Value of High-Dose Cytarabine During Interval Therapy of a Berlin-Frankfurt-Munster–Based Protocol in Increased-Risk Children With Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma: Results of the European Organization for Research and Treatment of Cancer 58881 Randomized Phase III Trial

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Purpose: The European Organization for Research and Treatment of Cancer 58881 study was designed to test in a prospective multicentric randomized trial the value of high-dose (HD) intravenous (IV) cytarabine (Ara-C) added to HD IV methotrexate (MTX) to reduce the incidence of CNS and systemic relapses in children with increased-risk acute lymphoblastic leukemia (ALL) or stage III and IV lymphoblastic lymphoma treated with a Berlin-Frankfurt-Munster (BFM)–based regimen.

Patients and Methods: After completion of induction-consolidation phase, children with increased-risk (risk factor $\geq$ 0.8 or T-lineage) ALL or stage III and IV lymphoblastic lymphoma were randomized to receive four courses of HD MTX (5 g/m² over 24 hours every 2 weeks) and four intrathecal administrations of MTX (Arm A) or the same treatment schedule with additional HD IV Ara-C (1 g/m² in bolus injection 12 and 24 hours after the start of each MTX infusion) (Arm B).

Results: Between January 1990 and January 1996, 653 patients with ALL (593 patients) or lymphoblastic lymphoma (60 patients) were randomized: 323 were assigned to Arm A (without Ara-C) and 330 to Arm B (with Ara-C). A total of 190 events (177 relapses and 13 deaths without relapse) were reported, and the median follow up was 6.5 years (range, 2 to 10 years). The incidence rates of CNS relapse were similar in both arms whether isolated (5.6% and 3.3%, respectively) or combined (5.3% and 4.6%, respectively). The estimated 6-year disease-free survival (DFS) rate was similar (log-rank $P = .67$) in the two treatment groups: 70.4% (SE = 2.6%) in Arm A and 71.0% (SE = 2.5%) in Arm B. The 6-year DFS rate was similar for ALL and LL patients: 70.2% (SE = 1.9%) versus 76.3% (SE = 5.6%).

Conclusion: Prevention of CNS relapse was satisfactorily achieved with HD IV MTX and intrathecal injections of MTX in children with increased-risk ALL or stage III and IV lymphoblastic lymphoma treated with our BFM-based treatment protocol in which cranial irradiation was omitted. Disappointingly, with the dose schedule used in this protocol, HD Ara-C added to HD MTX, although well tolerated, failed to further decrease the incidence of CNS relapse or to improve the overall DFS.

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C OMBINATION OF high-dose (HD) intravenous (IV) methotrexate (MTX) and intrathecal (IT) chemotherapy without cranial irradiation has been widely accepted for protection from CNS relapse in children receiving intensive chemotherapy for non–high-risk acute lymphoblastic leukemia (ALL).[1-3] In such patients, the rate of CNS relapses is 1.1% to 6.3%.[2,4,5] The addition of HD cytarabine (Ara-C)

to this prophylactic schedule may be useful to lower the incidence of CNS relapses because of in vitro antileukemic synergistic effect of Ara-C in combination with MTX[6,7] and good penetration of systemic HD Ara-C in CNS of leukemic patients.[8,9] However, in the late 1980s, no data were available on the clinical benefit of the addition of HD Ara-C. For this reason, the European Organization for

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Research and Treatment of Cancer (EORTC) Children's Leukemia Cooperative Group (CLCG) conducted a randomized trial to assess the value of HD Ara-C in combination with HD MTX and IT chemotherapy to reduce the incidence of CNS and systemic relapses in children with increased-risk ALL and advanced-stage lymphoblastic lymphoma treated with a Berlin-Frankfurt-Munster (BFM)–based regimen.

