VOLUME 29 · NUMBER 3 · JANUARY 20 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Response-Guided Induction Therapy in Pediatric Acute Myeloid Leukemia With Excellent Remission Rate

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Submitted May 25, 2010; accepted October 19, 2010; published online ahead of print at www.jco.org on December 13, 2010.

Written on behalf of the Nordic Society for Pediatric Hematology and Oncology.

Supported by The Children's Cancer Foundation, Sweden.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/11/2903-310/$20.00

DOI: 10.1200/JCO.2010.30.6829

ABSTRACT

Purpose
To evaluate the early treatment response in children with acute myeloid leukemia (AML) using a response-guided induction strategy that includes idarubicin in the first course.

Patients and Methods
All Nordic children with AML younger than 15 years (n = 151) were treated on the Nordic Society for Pediatric Hematology and Oncology (NOPHO) AML 2004 protocol. After the first course of idarubicin, cytarabine, etoposide, and 6-thioguanin, patients with good response were allowed hematologic recovery before the second course, whereas patients with a poor (≥ 15% blasts) or intermediate (5% to 14.9% blasts) were recommended to proceed immediately with therapy. Patients not in remission after the second course received fludarabine, cytarabine, and granulocyte colony-stimulating factor. Poor responders received allogeneic stem-cell transplantation (SCT) as consolidation.

Results
Seventy-four percent of patients had good response, 17% had intermediate response, and 7% had poor response after the first course. The overall remission frequency was 97.4%, with 92% in remission after the second course. The rate of induction death was 1.3%. Patients with an intermediate response had a lower event-free survival of 35% compared with good (61%) and poor responders (82%).

Conclusion
The NOPHO-AML 2004 induction strategy gives an excellent remission rate with low toxic mortality in an unselected population. Outcome is worse in patients with intermediate response but may be improved by intensifying consolidation in this group using SCT.

J Clin Oncol 29:310-315. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Despite significant progress, treatment results are still unsatisfactory in pediatric acute myeloid leukemia (AML). During the last 5 years, several groups have reported an event-free survival (EFS) of approximately 50% to 55%, with an overall survival (OS) approaching 65% at 5 years.[1-6] Recently two studies have shown even better results, with the Japanese AML99 study having an EFS and OS of 61% and 75%, respectively, and the AML02 study from St Jude having an EFS and OS at 3 years of 63% and 71%, respectively.[7,8]

Apart from the quest of finding new drugs and targeted therapy, efforts at improving prognosis have largely followed three main avenues. First, treatment intensification, particularly in the induction phase, both by drug exposure and timing, has been pursued by all cooperative groups and is probably (along with improvements in supportive care) the main reason for the increase in survival. Second, cytogenetics and the impact of early response to therapy has provided the basis for a better risk stratification allowing for different treatment approaches in risk groups.[9] Most groups are now investigating the role of minimal residual disease evaluation to improve future risk stratification.[8,10] Third, closely linked to risk grouping, researchers have sought to establish which patients benefit from allogeneic stem-cell transplantation (SCT) in first remission.[11] Currently, most treatment protocols reserve SCT for high-risk patients, although the definition of high-risk varies between groups.[12,13]

Since 1984, The Nordic Society for Pediatric Hematology and Oncology (NOPHO) has conducted consecutive population-based pediatric AML treatment studies in all five Nordic countries. The previous study, NOPHO-AML 93, was open 1993 to 2003 and gave satisfactory results with a

complete remission (CR) rate of 92% and EFS and OS at 5 years of 50% and 66%, respectively.[14]

In the current NOPHO-AML 2004 study, one of the aims was to improve prognosis by augmenting induction therapy. On the basis of studies showing that idarubicin gave an increased early blast clearance in children and on randomized studies showing increased efficacy in adults, idarubicin replaced doxorubicin in the first induction course.[15,16] The timing of the second course was guided by early response evaluation, but in contrast to NOPHO-AML 93, all patients received low-dose cytarabine and mitoxantrone as second course.

This article shows the results of this approach, which led to a CR rate of 97% with a low frequency of induction death and acceptable toxicity.

PATIENTS AND METHODS

In the Nordic countries, all children up to 15 years of age with AML have been treated on consecutive common protocols since 1984. In several centers, children up to 18 years of age are also included. The present study, NOPHO-AML 2004, commenced in January 2004 and had recruited 151 patients by September 2009.

