EUROPEAN JOURNAL OF CANCER 44 (2008) 2461–2469

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First isolated extramedullary relapse in children with B-cell precursor acute lymphoblastic leukaemia: Results of the Cooprall-97 study ☆

Carine Domenech[a,*], *Mariette Mercier*[b], *Emmanuel Plouvier*[c], *Marc Puraveau*[b], *Pierre Bordigoni*[d], *Gérard Michel*[e], *Yves Benoit*[f], *Guy Leverger*[g], *André Baruchel*[h], *Yves Bertrand*[a]

[a]*Service d'Immuno-hématologie Pédiatrique, Institut d'Hématologie et Oncologie Pédiatrique, Hospices civils de Lyon, Université Claude Bernard Lyon1, 1, Place Joseph Renaut, 69373 Lyon Cedex 08, France*
[b]*Unité de Recherche Clinique en Cancérologie, Besançon, France*
[c]*Service d'Hématologie Pédiatrique, Besançon, France*
[d]*Service d'Hémato-oncologie Pédiatrique, Nancy, France*
[e]*Service d'Immuno-hématologie Pédiatrique, La Timone, Marseille, France*
[f]*Service d'Haemato-oncology Pediatric, Ghent, Belgium*
[g]*Service d'Hémato-oncologie Pédiatrique, Trousseau, Paris, France*
[h]*Service d'Hémato-oncologie Pédiatrique, Saint Louis, Paris, France*

ARTICLE INFO

Article history:
Received 16 June 2008
Received in revised form 2 August 2008
Accepted 6 August 2008
Available online 18 September 2008

Keywords:
Isolated extramedullary relapses
ALL
Cooprall-97

ABSTRACT

We report on the efficiency of treatment of first isolated extramedullary relapse of B-cell precursor acute lymphoblastic leukaemia.

Sixty-eight children and adolescents were included in the trial COPRALL-97. Stratification criteria were time to relapse: first complete remission duration of less than 24 months for group G3A ($n = 35$), relapse beyond 24 months for group G3B ($n = 33$). Treatment consisted of risk-adapted alternating short course multiagent systemic and intrathecal chemotherapy and irradiation (18 Gy).

Event free survival (EFS) and overall survival (OS) for all registered patients at 6 years were 43% and 55%, respectively. EFS at 4 years for patients of group G3A and G3B were, respectively, 31% and 61% ($p = 0.0071$) while OS at 4 years were, respectively, 40% and 76% ($p = 0.065$). Our analyses highlighted two independent risks factors predictive of decreased EFS: early relapse and age at the initial diagnosis above 6 years. Early central nervous system relapses have a bad prognosis, and new therapeutic strategies are needed.

1. Introduction

Acute lymphoblastic leukaemia (ALL) is the most frequent malignant disease in childhood. The 5-year event-free survival rate (EFS) ranges now from 75% to 80%.[1–7] However, relapse of ALL remains one of the most common paediatric malignancies and 2–6%[1,7–9] of them occur exclusively isolated in extramedullary sites, more commonly in the central nervous system (CNS) and the testes.[1,7,10–13] In rare cases, relapse occurs in other sites (ovary, eye, kidney).[1,13] The prophylaxis of extramedullary leukaemia has increasingly become an important part of the first line treatment and the ability to

☆ A poster was presented at the 49th Annual Meeting of the American Society of Haematology, Atlanta, Georgia, December 8–11, 2007.

* *Corresponding author:* Tel.: +33 4 69 16 65 69; fax: +33 4 78 78 37 03.
E-mail address: carine_halfon@yahoo.fr (C. Domenech).

0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.08.007

achieve a second sustained complete remission (CR2) is now hampered by drug resistance and toxicity limits.[14] Furthermore, if a second complete remission is obtained, the rate of subsequent relapse is high. It is already well known that the prognosis of relapse depends on the site of relapse[1,5–7,12,15–17] and on the duration of the first complete remission (CR1).[1,6,10,17,18]

Here, we describe a prospective, stratified and multicentric study: the Cooprall-97. The Cooprall-97 was designed for ALL relapses. The patients were treated in three groups (G1, G2 and G3) according to the duration of CR1 and the site of relapse. The G3 group was designed for isolated extramedullary relapse. We report on the efficiency of a combination of chemotherapy and radiotherapy for the treatment of extramedullary relapses in children with B-cell precursor ALL.