PATIENTS AND METHODS

Patients

In July 1989, the EORTC-CLCG instituted a treatment protocol (EORTC 58881) for patients younger than 18 years of age with previously untreated ALL or lymphoblastic lymphoma. Patients with mature B-cell ALL or mature B-cell lymphoma were not eligible. A total of 28 centers from France, Belgium, and Portugal participated in this trial. According to their presenting features and the response to treatment, patients were stratified into three groups: low-risk, increased-risk, or very high-risk group. Low-risk group included leukemic patients with low tumor burden, defined as BFM risk factor (RF) (calculated as $RF = 0.2 \times \log_{10}$[blast cell count/mm^3 + 1] + 0.06 $\times$ cm of palpable liver + 0.04 $\times$ cm of palpable spleen) less than 0.8 and patients with stage I or II lymphoblastic lymphoma. Increased-risk group comprised ALL children with RF $\geq$ 0.8, patients with T-cell lineage ALL, and patients with stage III or IV lymphoblastic lymphoma. Very high-risk (VHR) group included children with at least one of the following criteria: more than 1×10^9/L blasts in peripheral blood at the end of the first week of prednisolone treatment and IT MTX injection, presence of acute undifferentiated leukemia features, presence of t(4,11) or t(9,22) translocation in leukemic cells, absence of complete remission, for ALL patients, or lack of good partial response, for lymphoblastic lymphoma patients, after completion of induction therapy. Increased-risk patients, without VHR features, were the subjects of the present study. Permission to include each child in the study was obtained by informed consent from the parents. The respective institutional review boards approved the protocol.

Definitions and Evaluations

When bone marrow involvement was observed, patients with less than 25% blasts in a bone marrow aspirate and none in the peripheral blood were considered to have lymphoma. Patients with lymphoblastic lymphoma were staged according to Murphy's classification using clinical and imaging criteria.[10] All cases were studied for specific lymphoblastic cell characteristics, including morphologic characteristics, immunophenotype, and cytogenetic features. Morphologic classification of the ALL was based on criteria of the French-British-American classification.[11] Classification of lymphomas was performed according to the Working Formulation and the Revised European-American Lymphoma Classification.[12,13] Frozen specimens or cell suspensions were evaluated for B- and T-lineage–associated antigens using standard techniques as previously reported.[14,15] Results were considered positive if more than 30% of the cells expressed a particular antigen. Cytogenetic analysis of the lymphoblastic cells was performed by R or G banding, and chromosomes were classified according to the International System for Human Cytogenetic Nomenclature.[16]

For ALL, complete remission (CR) was defined as less than 5% blasts in the bone marrow and recovery of normal hematopoiesis,

absence of blasts in peripheral blood, and no evidence of disease at any other site. For lymphoblastic lymphoma, CR was defined by the disappearance of all clinical, imaging, and cytologic signs of lymphoma, and good partial response was defined by the persistence of a residual mass in one tumor site, the main diameter of which could not exceed 30% of the initial diameter. Results of treatment were evaluated at completion of induction, consolidation, intensification, and maintenance phases.

CNS leukemia was diagnosed when neurologic abnormalities related to blastic infiltration of the CNS were observed and/or when blasts were identified on cytocentrifuge examination of CSF in which the WBC count was greater than 5 cells/μL. A CSF count and differential after cytocentrifugation were performed at the time of each administration of IT MTX. Routine surveillance of CSF analyses were not performed during maintenance therapy and thereafter, but in case of appearance of CNS symptoms or in case of systemic relapse. Infectious, renal, hepatic, and neurologic toxicities induced by the treatment were evaluated and graded according to the World Health Organization grading system.[17] Hepatic and renal toxicities were respectively defined as an increase in serum transaminase and creatinine levels greater than 1.25 $\times$ upper normal limit.

