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Mitoxantrone-Containing Regimen for Treatment of Childhood Acute Leukemia (AML) and Analysis of Prognostic Factors: Results of the EORTC Children Leukemia Cooperative Study 58872

Catherine Béhar, MD, Stefan Suciu, MS, Yves Benoit, MD, Alain Robert, MD, Etienne Vilmer, MD, Patrick Boutard, MD, Yves Bertrand, MD, Patrick Lutz, MD, Aline Ferster, MD, Erika Tokaji, MS, Anne-Marie Manel, MD, Gabriel Solbu, MS, and Jacques Otten, MD

The objective of this study was to evaluate the feasibility, the toxicity and the efficiency of a BFM-like treatment protocol for acute nonlymphoblastic leukemia (ANLL) of children in which mitoxantrone was substituted for conventional anthracycline. The chemotherapy called for induction (mitoxantrone, cytosine arabinoside, etoposide), consolidation (mitoxantrone, cytosine arabinoside, 6 thioguanine), followed by two intensification courses with cytosine arabinoside plus, respectively, mitoxantrone during the first and etoposide during the second courses. Maintenance therapy consisted of daily 6 thioguanine, four-weekly courses of cytosine arabinoside (s.c. daily during 4 days) and eight-weekly courses of mitoxantrone. The latter drug was pursued up to a total cumulative dose of 150 mg/sqm. Maintenance therapy was stopped at 2 years of diagnosis. Out of 108 patients, 84 (77%) achieved a complete remission, 10 died during induction of hemorrhage, sepsis or pulmonary infiltration by leukemic cells. A total of 32 relapses occurred. The median follow-up was 3.5 years. Actuarial event-free survival, disease-free survival and overall survival at 3 years as 41%, 52%, 56%, respectively. These results compare favorably with most reported data, and cytogenetic findings appear to be the most important prognostic factor. © 1996 Wiley-Liss, Inc.

Key words: mitoxantrone, acute myeloid leukemia, childhood, prognostic factors

INTRODUCTION

Acute myeloid leukemia (AML) is a relatively rare disease in childhood and there are quite a few large pediatric clinical trials. In spite of increasing treatment intensity, results have not matched those achieved for acute lymphoblastic leukemia in terms of complete remission rate or maintenance of remission.

All induction protocols call for at least cytosine arabinoside (ARAC) and anthracyclines, with daunorubicine (DNR) [1,2], and the latter drug is often further used through consolidation and/or intensification courses, but its cardiotoxicity limits the total cumulative dose which can safely be given.

Mitoxantrone (MITX) belongs to a new family of cytotoxic intercalating agents. It inhibits DNA and RNA synthesis through a complex mechanism comprising classical intercalation and interaction with single-strand DNA as well as nonintercalating electrostatic bindings [3–5].

It has shown marked antileukemic activity in relapsed and refractory acute nonlymphoblastic leukemia (ANLL) when used either as single agent [6] (10% to 40% remission rate) or in combination with ARAC and/or etoposide (VP16) [7–13]. From March 1984 to December 1987, a randomized trial had been performed, comparing MITX and DNR in untreated adult patients. The results were available in 1990 [14].

Noncumulative bone marrow depression (mostly of myelopoiesis) has been the dose-limiting toxicity. When combined with other drugs, it has usually be used at the dose of 10 to 12 mg/sqm.

In contrast with anthracyclines, MITX does not generate free radicals and it inhibits lipid peroxydation [3]. It may therefore be less cardiotoxic. Clinical abnormalities of the cardiac function [15] have been uncommon (less

From the Service d'Hémato-Oncologie Pédiatrique, American Memorial Hospital, Reims, France.

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Address reprint requests to Dr. Catherine Béhar, Service d'Hémato-Oncologie Pédiatrique, American Memorial Hospital, 45, rue Cognacq-Jay 51092 Reims Cédex, France.