2. Patients and methods

2.1. Patients

Between May 1997 and December 2002, 68 children and adolescents up to 20 years of age who had experienced a first isolated extramedullary relapse of acute B-cell (non-Burkitt) lymphoblastic leukaemia (ALL) were enrolled from 27 French, Belgian and Portuguese paediatric centres. All patients received therapy according to the Cooprall-97 protocol. Eligible patients had to have normal cardiac, pulmonary, kidney and liver function and had no neurological dysfunctions (grade >2 in the OMS graduation, normal values are available at www.who.int) except for clinical symptoms associated with leukaemia.

Patients transplanted during their first remission or suffering a second relapse were excluded from this study. Pregnant women were also excluded. Informed consent was obtained from the patient or the patients' guardians prior to the enrolment in the study. The Cooprall-97 protocol was approved by all the institutional ethical committee. All patients were treated with an intensive front line protocol (either EORTC CLG or FRALLE),[19,20] for a total of 24 months to 30 months. A few patients[5] received cranial radiation as CNS prophylaxis. Patient characteristics are summarised in Table 1.

2.2. Definition and diagnostics

Isolated extramedullary relapses were those with clinically overt extramedullary manifestation of leukaemia and less than 5% marrow infiltration (according to cytomorphologic criteria only). CNS relapse was defined as at least five leuko-

Table 1 – Patients characteristics and treatment

	Total number of patients N (%)	Group G3A N (%)	Group G3B N (%)
Total group	68 (100)	35 (51.5)	33 (48.5)
Sex			
Boys	50 (73.5)	20 (57.1)	30 (90.9)
Girls	18 (26.5)	15 (42.9)	3 (9.1)
Age at relapse			
<6 years	48 (70.6)	21 (60)	27 (81.8)
>or =6 years	20 (29.4)	14 (40)	6 (18.2)
Site of relapse			
CNS	45 (66.2)	33 (94.3)	12 (36.4)
Testis	22 (32.3)	2 (5.7)	20 (60.6)
Other	1 (1.5)	0	1 (3)
Immunophenotype			
Pro-B	3 (4.4)	1 (2.9)	2 (6.1)
Common	32 (47.1)	18 (51.4)	14 (42.4)
Pre-B	30 (44.1)	14 (40)	16 (48.5)
Biphenotypic	3 (4.4)	2 (5.7)	1 (3)
Front-line treatment			
Front-line protocol			
EORTC	33 (48.5)	21 (60)	12 (36.4)
FRALLE	35 (51.5)	14 (40)	21 (63.6)
Front-line CNS-irradiation			
No	63 (92.6)	32 (91.4)	31 (94)
Yes	5(7.4)	3 (8.6)	2 (6)
Treatment of relapse			
Chemotherapy/radiotherapy	53 (78)	21 (60)	32 (97)
Allogeneic SCT	14 (20.6)	13 (37.1)	1 (3)
Autologous SCT	1 (1.4)	1 (2.9)	0

Group G3A: Relapse before 24 months after the first complete remission.
Group G3B: Relapse beyond 24 months after the first complete remission.
SCT: Stem cell transplantation.
CNS: Central nervous system.

cytes per microliter in cerebrospinal fluid and a cytologic evaluation demonstrating lymphoblasts, or clinical signs of cranial nerve involvement regardless of cell count. Testicular and other extramedullary site (ovary) relapses were confirmed histologically. The distribution of immunological subtypes is included in Table 1.

Relapse occurring within 24 months after CR1 was defined as early relapse (group G3A), and otherwise it was categorised as a late relapse (group G3B).

Complete second remission (CR2) was defined as no blasts in the cerebro-spinal fluid (CSF) and white blood cell count <5 mm^3 in the CSF for the CNS, and normalisation of testis size for the testis (no repeated testicular biopsies), after the induction therapy (VANDA) for group G3A and after the first course of B2 for group G3B.

2.3. Treatment

Patients in group G3A received an induction regimen (VANDA). If an HLA identical related donor was available, induction was followed by stem cell transplantation (SCT) after one block B1 and one block B2. Otherwise, alternative treatment consisted in successive blocks (B1 + B2 + B3) repeated 3 times followed by radiotherapy and maintenance (for 2 years). Patients in group G3B received sequential blocks (B1 + B2 + B3) repeated three times followed by radiotherapy and maintenance (1 year). The treatment design is described in Table 2.

