Treatment of childhood acute lymphoblastic leukemia. Long-term results of the AIEOP-ALL 87 study

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Background and Objectives. In March 1987 AIEOP started the AIEOP-ALL-87 study, based on the previous AIEOP-ALL-82. The aim of this new study was to evaluate, for all risk groups: a) the efficacy of treatment intensification achieved by adding a fourth drug (daunomycin) in the induction phase and a 3-drug reinduction phase for all risk groups; b) the impact of the addition of three doses of intrathecal methotrexate during cranial radiotherapy and extended exposure to weekly high-dose L-asparaginase during late intensification in high risk patients. We report the long-term results of the AIEOP ALL-87 study.

Design and Methods. From 1987 to 1991, a total of 632 eligible and evaluable children (age 1 to ≤16 years) with non-B-cell acute lymphoblastic leukemia (ALL), were enrolled and stratified as follows: standard risk (SR, 79 patients, 12.5%) had WBC <10,000/mm^3, age ≥ 3 and <7 years, and FAB L1 morphology. The high risk (HR, 175 patients, 27.7%) group included patients with WBC ≥50,000/mm^3 or FAB L3 morphology or T immunophenotype or acute undifferentiated leukemia (AUL) or *leukemia-lymphoma syndrome*. All the remaining patients formed the intermediate risk group (IR, 378 patients, 59.8%). All patients received a 4-drug induction therapy; intermediate-dose methotrexate was given to HR patients; cranial radiotherapy was given to IR and HR patients, while SR patients received extended intrathecal methotrexate; all patients received a 3-drug reinduction phase; high dose L-asparaginase (HD-L-ASP; E.Coli, Bayer) was given to HR patients; continuation therapy with 6-mercaptopurine, i.m. methotrexate, and monthly vincristine and prednisone pulses was given to all patients. Treatment duration was 2 years.

Results. Six hundred and nineteen patients (97.9%) achieved complete remission. The remission rate was 98.7% in the SR group, 98.1% in the IR group, and 97.1% in the HR group. The overall 10-year survival and event-free survival (EFS) rates (SE) are 74.7% (1.8) and 62.8% (2.0) respectively; EFS rates by risk group are 67.5% (5.5) in SR, 62.8% (2.6) in IR, and 61.9% (3.8) for HR. The 10-year EFS for all eligible patients was 63.9% (1.9).

Interpretation and Conclusions. When compared to the results of the AIEOP-ALL-82 study, treatment intensification in the ALL-87 study has improved long-term survival and EFS from 66.4% and 53.6% to 74.7% and 62.8%, respectively. Failures were mostly due to marrow or extramedullary relapses suggesting that further treatment intensification, as being used in current therapeutic strategies, is appropriate, although patients relapsing after less intensive treatment may have better chances of rescue. These results, although obtained in a relatively large proportion of patients, in which infants were not included, indicate that the addition of high-dose L-asparaginase to a relatively non-intensive treatment may be of major benefit for HR patients and that the addition of intrathecal methotrexate during CRT, may improve the central nervous system-disease control with a marked reduction of nervous system relapses.

Key words: children, acute lymphoblastic leukemia, treatment intensification

The multicenter AIEOP-ALL-82 study for risk-directed therapy of childhood acute lymphoblastic leukemia (ALL), conducted during the early 1980s, resulted in an overall event-free survival (EFS) and survival of 54% and 66% at seven years, respectively.[1] Treatment intensity was limited according to contemporary standards. Standard risk (SR) patients (12%) received a 3-drug induction therapy, intrathecal methotrexate (IT-MTX), and continuation therapy

with oral 6-mercaptopurine, weekly intramuscular MTX, and monthly pulses with vincristine and prednisone. Intermediate risk (IR) patients (63%) received in addition cranial radiotherapy (CRT) and reinduction therapy with prednisone and three weekly doses of vincristine. Beginning from 1985, high risk (HR) patients (25%) were treated with a 4-drug induction therapy, intermediate dose MTX (0.5 g/m^2 q 10 days, $\times$ 3) and high-dose asparaginase (HD-L-ASP, 25,000 IU/sqm, weekly, $\times$20) during the reinduction and early continuation therapy; IT-MTX was not administered during CRT. EFS (standard error, SE) by risk group seven years after diagnosis was, respectively, 60.8% (4.7), 60.6% (4.3), and 46.1% (5.1). Results were characterized by unsatisfactory EFS in SR patients, and by a high rate of isolated central nervous system (CNS) relapses in HR patients.

