Haematologica 1998; 83:791-799 original paper

Intensive BFM chemotherapy for childhood ALL: interim analysis of the AIEOP-ALL 91 study

Valentino Conter,[1] Maurizio Aricò,[2] Maria Grazia Valsecchi,[3] Carmelo Rizzari,[1] Annamaria Testi,[4] Roberto Miniero,[5] Maria Teresa Di Tullio,[6] Luca Lo Nigro,[7] Andrea Pession,[8] Roberto Rondelli,[8] Chiara Messina,[9] Nicola Santoro,[10] Pier Giorgio Mori,[11] Giulio De Rossi,[12] Paolo Tamaro,[13] Daniela Silvestri,[3] Andrea Biondi,[1] Giuseppe Basso,[5] Giuseppe Masera[1]
for the "Associazione Italiana Ematologia Oncologia Pediatrica" (AIEOP)
Clinica Pediatrica dell'Università di: Milano, Ospedale S.Gerardo, Monza[1]; Pavia, IRCCS Policlinico S.Matteo[2]; Torino, Ospedale Infantile Regina Margherita[5]; Napoli, II Università, Servizio Autonomo di Oncologia Pediatrica[6]; Catania, Divisione di Onco-Ematologia Pediatrica[7]; Bologna[8]; Padova[9]; Bari[10]; Trieste, Ospedale Burlo Garofalo[13]; and from Istituto G. Gaslini, Genova[11]; Divisione di Ematologia Pediatrica, Ospedale Bambino Gesù, Roma[12]; Cattedra di Ematologia, Università La Sapienza, Roma[4]; Istituto di Statistica Medica e Biometria, Università di Milano[3]; Italy

Abstract

Background and Objective. **Since 1988 the AIEOP has used BFM-based chemotherapy for childhood ALL. Current organization and results and role of cranial irradiation in the AIEOP-ALL 91 study are reported.**

Design and Methods. **From 1991 to 1995, 1194 children (< 15 years) with non-B ALL, were enrolled and assigned to the standard risk [SR: age > 1 year, non-T-ALL, BFM risk factor (RF) < 0.8], intermediate risk (IR: RF ≥ 0.8 but < 1.7, or with RF < 0.8 and age < 1 year, or T-ALL), or high risk [HR: RF ≥ 1.7, or t(9;22), or t(4;11) or prednisone poor response or *late response* or CNS involvement] groups. All patients received initially protocol Ia. Thereafter SR patients received HD-MTX 2 g/m², a modified protocol II, and continuation therapy with triple intrathecal chemotherapy (TIT); IR patients received protocol Ib, HD-MTX 5 g/m², protocol II and continuation therapy with TIT; HR patients received 9 polychemotherapy blocks, cranial irradiation and continuation therapy. Duration of treatment was 24 months. A randomized study was conducted to evaluate the impact of high-dose asparaginase in non high risk patients: the results of this study cannot be disclosed yet.**

Results. **One thousand one hundred and fifty-two (96.5%) patients achieved CR. Overall EFS (SE) at 5-years was 71.0% (1.4), with a survival of 80.3% (1.3). Relapse occurred in 262 children (21.9%), either in the marrow (n=192 isolated and 32 with other sites, 18.7%), in the CNS (n=18, 1.5%), or elsewhere (n=20, 1.7%). 5-year EFS (SE) was 83.3% (2.4) in SR, 74.7% (1.8) in IR, and 39.7% (3.5) in HR groups, respectively.**

Interpretation and Conclusions. **Overall cure rate was higher than in the previous AIEOP-ALL 88 study. Treatment intensification with polychemotherapy blocks did not improve results in HR. Cranial irradiation can be safely omitted in over 80% of children treated with BFM based chemotherapy.**

Correspondence: Dr. V. Conter, Clinica Pediatrica, Ospedale Nuovo S. Gerardo, via Donizetti 102, 20052 Monza, Italy. Phone: international +39-039-2333513 • Fax international +39-039-2301646 • E-mail: masera@xquasar.it

Key words: children, acute lymphoblastic leukemia, BFM chemotherapy, cranial irradiation, prognostic factors

More than two thousand children with acute lymphoblastic leukemia (ALL) were treated in *Associazione Italiana di Ematologia ed Oncologia Pediatrica* (AIEOP) institutions in the period 1976-1986. About 50% of all patients enrolled in the three consecutive AIEOP-ALL studies '76, '79, '82, using non-intensive chemotherapy, survived free of disease five or more years.[1-3] In 1988 AIEOP introduced BFM-based intensive chemotherapy, similar to the BFM-ALL 86 study.[4] This study yielded an overall 6-year event-free-survival (EFS) of 67%, and showed that extended intrathecal methotrexate (IT-MTX) may replace cranial radiotherapy (CRT) for prevention of central nervous system (CNS) relapse in intermediate risk (IR) ALL children treated with BFM-based intensive chemotherapy.[5]

In 1991 a new study was started. The aims of this AIEOP-ALL 91 study were to assess: a) the effect of the addition of protracted high dose L-asparaginase to a BFM backbone, in non high risk (HR) patients evaluated in a prospective, randomized study; b) the effect of extended triple intrathecal chemotherapy (TIT) substitution for CRT in all non HR patients (i.e. >80% of the overall patient population); c) the clinical impact of a reduction of the treatment intensity in the standard risk (SR) group and of an intensification in the HR group by adopting a new therapeutic approach based on the experience of the BFM studies for ALL relapses.[6]

In a previous paper the experience in the treatment of IR, T-ALL patients in the AIEOP-ALL 91 study was

described, showing that CRT can be safely omitted in patients presenting with a white blood cell count not exceeding $100x10^9$/L.[7] In this paper the preliminary results of the AIEOP ALL 91 study are reported.

