Role of treatment intensification in infants with acute lymphoblastic leukemia: results of two consecutive AIEOP studies

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Fifty-two infants with acute lymphoblastic leukemia (ALL) enrolled in the AIEOP ALL-91 and ALL-95 studies were treated with the intermediate or high risk protocols according to their presenting features and early response to treatment. The 5-year event-free survival was 33.3% (95% CI 12.1-54.5), 53.5% (95% CI 35.7-71.3) and 45.0% (95% CI 31.3-58.7) in the ALL-91 and ALL-95 studies and in the overall cohort, respectively. In the ALL-95 high-risk group (BFM therapy intensified by three blocks and double protocol II) nine of 17 patients treated with chemotherapy only and three of four transplanted patients were alive and in complete remission. The corresponding figures for patients treated in the ALL-91 high-risk protocol (reduced induction and nine blocks) were one of seven patients treated with chemotherapy only and none of two who were transplanted.

Key words: infant, childhood, acute lymphoblastic leukemia, treatment, clinical trials.

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Cure rates in infant acute lymphoblastic leukemia (ALL) are currently in the range of 35-40% Such a dismal outcome is far behind the 75-80% cure rates obtained in the general population of childhood ALL and has been correlated with the typical high-risk presenting features of infant ALL.[1,2] Intensified chemotherapy and hematopoietic stem cell transplantation (HSCT)[3-16] have been tested in attempts to improve results in infant ALL. In a comparative evaluation of two successive AIEOP studies (ALL-91 and ALL-95), we previously reported a better treatment outcome for patients in the ALL-95 study who were at high-risk because of poor response to corticosteroids by using a full induction protocol I and by replacing the six alternating blocks of non–cross-resistant drugs with an eight-drug reinduction regimen (i.e. BFM protocol II), repeated twice, in the context of a traditional BFM-type intensive chemotherapy.[17] The main goal of the present study was to evaluate whether the treatment strategy adopted in the AIEOP ALL-95 study also improved the outcome in infants with ALL, compared to that in infants diagnosed and enrolled in the previous AIEOP ALL-91 study.

Design and Methods

Patients

From April 18, 1991 to September 7, 2000, 52 previously untreated patients younger than 12 months with newly diagnosed ALL, were registered from 22 AIEOP institutions in the ALL-91(n=21) and ALL-95 (n=31) studies and were eligible and evaluable for this analysis.

Diagnostic studies

The diagnosis of ALL was established according to standard morphologic, cytochemical, and immunologic criteria and centrally reviewed.[18] The t(4;11) translocation was identified by molecular screening of all samples.[19] Complete remission was defined as no physical signs of leukemia, no detectable leukemia cells on the blood smears, bone marrow with active hematopoiesis and less than 5% blast cells, and normal cerebrospinal fluid. In both studies infants could only be treated within the intermediate-risk or high-risk group. Patients who did not fulfill the high-risk criteria were thus stratified in the intermediate risk group. For this reason only high-risk criteria are listed here.

High-risk inclusion criteria for the ALL-91 study were BFM risk factor (calculated at diagnosis as $0.2\times\log_{10}$ [blast cell count + 1] + 0.06×centimeters of palpable liver + 0.04×centimeters of palpable spleen) ≥1.7 *or* CNS leukemia at diagnosis (*see above*) *or* t(4;11) *or* prednisone poor response (i.e. PPR, ≥1,000 blasts/mm^3 in the peripheral blood after 7 days of corticosteroids and one injection of intrathecal methotrexate) *or* failure to achieve CR after the first 6 weeks of induction therapy (protocol IA). *High-risk inclusion criteria for the ALL-95 study* were evidence of t(4;11) translocation *or* CD10 negative immunophenotype *or* PPR *or* failure to achieve complete remission after the first 6 weeks of induction therapy (protocol IA).

