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Outcome of very late relapse in children with acute lymphoblastic leukemia

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A B S T R A C T

Introduction and Objectives. Few data are available on the long-term outcome of children who present with a very late relapse of acute lymphoblastic leukemia, so treatment of these patients remains controversial. The present study was aimed at investigating clinical features and treatment outcome of children with very late relapse, diagnosed and treated in Italy in the last 20 years.

Design and Methods. All children diagnosed in Italian centers with a first relapse of acute lymphoblastic leukemia occurring ≥ 60 months after attainment of first complete remission were included in this study. These relapses were diagnosed between 1982 and 1997.

Results. Ninety-three patients (58 males, 62.4%) had a first very late relapse occurring at a median time of 6.1 years (range 5.8 - 13.7 years) after the initial diagnosis. At a median follow-up time of 9.1 years after relapse, the overall 5-year survival (SE) and event-free-survival (SE) were 55.6% (5.2) and 39.5% (5.1), respectively. In multivariate analysis the site of relapse was the only significant predictor of duration of the second complete remission. Patients with isolated bone marrow relapse fared worse than those with combined or isolated extramedullary relapse [5-year event-free survival (SE) 24.5% (5.9), 51.3% (11.1) and 68.4% (10.7), respectively; (p=0.004)]. All 7 patients who underwent an allogeneic bone marrow transplantation from a matched related donor are alive in second complete remission.

Interpretation and Conclusions. In this evaluation patients with a very late relapse isolated to the bone marrow had a poor outcome while re-treatment of extramedullary or combined relapse was associated with better cure rate. Our data suggest that patients with very late isolated bone marrow relapse should be treated intensively; bone marrow transplantation from a matched related donor may be indicated.

Key words: acute lymphoblastic leukemia, childhood, relapse, treatment.

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The prognosis of acute lymphoblastic leukemia (ALL) in childhood has improved greatly over the last decades. More than 95% of patients achieve complete remission (i.e. blast cells < 5% in the bone marrow and disappearance of signs and symptoms related to the disease) and over 70% are expected to be cured by current chemotherapy regimens. Given that the overall toxic death rate has been reduced to about 3%, leukemia relapse represents the main cause of treatment failure.[1,2] Relapses may occur in the bone marrow alone, in the bone marrow and additional sites or exclusively in extramedullary sites. The majority of relapses occur while the patients are still receiving treatment (which generally lasts 2 years) or during the first year after treatment withdrawal. The outcome of relapsing patients is related not only to the site of relapse but also to the time interval occurring between the initial diagnosis of ALL and the relapse. For example, patients with a bone marrow relapse during front-line treatment or soon after its discontinuation have a poor prognosis despite intensive chemotherapy;[3] by contrast, children with a bone marrow relapse later on have been reported to have a markedly higher probability of cure even with moderately aggressive re-treatment schedules.[4-7] From the 3rd year after the primary diagnosis, the relapse rate decreases steadily, so that the 5-year event-free survival is conventionally considered as a *cure rate*. However, approximately 2% of the patients may relapse beyond this time. According to previous definitions reported in the literature this type of relapse may be called a *very late relapse*;[8-11] since very few data are available on the long term outcome of these patients, optimal treatment remains controversial. The aim of this

retrospective study was to report the long-term outcome of a large group of consecutive children diagnosed in Italian pediatric hematology-oncology centers with a very late relapse of acute lymphoblastic leukemia.

Design and Methods

Study design and front-line therapy

In order to identify patients with very late relapse, the data-bases of 5 consecutive AIEOP (i.e. Associazione Italiana di Ematologia ed Oncologia Pediatrica) acute lymphoblastic leukemia front-line trials conducted in Italy between 1976 and 1990 were reviewed. Front-line treatment was gradually intensified through subsequent study generations (simplified outlines of these studies are showed in Figure 1). The results of these trials have already been reported elsewhere.[12-15] The use of cranial radiotherapy to prevent central nervous system relapses was partially replaced by extended intrathecal chemotherapy. The duration of front-line therapy was 2 years except in the ALL 76 study and in a subgroup of patients of the ALL 79 study who were treated for three years.

Diagnosis of relapse

Relapse of acute lymphoblastic leukemia was diagnosed by the presence of ≥ 25% in the bone marrow blasts (or ≥ 5% in the case of combined relapse) or > 5 cells/mm^3 (with unequivocal documentation of leukemic cells) in the cerebro-spinal fluid (CSF) or by biopsy of the involved site when the bone marrow was not involved. Immunophenotypic information was available for 73/93 patients. Cytogenetic analysis was not performed in most cases.