In March 1987 AIEOP started the AIEOP-ALL-87 study, aimed at improving the treatment results by intensifying the treatment. The major treatment modifications introduced, compared to the previous AIEOP-ALL 82 study, were: a) a 4-drug induction therapy with the addition of daunorubicin and a 3-drug (prednisone, vincristine, ASP) reinduction therapy was given also to non-HR patients; b) HD-L-ASP was given weekly for 20 weeks during reinduction and early continuation therapy to high risk patients; c) IT-MTX was administered during CRT (three doses) also in the HR group. We report the long term results of the AIEOP-ALL-87 study.

Design and Methods

From March 1987 to April 1991, patients more than 1 year and less than 16 years old, with newly diagnosed untreated non-B ALL (including those with undifferentiated ALL) from 34 participating institutions were registered in the study. Patients were stratified according to their presenting features into SR (8701), IR (8702), or HR (8703) groups. Patients defined as SR had a WBC <10,000/mm^3, age $\geq$ 3 and <7 years, FAB L1 morphology.[2] HR group included patients with WBC $\geq$50,000/mm^3 or FAB L3 morphology or T-immunophenotype or AUL or *leukemia-lymphoma syndrome* (LLS) defined as the contemporary presence of massive (under umbilical line) splenomegaly, or massive (lymph node: single > 3 cm or multiple > 5 cm) lymphadenopathy, or a mediastinal mass (mediastinal mass / thorax > 0.33) + one or more laboratory findings including: T-immunophenotype, Hb $\geq$10 g/dL, WBC >50$\times$10^9/L. The IR group was formed of all the remaining patients.

It should be mentioned that in March 1988 a group of AIEOP institutions began running the AIEOP-ALL-88 study, piloting the introduction of intensive, BFM-type chemotherapy in our co-operative group. The two studies are thus partly contemporary as already reported.[3] Infants were treated only in the 88 study.

Diagnostic studies

The diagnosis of ALL was based on morphologic, cytochemical and immunophenotype criteria. All patients had less than 3% blast cells positive for myeloperoxidase or Sudan black and were negative for non-specific esterase according to the FAB criteria.[2] Immunophenotyping was performed by flow cytometry using a large panel of commercially available monoclonal antibodies directed against the following surface and intracellular antigens: CD1a , CD3, CD4, CD5, CD7, CD10, CD13, CD14, CD15, CD19, CD20, CD24, CD33, CD34, CDw65, HLA DR, IgM, TdT.[4]

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 normal hematopoiesis, and <5% identifiable leukemic blast cells, and normal cerebrospinal fluid (CSF). Bone marrow aspiration was examined on day 28 for evaluation of CR. If leukemic blasts $\geq$5% but <25% were detectable, an additional bone marrow aspiration was evaluated for CR on day 35. Patients who did not attain CR by day 35 were taken out of the study and considered as induction failures.

Aims of the study

The AIEOP-ALL-87 study was designed on the basis of the previous AIEOP-ALL-82 study.[1] The aims of the study were to evaluate: a) the efficacy of treatment intensification achieved by adding a fourth drug (daunomycin) in the induction phase and a 3-drug reinduction phase for all risk groups; b) the impact of the addition of three doses of intrathecal methotrexate during cranial radiotherapy (CRT) and extended exposure to weekly HD-L-ASP during late intensification, in high risk patients.

Treatment schedule

The treatment schedule is described in Table 1. Briefly, all patients received a 4-drug induction therapy; intermediate dose MTX was given to HR patients; CRT was given to IR and HR patients, while SR patients received extended IT-MTX. All patients received a 3-drug reinduction phase; HD-L-ASP (E.Coli, Bayer) was given to HR patients; continuation therapy with 6-MP, i.m. MTX, monthly vincristine and prednisone pulses was given to all patients. Treatment duration was 2 years.

Statistical analysis

EFS and survival times are defined from the day of diagnosis until the date of failure. Patients were con-

Table 1. Treatment schedule.