Chemotherapy protocols

In the ALL-91 intermediate-risk protocol patients underwent 7 days of prephase steroid therapy followed by induction therapy (eight-

drug based BFM protocol IA+B), consolidation with four cycles of high-dose methotrexate (q2 weeks at 5 g/m^2), reinduction with the BFM protocol II and continuation therapy. Prophylaxis against central nervous system (CNS) disease consisted of extended triple intrathecal therapy with methotrexate+cytarabine+methylprednisolone (TIT). Cranial radiotherapy was not given. The total duration of treatment was 24 months.

In the ALL-91 high-risk protocol, the steroid prephase and protocol IA were followed by nine blocks of non-cross-resistant drugs; prophylaxis against CNS disease consisted of TIT administration during each treatment phase (including blocks) followed, in children ≥1 year at the beginning of the continuation phase, by cranial irradiation (12 Gy). Patients with CNS disease at onset received additional TIT administrations and higher doses of cranial radiotherapy (18 Gy). Children who were still < 1 year at the beginning of this phase were not irradiated and extended treatment with TIT was given during the continuation phase.

In the ALL-95 intermediate-risk protocol, patients underwent the same treatment as that in the ALL-91 intermediate risk protocol except for the consolidation phase (high-dose methotrexate was reduced to 2 g/m^2 for all patients other than those with CNS or testicular involvement, or T-immunophenotype at diagnosis, who received 5 g/m^2). Prophylaxis against CNS disease consisted of TIT administration during each treatment phase and was extended throughout the continuation phase.

In the ALL-95 high-risk protocol, patients underwent the same treatment as that in the ALL-91 high-risk protocol except for the additional use of protocol IB, the number of blocks (three instead of nine) and the addition of two protocols II. Cranial radiotherapy was given to children aged ≥1 year at the beginning of the interim continuation phase (between the two protocols II) whereas extended TIT was administered to children aged <1 year at that point. During the continuation phase monthly pulses of vincristine-prednisone were administered to all patients. The dosage of all chemotherapy agents was calculated in both studies according to the patient's body surface area. Both protocols were approved by the ethical committees of each single institution participating in the studies; consent was obtained from parents or legal guardians of all patients. The total treatment duration was 2 years in both studies. Further details on stratification, treatment strategy and results of the AIEOP ALL-91 and ALL-95 studies have been reported elsewhere.[17,20]

Transplant eligibility criteria

In the ALL-91 study any patient in the high-risk group in first complete remission was eligible for HSCT from a matched family donor, thus including patients bearing the t(4;11) translocation. In the ALL-95 study HSCT from a matched family donor was indicated for all patients < 1 year at diagnosis if they had one of the following features: t(4;11) clonal translocation; CD10-negative B-lineage immunophenotype; PPR associated with either a T-cell immunophenotype or a white cell count ≥100,000/μL; failure to achieve complete remission after the first 6 weeks of induction therapy (protocol IA)

Table 1. Main laboratory and clinical characteristics of the 52 infants treated in the AIEOP ALL-91 and ALL-95 studies, with related outcome (when adequate numbers were available).

	ALL-91 21 patients				*ALL-95 31 patients*			
	N.	*% pts.*	*N. events (SE)*	*3-year EFS°*	*N. pts.*	*%*	*N. events (SE)*	*3-year EFS°*
Gender								
Male	10	47.6	6	–	16	51.6	8	54.2 (12.9)
Female	11	52.4	8	–	15	48.4	6	66.7 (12.2)
Age at diagnosis								
0-5 months	10	47.6	7	–	10	32.3	6	–
6-12 months	11	52.4	7	–	21	67.7	8	71.4 (9.9)
WBC count at diagnosis								
<300,000/mm^3	17	81.0	11	47.1 (12.1)	22	71.0	8	68.2 (10.0)
≥300,000/mm^3	4	19.0	3	–	9	29.0	6	–
Immunophenotype								
B-lineage CD10$^+$	10	47.6	6	–	14	45.2	6	57.1 (13.2)
B-lineage CD10$^-$	10	47.6	7	–	10	32.3	3	–
B-lineage	1	4.8	1	–	5	16.1	4	–
Not classified								
T -lineage	0	–	–	–	2	6.4	1	–
t (4;11)								
Positive	4	19.0	3	-	8	25.8	5	–
Negative	17	81.0	11	47.1 (12.1)	22	71.0	9	68.2 (9.9)
Not known	0	–	–	–	1	3.2	0	–
CNS disease								
Yes	2	9.5	2	–	3	9.7	0	–
No	19	90.5	12	47.4 (11.5)	28	90.3	14	56.0 (9.5)
Prednisone response§								
PGR	16	76.2	10	50.0 (12.5)	16	51.6	8	56.3 (12.4)
PPR	3	14.3	2	–	14	45.2	6	64.3 (12.8)
Not known	2	9.5	2	–	1	3.2	0	–
Protocol administered								
Intermediate risk	12	57.1	6	66.7 (13.6)	10	32.3	5	–
High risk	9	42.9	8	–	21	67.7	9	66.7 (10.3)