2.4. Intrathecal therapy

All chemotherapy blocks contained intrathecal therapy. All patients with isolated extramedullary relapse received triple intrathecal therapy with methotrexate, prednisone and aracytine (Ara-C), according to their age. Patients with CNS-involvement received triple intrathecal therapy three times a week until leukaemic blasts disappeared, then every 2 weeks during the induction phase.

2.5. Local radiotherapy

Patients with testicular involvement received testicular radiation: both testicles were irradiated at a dose of 24 Gy (in 12 fractions) before the start of maintenance therapy.

Patients with CNS involvement over 2 years of age received cranio-spinal irradiation before the start of the maintenance therapy. Children received a dose of 18 Gy if they were not pre-irradiated (reduced to 15 Gy if pre-irradiated).

2.6. Stem-cell transplantation

Allogeneic stem-cell transplantation (SCT) was indicated in patients with an early isolated extramedullary relapse if an HLA-matched sibling donor was available. After a second CR (CR2) was achieved, these patients underwent SCT after two courses of intensification. SCT from unrelated donors and autologous transplants were not recommended during the study period. All transplanted patients, including those with CNS involvement, received conditioning regimens including total-body irradiation with 12 Gy.

Table 2 – Treatment courses

Drug	VANDA		Block B1		Block B2		Block B3		Maintenance*
	Dosage (per m^2 body surface)	Days drug was given	Dosage (per m^2 body surface)	Days drug was given	Dosage (per m^2 body surface)	Days drug was given	Dosage (per m^2 body surface)	Days drug was given	Dosage (per m^2 body surface)
Dexamethasone	10 mg	1–13	20 mg	1–5	20 mg	1–5	20 mg	1–5	–
Aracytine	2 g × 2	8–9	2 g × 2	5	2 g × 2	5	2 g × 2	1–2	–
Mitoxantrone	8 mg	10–11	–	–	–	–	–	–	–
Etoposide	150 mg	10–12	–	–	–	–	150 mg	3–5	–
L-Asparaginase	10,000 UI	14, 16, 18, 20	25,000 UI	6	25,000 UI	6	25,000 UI	6	–
6-Mercaptopurine	–	–	100 mg	1–5	–	–	–	–	–
Vincristine	–	–	1.5 mg	1, 6	–	–	–	–	–
Methotrexate+	–	–	1000 mg+	1	1000 mg +	1	–	–	20 mg
6-Thioguanine	–	–	–	–	100 mg	1–5	–	–	50 mg
Vindesine	–	–	–	–	3 mg	1	–	–	–
Cyclophosphamide	–	–	–	–	500 mg	6	–	–	–
Amsacrine	–	–	–	–	120 mg	5	–	–	–
Intrathecal therapy		1, 4, 12		1		1		5	

+: Infused for 36 h, with three rescue doses of folinic acid (hours 42, 48, and 54).
*: The children in conventional maintenance therapy received daily 6-thioguanine and methotrexate weekly.

2.7. Statistical methods

For comparison of patients' characteristics between groups, Fisher's exact test was performed. A two-tailed *P* value less than or equal to 0.05 was regarded as significant. The event-free survival (EFS) or the overall survival (OS) was estimated by Kaplan–Meier life-table analysis. The log-rank test was applied to compare the outcome between the different groups. The EFS time was calculated from the date of first relapse to the date of the end of the follow-up (15 December, 2006) or the date of an adverse event. Adverse events included any type of relapse or death by any cause during their CR2. Survival considered death alone (whatever the cause). In cases of a non-response to therapy or death during induction therapy, the EFS time was set to zero. To test the independence of prognosis factors of EFS, multivariate Cox-Regression analysis has been applied.

To exclude any time-to-transplant bias, the EFS difference between untransplanted and transplanted patients was tested by applying Cox's model using the EFS calculated from the date of the first relapse and the transplantation status was included in the model as a time dependent variable.

3. Results

Seventy two patients were registered. Four were excluded due to the first isolated extramedullary relapse of T-cell ALL. There were 45 cases of CNS relapses, 22 cases of testis relapses and one case of ovary relapse. The first relapse occurred at a median time of 24 months (range 0.4–125 months). The median age at the first relapse was 7.4 years (range 1.8–20.11 years). The higher number of males among patients with late relapse was due to testicular relapse, while relapse involving the ovary was rare in females. We did not find any statistical differences between the distribution of males and females with CNS involvement. Treatment results of the total cohort of registered patients are given in Table 3.

