival was worse in AML patients aged 61-65 years who received intensified induction therapy than in their older counterparts receiving conventional induction therapy (3.9 vs. 7.8 months; $p=0.23$). After 54 months, however, 15% of MAV/MAMAC recipients and 8% of DA/DA patients were alive ($p=0.78$) (Figure 1A).

The median disease-free survival was longer for MAV/MAMAC patients than DA/DA ones (18.6 vs. 11.6 months, $p=0.30$) resulting in a disease-free survival rate of 27% and 8% ($p=0.22$) after 51 months, respectively (Figure 1B). All long-term disease-free survivors had an intermediate or favorable risk karyotype.

Toxicity of MAV/MAMAC as compared to that of DA I/DA II induction therapy

Table 3 summarizes the non-hematologic toxicity greater than or equal to WHO grade 3 reported for the four different induction therapy courses. Thirty-one of 33 patients received the complete first induction course with MAV and 38/39 patients complete the first induction course with DA I. Nineteen patients in each group finished the second course of induction therapy. Whereas the proposed time interval between the two induction courses was 21 days according to the study protocol, the

A



B

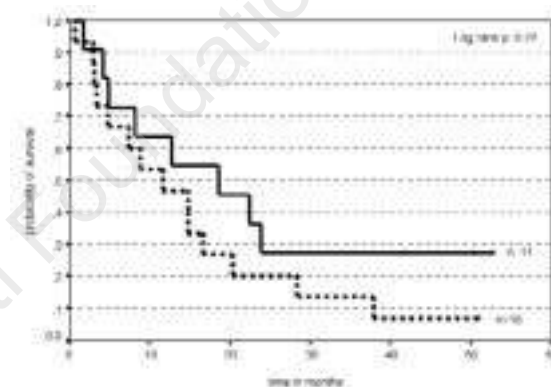


Figure 1. Overall survival (A) and disease-free survival (B) of AML patients aged 61-65 years receiving intensified induction therapy (solid line) and AML patients older than 65 years receiving conventional induction therapy (dotted line).

real median time interval was 24 days for MAV/MAMAC and 25 days for DA/DA patients ($p=0.28$). Thus, in 11 patients of each group the beginning of the second induction course was delayed. Severe pancytopenia or other toxicity was the reason in eight MAV/MAMAC patients and seven DA/DA ones. In the other patients the reasons for the delay were not known.

Fifteen patients (48%) in the MAV group experienced WHO grade 3 or 4 toxicity of the gastrointestinal tract and the liver as compared to eight patients (21%) in the DA I group ($p=0.02$). This difference was even more prominent comparing the second induction therapy courses, with 11/19 (58%) MAMAC recipients suffering grade 3 or 4

Table 3. Numbers of elderly AML patients experiencing non-hematologic toxicity related to the mentioned induction therapy courses according to WHO classification.

	1 st induction MAV (n=31) [†]	1 st induction DA I (n=38) [†]	2 nd induction MAMAC (n=19)	2 nd induction DA II (n=19)
Grade 3 or 4 toxicity [n]				
Hemorrhage	1	1	0	0
GI-tract and liver	15 (p=0.02 [§])	8	11 (p=0.005 [§])	2
Kidney and bladder	2	1	0	1
Lungs	4	7	2	2
Infections	9	9	8	2
Allergic reactions	0	0	0	0
Skin	0	0	1	0
Eye	0	0	0	0
Heart	1	5	2	1
Nervous system	2	2	0	0

[†]The p-value reflects a significant difference between the first induction therapy with MAV and DA I. [§]The p-value reflects a significant difference between second induction therapy with MAMAC and DA II. [†]treatment course was not completed for two MAV and one DA I patients.

toxicity of the gastrointestinal tract and the liver and 2/19 (11%) of those given DA II ($p=0.005$). Relevant symptoms and laboratory findings were nausea and vomiting, diarrhea, stomatitis, hyperbilirubinemia and elevation of liver enzymes. No significant differences could be found for toxicity of kidney and bladder, lung, skin, eye, heart, central nervous system, allergic reactions, infections or hemorrhage (Table 3). Myelosuppression was not different between the patients given the two induction treatment strategies. The median time to neutrophil recovery greater than $500/\mu\text{L}$ was 21 days for patients given MAV, 18 days for those given DA I, again 18 days for MAMAC and 13 days for DA II. Platelet recovery to greater than $20,000/\mu\text{L}$ was achieved after a median of 16 days for MAV, 19 days for DA I, 15 days for MAMAC and 8 days for DA II. The median number of transfused platelets or red blood cell concentrates was not significantly different between the induction therapy courses (Table 4). Transfusion triggers for platelets were active bleeding or a platelet count less than $10,000/\mu\text{L}$, and for red blood cells a hemoglobin level less than 5 mmol/L (8 g/dL).