Treatment

We used a BFM modified treatment protocol, but cranial irradiation was omitted.[5] The treatment protocol for the increased-risk patients is summarized in Table 1. In brief, after 1 week of prednisolone and one IT injection of MTX, all patients received induction therapy (daily prednisolone, weekly vincristine and daunorubicin, L-asparaginase twice weekly, and two IT injections of MTX) over a period of 4 weeks. During induction, the patients were randomized to receive Escherichia coli or Erwinia L-asparaginase (the dose for E coli and Erwinia preparations was the same in both arms). Patients with ALL or lymphoblastic lymphoma who achieved a CR and patients with lymphoblastic lymphoma who achieved a good partial response received 4 weeks of consolidation therapy (daily mercaptopurine, four 4-day courses of Ara-C, two courses of cyclophosphamide, and two IT injections of MTX). After consolidation therapy, patients in complete remission were assigned randomly to CNS prophylaxis regimen (interval therapy) with HD MTX alone (arm A) or HD MTX in combination with Ara-C (arm B). In arm A, patients received daily 6-mercaptopurine (25 mg/m^2) and four courses of HD MTX (5 g/m^2 every 2 weeks). HD MTX was given as a 24-hour IV infusion with alkaline hydration. Intrathecal administration of MTX was performed at the end of each MTX infusion. Folinic acid rescue (15 mg/m^2 given orally every 6 hours) was initiated 12 hours after the end of MTX infusion and was continued until the MTX plasma concentration was less than 0.2 10^{-6} mol/L. In arm B, patients received in addition IV HD Ara-C (1 g/m^2 as a 10-minute infusion) administered 12 and 24 hours after the start of each MTX infusion. Each course of MTX or MTX in combination with Ara-C was started if the WBC count was above 2 $\times 10^9$/L with more than 0.5 $\times 10^9$/L polymorphonuclear cell and the platelet count above 50 $\times 10^9$/L. According to the protocol, lower dose of Ara-C (2 $\times$ 750 mg/m^2) was administered in case of hematologic toxicity resulting in a delay of more than 7 days to perform the subsequent course of MTX Ara-C. Interval therapy was followed by a delayed intensification phase consisting of dexamethasone for 3 weeks, four weekly injections of vincristine and doxorubicin, and four injections of L-asparaginase followed by daily thioguanine (for 14 days), one course of cyclophosphamide, two 4-day courses of Ara-C, and one IT injection of MTX. Patients remaining in CR were randomized to receive maintenance treatment consisting of daily 6-mercaptopurine and weekly oral MTX

Table 1. Treatment Schedule for Increased-Risk Patients According to EORTC 58881 Protocol

Drug	Dose*	Applied on Days
Induction		
Prednisolone (orally)	60	1-7 (prephase)
Prednisolone (orally)	60	8-28, then tapered over 9 days
Vincristine (IV)	1.5 (max 2.5 mg)	8,15,22,29
Daunorubicin (IV)	30	8,15,22,29
L-asparaginase (IV) (*E. coli* or *Erwinia* according to randomization)	10,000 IU/m²	12,15,18,22,25,29,32,35
Methotrexate (IT)	According to age†	1,8,22
Consolidation		
Cyclophosphamide (IV)	1 g/m²	36 and 63
Cytarabine (IV)	75	38-41, 45-48, 52-55, 59-62
Methotrexate (IT)	According to age†	38 and 52
6-Mercaptopurine (orally)	60	36-63
Interval therapy		
Arm A		
6-Mercaptopurine (orally)	25	1-56
Methotrexate (24h infusion)	5 g/m²	8,22,36,50
Methotrexate (IT)	According to age†	9,23,37,51
Arm B		
6-Mercaptopurine (orally)	25	1-56
Methotrexate (24h infusion)	5 g/m²	8,22,36,50
Methotrexate (IT)	According to age†	9,23,37,51
Cytarabine (IV)	1 g/m² × 2	8,22,36,50
Intensification		
Dexamethasone (orally)	10	1-21 then tapered over 11 days
Vincristine (IV)	1.5 (max. 2.5 mg)	8,15,22,29
Doxorubicin (IV)	30	8,15,22,29
L-Asparaginase (IV) (*E. coli* or *Erwinia* according to the first randomization)	10,000 IU/m²	8,11,15,18
Cyclosphosphamide (IV)	1 g/m²	36
6-Thioguanine (orally)	60	36-49
Cytarabine (IV)	75	38-41, 45-48
Methotrexate (IT)	According to age†	38
Maintenance (up to 2 years after day 1 of induction)		
Arm M1: 6-Mercaptopurine (orally)	50	Everyday
Methotrexate	20	Once a week
Arm M2: 6-Mercaptopurine	50	Everyday
Methorexate (orally)	20	Once a week
6-Mercaptopurine (IV)	1 g/m²	Every 4 weeks