Materials and Methods

Patients

From March 1991 to April 1995, all untreated patients with newly diagnosed non-B ALL, less than 15 years old, from 37 participating AIEOP Institutions were to be centrally registered. One thousand two hundred and sixty seven children were registered: 22 were only registered, 25 were not eligible [because of: Down syndrome (14 pts), acute undifferentiated leukemia (1 patient), acute myeloid leukemia (2 pts), age more than 15 years (7 pts), antiblastic drug pretreatment (1 patient)]; 26 were not evaluable because of missing data. Thus, 1194 eligible and evaluable patients were included in the present report.

According to presenting features, patients were assigned to SR, IR, or HR groups of the AIEOP-ALL 91 study. SR group included patients aged > 1 year, non-T-ALL, with low tumor burden defined as BFM risk factor[4] [calculated as: RF= $0.2 \times \log_{10}$ (blast cell count +1) + $0.06 \times$ cm of palpable liver + $0.04 \times$ cm of palpable spleen] less than 0.8, who also were prednisone good responders (PGR: less than $1x10^9$/L blasts in the peripheral blood after 7 days of steroids and one injection of intrathecal methotrexate);[4] IR group included children with RF ≥ 0.8 but < 1.7, or with RF <0.8 and age <1 year or T immunophenotype. HR group included children with RF ≥ 1.7, or with t(9;22) or t(4;11) clonal translocations, or prednisone poor response (PPR), or who failed to achieve remission after the first part of induction therapy (protocol Ia).

CNS leukemia at diagnosis was defined as >5 mononuclear leukocytes/mm^3 and blast cells in a cytospin preparation of cerebrospinal fluid (CSF), or the presence of clinical signs of CNS involvement. Patients who presented with CNS involvement were only eligible for the HR group and received additional CNS directed therapy as specified below.

Diagnostic studies

From 1988 all AIEOP centers were given the opportunity to send samples from newly diagnosed patients to the referral laboratory.

The diagnosis of ALL was based on morphological, cytochemical and immunophenotype criteria. All patients had less than 3% blast cells positive for myeloperoxidase or Sudan black and were negative to non specific esterase according to the FAB criteria.[8]

Immunophenotyping was performed by flow cytometry using a large panel of commercial monoclonal antibodies directed against the following surface and intracellular antigens: CD1a (OKT6, Ortho), CD3 (Leu4, Beckton Dickinson), CD4 (OKT4A, Ortho), CD5 (Leu1, Beckton Dickinson), CD7 (3A1, Coulter), CD10 (J5, Coulter), CD13 (My7, Coulter), CD14 (My4, Coulter), CD15 (LeuM1, Beckton Dickinson), CD19 (B4, Coulter), CD20 (B1, Coulter), CD24 (OKB2, Ortho), CD33 (My9, Coulter), CD34 (HPCA 1, Beckton Dickinson), CDw65 (Vim2, Caltag), HLA DR (Ortho), IgM (μ chain, Southern Biotechnology), TdT (TdT, Supertechs). The positivity criteria were defined according to the BFM-family criteria, using the limit of 20% for surface antigens and 10% for intracellular markers.[9]

Although a prospective screening of cytogenetic abnormalities was not mandatory, patients who were identified as having t(4;11) or t(9;22) translocations were only eligible for the HR group.

Definition of remission. Complete remission (CR) was defined as no physical signs of leukemia, no detectable leukemic cells on the blood smears, a bone marrow with active hemopoiesis, and <5% identifiable leukemic blast cells, and normal CSF. Bone marrow aspiration was examined on day 42 for evaluation of CR. Patients who were not in CR by day 42 were assigned to the HR group; if CR was attained after block 1, patients were defined *late responders*. Patients who did not attain CR after block 1 were considered induction failures.

Treatment protocols

Treatment schedules are summarized in Tables 1a (for non-HR) and 1b (for HR patients). In brief, all patients received seven days of steroid pre-phase; prednisone good response was defined as <1,000 lymphoblasts/mm^3 after seven days of steroid (and one injection of IT-MTX) therapy.[4] Induction therapy included protocol Ia[4] for all patients. Thereafter SR patients received consolidation therapy with high dose methotrexate (HD-MTX), 2 g/m^2, reinduction therapy (modified protocol II: 2 doses of doxorubicin were given instead of 4), and continuation therapy with extended TIT; IR patients received protocol Ib, consolidation therapy with HD-MTX, 5 g/m^2, reinduction therapy (protocol II), and continuation therapy with extended TIT; SR and IR patients were randomized to receive or not protracted high-dose L-asparaginase (HD-L-ASP), i.e. 25,000 IU/m^2/week $\times$ 20. HR patients received 9 blocks of intensive polychemotherapy[6] followed by continuation therapy; the duration of treatment was 24 months for all patients. HR patients received CRT after ending block therapy (given as 12 Gy if aged ≥ 1 < 2 years, or 18 Gy if older than 2 years, in 12 or 14 fractions). Children with CNS leukemia at diagnosis were only eligible for the HR group. They received 2 additional doses of TIT during protocol Ia plus CRT, given after block therapy (18 Gy if aged ≥ 1 < 2 years, or 24 Gy if older than 2 years, in 12 or 14 fractions). For children younger than 1 year by the time of irradiation, extended TIT was substituted for CRT. For all HR patients, except for those eligible due to PPR only, when a matched familial donor was available, allogeneic bone marrow transplantation (BMT) was suggested.

Table 1a. Treatment schedule for non-high risk patients.