	Standard risk (SR)		Intermediate risk (IR)		High risk (HR)	
	mg/m²	Day	mg/m²	Day	mg/m²	Day
INDUCTION						
Vincristine †	2	0,7,14,21,28	2	0,7,14,21,28	2	0,7,14,21,28
Prednisone	40	–7 to 28°	40	–7 to 28°	40	–7 to 28°
Daunorubicine	30	0,7,14	30	0,7,14	30	0,7,14,21
Asparaginase°°	6,000	15,17,19, 22,24,26, 29,31,33	6,000	15,17,19 22,24,26,29,31,33	6,000	3,5,8,10,12,15,17,19,22
Methotrexate it	by age*	0,14,28	by age*	0,14,28	by age*	0,14,28
CONSOLIDATION						
Methotrexate it	by age*	42,49,56	by age*	42,49,56	by age*	35,45,55, 70,77,84
6–mercaptopurine	75	42–62	75	42–62	75	70–90
CRT#	–	–	18 Gy	42–55	18 Gy	70–84
Vincristine	–	–	–	–	2	35,42
Methotrexate iv	–	–	–	–	500	35,45,55
REINDUCTION						
Vincristine	2	63,70,77	2	63,70,77	2	91,98,105
Prednisone	40	63–77°	40	63–77°	40	91–105°
Daunorubicine	30	63,70,77	30	63,70,77	30	91,98,105
Asparaginase	–	–	–	–	25,000	91,98,105, 112,119
CONTINUATION§						
Vincristine	1.5	0	1.5	0	1.5	0
Prednisone	40	0–4	40	0–4	40	0–4
6–mercaptopurine	75	7–27	75	7–27	75	7–27
Methotrexate im	20	7,14,21	20	7,14,21	20	Weekly
Asparaginase##	–	–	–	–	25,000	weekly x 15
Methotrexate it	by age*	q 84 days				

*†Maximum dose 2 mg; °then tapered; °°(IU/m²); *age–adjusted doses of methotrexate: <1 year 6 mg, 1–2 years 8 mg, 2–3 years 10 mg, >3 years 12 mg; #CRT: patients with CNS involvement at the diagnosis received cranial irradiation at the dose of 24 Gy and spinal irradiation at the dose of 12 Gy. § Cycles repeated every 28 days. SR patients also received intrathecal MTX, age-dosed, every 84 days. ##High-dose asparaginase was given during reinduction and the initial phase of continuation therapy.*

sidered *off study* at any time during treatment in case of major protocol deviations, including treatment withdrawal and bone marrow transplantation (BMT) in first CR. The cut-off time for the current analysis was September 30, 1999. Time *on study* or to first event was calculated from the day of diagnosis. The terminal event for survival was death from any cause; the terminal events for EFS were induction failure, death during induction, death in continuous CR, relapse, and diagnosis of a second malignant neoplasm. Patients considered *off study* were censored in all curves at the date they were removed from the study. EFS and survival curves were obtained using the Kaplan-Meier method with standard errors (SE).[5] Differences in EFS were evaluated using the log-rank test.[6] Hepatomegaly and splenomegaly were defined as at or below the umbilical line. Variables showing a p value <0.01 in univariate analysis were evaluated in the multivariate analysis of prognostic factors.

Results

From March 1987 to April 1991, 694 children were registered from the 34 participating institutions. A total of 62 patients were considered not evaluable for analysis because they were not eligible (14) and/or the diagnosis was not fully documented (49). Thus a total of 632 patients were eligible and evaluable; their median follow-up time was 122 months (range: 0-150). The distribution according to risk-group was the following: SR, 79 patients (12.5%); IR, 378 patients (59.8%), HR, 175 patients (27.7%). The presenting clinical and laboratory features are shown in Table 2. CNS involvement at diagnosis was documented in 4 of the 613 patients investigated (0.6%); two of them were treated in the SR and two in the IR groups.

Treatment results are summarized in Table 3. One eligible child in the HR group died before starting therapy due to cerebral hemorrhage and 3 during induction therapy because of infection, hemorrhage, heart failure. Six hundred and nineteen patients (97.9%) achieved CR. CR rate was 98.7% in the SR group, 98.1% in the IR group and 97.1% in the HR group.

Two hundred and one (31.8%) patients subsequently relapsed, at a median time of 25 months (range 1-108

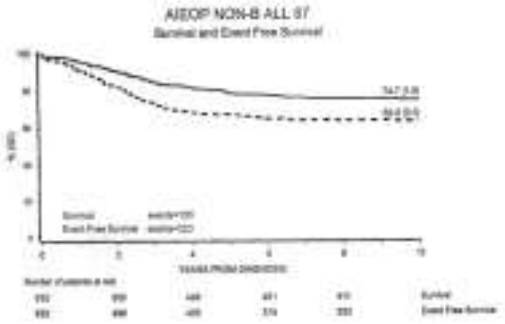

Figure 1. Event-free-survival (SE) and survival of the 632 children with non-B ALL treated in the AIEOP- ALL 87 study.