*Unless otherwise indicated, doses are given in milligrams per meters squared.

†Less than 1 year: 6 mg; 1 year: 8 mg; 2 years: 10 mg; 3 years and more: 12 mg.

or the same treatment with monthly IV 6-mercaptopurine. No cranial irradiation was performed. The total duration of the treatment protocol was 2 years.

Statistical Considerations

Randomization was performed centrally (EORTC Data Center, Brussels, Belgium) just before interval therapy treatment and was stratified according to center, RF (< 0.8, 0.8 to 1.19 $v \geq 1.2$), and previous randomized arm (*E coli* or *Erwinia* L-asparaginase). The primary end point was the disease-free survival (DFS) from the date of randomization until the date of first relapse or until death in CR. The secondary end points were the time to CNS relapse (time from randomization until CNS isolated or combined relapse, where patients with other types of relapse were censored at the moment of relapse) and

the duration of survival (the time from randomization until death, whatever the cause). The actuarial curves were computed using the Kaplan-Meier technique, and the SEs of the estimates were obtained via the Greenwood formula.[18] The differences between curves were tested for statistical significance using the two-tailed log-rank test or the log-rank test stratified by a categorical factor.[18] To summarize the overall treatment difference, the hazards ratio (HR) of having an event per time in arm B versus the one in arm A, along with its 95% confidence interval, was estimated via the Cox's proportional hazards model.[19] A total of 592 patients were initially planned to be randomized to detect a significant difference in terms of DFS at 5 years (70% v 80%), corresponding to a hazards ratio of 0.63 (alpha = 5%, beta = 20%); a total of 148 patients had to be followed until relapse or death in first CR before the final analysis. All analyses were performed

according to the intent-to-treat-principle. The Wilcoxon rank test was used for the treatment comparison regarding the duration of interval therapy. The rate of patients with an interval therapy exceeding 8 weeks was compared using the usual χ^2 test. The χ^2 from linear trend was used to compare the incidence of toxicities (graded as 0 v 1 to 2 v 3 to 4) in the two treatment arms.

RESULTS

Patients

Between January 1990 and January 1996, 27 centers of the EORTC-CLCG randomized a total of 656 patients to receive interval therapy with or without IV HD Ara-C. Two patients who were considered ineligible (one did not reach CR and one relapsed before randomization) and one who was considered unassessable (due to insufficient information about eligibility characteristics) have been excluded from further analyses. Among the remaining 653 patients, 323 were assigned to arm A (without Ara-C) and 330 to arm B (with Ara-C). Patient characteristics according to the treatment arm are listed in Table 2. There were 60 patients (39 boys and 21 girls; 12 months to 16 years old; median age, 7 years) with lymphoblastic lymphoma (42 patients with Murphy stage III and 18 patients with stage IV disease) and 593 ALL patients (343 boys and 250 girls; 3 months to 17 years old; median age, 4 years). Among the latter group there were 19 patients (7 in arm A and 12 in arm B) with RF less than 0.8. Patient characteristics were well balanced in the two treatment arms. The type of L-asparaginase administered during the induction and consolidation phase or the type of maintenance (with or without IV 6-mercaptopurine) were well balanced in the two treatment groups as well (data not shown).