	Standard risk (SR)		Intermediate risk (IR)	
	mg/m²	day	mg/m²	day
Induction				
VCR	1.5	8,15,22,29	1.5	8,15,22,29
PDN	60	1-28°	60	1-28°
DNM	30	8,15,22,29	30	8,15,22,29
L-ASP	10,000°°	19,22,25,28, 31,34,37,40	10,000°°	19,22,25,28, 31,34,37,40
CPM	-	-	1,000	43,71
6-MP	-	-	60	43-70
ARA-C	-	-	75	45-48,52-55 59-62,66-69
MTX it	by age*	1	by age*	1
TIT	by age*	15, 29	by age*	15, 29, 45,59
Consolidation				
MTX iv	2,000	8,22,36,50	5,000	8,22,36,50
CF (levo)	7.5	36,42,48#	7.5	36,42,48, 54,60
TIT	by age*	8,22,36,50	by age*	8,22,36,50
6-MP	25	1-56	25	1-56
Reinduction				
DXM	10	1-21°	10	1-21
VCR	1.5	8,15,22,29	1.5	8,15,22,29
ADM	30	8,15	30	8,15,22,29
L-ASP	10,000°°	8,11,15,18	Random	
6-TG	60	36-49	60	36-49
CPM	1,000	36	1,000	36
ARA-C	75	38-41,45-47	75	38-41,45-47
TIT	by age*	38,45	by age*	38,45
Maintenance				
L-ASP	Random		-	-
6-MP	50	Daily	50	daily
MTX im	20	weekly	20	weekly
TIT	by age*	q 8 weeks	by age*	q 8 weeks

*VCR: vincristine; PDN: prednisone; DNM: daunorubicin; L-ASP: L-asparaginase; CPM: cyclophosphamide; 6-MP: 6-mercaptopurine; ARA-C: cytarabine; MTX: methotrexate; CF: citrovorum factor; DXM: dexamethasone; ADM: adriamycin; 6-TG: 6-thioguanine; ° then tapered; °° (IU/m²); *Age-adjusted doses of TIT were for MTX, ARA-C and PDN respectively, as follows: <1 year 6/16/4 mg, ≥1<2 years 8/20/6 mg, ≥2<3 years 10/26/8 mg, >3 years 12/30/10 mg; **Patients with CNS leukemia had additional TIT on days 8 and 22. Random: L-ASP 25,000 IU/m² weekly for 20 doses: in the IR starting from reinduction week 1 and compared with 4 standard doses (10,000 IU/m² days 8,11,15,18); in the SR starting from maintenance week 1 and compared versus no L-ASP; #hours after HD-MTX infusion start.*

Table 1b. Treatment schedule for high risk patients.

	mg/m²	day
Protocol Ia		
VCR	1.5	8,15,22,29
PDN	60	1-28°
DNM	30	8,15,22,29
L-ASP	10,000°°	19,22,25,28, 31,34,37,40
MTX it	by age*	1
TIT	by age*	15, 29**
Block therapy		
	Block 1^	
	Block 2^^	
	Block 3^^^	
	Block 1^	
	Block 2^^	
	Block 3^^^	
	Block 1^	
	Block 2^^	
	Block 3^^^	
CRT	by age***	
Maintenance		
6-MP	50	daily
MTX im	20	weekly
TIT	-***	

Induction therapy consisted of Protocol Ia and of the first Block 1;
*VCR: vincristine; PDN: prednisone; DNM: daunorubicin; L-ASP: L-asparaginase; CPM: cyclophosphamide; 6-MP: 6-mercaptopurine; ARA-C: cytarabine; MTX: methotrexate; CF: citrovorum factor; DXM: dexamethasone; 6-TG: 6-thioguanine; CRT: cranial irradiation; °then tapered; °°(IU/m²); *Age-adjusted doses of TIT were for MTX, ARA-C and PDN respectively, as follows: <1 year 6/16/4 mg, >1<2 years 8/20/6 mg, >2<3 years 10/26/8 mg, >3 years 12/30/10 mg; **Patients with CNS leukemia had additional TIT on days 8,22. ***CRT was given at the following doses: age >1<2 years 12 Gys (18 Gys if CNS+ at diagnosis); age >2 years 18 Gys (24 if CNS+); for high risk with age <1 year extended TIT during maintenance was substituted for CRT.*
^Block 1: VCR 1.5 mg/m² days 1,8, DXM 20 mg/m² days 1-5, 6-MP 100 mg/m² days 1-5, MTX 5 g/m² day 1, CF: 7.5 mg/m² (levo) at 36, 42, 48 hrs after MTX infusion start, ARA-C 2+2 g/m² day 5, L-ASP 25,000 IU/m² day 6, TIT day 1.
^^Block 2: Vindesine 3 mg/m² day 1, DXM 20 mg/m² days 1-5, 6-TG 100 mg/m²days 1-5, MTX 5 g/m² day 1, CF 7.5 mg/m² (levo) at 36, 42, 48 hrs after MTX infusion start; DNM 50 mg/m² day 5, L-ASP 25,000 IU/m² day 5, CPM 150 mg/m² days 1-5, TIT day 1.
^^^Block 3: DXM 20 mg/m² days 1-5, ARA-C 2+2 g/m² days 1-2, L-ASP 25,000 IU/m² day 6, etoposide 150 mg/m² days 3-5, TIT day 5.

Data management

Patient data were collected on protocol-specific forms and reviewed before the input. The data-base was organised by VENUS. The data center was responsible for assigning the randomized treatment upon request of the clinician (by phone) and checking the eligibility criteria.

Statistical analysis

The EFS and survival curves were estimated according to Kaplan-Meier. The starting point for the observation time was the date of study entry at ALL diagnosis. For EFS, death during induction, induction failure (resistant disease), death in continuous CR (CCR), and relapse or secondary malignancy, were counted as failures. Death from any cause was considered a failure in calculating survival time. For both analyses, the observation time was censored at last follow-up date if no failure was observed, or if the patient was lost to follow-up. In a sub-analysis, the EFS observation time was censored at the date of BMT in first CR.