Sixty-four of 68 eligible patients achieved a second complete remission (94%). Of the 64 children who achieved a CR2, 28 (43.7%) suffered a second relapse. Most of these relapses ($n = 10$, 35.7%) occurred in the bone marrow (BM), whereas eight relapses (28.6%) were combined and nine relapses (32%) were isolated extramedullary (Table 3).

Of the 68 eligible patients, 31 patients (45.6%) were in their second complete continuous remission (CCR) at a median follow-up time of 7.2 years (range: 4–9.7 years). After their second relapse, 22 children subsequently died and six are living in their third (or more) CCR (Table 4). The subsequent relapses occurred within a median of 18 months (range: 4–70 months). Five patients died during their second CR because of treatment-related complications (three of them after SCT).

3.1. Group G3A

Thirty-five patients were treated in group G3A. In this group, all children relapsed before the completion of the frontline protocol (FRALLE or EORTC). Thirty-three (94.3%) patients had a CNS relapse and 2 (5.7%) a testicular relapse. Thirty-three patients achieved a CR2 (94%). There was one death during the induction period and one non-responder.

Fifteen patients underwent SCT in CR2. Twelve children received a graft from an HLA identical sibling donor, two were transplanted with an HLA-identical unrelated donor and one received an autologous graft. Two children with transplants suffered a treatment-related death (after SCT), eight children subsequently relapsed (4 BM, 3 combined, 1 isolated extramedullary), and 5 children remained disease-free in second CCR. So far, the patient who benefited an autologous graft is still in second CCR.

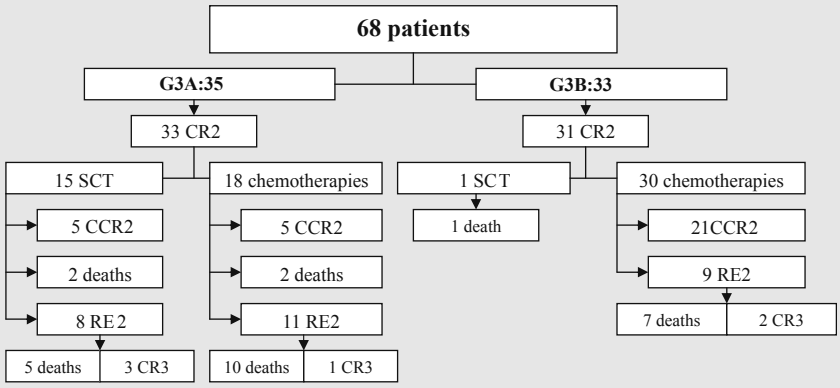
Nineteen of 33 patients who achieved a second CR, suffered a subsequent relapse (15 died and 4 are living in third CCR). The median time between the first and the second relapse was 20 months (range: 4–70 months). Of the four toxic deaths in CR, two occurred after SCT.

Table 3 – Outcome of 68 children with extramedullary relapse of B-cell precursor acute lymphoblastic leukaemia after the first relapse

	Total number of patients *N* (%)	Group G3A *N* (%)	Group G3B *N* (%)
Events	**68** (100)	**35** (100)	**33** (100)
Induction death	2 (2.9)	1 (2.8)	1 (3)
Non-response	2 (2.9)	1 (2,8)	1 (3)
Relapse	28 (41.2)	19 (54.3)	9 (27.3)
Death in CR	5 (7.4)	4 (11.5)	1 (3)
CCR+	31 (45.6)	10 (28.6)	21 (63.7)
Site of the second relapse	**28** (100)	**19** (100)	**9** (100)
BM isolated	10 (35.7)	6 (31.6)	4 (44.4)
BM combined	8 (28.6)	8 (42.1)	–
Extramedullary isolated	9 (32.1)	4 (21)	5 (55.6)
No data	1 (3.6)	1 (5.3)	–

CR: complete remission; CCR: continuous complete remission; BM: bone marrow.
+: Two boys underwent an right orchidectomy and one girl underwent an ovariectomy in group G3B.
/: In group G3A:There were 1 CNS relapse (RE2) after a testis relapse in RE1 and 3 CNS relapses (RE2) after CNS relapses in RE1.
In group G3B: there were 2 CNS relapses (RE2) after CNS relapses in RE1; 2 testis relapses after testis relapses in RE1 and 1 bone + kidney relapse (RE2) after a testis relapse in RE1.
Group G3A: Relapse before 24 months after the first complete remission.
Group G3B: Relapse beyond 24 months after the first complete remission.