Treatment Outcome

At the time of final analysis, the median follow-up was 6.5 years (range, 2 to 10 years), and 190 events (comprising 177 relapses and 13 deaths in first CR) were reported. Site-specific relapse rates are listed in Table 3 according to the arm of randomization. The distribution of the relapse sites was similar in the two treatment groups. Isolated bone marrow relapse was the main cause of treatment failure in both arms (12.4% and 14.3%). In arm A and arm B, the incidences of CNS relapses were quite similar, whether isolated (5.6% and 3.3%, respectively) or combined (5.3% and 4.6%, respectively). Three patients (0.9%) in arm A and 10 (3%) in Arm B died while in CR as a result of the treatment toxicity (mainly infection). Four patients died (one in arm A and three in arm B) during intensification phase, eight patients died (one in arm A and seven in arm B) during maintenance therapy, and only one patient died (in arm A) during interval therapy.

Considering the time-to-event analysis, the estimated 6-year DFS rate was 70.4% (SE = 2.6%) for the patients assigned to arm A and 71.0% (SE = 2.5%) for those assigned to arm B (Fig 1). The estimated hazards ratio was 1.06 (95% confidence interval, 0.8 to 1.41). The log-rank test yielded a nonsignificant result ($P = .67$). Because of the good balance of different features in the two treatment groups, these findings were not influenced when the treatment comparison was stratified by the initial WBC count, risk factor, immunophenotyping, or disease (data not shown). The 6-year DFS rate was similar for ALL and LL patients: 70.2% (SE = 1.9%) versus 76.3% (SE = 5.6%).

Table 2. Patient Characteristics According to the Randomized Arm

	Arm A (without Ara-C) (n = 323)		Arm B (with Ara-C) (n = 330)	
	No. of Patients	%	No. of Patients	%
Sex				
Male	190	59	202	58
Female	133	41	144	42
Age				
< 1 years	7	2	1	< 1
1-9 years	266	82	280	85
10-18 years	50	15	49	15
Disease				
LL	31	10	29	9
ALL	292	90	301	91
ALL patients only				
WBC				
< 25 × 10⁹/L	160	55	182	61
25-100 × 10⁹/L	97	33	91	30
≥ 100 × 10⁹/L	35	12	28	9
RF				
< 0.8	7	2	12	4
0.8-1.19	157	54	158	52
≥ 1.2	128	44	131	44
CNS involvement	1	< 1	0	0
Immunophenotype				
B lineage	258	88	255	85
T lineage	34	12	46	15
Chromosome findings				
Successful examination*	206	64	219	66
Diploid	69	34	77	36
Pseudodiploid	34	17	57	26
Hypodiploid	8	4	14	7
Hyperdiploid 47-50	26	13	19	9
Hyperdiploid 51-66	65	32	49	23
Other	4	2	3	1

*Percentages were computed for those with a successful cytogenetic examination.

Table 3. Outcome According to the Randomized Arm

	Arm A (without Ara-C) (n = 323)		Arm B (with Ara-C) (n = 330)	
	No. of Patients	%	No. of Patients	%
Continuous CR	230	71.2	233	70.6
Death in CR	3	0.9	10	3.0
Relapse	90	27.9	87	26.4
Bone marrow, isolated	40	12.4	47	14.3
CNS, isolated	18	5.6	11	3.3
CNS, combined	17	5.3	15	4.6
Other isolated	10	3.1	7	2.1
Other combined	5	2.0	7	2.1