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TABLE I. Treatment Schedule of EORTC 58872 Study

	Induction	Consolidation	First intensification	Second intensification	Maintenance[a]
ARAC continuous infusion	100 mg/sqm/day Day 1, 2				40 mg/sqm s/cut 4 days/months
ARAC bolus	100 mg/sqm/12 h D 3 to 8	75 mg/sqm D 1 to 4, 8 to 11, 15 to 18, 29 to 32 36 to 39, 43 to 46			
HDRARAC i.v. 3 h			2 g/sqm/12 h D 1, 2, 3	2 g/sqm/12 h D 1, 2, 3	
VCR		1,5 mg/sqm D 1, 15, 29, 43			
6 Thioguanine		60 mg/sqm/day D 1 to 46			40 mg/sq/day
MITX	10 mg/sqm D 3, 4, 5	10 mg/sqm D 1, 15, 29, 43	10 mg/sqm D 3, 4, 5		10 mg/sqm D 1 of ARAC/8 weeks (total dose = 150 mg/sqm)
VP 16	150 mg/sqm D 6, 7, 8			125 mg/sqm D 2, 3, 4, 5	
ARAC intrathecal	D 1	D 1, 15, 29, 43			

[a]Total duration of maintenance = 24 months after diagnosis.

than 3%) at cumulative doses up to 100 mg/sqm in patients previously treated with anthracyclines and of up to 160 mg/sqm in untreated patients [16]. We have therefore substituted MITX for DNR in a protocol derived from the 1983 BFM ANLL [17] study in order to evaluate the feasibility, the acute toxicity and the efficiency of this hopefully less cardiotoxic new regimen.

PATIENTS AND METHODS

Patients

Children less than 18 years of age with newly diagnosed AML, excluding secondary leukemia, were registered centrally and prospectively at the EORTC Data Center. The study was opened to patients entered from January 1988 to December 1991.

Diagnosis

The FAB classification was used for the diagnosis of AML and its subtypes. The morphologic subgroups were identified on May-Grünwald Giemsa and cytochemical staining of bone marrow and blood smears. Cytologic material was reviewed by a panel of cytologists. Whenever feasible, cytogenetic analysis of blood and/or bone marrow blasts was performed. Central nervous system (CNS) involvement was looked by lumbar puncture carried out at diagnosis.

Treatment

An outline of the protocol doses and timing is shown in Table I. The induction treatment consisted of ARAC, MITX and VP16. After a treatment-free interval of one or two weeks, Vincristine (VCR), MITX, ARAC and 6 thioguanine were given in combination with CNS prophylaxis which consisted of four intrathecal injections of ARAC. The duration of this consolidation was 46 days.

Patients who were in complete remission (CR) after induction and consolidation received two courses of intensification consisting of high doses of ARAC (HDARAC) with MITX for the first one and VP16 for the second one. Maintenance therapy was started after the second intensification with 6 thioguanine, ARAC and

TABLE II. Patient Characteristics: 108 Patients

Median age	5 years (0–15) (14 < 1 year)
Sex ratio	51 males/57 females
Positive CNS	25
Other extra medullary involvement	36
WBC median	19.8 × 10^9/l (0.8–893)

TABLE III. FAB Subtypes

M1	15
M2	28
M3	5
M4	14
M5	31
M6	5
M7	2
AUL	4
Unclassified	4
Total	108

TABLE IV. Cytogenetic Findings

67	NN
40	AN + AA
6 7q−	4 t (15,17)
6 8+	4 t (9,11)
9 t (8,21)	3 t (10,11)
	3 y−
4 inv 16	1 t (9,22)

NN = 100% Normal metaphases. AN = at least 3 abnormal metaphases. AA = 100% abnormal metaphases.

TABLE V. Overall Results

Patients	108
Deaths before start of treatment	2
Treatment started	106
Death	10
during induction	6
during hypoplasia	4
PR/Resistance	12
CRs	84 (77.8%; S.E. = 4%)
after first induction	70 (64.8%; S.E. = 4.6%)
Allo BMT/ABMT performed in first CR	13/2
Relapse	32
BM	18
isolated CNS	7
BM + CNS	4
isolated skin relapse	2
other localisation	1
Death in first CR	6
In CCR	46
Survival at 3 years	56% (S.E. = 4.9%)
DFS at 3 years	52% (S.E. = 5.7%)
EFS at 3 years	41% (S.E. = 4.9%)
Median follow-up (years)	3.5

MITX (to a cumulative dose of 150 mg/sqm). Total duration of the treatment was 2 years after diagnosis.

Patients who were in failure (blasts > 15%) after induction, or in partial remission (5% ≤ blasts ≤ 15%) after consolidation, received a salvage therapy with HDARAC and amsacrine. Allogenic bone marrow transplantation from a HLA-matched sibling was recommended in patients who had failed to achieve complete remission at the end of induction and consolidation.