A diagnosis of AML, fulfilling the criteria of the WHO classification, was based on examination of bone marrow smears with appropriate cytogenetic and flow cytometry analyses. CNS involvement was defined as either five or more leukocytes per μL of CSF and presence of leukemic cells on cytospin preparation or cranial nerve involvement. Children with Down syndrome, acute promyelocytic leukemia, isolated granulocytic sarcoma, or secondary AML were excluded.

Induction Treatment

All patients received an initial 6-day induction course with low-dose cytarabine, etoposide, 6-thioguanine, and idarubicin (AIET). A detailed description of the induction courses is shown in Table 1. Bone marrow evaluation was performed on day 15. If blast counts were less than 5% as assessed by morphology, treatment was postponed until hematologic recovery, during which time weekly bone marrow controls was recommended. For patients with $\geq$ 5% blast cells, the second induction course was to be given immediately. All patients received low-dose cytarabine and mitoxantrone (AM) as the second induction course. Children not in remission after these courses were given fludarabine, cytarabine, and granulocyte colony-stimulating factor (FLAG) as a third induction course, whereas those in remission proceeded to consolidation therapy. Children with CNS involvement received twice-weekly triple intrathecal therapy until 1 week after blast clearance and subsequently one methotrexate injection with every treatment course. Children without CNS disease received prophylactic intrathecal therapy with methotrexate each course. It was recommended that all patients receive fluconazole as antifungal prophylaxis during neutropenic periods and trimethoprim-sulfamethoxazole throughout treatment.

Table 1. Overview of the First (AIET) and Second (AM) Induction Courses

Course and Drug	Dose (mg/m^2)*	Administration	Days
AIET			
Cytarabine	200	24-hour IV	1-4
Etoposide	100	24-hour IV	1-4
6-thioguanine	100	Orally every 12 hours	1-4
Idarubicin	12	4-hour IV	2,4,6
AM			
Cytarabine	100	24-hour IV	1-5
Mitoxantrone	10	30-minute IV	1-3

Abbreviations: AIET, cytarabine, etoposide, 6-thioguanine, and idarubicin; AM, cytarabine and mitoxantrone; IV, intravenous.
*Children younger than 1 year of age or weighing less than 10 kg received doses calculated according to body weight (1 m^2 = 30 kg).

Treatment Response

Evaluation of bone marrow was first done on day 15. This is a difficult analysis because most bone marrow is severely hypoplastic at this time. The blast cell count on morphology was the main determinant, but in all patients, flow cytometry was used to help judge whether the blast cells were leukemic.

Patients with $\geq$ 15% leukemic cells after AIET or $\geq$ 5% after AM were considered poor responders. Those with 5% to 14.9% after AIET were classified as intermediate responders, and those with less than 5% were classified as good responders.

CR was defined as a bone marrow blast count of less than 5% on morphologic examination and supported by flow cytometry, with absolute neutrophil count $\geq$ 1,000/μL and platelets $\geq$ 80/μL and no evidence of extramedullary disease.

Risk Stratification

Risk grouping was based solely on treatment response and cytogenetics. Patients with $\geq$ 15% blasts after the first AIET course or not in remission after AM were considered poor responders and stratified to the high-risk group. An exception was patients with t(8;21) and inv(16) who were assigned to the standard-risk group if they were in remission after AM regardless of response to AIET.

Patients with mixed-lineage leukemia (MLL) rearrangements other than t(9;11) were always assigned to the high-risk group. All other patients were treated as standard risk.

After induction, standard-risk patients received four high-dose cytarabine–containing courses (course 1, cytarabine 1 g/m^2 every 12 hours days 1 through 3 and mitoxantrone 10 mg/m^2 days 3 through 5; courses 2 and 4, cytarabine 2 g/m^2 every 12 hours days 1 through 3 and etoposide 100 mg/m^2 days 2 through 5; course 3, cytarabine 3 g/m^2 every 12 hours days 1 through 3), after which patients were randomly assigned to receive two courses of gemtuzumab ozogamicin or to stop treatment. High-risk patients were offered SCT if any suitable matched related or unrelated donor was identified.

The protocol was approved by the national ethics boards in the Nordic countries, and informed consent was obtained from the guardians.