Table 4. Hematologic toxicity with duration of granulocytopenia (days to neutrophile count $>500/\mu\text{L}$) and thrombocytopenia (days to platelet $>20,000/\mu\text{L}$) and amount of transfused blood products in elderly AML patients after the specific courses of induction therapy.

	1 st induction MAV (N=31) [†]	1 st induction DA I (N=38) [†]	2 nd induction MAMAC (n=19)	2 nd induction DA II (n=19)
Granulocytopenia [days]				
Median	21	18	18	13
Range	10-124	6-50	8-30	3-44
Thrombocytopenia [days]				
Median	16	19	15	8
Range	8-31	5-46	7-44	3-66
Transfused platelet concentrates [‡] [n]				
Median	6	5	5	4
Range	0-20	0-28	0-10	0-25
Transfused red blood cell concentrates [n]				
Median	8	8	6	5
Range	0-26	0-14	0-12	0-21

Differences between MAV and DA I and between MAMAC and DA II were all not significant. [‡]If available all platelet concentrates were apheresis products; [†]treatment course was not completed for two MAV and one DA I patients.

The early death rate was higher in the group of patients given intensified induction than in the group given conventional induction therapy. Within the first 6 weeks after treatment had been started 8/33 (24%) of MAV/MAMAC patients had died as compared to 5/39 (13%) of the DA I/DA II patients. This difference was most prominent after 12 weeks with 42% deaths shortly after or during MAV/MAMAC therapy and only 18% after DA I/DA II ($p=0.04$).

Deaths were mainly due to infectious complications, hemorrhage or organ failure.

Discussion

We present the results of 33 AML patients aged 61-65 years treated within a multicenter trial who received intensified double induction therapy according to the regimen used for patients younger than 60 years. The age range of 61-65 was chosen because it is thought that, within elderly AML patients, those up to the age of 65 form a subgroup with a better prognosis.¹⁶ The treatment results were compared with those of 39 patients older than 65 years who were treated with con-

ventional double induction therapy including daunorubicin and cytarabine within the same time period. Both groups had comparable performance status, cytogenetics and *mdr1* expression.

Since Rees *et al.*⁹ showed that intensification of induction therapy using higher doses of daunorubicin led to higher CR rates and longer survival in AML patients older than 60 years, more intensive induction treatment strategies seem to be a tool to improve the so far disappointing treatment results in such patients. The same effect was recently demonstrated by the German AMLCG with an improved CR rate in elderly AML patients receiving higher doses of daunorubicin. The disease-free survival, however, was not influenced by the daunorubicin dosage.¹⁷ The intensified induction therapy used in our study consisted of a first course of mitoxantrone (total dose 50 mg/m²), cytosine arabinoside and VP-16 (MAV) and a second course of high dose cytosine arabinoside (total dose 10 g/m²) and m-amsacrine (MAMAC). The MAV combination proved to be a highly active anti-leukemic treatment even in relapsed and refractory AML.¹⁸ In a pilot study using a slightly lower mitoxantrone dosage (30 mg/m²) this MAV combination induced a high CR rate with acceptable toxicity in patients older than 60 years.¹⁹ So far, high dose ara-C within induction therapy has been used in younger AML patients and improved disease-free survival substantially.²⁰

In the study here presented, CR rate, overall and disease-free survival of patients between 61-65 years after intensified induction therapy was not significantly better than those of patients older than 65 years who received standard induction therapy. However, the early death rate was significantly higher in the intensified induction group because of considerable toxicity to the gastrointestinal tract and the liver. Therefore, the intensified induction treatment arm for AML patients aged 61-65 years was closed after 1.5 years of recruitment. Subsequently, AML patients aged 61-65 years were treated with standard induction therapy (DA I/ DA II) with no difference in overall survival after 40 months compared to that in the closed intensified induction therapy group (*data not shown*).