Cardiac Monitoring

Echocardiography [18] was required for all patients at diagnosis and before each MITX injection. The measured shortening fraction (SF) ≥28% was the criterium to continue therapy. If 20% < SF < 28%, MITX was stopped until SF improved. In rare cases of patients with borderline stable SF (around 28%), each team was free to reduce MITX.

STATISTICAL ANALYSIS

Duration of survival of all patients was calculated from the date of diagnostic until death. For patients who achieved CR after induction or salvage, the disease-free survival (DFS) was calculated from the date of first CR until the date of first relapse or the date of death in first CR, whatever subsequent treatment (chemo or BMT). The event-free survival was the time from end of induction or salvage until event: relapse, death in CR or non-achievement of CR (patients who did not reached CR were considered as failures at time 0).

Actuarial curves were calculated according to the Kaplan-Meier technique [19] and the standard error of the estimate was computed using the Greenwood formula [19]. The differences between curves were statistically tested using the two-tailed log rank test [19]. For ordered variables the log rank test for linear trend was used [19]. The standard error of the proportion of patients who reached CR was calculated based on usual formula (Vp* (1 − p)/N, where p = observed proportion and N the total number of patients).

RESULTS

Patient Characteristics

One hundred and eight children were included by 20 centers of the EORTC children leukemia group. The patients' major clinical and hematologic features are summarized in Tables II, III. The median age was 5 years with a sex ratio of 51 males for 57 females. Twenty-five patients had initial CNS involvement based on clinical signs and/or unequivocal blast cells in the CSF.

Median leukocyte count ($\times 10^9$/l) was 19.8 and the range was 0.8 to 893. The distribution of the AML subtypes is presented in Table VI; as in other pediatric series, the high proportion of M5 is obvious. Chromosome analysis was performed for 67 children; 40 show abnormalities (Table IV).

Overall Results

The overall results are presented in Table V. Among 108 evaluable patients, 84 (77%) achieved complete remission: 70 after induction alone, 14 after induction and consolidation or salvage therapy. Six patients died in first CR: two during induction, four during consolidation, from sepsis and interstitial pneumonia (pneumocystis carinii and streptococcus). Overall survival of all patients is 56% at 3 years with an event-free survival (EFS) of 41% and a DFS of 52% with a median follow-up of 3.5 years (Fig. 1).

Prognostic Factors

The prognostic value of different initial factors were studied: FAB subtype did not appear to be of prognostic importance. The M5 subclass had a comparable outcome as the others (Fig. 2).

The risk groups as defined by Creutzig et al. [2]: good group = M1 with Auer Rods, M2 with WBC < 20.10^9/l,

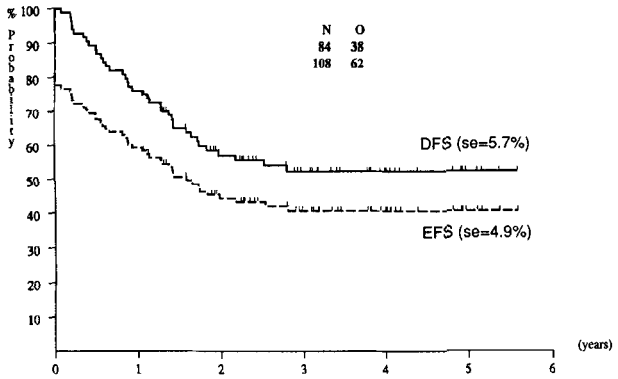

Fig. 1. Disease-free survival (DFS) and event-free (EFS) survival. N, number of patients at risk; O, observed events.

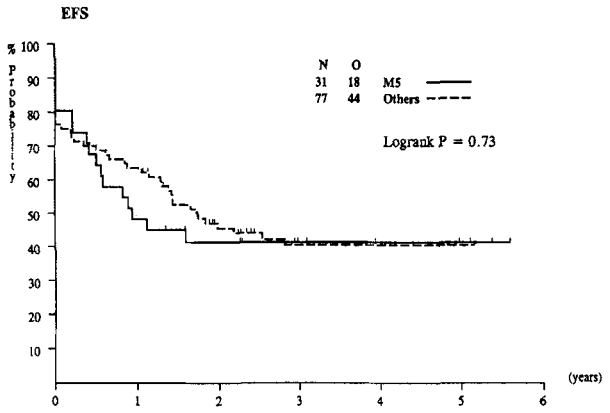

Fig. 2. Event-free survival of M5 patients.