Follow-up was updated as of December 31, 1997 and thus the minimum potential observation time

Table 2. Characteristics of the 1194 patients and their distribution in the risk groups.

	SR		IR		HR		Total	
	N	%	N	%	N	%	N	%
Total	290	24.3	706	59.1	198	16.6	1194	
Sex								
Male	159	54.8	381	54.0	131	66.2	671	56.2
Female	131	45.2	325	46.0	67	33.8	523	43.8
Age								
< 1 year	0	0.0	12	1.7	9	4.5	21	1.8
1 - 10 years	249	85.9	596	84.4	138	69.7	983	82.3
≥10 years	41	14.1	98	13.9	51	25.8	190	15.9
WBC								
$< 10\times10^9$/L	268	92.4	270	38.2	25	12.6	563	47.2
$10<50\times10^9$/L	21	7.3	323	45.8	58	29.3	402	33.7
$50<100\times10^9$/L	1	0.3	60	8.5	23	11.6	84	7.0
$\geq100\times10^9$/L	0	0.0	53	7.5	92	46.5	145	12.1
Immunophenotype								
Common	210	72.4	425	60.2	59	29.8	694	58.1
pre-B	42	14.5	129	18.3	32	16.1	203	17.0
T	0	0.0	71	10.0	73	36.9	144	12.1
AHL	26	9.0	52	7.4	18	9.1	96	8.0
pre-pre-B	12	4.1	28	4.0	16	8.1	56	4.7
AUL	0	0.0	1*	0.1	0	0.0	1	0.1

AHL = acute hybrid leukemia; AUL = acute undifferentiated leukemia; (*) patient not eligible, but erroneously randomized.

Table 3. Treatment results and status of the patients by risk group.

	SR		IR		HR		Total	
	N	%	N	%	N	%	N	%
On study	290	24.3	706	59.1	198	16.6	1194	100.0
Deaths in pre-phase and in phase Ia	2	0.7	2	0.3	12	5.7	16	1.3
Lost to f-up in pre-phase and in phase Ia	1		3		0		4	0.3
Resistants after block I					22	11.3	22	1.8
CR after induction	287	99.0	701	99.3	164	82.8	1152	96.5
Relapses	41	14.1	148	21.0	73	36.9	262°	21.9
BM	29		109		54		192	
BM + other	5		17		10		32	
CNS	2		14		2		18	
Testis	3		5		3		11	
Other	2		3		4		9	
Second malignant neoplasm	1*	0.3	0		0		1	0.1
Deaths in CCR	0		9	1.3	13	6.6	22#	1.8
Lost to follow-up in CCR	5	1.7	14	2.0	0		19	1.6
Alive in CCR (December 31, 1997)	240	82.8	530	75.1	78	39.4	848	71.0

**Rhabdomyosarcoma, 45 months after diagnosis; #6 of these deaths were due to transplant related events in HR patients; °8 of these relapses occurred after BMT in first CR.*

was 32 months; overall, 23 patients (1.9%) were lost to follow-up. The log-rank test was applied for comparing the outcome of different groups. The presence of major departures from the proportional hazards assumptions was excluded by graphical checks. Thus the Cox regression model was applied to investigate the prognostic role of different variables (WBC count, age, sex, T-immunophenotype) on the EFS time.[10] The analyses were carried out with the SAS package.

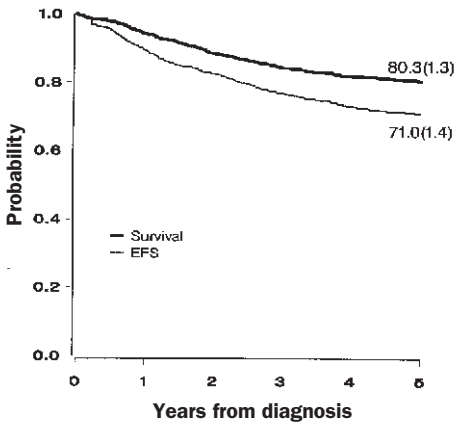

Figure 1. Event-free-survival (SE) and survival of the 1194 children with non-B ALL treated in the AIEOP- ALL 91 study.

Results

The presenting clinical and laboratory features of the 1,194 patients are shown in Table 2; 290 (24.3%) patients were treated in the SR arm, 706 (59.1%) in the IR, and 198 (16.6%), including 39 (3.3%) patients presenting with CNS disease, in the HR arm. Median follow-up time was 53 months.

Overall results

The overall outcome of the patients is reported in Table 3 and Figure 1. Sixteen patients (1.3%) died during induction therapy: 10 of infection (pneumonia n=7, brain abscess n=1, septicemia n=1, varicella n=1), 3 of hemorrage (DIC n=2, brain hemorrhage n=1), 3 of cerebral leukostasis.

Of the 1,152 (96.5%) children who achieved CR, 23 (1.9%) had an adverse event other than relapse. Twelve died of infection: septicemia (n=6, including one child with congenital immunodeficiency), typhlitis, encephalitis, varicella, pneumonia, interstitial pneumonia, CMV enteritis (one case each); other reasons were: hemolytic-uremic syndrome, respiratory failure, cardiac arrest and cerebral hemorrhage (one case each); 6 patients died of BMT related complications; one patient developed rhabdomyosarcoma as a second malignant neoplasm. Overall EFS (SE) at 5 years from diagnosis was 71.0% (1.4), with a survival of 80.3% (1.3). When events (6 deaths in CR and 8 relapses) after BMT in first CR were not accounted for EFS, due to censoring at BMT, the estimated 5-year EFS was 71.5% (1.4).