PGR: prednisone good response; PPR: prednisone poor response; WBC: white blood cell; CNS: central nervous system; EFS: event-free-survival; SE: standard error. °Even free survival (EFS) comparisons in subgroups within the AIEOP ALL-95 protocol were performed for gender and prednisone response and did not reach statistical significance (at the 0.05 level). §The distribution of prednisone response was significantly different in the two series of infants (p-value =0.027). No other comparison showed a statistically significant difference in distributions of characteristics between the two studies.

Statistical analysis

Event-free survival from diagnosis and disease-free survival from complete remission were estimated with the Kaplan-Meier method. Death in induction, treatment resistance, relapse, death in continuous complete remission, and secondary malignancy were considered events in the event-free survival analysis whereas only the latter three types of events were considered for the disease-free survival. The observation time was censored at the last follow-up date if no event was noted. Follow-up was up-dated as of December 31, 2001 for the ALL-91 study and as of December 31, 2003 for the ALL-95 study; no patient was lost to follow-up. The log-rank test was used for univariate comparisons.

Results

The main laboratory and clinical characteristics of the 52 patients treated in the ALL-91 and ALL-95 studies are shown in Table 1. The events, transplants and current status of study patients are presented in a flow dia-

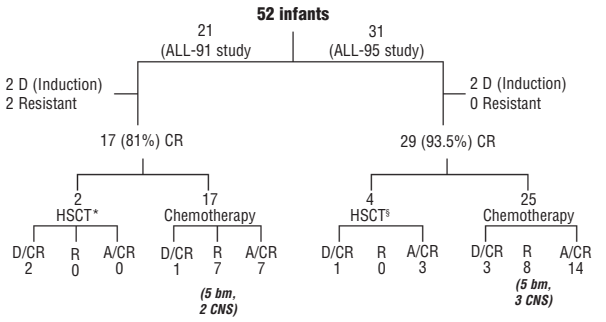

Figure 1. Flow diagram of the management and outcome of the 52 infants treated in the AIEOP ALL-91 and ALL-95 studies. HSCT: hematopoietic stem cell transplantation in first complete remission; BM: bone marrow; CNS: central nervous system; D: death, R: relapse, CR: complete remission; A: Alive. *one from a mismatched family donor and one from a matched family donor. §one from a mismatched family donor, two from matched family donors and one from a matched unrelated donor.

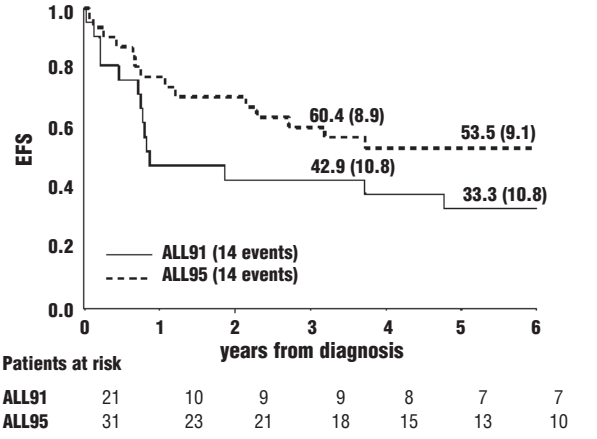

Figure 2. Event-free-survival (SE) of infants enrolled in the AIEOP ALL-91 and ALL-95 studies.