Table 4 – Outcome of 68 children with extramedullary relapse of B-cell precursor acute lymphoblastic leukaemia after the first relapse



G3A: Relapse before 24 months after the first complete remission.
G3B: Relapse beyond 24 months after the first complete remission.
CR2: Second complete remission.
CCR2: Second continuous complete remission.
CR3: Third complete remission.
SCT: Stem cell transplantation.
RE2: Second relapse.

3.2. *Group G3B*

Thirty-three patients were treated in group G3B. There were 12 CNS (36.4%), 20 testicular (60.6%) and one ovary (3%) relapse. Thirty-one patients reached a second CR (94%). Nine of 31 patients who had achieved a CR2, suffered a subsequent relapse (7 died and 2 are living in the third CCR). The patients who relapsed had all received chemotherapy. The median time between the first and the second relapse was 16 months (range: 7–44 months). One patient underwent SCT.

3.3. *Event free survival (EFS) and overall survival (OS) in the groups G3A and G3B*

The EFS and OS for all eligible patients at 6 years were 43% (IC 95%: 0.31–0.55) and 55% (IC 95%: 0.43–0.67), respectively (Fig. 1). The EFS and OS at 4 years for group G3A were, respectively, 31% (IC 95%: 0.16–0.47) and 40% (IC 95%: 0.24–0.56) (Fig. 2). The EFS and OS at 4 years for group G3B were, respectively, 61% (IC 95%: 0.44–0.77) and 76% (IC 95%: 0.61–0.90) (Fig. 2).

The EFS and OS of group G3A were significantly less than those of group G3B ($p = 0.0071$ and $p = 0.0065$, respectively).

3.4. *Prognostic factors*

Several parameters of relapse (time of relapse, age at initial diagnosis, immunophenotype and sex), and the performance of SCT were analysed for their impact on the prognosis. 6-year EFS was not significantly affected by gender (in CNS involvement) (males 54%, females 50.5%, $p = 0.512$). CNS relapses were essentially in the group of early relapses and testes relapses in the other group. This strong correlation precluded further analysis of the value of relapse site as a risk factor.

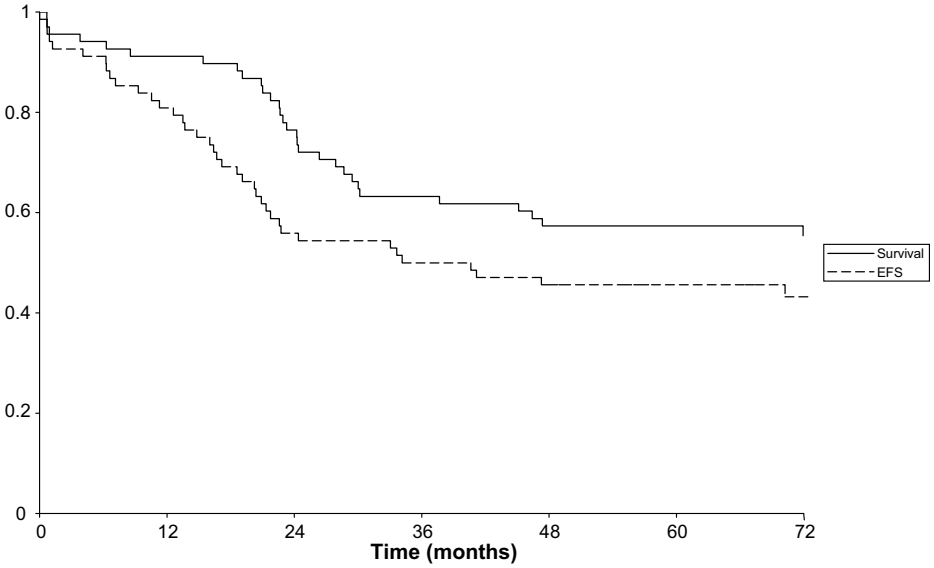
In multivariate Cox regression analysis, the time of relapse and the age at initial diagnosis above 6 years were found to be independent prognosis factors of EFS ($p = 0.05$ and $p = 0.01$, respectively) (Figs. 2 and 3). Indeed, patients above 6 years at initial diagnosis had a worse prognosis (4 year EFS: 15%, IC 95%: 0–0.3) than those under 6 years (4-year EFS: 58%, IC 95%: 0.44–0.72). The other factors, such as the immunophenotype, sex and stem cell transplantation were not significant.