Relapse was the most common cause of treatment failure. It occurred in 262 children (21.9%) at a median time of 19 months after attainment of CR (range 1-65 months). Site specific relapse rates are described in Table 3. Most of the relapses occurred in the marrow (192 isolated, 32 combined); isolated relapses in the CNS and in the testes occurred in 18 and 11 patients, respectively. Further details are described in Figures 2-4. In SR patients, 5-year EFS (SE) was 83.3% (2.4), and survival was 91.9% (1.7). Isolated CNS relapse occurred in 2 children (0.7%), and testes relapse in 3 (1.9% of males). In IR patients, 5-year EFS (SE) was 74.7% (1.8); isolated CNS relapse occurred in 14 (2.0%) children (10 during treatment); isolated CNS relapse occurred in 0.6% of the IR patients presenting with RF <1.2; isolated testicular relapse occurred in 5 IR children (1.3% of males). In HR patients, 5-year EFS (SE) was 39.7% (3.5). The corresponding figure, when EFS was censored at BMT in first CR, was 39.1% (3.9). Details concerning BMT in HR patients are reported below. Isolated relapse occurred in the CNS in 2 children (during the treatment), and in the testis in 3 (one during treatment).

The results obtained in the two arms of the randomized studies of patients in the SR and IR groups cannot be disclosed yet.

Chromosomal abnormalities

Nineteen patients were identified as having the t(9;22) translocation; 10 were PGR: all of them achieved CR, 1 died in remission after BMT from a matched unrelated donor, 2 relapsed, and 7 remain in first CR (6 after BMT); 6 were PPR: of them only one achieved CR and relapsed; in 3 patients prednisone response was not evaluated: one was resistant to induction therapy, one relapsed and one remains in first CR.

Nine patients were identified as having the t(4;11) translocation (including 4 infants): 7 were PGR and achieved CR: one died in remission (after BMT from mismatched donor), 3 relapsed, and 3 remain in first CR (one after allogeneic BMT); one was a PPR, achieved CR and relapsed; in one patient prednisone response was not evaluated: he died in CR after allogeneic BMT.

Bone marrow transplantation

Twenty-nine HR patients underwent allogeneic BMT in first CR: 26 from a matched familial donor (1 from a syngeneic donor), 2 from a matched-unrelated donor, and one from a mismatched familial donor; of the 26 HR patients engrafted from a matched familial donor, 3 died, 7 relapsed, and 16 remain in first CR after a median time of 55 months from BMT; all of the remaining three HR patients transplanted with an alternative donor failed due to transplant related complications. Although not recommended, two IR patients underwent BMT, one autologous (followed by relapse) and one from a matched familial donor (still in first CR).

Prognostic factors

As this is a large case series, it was possible to evaluate the role of different variables in different risk groups. According to the univariate analyses, sex seemed to play a prognostic role in the SR group, as

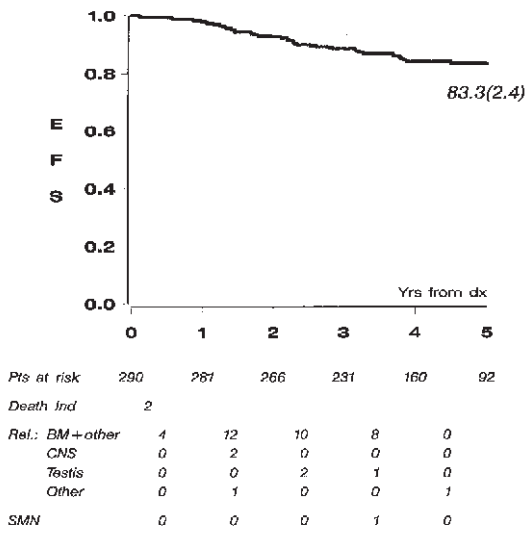

Figure 2. Event-free-survival (SE) of the 290 children treated in the standard risk group.

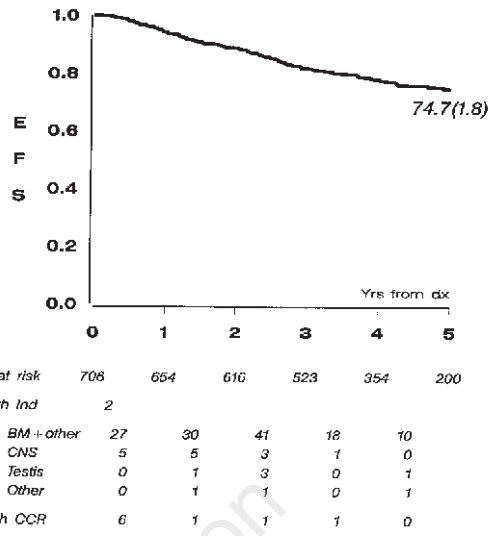

Figure 3. Event-free-survival (SE) of the 706 children treated in the intermediate risk group.

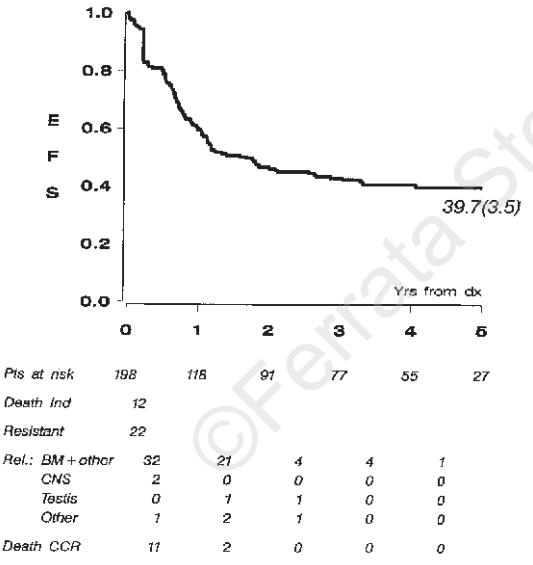

Figure 4. Event-free-survival (SE) of the 198 children treated in the high risk group.

the estimated 5-year EFS (SE) was 87.8% (3.1) and 79.5% (3.4) for females and males, respectively (p value = 0.03). Also, a significant difference in EFS was related to age, with an estimated 5-year EFS (SE) of 87.4% (2.2) and 60.9 (8.1) for children aged 1-10 years and 10-14 years, respectively (p-value <0.001). A Cox model was fitted to the SR group data with regressors for sex, age and WBC count. WBC count was not significantly related to outcome (note that, by definition, the SR group is rather homogeneous with respect to WBC count), while the other two variables retained their significant prognostic role. The model estimated a 2-fold increase in the failure rate for males with respect to females [hazard ratio = 2.1, p value=0.03], and more than a 3-fold increase related to older age (hazard ratio = 3.5, p value <0.001).