The type of L-asparaginase administered during the induction or the type of maintenance (with or without a monthly administration of IV 6-mercaptopurine) did not influence the treatment difference either (data not shown). The treatment difference in terms of time to CNS relapse was not significant ($P = .29$) (Fig 2). The actuarial cumulative 6-year CNS relapse rate was 12.0% (SE = 1.9%) in arm A and 8.6% (SE = 1.6%) in arm B. The estimated hazards ratio was 0.76 and the 95% confidence interval was quite large (0.46 to 1.26) as the total number of CNS relapses was relatively low. In ALL and LL, the overall 6-year CNS relapse rates were 10.8% (SE = 1.3%) and 5.6% (SE = 2.8%), respectively. The duration of survival was not significantly different ($P = .55$) between the two treatment groups, as shown in Fig 3. The estimated 6-year survival rates were practically identical in each arm, 83.5% (SE = 2.2%) versus 84.0% (SE = 2.0%), the estimated hazards ratio was 1.12, and the 95% confidence interval was 0.77 to 1.63. These later numbers remained unchanged by performing an adjustment by disease. The 6-year survival of ALL

Fig 2. Cumulative risk of CNS relapse according to arm A or arm B. Abbreviations: O, observed number of events (CNS relapse, either isolated or combined with other sites); N, number of patients at risk.

patients was 84.1% (SE = 1.5%) versus 79.9% (SE = 5.5%) for LL patients.

Protocol Compliance and Toxicity

In arm A, all but six patients (2%) did not receive Ara-C during the interval therapy, whereas in arm B, Ara-C was not administered to 11 patients (3%), and in nine cases the doses of Ara-C could not be checked, as the forms were not available. The toxic side effects occurring during the interval therapy in the two treatment groups are listed in Table 4. In most cases, the toxicity was absent or only mild to moderate (grade 1 to 2). The incidence and the degree of infections and of increased serum creatinine levels were similar in the two treatment groups. Increased serum transaminase levels were slightly higher in arm B than in arm A (χ^2 for linear trend, $P = .12$). The incidence of neurotoxicity was rare in the two arms (less than 1%). Twenty-eight courses of reduced dose of Ara-C were administered in 16 patients because of hematologic toxicity.
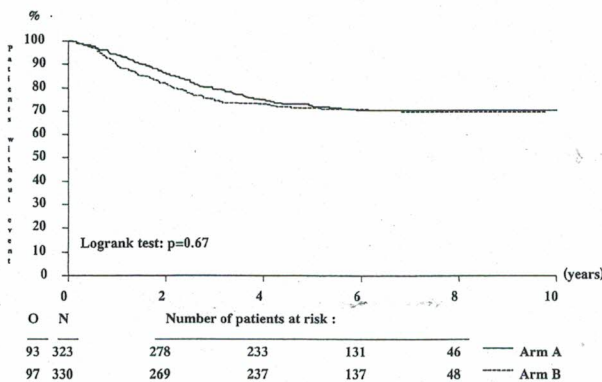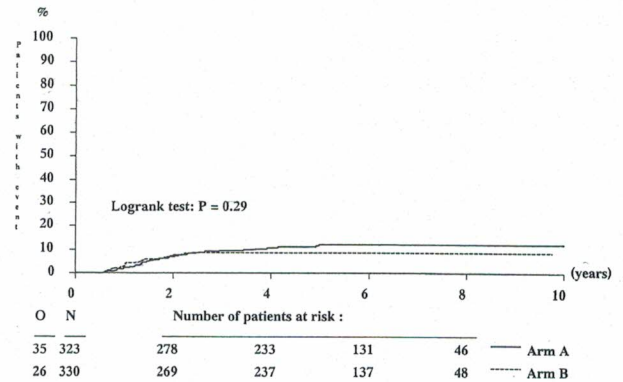