Treatment of relapse

Given the long period of time considered, treatment of relapse was not uniform. During the early 1980s most patients were enrolled in a national AIEOP acute lymphoblastic leukemia trial for relapsing patients. This trial included a multi-drug approach for the induction of remission and a randomized study of two different continuation regimens.[16] Patients with extramedullary relapse also received local irradiation. The total duration of chemotherapy was 2 years. Due to the lack of a specific co-operative study, from the mid 1980s onward most patients were treated with more intensive chemotherapy schedules derived from front-line or relapse protocols of the German Berlin-Frankfurt-Münster (BFM) group.[10,11] A decision whether to perform bone marrow transplantation was taken in each institution based on local treatment policies.

Statistical analysis

Event-free survival was estimated by the Kaplan-Meier method after calculation of the time from the date of first relapse to the date of death in induction, resistance, second relapse, second malignant neoplasm or death in second complete remission, whichever occurred first. Survival probability estimates considered the time from first relapse to the date of death from any cause. The follow-up was updated as of June 30, 2002. The log-rank test was applied to compare the outcome of different groups. After excluding the presence of major departures from the proportional hazards assumptions by means of graphical checks, the Cox regression model was applied to investigate the prognostic role of sex, age at the time of relapse and site of relapse. Results are expressed as hazard ratios (HR) and corresponding *p*-values were calculated according to Wald's test.[17] The analyses were carried out using the SAS package.

Results

Patients' characteristics

Among 3,173 patients enrolled in the 5 front-line AIEOP acute lymphoblastic leukemia studies, a very late relapse occurred in 93 (2.9%) patients between 1982 and 1997. Interestingly, this rate was not homogeneous across the post-diagnosis periods, with 39 relapses in the 6th year (1.2%), 27 in the 7th year (0.8%), 14 in the 8th year (0.4%), 6 in the 9th year (0.2%) and 7 thereafter, between the 10th and the 14th year after diagnosis. All 93 patients [58 males and 35 females, aged 1-14.8 years (mean 6.0, SD 3.2)] had been diagnosed with acute lymphoblastic leukemia between 1976 and 1990. Their main clinical and biological features at diagnosis are summarized in Table 1.

Seventy-five (81%) patients were treated with standard/intermediate risk acute lymphoblastic leukemia protocols and 18 (19%) with high-risk protocols. First relapse occurred at a median time of 6.1 years after attainment of first complete remission (range 5.8-13.7 years). The median age at first relapse was 12.0 years (range 7.4 - 26.1 years).

Fifty-three patients (57%) experienced isolated bone marrow relapse and 40 (43%) extramedullary relapse, either isolated (n=21) or combined with marrow involvement (n=19). The testes were involved in 22 cases (24%, isolated in 11 cases) and the central nervous system in 15 patients (16%, isolated in 5 cases). The higher number of males among patients with very late relapse was due to testicular relapse, either isolated or combined, while relapses involving the uterus or ovaries were rare in females. When all these relapses were excluded, no major difference in the relapse site distri-