In the IR group, we investigated, by applying the Cox model, the variables WBC count and age at diagnosis, sex, and T immunophenotype; all of them, but sex, were significantly related to prognosis. Specifically, children with WBC count >100×10^9/L had about a 2-fold increase (hazard ratio = 2.2, p value <0.002) of the failure rate with respect to children with WBC count <10×10^9/L; their outcome was not significantly worse than that of children with intermediate tumor burden (10×10^9/L <WBC <100×10^9/L). Both groups of children aged 1-10 years and 10-14 years had a better prognosis than infants, but only for the younger group was the difference significant (hazard ratio = 0.38, p value=0.03). T-cell leukemia had the worst prognosis, with a more than 2-fold increase of the failure rate (hazard ratio = 2.6, p value<0.001). However, as noted in a recent specific paper, which was based on a joint work with the BFM group,[7] the prognosis of T-cell leukemia patients was significantly different according to the related tumor burden: the results of the Cox model on this updated data set still indicated that there is a significant interaction (p value<0.001) between these two variables.

Discussion

The overall results achieved by the AIEOP-ALL 91 study are comparable to those obtained by major international pediatric oncology groups, with an improvement of about 5% in the 5-year EFS with respect to the previous study AIEOP-ALL 88.[5] When evaluating these results it should be taken into account that, given the number of patients enrolled, a positive selection of patients can be safely excluded. In fact, this study recruited about 90% of the children with newly diagnosed ALL expected in Italy during the study period. Interestingly, the results are also quite similar in the 37 participating centers, probably due to the learning effect, as application of intensive, BFM-based chemotherapy, continues on a national basis. This is also reflected in the trend of the HR group experience. The incidence of treatment-related mortality in these patients was 18% in the subset of patients recruited during the first 13 months versus 6% observed in the patients recruited later on. Interestingly this change was not dependent on any significant modification in treatment schedule or supportive measures.

Results obtained in the SR group (5-year EFS in the range of 80%) are slightly lower than expected. Although a fraction of SR patients who underwent this treatment can still be rescued by second line treatments, these data suggest that selection of patients and reduction of treatment intensity for childhood SR-ALL should be applied with great caution. In the current AIEOP-ALL 95 study, SR patients are selected not only according to the tumor burden, but also based on favorable biological features, such as high DNA content and early response to treatment. The IR group, including about 60% of the patients, achieved over 70% EFS. A subanalysis performed on patients with lower tumor burden (i.e. RF between 0.8 and 1.2) confirmed that CRT may be safely replaced by extended TIT as reported for the AIEOP-ALL 88 study.[5] Conversely, as previously reported in a joint AIEOP-BFM study, IR patients with T-ALL and higher leukocyte count (who account for only 1% of the total population) may require CRT, as currently given in the AIEOP-ALL 95 study, to achieve optimal results.[7]

In the attempt to improve the cure rate of HR ALL, chemotherapy in the AIEOP-ALL 91 study was intensified compared to that given in the previous AIEOP-ALL 88 study and was based on the block-therapy used in the BFM ALL 90 study,[11] derived from the BFM REZ study for relapsed ALL.[6] This therapeutic effort was associated with severe toxicity and prolonged hospitalization. Nonetheless, due to an excess of marrow relapses, unsatisfactory results were obtained. This treatment did not improve results obtained in the HR arm of the previous AIEOP-ALL 88 study with conventional BFM chemotherapy, suggesting that intensive intermittent therapy may be less effective than conventional BFM consolidation and reinduction treatment. Based on this experience in the current AIEOP-ALL 95 study the HR patients are given a more traditional BFM backbone therapy with the introduction of the repeated protocol II,[13] similarly to the current CCG strategy.[12] In this setting also BMT resulted of limited benefit on the overall outcome of HR group patients. This can be attributed partly to the fact that only a minority of HR patients have the chance to undergo matched familial donor BMT in first CR. A second reason may be that the benefit becomes smaller with longer intervals between diagnosis and time of BMT procedure. Other aspects of interest regard research issues and the organizational aspects achieved in this study. Besides the already mentioned role of CRT,[7] studies have been conducted on asparagine depletion,[14] the prognostic value of early marrow response[15] and of expression of myeloid markers,[16] and clinical and biological effects associated with the use of Erwinia L-asparaginase.[17-19]

The organizational setting of this study allowed central confirmation of diagnosis in over 90% of cases and storage of biological material from 65% of cases in the central repository for further investigations. This provided the basis for the current study 95, in which prospective screening is performed successfully for t(4;11) and t(9;22) clonal translocations in 90% and for DNA content in 95% of the patients. Such excellent compliance and results not only define a high quality of diagnosis of ALL, but also provide opportunities for further research. Prompt availability of such a large number of ALL cases, prospectively followed, allows the group to test, timely and properly, new hypotheses raised in this field, as recently occurred for the t(12;21) translocation.[20] This setting allows the group to participate in large intergroup studies, which are necessary to investigate small subsets of childhood ALL, and thus to make further progress in this field. The ongoing AIEOP-ALL 95 study has been designed in the frame of the International BFM Study Group (I-BFM-SG), to explore in a prospective randomized intergroup trial the role of vincristine + dexamethasone pulses during continuation therapy for intermediate risk ALL, with the support of prospective meta-analysis.[21] In the same setting, the role of allogeneic BMT from a sibling donor for a selected subgroup of high risk patients in first remission is also being assessed.