Fig 1. Disease-free survival according to arm A or arm B. Abbreviations: O, observed number of events (relapses or deaths in CR); N, number of patients at risk.
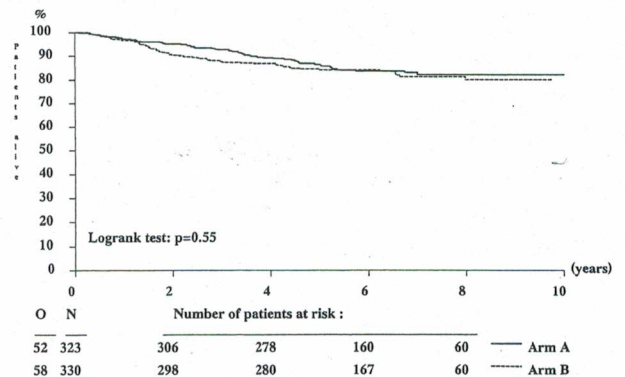

Fig 3. Survival according to arm A or arm B. Abbreviations: O, observed number of deaths, whatever the cause; N, number of patients at risk.

Table 4. Toxic Side Effects (WHO grading) Reported During the Interval Therapy* According to the Randomized Arm

	Arm A (without Ara-C) (n = 311)		Arm B (with Ara-C) (n = 315)	
	No. of Patients	%	No. of Patients	%
Infection				
Grade 1-2	72	23	87	28
Grade 3-4	8	3	14	4
Increase of transaminases				
Grade 1-2	95	30	105	37
Grade 3-4	6	2	12	4
Neurotoxicity				
Grade 1-2	17	5	18	6
Grade 3-4	3	1	0	0
Increase of creatinine				
Grade 1-2	55	18	63	20
Grade 3-4	4	1	3	1

*Patients with the documented forms received were included in this analysis.

The duration of interval therapy was statistically longer (Wilcoxon test, $P = .0001$) for patients randomized in arm B (the quartiles 50%, 75%, and 90% were 55 days, 56 days, and 61 days, respectively) than for those in arm B (the quartiles 50%, 75%, and 90% were 55 days, 60 days, and 68 days, respectively). The rate of patients with a prolonged interval therapy exceeding the normal 8-week period was 33% in arm B versus 17% in arm A (χ^2 test, $P < .001$).

DISCUSSION

Cranial irradiation may induce neuropsychologic and neuroendocrinologic damages, especially in young children, and secondary brain tumors.[20,21] Previous trials have indicated that intermediate and HD IV infusion of MTX and/or IT injection of chemotherapy may replace prophylactic CNS radiotherapy without compromising efficacy in children with ALL.[1,22] In the EORTC 58832 randomized trial, we demonstrated that the omission of cranial irradiation did not influence the risk of CNS relapse or the treatment outcome in intermediate and high-risk patients.[23] The combination of IV 1 g/m² MTX and IT MTX injections has been shown to be as effective as cranial irradiation in preventing CNS relapse in children with favorable-risk ALL.[1] Interestingly, use of IV intermediate- or high-dose MTX in patients with B-cell progenitor has been reported to prolong CR duration and to prevent leukemic relapse in the testes.[22,24] Theoretically, administration of IV HD MTX may provide control of CNS sanctuary sites, because cytotoxic levels of the drug can be achieved in CSF in leukemic patients.[25] However, we reported in a previous study that patients who achieve adequate MTX level in CSF at the end of a 24-hour infusion of 5 g/m2 MTX do not seem to be protected against CNS relapse.[26]

Results of previous studies have indicated that cranial irradiation can be omitted in intermediate-risk ALL as well. Conter et al[2] have shown that HD MTX with extended intrathecal chemotherapy is effective for protection from CNS relapse in children receiving intensive chemotherapy. Tubergen et al[27] demonstrated that the frequency of CNS isolated relapses is strongly influenced by the intensity of the systemic therapy in patients with intermediate-risk ALL in which cranial irradiation is omitted. A lower rate of CNS isolated relapse was observed in patients receiving the more intensive therapy regimens. Standards are less established for combined-site CNS relapse prevention.