4. Discussion

Isolated extramedullary relapses usually occur in the CNS or testis, organs in which there is a blood–tissue barrier. Indeed, such a functional barrier alters the bioavailability of cytotoxic agents administered. The Cooprall-97 therapy (derived from ALL-REZ BFM therapy, [16]) consisted of risk-adapted alternating short courses of multi-agent chemotherapy through systemic and intrathecal ways. It was followed by a local irradiation therapy (18 Gy) and a conventional maintenance therapy or stem cell transplantation when indicated. This concept of block therapy has been shown to be of significant benefit and is relatively well tolerated.[4,16]

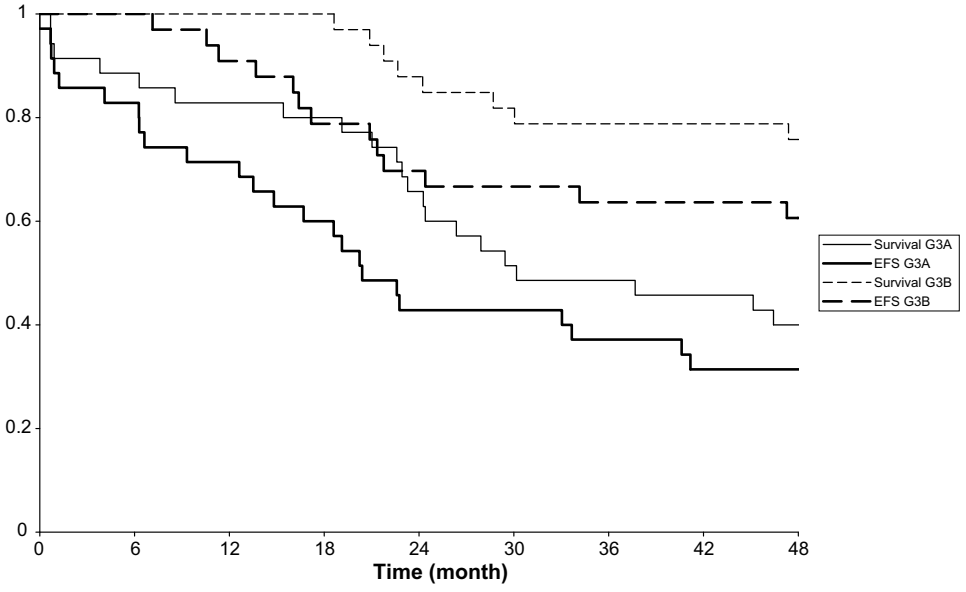
In our study, most of the patients (94%) achieved a CR2. These results are comparable to other published data.[2,5,6,16] However, long-term CR could only be maintained in 45.6% of the children. The major adverse event for patients during CR2 was subsequent BM relapse. These second relapses probably occurred following a refractory BM disease. BM disease is probably derived from leukaemic cells that survived the 2nd line chemotherapy and then became refractory to the drugs used to treat ALL relapses.

Several risk factors influenced the probability of achieving a prolonged EFS after CR2. The characterisation of these factors is essential to establishing new treatment stratifications