Appendix

The following institutions enrolled patients in the AIEOP-ALL 91 study:

- *Ancona, Clinica Pediatrica (Dr. L. Felici, Dr. P. Pierani);*
- *Ancona, Divisione di Pediatria (Prof. G. Caramia, Dr. Iorini);*
- *Bari, Clinica Pediatrica I (Prof. F. Schettini, Dr. N. Santoro);*
- *Bari, Clinica Pediatrica II (Prof. N. Rigillo, Dr.ssa S. Bagnulo);*

- *Bergamo, Div. Pediatria (Prof. F. Bergonzi, Dr. P.E. Cornelli), Ematologia (Prof. T. Barbui).*
- *Bologna, Clinica Pediatrica (Prof. G. Paolucci, Dr. A. Pession, Dr. R. Rondelli);*
- *Bologna, Divisione di Pediatria, Ospedale Maggiore (Prof. G. Ambrosioni);*
- *Brescia, Clinica Pediatrica (Prof. A.G. Ugazio, Dr. A. Arrighini);*
- *Cagliari, Servizio di Oncoematologia Pediatrica (Prof. P.F. Biddau, Dr.ssa R. Mura);*
- *Catania, Divisione di Onco-Ematologia Pediatrica (Prof. G. Schilirò, Dr. L. Lo Nigro);*
- *Catanzaro, Div. di Ematologia (Prof. S. Magro, Dr.ssa C. Consarino);*
- *Firenze, Ospedale Meyer, Dipartimento di Pediatria, U.O. Oncoematologia Pediatrica (Prof.ssa G. Bernini, Dr.ssa A. Lippi);*
- *Genova, Ist. "G.Gaslini" (Prof. P.G. Mori, Dr.ssa C. Micalizzi);*
- *Genova Galliera (Prof. A. Rasore Quartino, Dr. M. Cominetti);*
- *Modena, Clinica Pediatrica (Prof.ssa F. Massolo, Dr.ssa M. Cellini);*
- *Monza, Clinica Pediatrica (Prof. G. Masera, Dr. V. Conter, Dr. C. Rizzari, Dr. M. Jankovic);*
- *Napoli, Ospedale Pausilipon (Prof. V. Poggi, Dr.ssa M.F. Pintà Boccalatte);*
- *Napoli, II Università, Dipartimento di Pediatria, Servizio Autonomo di Oncologia Pediatrica, (Prof.ssa M.T. Di Tullio, Dr.ssa F. Casale, Dr.ssa A. Murano);*
- *Napoli, Clinica Pediatrica II (Prof. S. Auricchio, Dr. A. Fiorillo, Dr.ssa R. Migliorati);*
- *Napoli, Ospedale SS. Annunziata (Prof. F. Tancredi, Dr. A. Correra);*
- *Padova, Clinica Pediatrica II (Prof. L. Zanesco, Dr.ssa C. Messina);*
- *Palermo, Clinica Pediatrica I (Prof.ssa M. Lo Curto, Dr.ssa G. Fugardi);*
- *Parma, Clinica Pediatrica (Dr. G. Izzi, Dr.ssa P. Bertolini);*
- *Pavia, Clinica Pediatrica (Prof.ssa F. Severi, Dr. M. Aricò);*
- *Perugia, Divisione di Oncoematologia Pediatrica, Ospedale Silvestrini (Dr. A. Amici, Dr. P. Zucchetti);*
- *Pescara, Divisione di Ematologia (Dr. A. Di Marzio, Dr. R. Di Lorenzo, Prof. G. Torlontano);*
- *Pisa, Clinica Pediatrica III (Prof. P. Macchia, Dr. C. Favre);*
- *Reggio Calabria, Divisione di Ematologia, Ospedali Riuniti (Prof. F. Nobile, Dr.ssa M.Comis);*
- *Roma, Divisione di Ematologia Pediatrica, Ospedale "Bambino Gesù" (Prof. G. De Rossi, Dr. C. Miano);*
- *Roma, Cattedra di Ematologia (Prof. F.Mandelli, Dr.ssa A.M. Testi);*
- *Roma, Clinica Pediatrica (Prof. G. Multari, Dr.ssa B. Werner);*
- *S.Giovanni Rotondo, Ospedale "Casa Sollievo della Sofferenza", Divisione di Pediatria, Sezione di Ematologia ed Oncologia Pediatrica (Prof. M. Carotenuto, Dr. S. Ladogana);*
- *Sassari, Clinica Pediatrica (Prof. D. Gallisai, Dr. C. Cosmi);*
- *Siena, Clinica Pediatrica (Prof. G. Morgese, Dr. A. Acquaviva, Dr. A. D'Ambrosio);*
- *Torino, Clinica Pediatrica (Prof. E. Madon, Prof. R. Miniero, Dr.ssa E.Barisone, Prof. G.Basso);*
- *Trieste, Clinica Pediatrica (Prof. P. Tamaro, Dr. G.A. Zanazzo);*
- *Varese, Clinica Pediatrica (Prof. L. Nespoli, Dr.ssa S. Binda);*
- *Verona, Clinica Pediatrica (Prof. L. Tatò, Dr. Marradi).*

Funding

This work was conducted within the framework of CNR (Italian Research Council) applied project ACRO (grants n. 94.01262,PF39; 96.00694,PF39) and with contributions from the Fondazione Tettamanti per lo studio delle leucemie ed emopatie infantili and the Associazione Italiana per la Ricerca sul Cancro (AIRC).