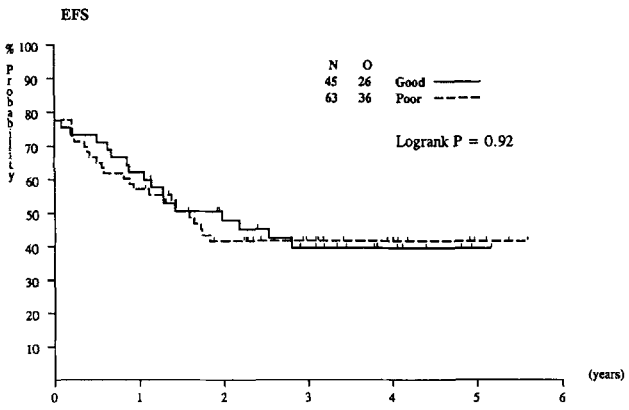

Fig. 3. Event-free survival according to Creutzig risk groups.

all M3, M4 with EO ≥ 3%, all M6; poor group = M1 without Auer Rods, M2 with WBC ≥ 20.10^9/l, M4 with EO < 3%, all M5, did not discriminate the outcome in our series (Fig. 3).

Patients were classified according the Keating cytogenetic criteria [20]: favorable, t(8,21) t(15,17) inv 16,

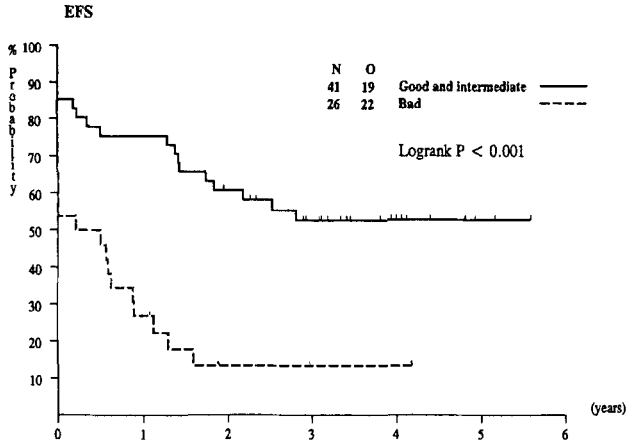

Fig. 4. Event-free survival according to cytogenetic prognostic groups of Keating.

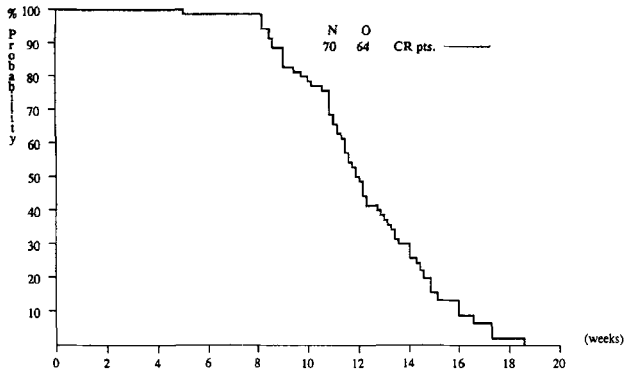

Fig. 5. Time to recovery PMN > 0.5 × 10^9/l after consolidation.

intermediate normal karyotype, and poor, all other abnormalities. Those with favorable features had a higher chance to reach and to remain in CR (85% vs. 54%; Fig. 4).

Myelotoxicity

Acute myelotoxicity occurred as expected after induction; the median time to recovery PMN > 0.5 × 10^9/l or platelets > 50 × 10^9/l was 4 weeks. On the contrary, the consolidation phase, calling for fortnightly MITX in addition to ARAC and 6TG, induced severe and protracted myeloid aplasia; median time to recovery PMN > 0.5 × 10^9/l was 12 weeks (range from 4 to 18; Fig. 5).