The reasons for testing the effect of the combination of IV MTX and Ara-C in the present study were based on experimental and pharmacokinetic data. In vitro studies indicated that these drugs act synergically against L1210 murine leukemic cells.[7] This synergistic effect results from increased intracellular accumulation of Ara-C and enhancement of phosphorylation of Ara-C to its active metabolite in leukemic cells exposed to MTX. However, some studies do not find synergism.[28] In vitro synergistic cell kill requires that MTX administration precede Ara-C administration and that the concentration of MTX be high (1×10^{-6} mol or greater), indicating that dose and schedule of administration of these two drugs are critical.[7] Moreover, pharmacokinetic and clinical studies have demonstrated that IV administration of HD Ara-C provides a high degree of penetration of the drug in the CSF with prolonged cytotoxic concentrations.[8,9] We previously reported that administration of HD Ara-C in combination with HD MTX did not seem to modify the CSF MTX concentrations in a study conducted in 114 children with ALL.[26] HD IV Ara-C was reported to be effective in patients with meningeal leukemia.[29] Very few data are available concerning the use of HD MTX in combination with Ara-C as CNS prophylactic measure in patients with ALL. Cortes et al[30] reported CNS relapses in 3% of 92 adults with ALL receiving high-dose systemic chemotherapy (MTX 1 g/m² and Ara-C 12 g/m²) with IT injection chemotherapy as CNS prophylactic measure. A pilot study of the Pediatric Oncology Group reported a tolerable toxicity and a low incidence (3%) of CNS relapse in nonirradiated children with standard- and poor-risk B-precursor cell ALL receiving three-drug IT therapy and combination of IV MTX (1 g/m²) and IV Ara-C (1 g/m²) after documentation of CR.[31] In a randomized trial, this group demonstrated that patients receiving six pulses of similar treatment with IV MTX and Ara-C administered every 3 weeks have the same CR duration but higher CNS

toxicity than those who received this combination every 12 weeks.[32] Of the 428 patients with standard- and poor-risk B-precursor cell ALL of this study, 4.2% developed isolated CNS relapse. The same group reported that RBC MTX concentrations were lower in low-risk children receiving intermediate dose of MTX in combination with Ara-C than in patients receiving MTX·alone.[33] In this study, lower RBC MTX concentration was associated with a worse event-free survival, suggesting that Ara-C altered MTX pharmacology in the therapeutic schedule used.

In the present study, the 5.6% incidence rate of isolated CNS relapse in children receiving HD MTX alone during interval therapy is comparable to the rate (3.3%) observed in those receiving combination of HD MTX and Ara-C. These rates are within the range usually accepted as demonstrating efficacy for any regimen of CNS prophylaxis in children with increased-risk ALL.[4,5] Recently, the BFM group reported isolated CNS relapses in 0.8% of medium-risk children receiving a reduced (12 Gy) prophylactic cranial irradiation.[34] In the present study, the addition of HD Ara-C did not reduce the systemic marrow relapse rate and did not result in a significant advantage in terms of general outcome. The DFS in our two treatment groups of patients compares favorably with those achieved in studies with BFM-based regimens.[2,4,5] It is noteworthy that the current report included patients with high leucocyte count, T-ALL, or lymphomatous features that were reported to have a worse prognosis.[35,36]

The duration of interval therapy was statistically longer for patients receiving HD Ara-C, indicating that courses of MTX and Ara-C were more frequently delayed than courses of MTX alone. Toxic events such as infections and abnormal transaminases levels, which were more frequent in this treatment group, could explain the delay in treatment realization. Interestingly, the addition of HD Ara-C to HD MTX did not enhance the neurotoxicity of this drug. We previously reported that children receiving HD Ara-C during interval therapy did not exhibit impairment of biogenic amines metabolites concentrations in CSF (abnormalities of these biochemical compounds being reported in some patients with MTX-induced neurotoxicity).[37]

In conclusion, the addition of HD Ara-C to HD MTX could not provide better protection of CNS relapse and less systemic relapses as compared with HD MTX alone in children with increased-risk ALL or stage III and IV lymphoblastic lymphoma.

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