No significant differences in toxicity were observed by the MRC AML11 study group when comparing a total of 60 mg/m² mitoxantrone with daunorubicin in different induction therapy arms for patients older than 60 years.²¹ Increasing the dosage of ara-C within post-remission therapy for

AML patients older than 60 years, as done by the CALGB group, again did not lead to increased toxicity.²² Neither study, however, showed a benefit of either high dose mitoxantrone or high dose ara-C on survival of older AML patients.^{21,22}

In the context of these recently published studies our group found that the combination of both treatment principles, i.e. high dose mitoxantrone and high-dose Ara-C too toxic for even AML patients aged 61-65 years.

Although escalation of daunorubicin dosage improved treatment results in older AML patients in the past,^{9,17} our data suggest that further escalation of induction treatment is generally not feasible in patients older than 60 years and alternative treatment strategies are needed. In this context appropriate consolidation therapy might be one point to discuss as the relapse rate in older AML patients is high and outcome of salvage therapy is very poor.²³ However, we feel that many physicians are reluctant to apply aggressive consolidation therapy to older patients. Furthermore, as proposed by Estey,¹⁶ treatment strategies for older AML patients should be stratified according to risk factors, such as younger old age, *mdr1* expression, performance status and cytogenetics. Thus, some *young elderly* patients with good risk factors might benefit from further treatment intensification. Indeed, survival was better in patients who reached CR after intensified induction therapy than in the conventionally treated patients in our study. This might reflect a better quality of CR after intensified induction therapy. However, given the small number of patients in each study arm, this difference was not statistically significant in the log rank test. Interestingly, all long-term survivors had intermediate or favorable risk cytogenetics. Leith *et al.*⁴ found that response to induction treatment in old AML patients depends on cytogenetics and *mdr1* expression. Patients who were negative for *mdr1* and did not have high risk cytogenetics had a CR rate comparable to that of younger patients whereas *mdr1* positive high-risk cytogenetic patients had almost completely therapy-resistant disease. In addition, our group showed that *mdr1* expression predicted induction treatment failure independently of age in a multivariate analysis of AML patients.¹¹ Recently, Grimwade *et al.* reported cytogenetics as being a critical independent determinant of outcome in older AML patients.¹⁵ Whether induction treatment intensification may be applicable in distinct subgroups of older AML patients with favorable or intermediate risk cytogenetics or other good prognostic factors

and whether it may produce long-lasting complete remissions remain to be proven in prospective, randomized studies in the future.

For the high-risk elderly AML patients alternative treatment strategies, such as *mdr1* modulation,²⁴ monoclonal antibodies²⁵ or early non-myeloablative allogeneic stem cell transplantation²⁶ should be further investigated.

In conclusion, further induction treatment intensification with high dose mitoxantrone and high dose ara-C in AML patients aged 61-65 years is not feasible in all patients because of marked non-hematologic toxicity. *The more intensive the better* is not the way to improve treatment results in the elderly AML population. Therefore risk-adapted or alternative treatment strategies are needed in the future.

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MS, TI, GE were the principal authors. They were primarily responsible for this work, from conception and design of the study to submitted manuscript. The remaining authors qualified for authorship according to the World Association of Medical Editors (WAME) criteria and have taken specific responsibility for the following parts of the content: WA, HB, MC, AN, US, HW, collection of patients' data and contributions to the conception and design of the study; RR, CD34 analyses; SS, statistical analyses.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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PEER REVIEW OUTCOMES

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What is already known on this topic

Several studies have suggested that increased doses of ara-C produce undue toxicity, including death, in older patients with newly-diagnosed AML. It has been suggested however that increased doses of drugs such as mitoxantrone may be beneficial.

What this study adds

This study explores that possibility in patients between 61 and 65 years of age. The results indicate that, as with ara-C, increasing the dose of mitoxantrone or etoposide is unlikely to be productive.

Potential implications for clinical practice

As the authors conclude, the implications for clinical practice are that strategies other than dose-intensification should be pursued in elderly patients with untreated AML.

Elihu Estey, Associate Editor