gram (Figure 1). Seven of the 21 patients in the ALL-91 study (median follow-up 7.5 years) remain in continuous complete remission, whereas 17 of the 31 patients in the ALL-95 study (median follow-up 6 years) are still in continuous complete remission. The event-free survival rates 5 years after diagnosis were 45.0%(95% CI 31.3-58.7) in the overall cohort, 33.3% (95% CI 12.1-54.5) in the ALL-91 study group and 53.5% (95% CI 35.7-71.3) in the ALL-95 study (Figure 2) (p-value=0.13). Although the relatively small number of patients in the two studies precludes meaningful statistical comparison of further subgroups, in the ALL-95 study a tendency to a better outcome – compared to the same sub-groups treated in the ALL-91 study – was noted for infants aged 6-12 months, those with a white cell count at onset <300,000/mm^3, those who were t(4;11) negative and those with a PPR. Results obtained in the intermediate-risk groups of the two studies were similar while a better outcome was observed for patients recruited in the high-risk group of the ALL-95 study, as shown in Table 1. The event-free survival curves in both studies did not change substantially when data were censored at the time of HSCT. In a retrospective evaluation which included infants treated not uniformly (patients belonged to three different studies conducted between 1983 and 1995), BFM investigators found that PPR was a strong and independent negative prognostic indicator.[8] In the present analysis the results obtained in infants treated within the AIEOP ALL-91 and ALL-95 studies were compared. It was found that the improved outcome previously reported for high-risk patients with a PPR enrolled in the AIEOP ALL-95 study[17] was extended to infants with high-risk ALL. In fact, infants with a PPR had the greatest benefit from the ALL-95 modified chemotherapy regimen, while this benefit was not extended to other subgroups of patients, such as those aged less than 6 months, those with extreme hyperleukocytosis (>300,000/mm^3), those who failed to achieve complete remission at the end of protocol IA or those with the t(4;11) translocation. Since encouraging results have recently been reported on the role of HSCT in infants, with 3-year disease-free survival rates of 76%[15] and 64.4%,[16] we also evaluated the impact of HSCT in our series from the ALL-91 and ALL-95 studies. Overall, six patients underwent an HSCT procedure (two from a mismatched family donor, three from a matched family donor and one from a matched unrelated donor). Three out of these six transplant recipients are still in continuous complete remission. The disease-free survival at (SE) at 3 years after first complete remission was 59.4% (7.9) with chemotherapy only (censoring HSCT) in 46 patients who achieved complete remission. If only patients surviving at 5 months after complete remission were considered, in order to mimic the selection induced by the waiting time to transplant, the overall rate of disease-free survival increased to 63.9% (8.0). For this reason, the indications for HSCT in infants still need, in our opinion, to be balanced against recent improvements obtained with modern chemotherapy regimens, as also confirmed in our recent experience with the AIEOP ALL-95 study regarding some high-risk subgroups such as patients with a PPR only.[17]

AB: planned the study, contributed to data analysis and wrote the manuscript with CR; MGV was the study statistician, analyzed the study results and contributed to writing the manuscript. PDL was in charge of data checking, study reporting and statistical analyses; MA', FL, LLN and GDR contributed to the study design, data evaluation and to reviewing of the manuscript; AB and GB were the coordinators of the central laboratories where diagnostic analyses were performed; GM was the ALL Committee Chairman of the AIEOP group, planned the study, coordinated the study in Italy and reviewed the report. The authors declare that they have no potential conflict of interest. We thank M. Spinelli from Clinica Pediatrica, Università di Padova and V. Rossi from Clinica Pediatrica, Università Milano-Bicocca, for their excellent contribution to this study.

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