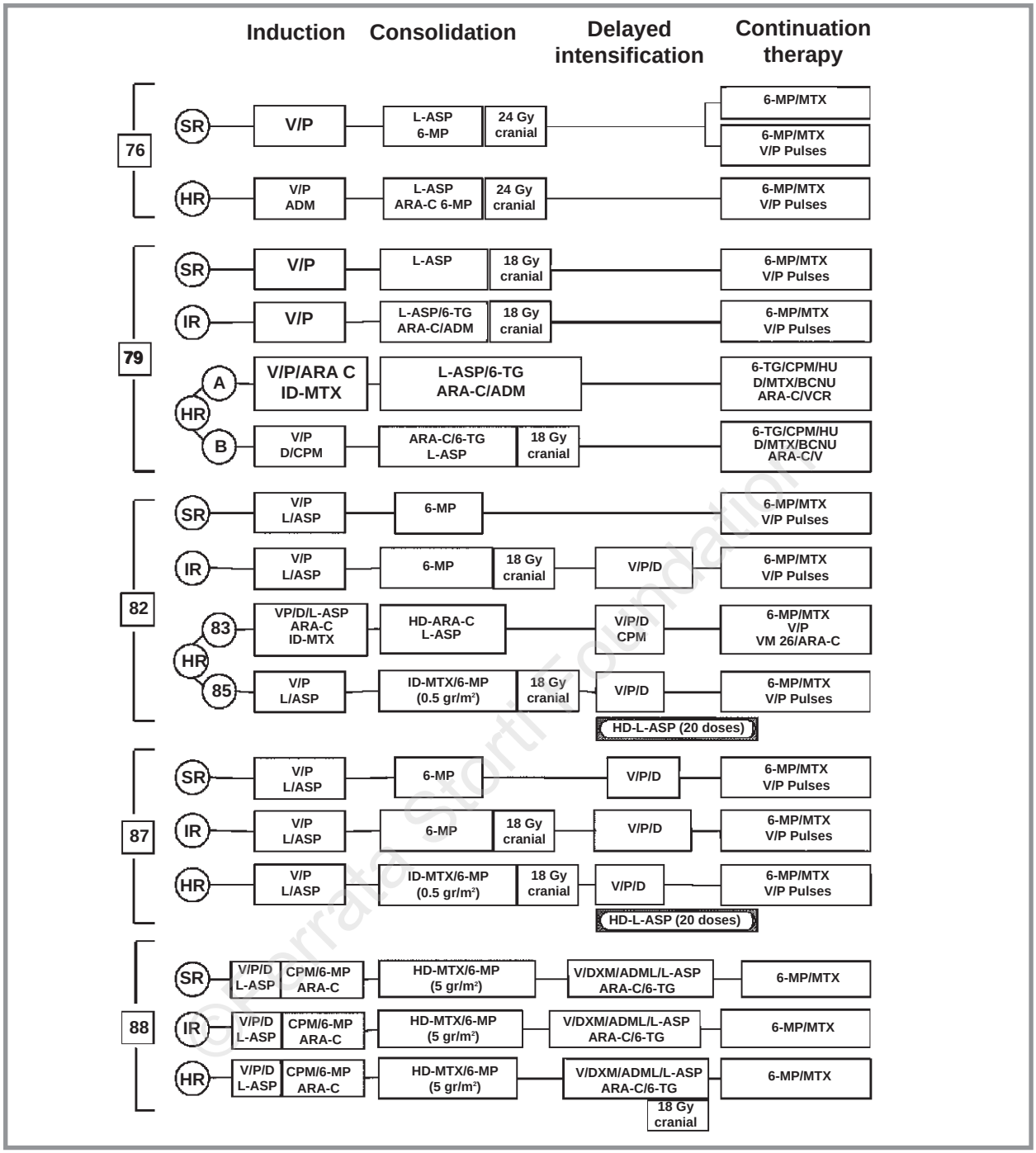

Figure 1. Simplified outlines of the 5 consecutive AIEOP ALL front-line studies conducted in Italy between 1976 and 1990. SR: standard risk; IR: intermediate risk; HR: high risk; V: vincristine; P: prednisone; L-ASP: L-asparaginase; 6-MP: 6-mercaptopurine; Gy: Grays; MTX: methotrexate; ADM: adriamycin; ARA-C: cytosine arabinoside; 6-TG: 6-thioguanine; ID-MTX: intermediate dose MTX; HD-MTX: high dose MTX; CPM: cyclophosphamide; HU: hydroxyurea; D: daunomycin; BCNU: carmustine; HD-ARA-C: high dose cytosine arabinoside; VM-26: teniposide; DXM: dexamethasone.

bution was seen between males and females (isolated bone marrow relapses accounted for 76% and 78% of the very late relapses in females and males, respectively). Details on relapse site by gender are outlined in Table 2.

Outcome

As illustrated in Table 3, ten patients failed to achieve a second complete remission either because of death in induction (n=3) or resistance to treatment (n=7). These latter patients subsequently died of resistant disease,

Table 1. Main clinical and biological features at initial diagnosis of ALL in 93 patients with subsequent very late relapse.

	Total	
	n	%
Total	*93*	*100*
Gender		
Male	58	62.4
Female	35	37.6
WBC count/μL*		
≤ 10,000	48	52.2
10 - 50,000	30	32.6
> 50,000	14	15.2
Immunophenotype		
Non-T	76	81.7
T	8	8.6
NK	9	9.7
Age at diagnosis (years)		
≤ 10	23	24.7
10 - 14	41	44.1
> 14	29	31.2

**data missing for one patient.*

Table 2. Sites of very late relapse of acute lymphoblastic leukemia according to gender.