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

Manuscript received on January, 21, 1998; accepted June 8, 1998.

References

1. ALL Steering committee of the AIEOP: G. Paolucci, G. Masera, V. Vecchi, et al. Treating childhood acute lymphoblastic leukemia (ALL): summary of ten years' experience in Italy. Med Pediatr Oncol 1989; 17:83-91.
2. Vecchi V, Aricò M, Ceci A, et al. for the "Associazione Italiana Ematologia Oncologia Pediatrica". Risk-directed therapy for childhood acute lymphoblastic leukemia: results of the AIEOP '82 studies. Cancer 1993; 72:2517-24.
3. Vecchi V, Pession A, Rosati D, et al. Childhood acute lymphoblastic leukemia (ALL). Results of AIEOP 87 protocol generation. Med Pediatr Oncol 1992; 20: 390.
4. Reiter A, Schrappe M, Ludwig R, et al. Chemotherapy in 998 unselected childhood acute lymphoblastic leukemia patients. Results and conclusions of the multicenter trial ALL-BFM 86. Blood 1994; 84:3122-33.
5. Conter V, Aricò M, Valsecchi MG, et al. for the "Associazione Italiana Ematologia Oncologia Pediatrica" (AIEOP). Extended intrathecal methotrexate may replace cranial irradiation for prevention of CNS relapse in intermediate risk ALL children treated with BFM-based intensive chemotherapy. J Clin Oncol 1995; 13:2497-502.
6. Henze G, Fengler R, Hartman R, et al. Six-year experience with a comprehensive approach to the treatment of recurrent childhood acute lymphoblastic leukemia (ALL REZ BFM 85). A relapse study of the BFM group. Blood 1991; 78:1166-72.
7. Conter V, Schrappe M, Aricò M, et al. for the "Associazione Italiana Ematologia Oncologia Pediatrica" (AIEOP) and the Berlin-Frankfurt-Münster (BFM). The role of cranial radiotherapy for childhood T-cell acute lymphoblastic leukemia with high WBC count and prednisone good response. J Clin Oncol 1997; 15: 2786-91.
8. Bennett JM, Catovsky D, Daniel M-T, et al. Proposals

for the classification of the acute leukemias. French-American-British Cooperative group. Br J Haematol 1986; 33:451-8.
9. van-der-Does van-den-Berg A, Bartram CR, Basso G, et al. Minimal requirements for the diagnosis, classification, and evaluation of the treatment of childhood acute lymphoblastic leukemia (ALL) in the "BFM Family" Cooperative Group. Med Pediatr Oncol 1992; 20: 497-505.
10. Marubini E, Valsecchi MG. Analysing survival data from clinical trials and observational studies. J. Wiley & Sons, Chichester, 1995 (chapters 3, 4, 6).
11. Schrappe M, Reiter A, Sauter S, et al. Konzeption und Zwischenergebnis der therapiestudie ALL-BFM 90 zur behandlung der akuten lymphoblastichen leukämie bei kindern und jugendlichen: die bedeutung des initialen therapieansprechens in blut und knochenmarck. Klinische Pädiatr 1994; 206:208-21.
12. Nachmann J, Sather HN, Gaynon PS, et al. Augmented Berlin-Frankfurt-Münster therapy abrogates the adverse prognostic significance of slow early response to induction chemotherapy for children and adolescents with acute lymphoblastic leukemia and unfavorable presenting features: a report from the Children's Cancer Group. J Clin Oncol 1997; 15: 2222-30.
13. Aricò M, Conter V, Valsecchi MG, et al. Treatment intensification with repeated BFM-protocol II may prevent early relapse in very high risk (HR) AIEOP-ALL 9503 study. Blood 1997; 90:236b.
14. Gentili D, Conter V, Rizzari C, et al. L-Asparagine depletion in plasma and cerebro-spinal fluid of children with acute lymphoblastic leukemia during subsequent exposures to Erwinia L-asparaginase. Ann Oncol 1996; 7: 725-30.
15. Cantù Rajnoldi A, Gornati G, Basso G, et al. Role of bone marrow evaluation at day 15 in children with acute lymphoblastic leukemia treated with AIEOP-ALL 91 protocols. Med Pediatr Oncol 1997; 29: 460.
16. Putti MC, Rondelli R, Cocito MG, et al. for the AIEOP: Expression of myeloid markers lacks prognostic impact in children treated for acute lymphoblastic leukemia. AIEOP experience in BFM-oriented ALL 88-91 studies. Blood 1998; 92:795-801.
17. Rizzari C, Scarpa A, Conter V, et al. IgG antibodies formation after repeated exposures to Erwinia C. L-asparaginase in children with acute lymphoblastic leukemia. Med Pediatr Oncol 1996: 27, 392.
18. Bossi G, Larizza D, Conter V. Thyroid function is not affected by second exposure to Erwinia asparaginase for childhood acute lymphoblastic leukemia. Haematologica 1997; 82:507-8.
19. Rizzari C, Conter V, Colombini A, et al. Systemic allergic reactions in children with acute lymphoblastic leukemia (ALL) undergoing a second exposure to Erwinia C. L-asparaginase may occur more frequently if the drug is given intravenously. Blood 1997; 90: 233b.
20. Borkhardt A, Cazzaniga G, Viehmann S, et al. Incidence and clinical relevance of TEL/AML1 fusion genes in children with acute lymphoblastic leukemia enrolled in the German and Italian multicenter therapy trials. Associazione Italiana Ematologia Oncologia Pediatrica and the Berlin-Frankfurt-Münster Study Group. Blood 1997; 90: 571-7.
21. Valsecchi MG, Masera G. A new challenge in clinical research in childhood ALL: the prospective meta-analysis strategy for intergroup collaboration. Ann Oncol 1996; 7:1005-8.