Statistical Methods

Differences in proportions were evaluated with the Fisher's exact test for 2 $\times$ 2 contingency tables and Pearson's χ^2 for higher order tables. Median values were compared using Mann-Whitney *U* or Kruskal-Wallis test as appropriate. EFS was defined as the time from start of treatment to any event (induction failure, relapse, second malignancy, death from any cause). The Kaplan-Meier method was used to construct EFS curves, and differences in factors were assessed using the log-rank test. Estimates of EFS are shown as percent $\pm$ SE. Cox regression was used to evaluate the impact of continuous and categorical variables on EFS. All *P* values were two-sided and considered significant when less than .05.

RESULTS

All 151 Nordic patients who entered the NOPHO-AML 2004 protocol between January 2004 and September 2009 and were evaluable for response to induction as of November 30, 2009, were included. Table 2 shows demographic and disease characteristics for the patients. There was a comparatively large proportion of children younger than 2 years of age (31%) and also a high frequency of CNS disease (13%). All patients had evaluable cytogenetic examinations, and 26% had core-binding factor AML, 25% had MLL rearrangements, and no cytogenetic aberrations were detected in 19%. In 115 patients analyzed for *FLT3* mutations by polymerase chain reaction, nine (7.8%) had internal tandem duplication (ITD), and six (5.2%) had point mutations.

Table 2. Patient Characteristics and Response to First Treatment Course

Characteristic	No.	%	Response to First Course (AIET)						Died
			Good		Intermediate		Poor		
			No.	%	No.	%	No.	%	
Sex									
Male*	80	53	55	69	16	20	9	11	0
Female	71	47	57	80	9	13	3	4	2
FAB type									
M0	12	8	9	75	2	17	1	8	0
M1	16	11	10	63	5	31	1	6	0
M2	39	26	28	72	8	21	3	8	0
M4	28	19	20	71	5	18	3	11	0
M5	37	25	30	81	2	5	3	8	2
M6	4	3	4	100	0	0	0	0	0
M7	12	8	9	75	3	25	0	0	0
Unknown	3	2	2	67	0	0	1	33	0
CNS involvement									
Yes	20	13	13	65	5	25	1	5	1
No	128	85	97	76	19	15	11	9	1
Unknown	3	2	2	67	1	33	0	0	0
Extramedullary involvement									
Yes	31	21	25	81	4	13	1	3	1
No	118	78	85	72	21	18	11	9	1
Unknown	2	1	2	100	0	0	0	0	0
Cytogenetics									
t(8;21)	25	17	22	88	3	12	0	0	0
inv(16)	14	9	12	86	1	7	1	7	0
t(9;11)	19	13	17	90	1	5	0	0	1
11q23 non t(9;11)	18	12	13	72	2	11	2	11	1
Other aberrations	47	31	31	66	10	21	6	13	0
Normal karyotype	28	19	17	61	8	29	3	11	0
WBCs $\times 10^9$/L									
≥ 100	17	11	12	71	2	12	3	18	0
50-100	25	17	19	76	3	12	2	8	1
20-50	36	24	28	78	5	14	3	8	0
< 20	73	48	53	73	15	21	4	6	1
Age, years									
< 2†	46	31	39	85	5	11	1	2	1
2-9	62	41	46	74	10	16	5	8	1
10-17	43	29	27	63	10	23	6	14	0
Risk group									
Standard risk	122	81	100	82	21	17	1	1	NA‡
High risk	27	18	12	44	4	15	11	41	NA
Poor response alone	11	7	0	0	2	18	9	82	NA
MLL + poor response	3	2	0	0	1	33	2	67	NA
MLL	13	9	12	92	1	8	0	0	NA

NOTE. Good response, < 5% blasts; intermediate response, 10% to 14.9% blasts; poor response, ≥ 15% blasts after AIET.
Abbreviations: AIET, cytarabine, etoposide, 6-thioguanine, and idarubicin; FAB, French-American-British; NA, not applicable; MLL, mixed-lineage leukemia rearrangement.
*Trend to fewer male patients with good response compared with females, $P = .051$.
†Significantly higher proportion of good response compared with older children, $P = .017$.
‡Risk grouping not applicable for patients with early death.