Site of relapse	*Females*		*Males*		*Total*	
	N	*(%)*	*N*	*(%)*	*N*	*(%)*
Total	35	(100)	58	(100)	93	(100)
Isolated bone marrow	25	(71.4)	28	(48.3)	53	(57.0
Bone marrow + testes	–	–	11	(19.0)	11	(11.8)
Testes	–	–	11	(19.0)	11	(11.8)
Central nervous system	0	0	5	(8.6)	5	(5.4)
Bone marrow + central nervous system	5	(14.3)	3	(5.2)	8	(8.6)
Central nervous system + skin	1	(2.9)	0	(0	1	(1.1)
Central nervous system + eye	1	(2.9)	0	(0)	1	(1.1)
Bone marrow + pelvis	1	(2.9)	0	(0)	1	(1.1)
Bone marrow + uterus	1	(2.9)	–	–	1	(1.1)
Ovaries	1	(2.9)	–	–	1	(1.1)

Table 3. Outcome of 93 children with very late relapse of acute lymphoblastic leukemia.

	Chemo therapy*	*Bone Marrow Transplantation**	*Total (%)*
	69	*14*	*83*
Relapses	34	3	37 (39.8)
Bone marrow	21	1	22
Central nervous system	70	7	
Bone marrow + CNS	2	2	4
Testes	1	0	1
Bone marrow + Testes	1	0	1
CNS + lymph node + muscle	1	0	1
Eye	1	0	1
Secondary malignancy	1	1	2 (2.1)
Death in complete remission	9	1	10 (10.8)
Continuous complete remission	25	9	34 (36.6)
Patients			93 (100)
Death in induction			3 (3.2)
Resistance			7 (7.5)
Second complete remission			83 (89.3)

*CNS: central nervous system. *Treatment performed after achieving 2nd complete remission.*

including two who underwent allogeneic bone marrow transplantation while disease was still present. Eighty-three patients (89%) reached a second complete remission. Thereafter, 69 were treated with chemotherapy: 9 of these died 0.4 to 20 months after achieving the second complete remission due to infection (n=6), hemorrhage (n=2) or heart failure (n=1). Thirty-four children had a second relapse. Interestingly, 24/34 were very late isolated bone marrow relapses; 21/24 entered a 3rd complete remission thus suggesting that disease was still responsive to chemotherapy treatment. Fourteen patients underwent bone marrow transplantation while in 2nd complete remission: 7 patients with a very late relapse [bone marrow (n=3), central nervous system (n=2) and combined (n=2)] underwent autologous bone marrow transplantation (1 died of interstitial pneumonia, 3 had a second relapse, 2 are alive in 2nd complete remission, 1 developed a non-Hodgkin's lymphoma). All 6 patients (bone marrow n=3, central nervous system n=2 and combined n=2) who underwent allogeneic bone marrow transplantation from a matched family

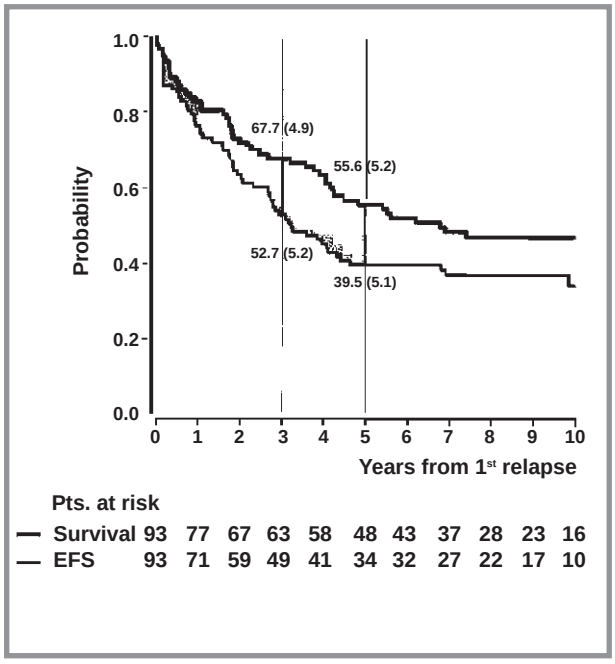

Figure 2. Outlines of the Kaplan-Meier plots of overall survival and event-free-survival for the 93 patients with very late relapse of acute lymphoblastic leukemia.