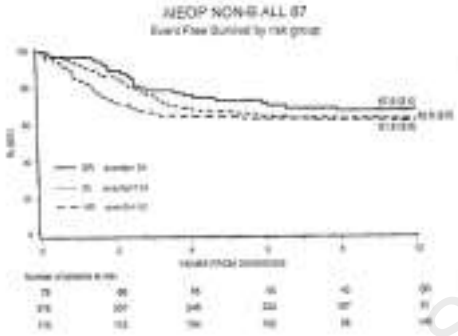

Figure 2. Event-free-survival (SE) according to risk groups.

months). Most of the relapses involved bone marrow (92 isolated, 33 combined); isolated CNS-relapses occurred in 50 patients (7.9%): 8 in SR patients (10.1%), 28 in IR patients (7.4%) and 14 in the HR (8.0%) group. Isolated testicular relapse occurred in 18 of 358 males (5.0%); other sites (ovary, lymph nodes, eye) were involved in 10 cases. Seven patients (1%) died in continuous CR, due to infection (EBV infection, interstitial pneumonia, systemic candidiasis) or other causes (acute respiratory failure, pancreatitis, encephalopathy); 18 patients were censored at the time they were lost to follow-up; 19 patients in CR were considered *off study* because of protocol violations (17 cases: 3 SR, 7 IR, 7 HR patients) or BMT (2 cases: 1 IR, 1 HR).

The overall 10-year survival and EFS rates are 74.7% (1.8) and 62.8% (2.0) respectively (Figure 1), with EFS by risk group being 67.5% (5.5) in the SR group, 62.8% (2.6) in the IR group, and 61.9% (3.8) in the HR (Fig-

Table 2. Characteristics of the 632 patients and their distribution in the risk groups.

	SR		IR		HR		TOTAL	
	N	%	N	%	N	%	N	%
Total	79	12.5	378	59.8	175	27.7	632	100
Sex								
Male	41		214		103		358	56.6
Female	38		164		72		274	43.4
Age								
1-5 years	70		234		90		394	62.3
6-9 years	9		83		47		139	22.0
10-15 years	-		61		38		99	15.7
WBC/mm^3								
< 10,000	79		168		33		280	44.3
10-49,999	-		210		23		233	36.9
50-99,999	-		-		63		63	10.0
≥100,000	-		-		55		55	8.7
Unknown	-		-		1		1	0.1
Immunophenotype								
Common	69		324		70		463	73.3
Pre-B	9		35		20		64	10.1
T	-		-		63		63	10.0
Pre-T	-		5		6		11	1.7
Non T-non B	-		2		-		2	0.3
Early pre-B	1		12		3		16	2.5
Undifferentiated (AUL)	-		-		13		13	2.1
CNS involvement	2		2		-		4	0.6

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

	SR		IR		HR		TOTAL	
	N	%	N	%	N	%	N	%
On Study	79		378		175		632	100.0
Deaths during induction	-		1		3		4	
Lost to follow-up in induction	1		-		-		1	
Resistant	-		6		2		8	
CR AFTER INDUCTION	78	98.7	371	98.1	170	97.1	619	97.9
Relapses	24		124		53		201	31.8
- BM	8		63		21		92	
- BM + other	5		20		8		33	
- CNS	8		28		14		50	
- TESTIS	2		11		5		18	
- Other	1		2		5		8	
Second malignant neoplasm	-		-		-		-	
Deaths in CCR	-		4		3		7	
Lost to follow-up in CCR	1		10		6		17	
Off-study*	3		8		8		19	
ALIVE IN CCR (at 9/1999)	50		225		100		375	59.3

**Patients considered off study by risk group and reason: SR group: 1 toxic event, 1 major protocol violation, 1 major side effects. IR group: 1, BMT; 4, toxic event; 3, major protocol violation. HR group: 1, BMT; 3 toxic event; 4, major protocol violation.*

Table 4 EFS. Univariate and multivariate analysis of prognostic factors.