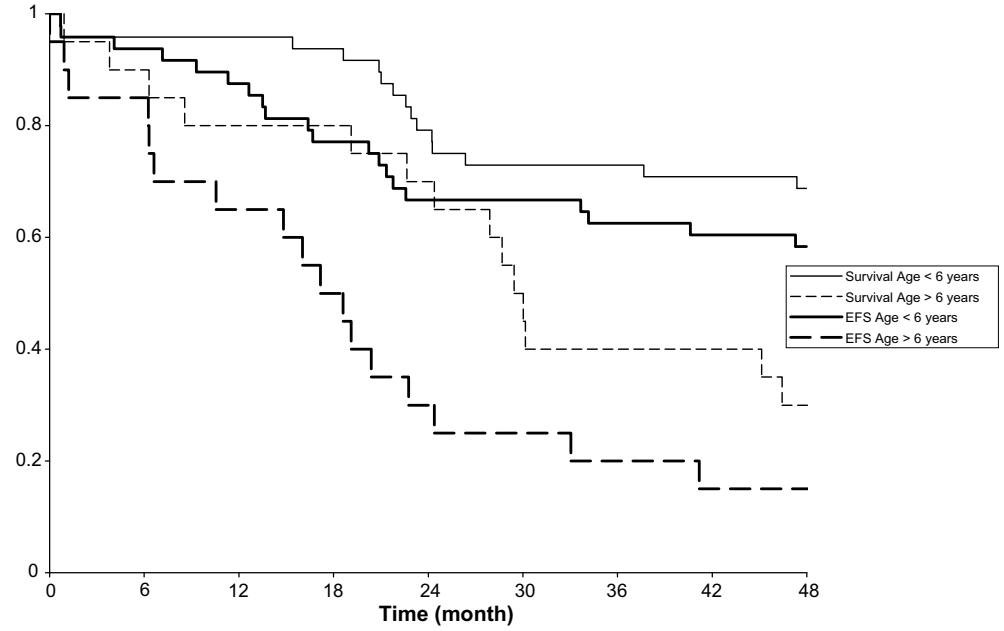
Survival (months)	0	12	24	36	48	60	72
Patients at risk	68	62	52	43	38	38	28
Cumulative events	0	6	16	25	29	29	30
EFS (months)	0	12	24	36	48	60	72
Patients at risk	68	55	38	34	30	30	18
Cumulative events	0	13	30	34	37	37	38

Fig. 1 – Event-free survival and overall survival for all registered patients.



Survival (months)		0	12	24	36	48
Group G3A	Patients at risk	35	29	23	17	14
	Cumulative of events	0	6	12	18	21
Group G3B	Patients at risk	33	33	29	26	25
	Cumulative of events	0	0	4	7	8
EFS (months)						
Group G3A	Patients at risk	35	25	15	13	11
	Cumulative of events	0	10	20	22	24
Group G3B	Patients at risk	33	30	23	21	20
	Cumulative of events	0	3	10	12	13

Fig. 2 – EFS and overall survival according to the group G3A and G3B.



Survival (months)		0	12	24	36	48
Age< 6years	Patients at risk	48	46	38	35	33
	Cumulative events	0	2	10	13	15
Age> or =6years	Patients at risk	20	16	14	8	6
	Cumulative events	0	4	6	12	14
EFS (months)						
Age< 6years	Patients at risk	48	42	32	30	28
	Cumulative events	0	6	16	18	20
Age> or =6years	Patients at risk	20	13	6	4	3
	Cumulative events	0	7	14	16	17

Fig. 3 – EFS and OS according to the age at the initial diagnosis.

in future clinical trials. Both the time of relapse and the age at the initial diagnosis are significant predictors of EFS. These parameters proved to be independent risk factors using a multivariate analysis. This study confirms early reports that late relapses are associated with a better EFS and survival rate than the early relapses for both sites of relapse.[1–7,12,13,16,17] Indeed, similar results were obtained by Schroeder and colleagues[5] for the isolated CNS relapses: EFS at 8 years: 21% (±10%) for the early relapses *versus* 61% (±13%) for the late relapses. Similarly, in the Children's Cancer Group, Gaynon and colleagues[3] reported for isolated CNS relapses a 52% (±11%) EFS (early relapses) and a 81% (±5%) EFS (late relapses) at 7 years. Barredo and colleagues[2] reported similar results for the isolated CNS relapses. Gaynon and colleagues[3] found that once the adjustments for time and site of relapse effects were made, the initial age (>= at 10 years) and sex (male) were significantly associated with an adverse prognosis ($p < 0.01$). Wofford and colleagues[8] reproduced the same results regarding the age at the initial diagnosis, as well as Tsurusawa and colleagues.[21] Finally, Barredo and colleagues showed that the NCI risk group was an independent prognostic factor in isolated CNS relapses of ALL.[2] We found that two ages (6 and 10 years) might be used as prognosis factors, but only the age >= 6 years was highly significant (respectively, $p = 0.01$ and $p = 0.02$). As reported by Barredo and colleagues, we did not find the gender to be a prognosis factor.[2]

Contrary to the case of systemic relapses, the therapeutic benefit of an allogenic SCT as a treatment for isolated extramedullary relapse has not yet been assessed in a large cohort study.[22–24] In our prospective study, we were unable to detect a statistically significant difference favouring SCT over conventional therapy, as also reported by Eapen and colleagues.[25]

Overall, the results of the Cooprall-97 therapy are consistent with the previously published studies. The therapeutic results are quite good for group G3B but disappointing for group G3A.