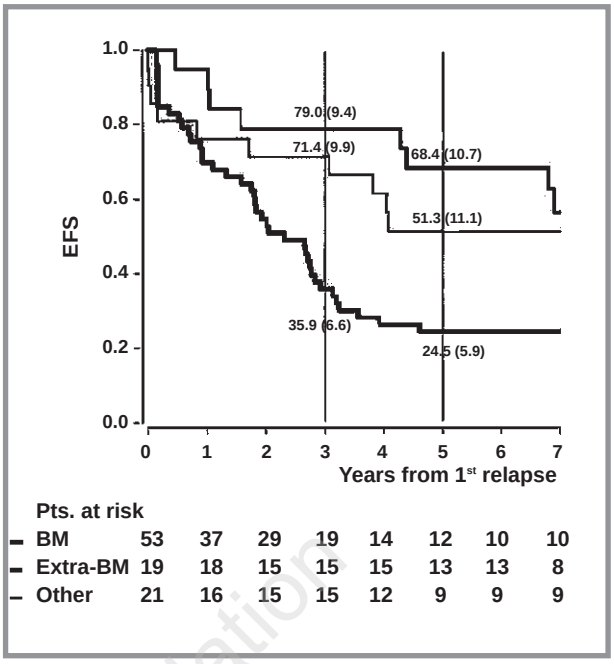

Figure 3. Kaplan-Meier plots of event-free survival for the 93 patients with very late relapse of acute lymphoblastic leukemia according to the site of relapse.

Table 4. Results of the Cox model analysis of event-free survival in 93 children with very late relapse of acute lymphoblastic leukemia in terms of estimated hazard ratios (HR) and 95% confidence intervals (CI).

Variable	*Estimated*		
	HR	*95% CI*	*p value*
Age at relapse (yrs)			
10-14 ≤ 10	1.35	0.65-2.83	0.420
15-24 ≤ 10	1.84	0.85-4.00	0.124
Gender			
Female vs male	1.11	0.65-1.89	0.706
Site of relapse			
Extramedullary vs isolated BM	0.37	0.17-0.83	0.015
BM + extramedullary vs isolated BM	0.58	0.28-1.23	0.157

donor are alive in 2nd complete remission, 5 to 12 years after transplant. One patient (bone marrow+central nervous system) who received a syngeneic transplant is alive after 11 years. Overall, after a median follow-up of 9.1 years, 44 of the 93 patients are alive, of whom 34 in 2nd complete remission (25 in the chemotherapy group and 9 in the bone marrow transplantation group). The 5-year survival and event-free survival with their relative SE are 55.6% (5.2) and 39.5% (5.1), respectively (Figure 2). Similar survival and event-free survival results were obtained for patients who received chemotherapy alone, censoring data for the 14 patients given bone marrow transplantation at the time of the transplant [52.9% (5.6) and 35.1% (5.4) for survival and event-free-survival, respectively].

Prognostic factors

In univariate analysis, 5-year event free-survival (SE) was not significantly affected by gender [males 48.1% (6.6), females 25.7% (7.4); p=0.13] or age at relapse [52.2% (10.4), 43.5% (7.8) and 24.1% (8.0) for patients aged 7-9, 10-14 and 15-24 years, respectively; (p=0.07)]. There was a significant difference (p=0.004) in the outcome according to the type of relapse: patients with isolated bone marrow relapse fared worse [5-year event-free survival (SE) 24.5% (5.9)] than those with either combined bone marrow [51.3% (11.1)] or extramedullary relapse [68.4% (10.7)] (Figure 3). With regard to isolated bone marrow relapses, the 5-year event-free survival (SE) in males and females was 25.0% (8.2) and 24.0% (8.5), respectively. In multivariate analysis, performed using a Cox regression model (Table 4), the site of relapse was also found to have a significant influence on the event-free survival, with extramedullary very late relapses having a 60% lower risk of failure than did isolated marrow relapses (*see Table 4 for details*). Figure 4 shows a chart of response and outcome of the 93 children with very late relapse of acute lymphoblastic leukemia.