Variables	#	events	Univariate RR	Univariate P	Multivariate RR	Multivariate P
WBC						
< 20,000/mm³	407	131	1.23	0.005	1.45	0.01
> 20,000/mm³	224	89				
unknown	1	0				
Age						
1-9 years	533	167	1.71	0.0001	2.02	0.0001
10-15 years	99	53				
Sex						
Females	274	68	1.71	0.0001	1.94	0.0001
Males	358	152				
Hepatomegaly						
No	510	168	1.36	0.0031	1.27	0.20
Yyes	112	50				
unknown	10	2				
Splenomegaly						
No	454	146	1.31	0.0011	1.31	0.10
Yes	175	74				
unknown	3	0				
Mediastinal mass						
No	608	208	1.53	0.004	1.46	0.28
Yes	21	11				
Unknown	3	1				
Immunophenotype						
non-T	558	188	1.28	0.0033	1.22	0.36
T	74	32				

ure 2) group. The 10-year EFS for eligible patients without any censoring was 63.9% (1.9).

Prognostic factors

In the univariate analysis the 10-year EFS was significantly inferior for older patients [44.6% (5.1) in children aged 10-15 years versus 66.7% (2.1) for those aged 1-9 year (p=0.0001)], those of male gender [55.7% (2.7) versus 73.2% (2.8) female gender (p=0.0001)], patients with a higher leukocyte count [57.3.2% (3.4) versus 66.2% (2.4) for those with a count <20,000/mm³ (p=0.005)], those with hepatomegaly [52.5% (4.9) versus 65.1% (2.2) for those with no hepatomegaly (p=0.0031)], splenomegaly [48% (3.9) versus 66.1% (2.3) no splenomegaly (p=0.0011), mediastinal mass [43.0% (11.4) versus 63.9% (2.0) no mediastinal mass (p=0.004)], T-immunophenotype [53.1% (6.1) versus 64.4% (2.1) for non-T ALL (p=0.0033)], LLS [53.7% (6.8) versus 63.9% (2.1) for the non-LLS group (p=0.022)].

In the multivariate analysis age ≥10 years (p=0.0001), male sex (p=0.0001) and a WBC count >20,000/mm³ (p=0.01) retained their significantly adverse prognostic value (Table 4).

Discussion

The long-term overall results of the AIEOP-ALL-87 study, with EFS and survival rates of 62.8% (2.0) and 74.7% (1.8), respectively, represent a marked improvement over those achieved by the previous AIEOP-ALL-82 study, in which EFS and survival were, respectively, 52.7 (1.7) and 63.7% (1.6).[1,5] Since the stratification of patients in these two studies was the same, the improvement can be attributed to the treatment applied. The higher rate of CR (97.9% vs. 94.7%) is explained partly by a lower incidence of deaths during induction (0.63% versus 2.2% in study 82) and partly by the lower rate of resistance to induction therapy (1.26% versus 2.7% in study 82), confirming that the introduction of an anthracycline as a fourth drug during induction therapy for all risk groups may be safe and beneficial.[7]

The 10-year EFS in SR patients was 67.5% (5.5), which compares favorably with the 60.8% (4.7) at 7 years in the SR group of study 82.[1] Treatment intensification achieved with a 4-drug induction and introduction of a reinduction phase may explain better leukemia control in this group.

The IR group had a 10-year EFS of 62.8% (2.6), with a minor improvement compared to that of study 82 [7-year EFS: 60.6% (2.3)]. Differences in treatment between studies 82 and 87 in this group consisted only in the addition of an anthracycline during induction and reinduction therapy.

Results obtained in both SR and IR groups do, however, remain inferior to contemporary results obtained by other groups with more intensive treatment.[8-11] Failures in these groups are largely explained by an excess of extramedullary relapses, either in the CNS or in the testes; this pattern of relapses can be connected to the limited use of intrathecal chemotherapy together with the lack of high-dose methotrexate (HD-MTX).[8-11] Starting from study 88 the AIEOP introduced the use of extended intrathecal therapy, together with HD-MTX for all risk groups.[3]

The HR group included 27% of the total patient population, a proportion which is slightly superior to the 24.5% enrolled in the HR group in study 82. The treatment strategy for these patients, which included intermediate dose MTX and protracted HD-L-ASP, was the same as that applied since 1985 except for the addition of 3 doses of IT-MTX during CRT. Results in this group of patients have been a very favorable 10-year EFS [61.9% (3.8)] with a marked reduction of isolated CNS relapse, which fell from 19% in the HR group (8503) of the AIEOP-ALL-82 study to 8%. These results confirm that the addition of HD-L-ASP to a relatively non-intensive treatment may be of major benefit for HR patients older than one year, in keeping with the findings of the previous 8503 study; they also indicate that the addition of IT-MTX during CRT may improve CNS-disease control.