It is assumed that isolated EM relapses may be an early manifestation of the recurrent systemic disease.[13] For decades it has been known that treatment of the EM relapse only is not sufficient to maintain the patient in remission and that subsequent BM relapse will follow. Also, investigations using polymerase chain reaction for leukaemia specific sequences have shown that malignant cells can already be present in the BM at the moment of EM recurrence, while the BM is

microscopically still in remission.[16,17,26–28] Indeed, despite the seemingly isolated nature of these relapses, most patients will rapidly develop a haematological relapse when the search for a minimal residual disease (MRD) in the BM is positive. Thus, the absence of MRD also identifies a group of patients with a likelihood of reduced risk of relapse who might benefit from a less intensive therapy (i.e. no SCT) that aims to reduce long term toxicity.[29]

Future protocols for the isolated extramedullary relapses should include a systematic evaluation of BM MRD: patients with a positive MRD would be treated as combined systemic relapses currently are. For relapses with a negative MRD (truly isolated EM relapses), other therapeutic options should be considered.

Each of the three groups should benefit from an intensive systemic chemotherapy using drugs with good penetration of the blood–tissue barrier in order to reach the 'sanctuary sites' and avoid the second relapses. In the MRD positive group, allogenic SCT would follow intensive chemotherapy as in the current BM relapse protocols.

Furthermore, the group with truly isolated and early EM relapses could benefit from delayed intensive radiation or autologous stem cell transplantation (ASCT) in association with the intensive chemotherapy previously described. Barredo and colleagues recently reported good results for isolated CNS using a similar protocol and a delay prior to radiotherapy of 12 months.[2] Also, there is evidence that ASCT might contribute to curing relapsed children.[9,22,24] Rossetti and colleagues have reported 12 children who received high doses of Ara-C and TBI before ASCT. Eight of them were in CCR at 2 years median observation time.[24] Messina and colleagues also reported 19 children experiencing an early isolated CNS relapse who underwent ASCT, the 5-year EFS was 56.3% for this group (compared to 12.6% for the group treated only with chemotherapy (41 children)).[9]

Because the prognosis could be better for the 'true' isolated and late relapses, this group may benefit from a systemic and intrathecal chemotherapy followed by radiotherapy with reduced doses. Barredo showed that the reduction of radiation therapy was feasible for patients with CR1 of at least 18 months, hence reducing the long term side-effects of spinal axis radiotherapy.[2] Furthermore, Van den Berg[26] and colleagues reported a cohort of five boys in whom the testicular irradiation was replaced by high-doses of methotrexate, with apparent continued testicular remission.

5. Conclusion

Our results are in line with the previous studies. Results on the late EM relapses are encouraging but the outcome after early EM relapses is still poor. To improve the results, particularly for early relapses, further trials should include the data for MRD[30] and the value of SCT and ASCT must be evaluated prospectively in a cohort of homogeneous patients. Better results could also be obtained with a better use of drugs with systemic and local (CNS, testes) efficacy.

Because current therapies lead to increased EFS in childhood ALL, any attempt of a prospective trial to assess the efficiency of a new therapeutic scheme will require an international cooperation. It will also be of interest to study the biological characteristics of the leukaemia cells involving extramedullary sites.

Conflict of interest statement

All authors disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work.

Acknowledgments

We thank the following centres and their teams for their participation in the Cooprall-97 study:

Besançon (Dr. Plouvier), Bordeaux (Pr. Perel), Bruxelles (Pr. Cornu), Clermont-Ferrand (Pr. Demeocq), Ghent (Pr. Benoit), Grenoble (Pr. Plantaz), Leuven (Dr. Uyttebroeck), Liège (Dr. Houyoux), Lille (Dr. Nelken), Limoges (Pr. De Lumley), Lyon (Pr. Bertrand), Marseille (Pr. Michel), Montpellier (Dr. Margueritte), Nancy (Pr. Bordigoni), Nantes (Dr. Mechinaud), Nice (Dr. Sirvent), Paris R. Debré (Pr. Vilmer†), Paris Saint-Louis (Pr. Baruchel), Paris Trousseau (Pr. Leverger), Poitiers (Dr. Millot), Porto (Dr. Norton), Reims (Dr. Behar), Rennes (Pr. Le Gall), Rouen (Pr. Vannier), Saint-Etienne (Pr. Stephan), Strasbourg (Dr. Babin) and Toulouse (Dr. Robert and Dr Rubie).

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