Cardiotoxicity

The evolution of 15 patients, showing a SF ≤ 28% at any time during treatment, is summarised in Table VI: two had a pathological SF at diagnosis before any treatment; for one, autopsy revealed congenital endocardiac

TABLE VI. Evolution of Patients Showing SF ≤ 28% at Any Time of Treatment

Patient no.	Diagnosis	Induction	Consolidation	1st Intensification	2nd Intensification	Maintenance	Salvage	Off therapy	Comment
1	40	32	32	32	31	27		31	MITX delayed 150 mg/sqm
2	42				21	26		25	MITX stopped 120 mg/sqm
3	36	32	31	51 (?)	27	27		33	MITX stopped 94 mg/sqm
4	33	33	36	36		28		32	MITX delayed 150 mg/sqm
5	30			28					No follow up
6	34	34	25				32		Relapse–death aspergillus
7	27	29					24		Failure–death endocardiac fibroelastosis
8	25	28	28						No follow up
9	50	35	35	21	32			34	Sepsis + myocarditis Streptococcus
10	34	30	28						Failure–death infection
11	30		28	35		25		35	MITX delayed 150 mg/sqm
12	42			25			32		Relapse–death infection
13	37	45	40	40	40	37	28		Relapse–death infection
14	34	31	29	29	28				No modification of dosage
15	37	37	32		28	25			MITX stopped 130 mg/sqm

fibroelastosis (MITX had been administrated in spite of the SF level); the other did not present any underlying cardiopathy. Three patients had a SF ≤ 28% during consolidation, and three others during the first intensification; patient 9 presented a severe interstitial pneumonia with myocarditis which explained the very low SF (21%); after appropriate antibiotherapy, the SF recovery occurred, allowing the continuation of MITX.

During the second intensification (free of MITX), three children had a SF decrease, confirmed during maintenance; none of them had cardiac symptoms. MITX was definitely stopped; one has already a normal SF, all are on follow-up.

During maintenance, three patients showed a SF ≤ 28%; MITX injection was delayed but treatment could be achieved to a total dose of 150 mg/sqm. All have a normal SF off therapy. So far, MITX has been stopped only for three children on echocardiographic criteria. They are still asymptomatic and followed by echocardiography. None of the patients died from chemotherapy cardiotoxicity.

DISCUSSION

The response to induction therapy in this study was comparable to but no better than currently reported results of induction courses combining ARAC, anthracyclines with or without supplementary drugs such as 6TG or etoposide. On the other hand, the DFS and overall survival favourably compare to most reported data [21–23] and match those of Creutzig et al. [17,24] whose protocol design was used as a framework for ours; EFS at 3 years is 41%.

Concerning toxicity substitution of 3 × 10 mg MITX/sqm for 3 × 45 mg DNR/sqm during the induction phase does not seem to have modified the duration or the severity of the postinduction aplasia. By contrast, the consolidation phase, calling for fortnightly MITX in addition to ARAC and 6TG, induced severe and protracted myeloid aplasia which, in some patients, entailed considerable postponement of intensification courses, up to 5 months, and was accompanied by a great incidence of toxic deaths: 4/70 patients. This unexpected severity of the myelotoxicity during this phase might be related to the design of the protocol rather than to the total dose of MITX given. The fortnightly administration of this very slowly eliminated drug [25–29] may have led to very long-term exposure of the hemopoietic progenitors. Whether the antileukemic effect may have matched that on normal hemopoietic cells can be only speculated.

Concerning cardiotoxicity, the drop of the SF < 28% occurred uniformly during all the treatment steps, with-

out any acute clinical signs. All patients recovered a normal SF after discontinuation or delay of MITX administration. These data have to be confirmed by a long-term follow-up. Recent studies suggest that peak value of the blood anthracycline concentration is responsible for cardiac complications. Therefore, it might be worthwhile to replace the bolus administration by continuous infusion without losing the therapeutic effect.

We could not confirm the prognostic significance of the features identified as predictive by Creutzig for EFS and accordingly we were unable to find any difference in outcome between the two risk groups. This is surprising since both studies and overall outcome are similar. Furthermore, in our study, patients with M5 AML have a comparable EFS to the other subtypes. This is unexpected since M5 subtype is usually considered as a bad prognostic factor. On the contrary, cytogenetic characteristics appeared to be the most important factor. Our data confirm the predictive value of Keating's classification: the favorable group had EFS of 52% at 3 years.

CONCLUSION

This protocol is very efficient for AML in childhood compared to others. The major problem is its myelotoxicity during the consolidation phase; this has been taken into consideration for our present protocol. Whether it will eventually be less cardiotoxic requires much longer follow-up. Considering the importance of the prognostic significance of cytogenetic groups, treatment-adapted protocols should be considered in future studies.

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