Treatment Response

Figure 1 shows an overview of treatment response and the flow of patients through induction therapy. In the 151 children, 112 (74%) had a good response with less than 5% blasts, 25 (17%) had an intermediate response, and 12 (7%) had a poor response after AIET. Of the good responders, one did not receive AM because of prolonged pancytopenia, but all were in CR after AM. In addition, five of the 12 patients with poor response and 22 of the 25 with intermediate response achieved CR after AM. Two patients died from bleeding within 3 days after starting AIET treatment. Thus 138 (92%) of the 150 evaluable patients were in remission after AM. Of the 10 patients not in CR after AM, eight achieved remission after FLAG therapy, giving an overall CR frequency of 97.4%.

In general, patients with an intermediate response were more difficult to classify on day 15 marrow examination as a result of hypoplasia. If the absolute count of suspected blasts was very low,

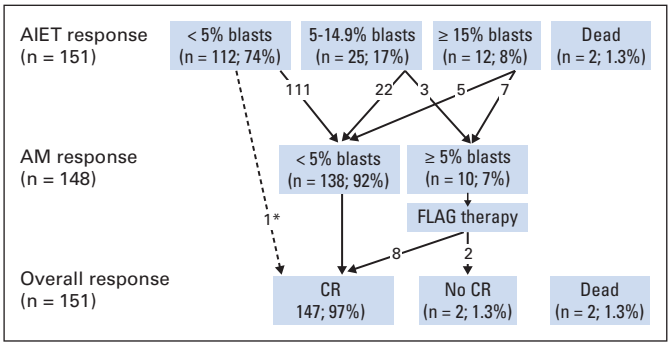

Fig 1. Overview of treatment response and flow of patients during induction therapy in Nordic Society for Pediatric Hematology and Oncology AML 2004. Cytarabine, etoposide, 6-thioguanine, and idarubicin (AIET) is the first course, and cytarabine and mitoxantrone (AM) is the second course. Fludarabine, cytarabine, and granulocyte colony-stimulating factor (FLAG) was given to those not in remission after AM. *One patient proceeded to consolidation without receiving AM because of prolonged aplasia after AIET. CR, complete remission.

despite being more than 5%, a repeat examination was performed after a week. Of the 29 patients who, at any time point between AIET and AM, had 5% to 15% blasts, four proved to have a good response on repeat examination.

Univariate analysis showed that the median age was higher in patients with a poor (9.0 years) or intermediate response (8.0 years) than in those with good response (3.0 years, $P = .017$). There was also a trend for a lower frequency of good response among boys ($P = .051$). As shown in Table 3, age and sex interacted with a higher median age for boys, but logistic regression showed that only age had an independent significant effect on treatment response ($P = .034$).

There was no difference in initial white cell counts, frequency of specific cytogenetic aberrations, French-American-British type, or CNS disease in the response groups (Table 2). Of the nine patients with *FLT3*-ITD, three had a poor response and one an intermediate response to AIET.

The median time between treatment courses AIET and AM was 32 days (range, 13 to 141 days) in patients with good response to AIET, 28 days (range, 17 to 47 days) in intermediate responders, and 18 days (range, 13 to 25 days) in poor responders.

Early Treatment Response and Outcome

Although the median follow-up still is short and the final outcome of the protocol cannot be evaluated yet, we compared the outcome stratified for early treatment response. Thirty-three (29%) of 112 patients with good response have experienced an event (29 relapses, four patients dead in CR), 15 (60%) of 25 patients with intermediate response have experienced an event (all relapses), and two (17%) of 12 patients with poor response have experienced an event (one death in CR, one relapse). For all patients, EFS and OS at 3 years was 57% ± 5% and 69% ± 5%, respectively. Figure 2 shows a significant effect of treatment response on EFS ($P = .047$) and that patients with a poor response have a 3-year EFS of 82% ± 12%, patients with an intermediate response have a 3-year EFS of 35% ± 10%, and patients with a good response have a 3-year EFS of 61% ± 6%. Cox regression did not show an independent effect of age or sex on EFS. SCT was performed in first remission in 10 of 12 patients with poor response, four of 25 patients with intermediate response, and eight of 112 patients with good response. In the latter groups, the indication for SCT was MLL rearrangement in seven patients and at the discretion of the treating physician in five patients. Of the 22 patients with SCT in first CR, four patients received grafts from a sibling and 18 patients received grafts from an unrelated donor. The conditioning regimen was busulfan-based in 16 patients and total body irradiation–based in six patients. Three patients have experienced an event (one in each response group). Thus only seven of 21 patients in the intermediate response group treated without SCT remain in first CR. The estimated OS at 3 years in good, intermediate, and poor responders was 72.7% ± 5.3%, 49.8% ± 14.2%, and 81.8% ± 11.6%, respectively (nonsignificant).