Multivariate analysis of the evaluated prognostic factors confirmed that only age, sex, and leukocyte count retained independent prognostic values.

Another aspect of interest is that although EFS of this study remains mildly inferior to that obtained by some contemporary studies with the use of more intensive chemotherapy schedules, the overall survival is rather similar. This can be explained by the sizeable proportion of patients achieving a second CR (212 of 243), and CCR (43 of 137 patients treated with chemotherapy only and 13 of 19 patients who underwent BMT). Although it is clear that ALL relapse is an highly unfavorable event which should be prevented, our data suggest that patients relapsing after less intensive treatment may have a higher potential for rescue than patients relapsing from current, very intensive regimens.

In conclusion these data show that treatment intensification has improved results confirming the concept that, at least within certain treatment settings, *more is better*.[12] Failures were mostly due to marrow or extramedullary relapses suggesting that further treatment intensification as being applied in current therapeutic strategies, is appropriate, although patients relapsing after less intensive treatment may have better chances of rescue. The combination of the stratification criteria and treatment results of this study did not allow selection of subgroups at very high risk of leukemia relapse who might have benefited from very aggressive therapy (including BMT in first remission), confirming that these subgroups may be identified more efficiently by biological markers or initial treatment response.

Contributions and Acknowledgments

GP was the current AIEOP Chairman at the time the study was run; VV served as the clinical study co-ordinator; EM, AP, G.DR, LLN, FP, NS, PI were the clinicians who gave the most relevant contribution to the conception of the study, acquisition and interpretation of the data; RR was responsible for the statistical analysis; GB was responsible for the centralized laboratory of the AIEOP; CF, RM, VC and MA were responsible for drafting the article.

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Disclosures

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Potential implications for clinical practice

Evaluation of long-term results of therapeutic studies on large unselected series of patients is helpful for comparative evaluation of different therapeutic strategies and for devising new studies.

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Appendix

The following institutions enrolled patients in the AIEOP-ALL-87 study.

- *Ancona, Clinica Pediatrica (Prof. G.V. Coppa, 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. G. Surico);*
- *Bergamo, Div. Pediatria (Dr. P.E. Cornelli);*
- *Bologna, Clinica Pediatrica (Prof. G. Paolucci, Dr. A. Pession, Dr. R. Rondelli);*
- *Brescia, Clinica Pediatrica (Prof. L. Notarangelo, Dr. F. Porta,);*
- *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" (Dr. G. Dini, Prof. P.G. Mori, Dr.ssa C. Micalizzi);*
- *Milano, Clinica pediatrica (Prof. V. Carnelli, Dr. F .Portaleone);*
- *Modena, Clinica Pediatrica (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 Pediatrica, 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);*
- *Padova, Clinica Pediatrica II (Prof. L. Zanesco, Prof. G. Basso, Dr.ssa C.Messina);*
- *Palermo, Clinica Pediatrica I (Prof. La Grutta, Dr.ssa G. Fugardi);*
- *Parma, Clinica Pediatrica (Dr. G. Izzi, Dr.ssa P. Bertolini);*
- *Pavia, Clinica Pediatrica (Dr. F. Locatelli, Dr. M. Aricò);*
- *Perugia, Divisione di Oncoematologia Pediatrica, Ospedale Silvestrini (Dr. A. Amici, Dr. P. Zucchetti);*
- *Pescara, Divisione di Ematologia (Dr. G. Fioritoni, Dr. A. Di Marzio, Dr. R. Di Lorenzo);*
- *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 (Dott. Paolo Paolucci Dr. S. Ladogana);*
- *Siena, Clinica Pediatrica (Prof. G. Morgese, Dr. A. Acquaviva, Dr. A. D'Ambrosio);*
- *Torino, Clinica Pediatrica (Prof. E. Madon, Dr.ssa E. Barisone);*
- *Trieste, Clinica Pediatrica (Prof. P. Tamaro, Dr. G.A. Zanazzo);*
- *Verona, Clinica Pediatrica (Prof. L. Tatò, Dr. Marradi)*