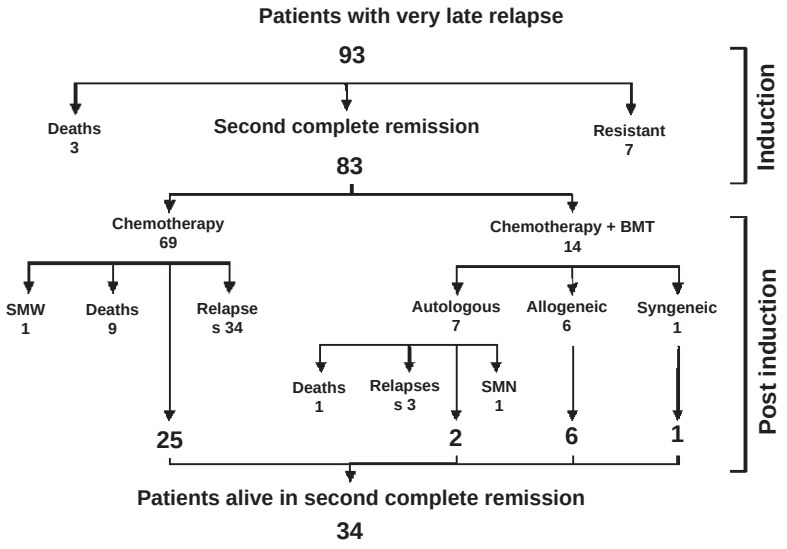

Figure 4. Flow-chart of response and outcome of 93 patients with very late relapse of acute lymphoblastic leukemia. SMN: secondary malignant neoplasm; BMT: bone marrow transplantation.

Discussion

In the present study, which to our knowledge represents the largest cohort reported to date, acute lymphoblastic leukemia relapse occurred 5 or more years after the initial diagnosis in 2.9% of patients treated in five consecutive AIEOP acute lymphoblastic leukemia studies carried out in Italy between 1976 and 1990. It is well known that the risk of relapse in acute lymphoblastic leukemia patients steadily decreases during the first 5 years of follow-up, but that relapses may still occur even after 10 years or more.[18] A short duration of first complete remission has been reported to be associated with a significantly worse prognosis because of the higher risk of a second relapse.[19] Based on this concept, the prognosis for very late relapse has been considered less severe or even quite good; thus, in the past, moderately intensive treatment schedules have often been considered adequate for re-treating patients who develop a very late relapse.[20] However, the results of the present study show that after a median follow-up of 9.1 years, less than one half of these patients are alive, and only 36% remain in 2nd complete remission. The lack of a plateau in the survival curves, due to the late events occurring after 3 years, with an additional 12% drop over the next two years, highlights the need for extended follow-up of these patients to evaluate their outcome properly.

In previous reports focusing on *late* relapses of acute lymphoblastic leukemia, analysis of prognostic factors showed that isolated bone marrow relapse has a worse prognosis than extramedullary or combined relapses.[10] Our findings are similar, with the risk of failure being 60% lower in children with extramedullary relapse than in those with isolated bone marrow relapse. The limited intensity of second-line chemotherapy treatment schedules adopted in our patients might partially explain the inadequate leukemia control achieved in these patients. Better results, which compare favourably with those obtained in patients treated with bone marrow transplantation,[21-24] have been observed by using intensive second-line chemotherapy regimens.[8,9,11] However, our experience with bone marrow transplantation, albeit in a limited number of patients, has been very encouraging; all 7 patients with very late relapse who were given a matched family donor (n=6) or syngeneic (n=1) bone marrow transplantation are in fact disease-free 5 to 12 years after bone marrow transplantation.

Our data therefore suggest that patients with very late relapse should be treated intensively. Evaluation of minimal residual disease, which has recently proven to be useful in predicting treatment failure in relapsed acute lymphoblastic leukemia trials,[25] could be used to identify patients with very late relapse who could benefit from allogeneic bone marrow transplantation.

All the authors contributed substantially to the study. In particular CR, MA, RoMi and VC designed the study, contributed to data analysis and wrote the manuscript. SG and MGV carried out the statistical analysis, contributed to study design and critically reviewed the manuscript. CM, GDR, AMT, RoMu, and FL were involved in the diagnosis and recruitment of patients and critically reviewed the manuscript. AB contributed in drafting and reviewing the paper.

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Appendix

The following institutions enrolled patients in the AIEOP acute lymphoblastic leukemia studies:

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 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); Napoli, Ospedale SS. Annunziata (Prof. F. Tancredi, Dr. A.Correra); Padova, Clinica Pediatrica II (Prof. L.Zanesco, Prof. G.Basso, 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. F.Locatelli, 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. M. Luciani); 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); 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).

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