Toxicity

Only two (1.3%) induction deaths were observed, both caused by bleeding in patients with French-American-British M5 during the first 3 days of treatment. No patient died during cytopenia after AIET. Thus 149 patients were evaluable for toxicity after AIET, but for a few patients, data were missing in the database. Of 146 patients with recorded data, all had received at least one platelet transfusion. A total of 145 of 146 patients had neutropenic infection requiring intravenous antibiotic therapy, and in 13 patients (9%), signs of septic shock occurred. No acute cardiac toxicity related to therapy was observed. Granulocyte-macrophage colony-stimulating factor was not routinely recommended but was used in 26 (18%) of 144 patients. The median time to neutrophil counts $\geq 0.5 \times 10^9$/L in the patients with good response (who were allowed to regain peripheral counts) was 27

Table 3. Relation Between Age Group, Sex, and Treatment Response After the First Induction Course (AIET)

Age and Sex	Good		Intermediate		Poor		
	No.	%	No.	%	No.	%	Total No.
< 2 years	39	87	5	11	1	2	45
Male	15	94	1	6	0	0	16
Female	24	83	4	14	1	3	29
2-9 years	46	75	10	16	5	8	61
Male	22	67	7	21	4	12	33
Female	24	86	3	11	1	4	28
10-17 years	27	63	10	23	6	14	43
Male	18	58	8	26	5	16	31
Female	9	75	2	16	1	9	12

NOTE. Good response, < 5% blasts; intermediate response, 10% to 14.9% blasts; poor response, ≥ 15% blasts after AIET.
Abbreviation: AIET, cytarabine, etoposide, 6-thioguanine, and idarubicin.

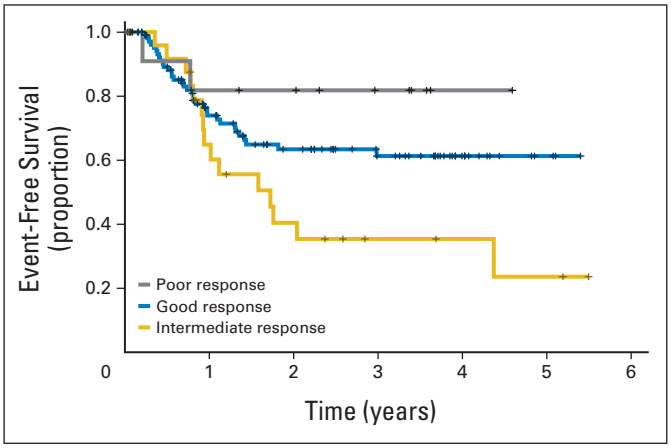

Fig 2. Kaplan-Meier curve of event-free survival stratified according to the response to the first induction course. Patients with an intermediate response had a significantly worse outcome than those with good or poor response ($P = .047$).

days (range, 13 to 141 days), and the median time to the last platelet transfusion was 21 days (range, 13 to 141 days).

After AM, 123 (87%) of 142 patients received intravenous antibiotics as a result of neutropenic fever, and three (2.1%) of these cases were life-threatening. No acute cardiac toxicity was recorded. The median time to neutrophil counts $\geq 0.5 \times 10^9$/L in the patients who were in remission after AM was 22 days (range, 0 to 49 days), and the median time to the last platelet transfusion was 15 days (range, 0 to 58 days).

DISCUSSION

The NOPHO-AML 2004 induction therapy gave an excellent remission frequency of 97% in pediatric patients with AML. Several other groups, including the Berlin-Frankfurt-Münster, Medical Research Council (MRC), and Leucemie Aigue Myeloblastique Enfant have reported total CR rates between 88% and 93%, and the Japanese AML99 study had a rate of 94.6%.[2,4,7,17] All these studies included populations with similar disease and demographic characteristics, but one important aspect is that the NOPHO study is population-based, and no children younger than 15 years were treated on other protocols. Thus our data show that it is possible to obtain a very high CR rate in an unselected population of children with AML.

Our previous study NOPHO-AML 93 had an overall CR rate of 92%.[14] The only differences in treatment were the substitution of idarubicin (3×12 mg/m^2) for doxorubicin (75 mg/m^2) in the first course and that children not in remission after two courses obtained FLAG as a third induction course in NOPHO-AML2004 instead of a course of high-dose cytarabine and etoposide. It is possible that both factors contributed, because the CR rate after the first course was 67% in NOPHO-AML 93 compared with 74% in this study, and FLAG induced remission in eight of 10 patients who were not in CR after AIET and AM.

Although almost all pediatric AML protocols include an anthracycline for induction therapy, it is still unresolved whether any specific anthracycline gives superior outcome. Idarubicin was introduced in NOPHO-AML 2004 because several randomized studies in adults had shown increased remission frequency and median survival, and in the Berlin-Frankfurt-Münster 93 study, idarubicin increased the proportion of rapid early responders as compared with daunorubicin.[18-20] Since then, the Children's Cancer Group 2941 study has confirmed an improved early blast clearance, although in association with high toxicity, and a recent report in adults showed better outcome with idarubicin. However, no pediatric study has provided conclusive evidence for improved long-term results with idarubicin.[21,22] It should be noted that in the Japanese AML99 study, a 12-day long induction course including mitoxantrone gave a CR rate of 86% after one course. Currently, most pediatric AML protocols use idarubicin or mitoxantrone as part of induction therapy.

The NOPHO-AML 2004 protocol used a response-based induction strategy. Those in remission after AIET were allowed hematologic recovery before proceeding with therapy, whereas those with more than 5% blasts in the bone marrow were to be treated immediately. However, this concept was not fully implemented because of the fact that the bone marrow on day 15 frequently displayed severe hypoplasia, and patients often were ill from neutropenic fever at this time. Therefore, treatment was sometimes withheld and a repeat marrow examination was performed, which is reflected in the difference in median time between courses for intermediate and poor responders. On repeat marrow examination, only four of the 29 patients with blasts counts more than 5% on day 15 converted to good responders, and the remaining 25 patients still showed intermediate response.

For risk stratification, the NOPHO protocol adopted a cutoff of $\geq$ 15% marrow blasts after the first course for assignment to the high-risk group. Patients in the high-risk group, which also included those with MLL rearrangements other than t(9;11), were treated with allogeneic SCT as consolidation. Overall, 14% of all patients received SCT in first CR, and the outcome for these patients was excellent, including the poor responders in the high-risk group (Fig 2). The small sample size precludes definite conclusions, but probably improved supportive care contributes to the good transplantation results.

Because the MRC showed that patients with 5% to 15% blasts after the first course comprise an intermediate-risk group with a survival of 65% (provided such patients enter remission subsequently), we chose to treat our intermediate responders with standard consolidation using four high-dose cytarabine–containing courses.[2] Although 88% of our intermediate responders entered remission after the second course of AM, the majority subsequently experienced a relapse. This emphasizes both the importance of rapid response and the concept of remission quality for long-term outcome. The AML02 study also showed a poor outcome for patients with minimal residual disease more than 1% after the first course.[8] The better outcome for intermediate responders in the MRC trials could be explained by differences in consolidation therapy but may also reflect the difficulties associated with assessment of morphologic response after AML induction.

The AIET induction course was very toxic, with a median duration of neutropenia of 27 days. All but one patient had neutropenic infections, and the treating physicians were very concerned about the condition of the patients, particularly in the early days of the protocol. Nonetheless, the induction death rate was very low, and both deaths (early bleedings) were attributed to the disease and not the treatment.

The second course was less toxic and was well tolerated, even in patients who received AM immediately after the day 15 marrow

examination. To further improve remission quality, particularly for those with intermediate response, it seems feasible to fortify this course.

In conclusion, the 97% CR rate in the NOPHO-AML 2004 protocol is one of the best reported. Early bone marrow examination can identify a group with intermediate response after course 1 with a very high risk of relapse after conventional chemotherapy. This group will require additional treatment either by SCT in first CR or by intensification of conventional therapy. Furthermore, most poor responders can achieve remission after FLAG and have good long-term results after SCT.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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