Keep in mind quality of life: outcome of a 10-year series of post-transplant early relapses in childhood acute lymphoblastic leukemia A report from the GOCE, the Grand Ouest oncology study group for children in France

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Short title: quality of life of early post-transplant relapses in childhood lymphoblastic leukemia

S.Haro, MD[1*], A.Tavenard[2], F.Rialland, MD[3], S.Taque, MD[4], G.Guillerm, MD[5], P.Blouin, MD[6], M.Esvan[2], I.Pellier, MD-PhD[7], V.Gandemer, MD-PhD[4]

[1] Department of Pediatrics and Genetics, University Hospital of Brest, Brest, France;

[2] GOCE biostatistic unit, University Hospital of Rennes, France

[3] Department of Pediatric Hematology/oncology, University Hospital of Nantes, Nantes, France

[4] Department of Pediatric Hematology/oncology, University Hospital of Rennes, Rennes 1 University, France

[5] Department of Clinical Haematology, Institute of Cancerology and Hematology, University Hospital Brest, Brest

[6] Department of Pediatric Onco hematology, University Hospital of Tours,Tours, France

[7] Department of Pediatric Onco hematology, University Hospital of Angers, Angers, France

* Correspondence and reprint requests: Sophie Haro, MD, department of Pediatric Onco Hematology, University hospital of Brest, 2 avenue Foch, 29200 Brest, France, Email : sophie.haro@chu-brest.fr

Abstract

Acute lymphoblastic leukemia (ALL) relapses early after hematopoietic stem-cell transplants in children are uncommon, but associated with a very poor prognosis. Whereas there are no current recommendations for the management of these relapses, the children's quality of life is an important issue. We studied the outcomes, including one-year overall survival, complete remission and quality of life, of 19 children with ALL who relapsed within the year following their transplant treated in the 5 participating centers between 2000 and 2011 Patients were distributed as follows: supportive care only (group A), outpatient treatment (mainly steroid and vincristine; group B) or intensive inpatient treatment (group C). There were no significant differences in one-year overall survival (31.5% for the entire cohort) or remission rate for time between transplant and relapse (<6 months or 6–12 months), transplant or disease characteristics or treatment group. However, time spent in hospital (for treatment and complications) significantly differed between treatment groups B and C (20.8%+/-13.0 versus 59.1% +/-32.9, respectively; $p<0.05$). No differences in organ toxicities, school attendance or Lansky score were found between treatment groups. Our sample size-limited data indicate, in a pre-personalized medicine era, that children treated with steroid and vincristine have the same prognosis as those treated with intensive therapy, but may benefit from improved quality of life. Nevertheless, new therapeutic strategies are required and future prospective trials would help to establish recommendations.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) accounts for 80% of acute leukemia in children. Cure is achieved in over 85% of children. Because of the risk of acute complications and long-term sequelae, hematopoietic stem-cell transplantation (HSCT) is limited to certain high-risk patients. However, relapse after HSCT occurs in 20 to 40% of these patients [1–4]. Several risk factors for relapse after transplantation have been identified, including the absence of chronic graft versus host disease (cGVHD) and the type and intensity of immunosuppression [5]. Over the last decade, pre-transplant minimal residual disease (MRD), evaluated in bone marrow samples by multiparameter flow cytometry or real-time quantitative polymerase chain reaction for immunoglobulin IgH/T-cell receptor (TCR), has emerged as a major predictor of outcome [6–8]. For instance, the French pediatric group of HSCT has recently demonstrated that a pre-transplant MRD $\geq 10^{-3}$ increased the 5-year cumulative incidence of relapse from 16.7% to 43.6% [9].

Previous findings have shown that ALL which relapse early after HSCT has a very poor prognosis; indeed, treatment is rarely effective or well-tolerated in such cases [7,8]. The time between HSCT and relapse is a major factor affecting outcome, with a 1-year survival rate of less than 5% for patients relapsing within 6 months post-transplant [9]. Post-transplant relapse strategies usually firstly include immune modulation, namely withdrawing immune suppression and/or performing donor lymphocyte infusion (DLI) [10,11]. Secondly, chemotherapy may be initiated, depending on residual transplant toxicity, with the aim of obtaining complete remission. Finally, a second HSCT may be proposed.

No recommendations for the treatment of early relapse (relapse occurring within 1 year after transplantation) after HSCT have been published. Currently in France, treatment is decided on a case-by-case basis after multidisciplinary discussion. The standardization of treatment

following early relapse is difficult due to the low frequency of such relapse events and because it is difficult to know how well a patient may endure intensive treatment. Regardless of the prognosis, the quality of life of these children remains a major issue.

In a multicenter study, we investigated the outcome, in terms of one-year outcome (overall survival (OS)) and the clinical status at 6 months, of early post-transplant relapses in children with ALL receiving different treatment strategies.

MATERIALS AND METHODS

Patients and study design

All patients under 18 years of age at relapse, treated in 1 of the 5 participating centers of the Grand Ouest network GOCE, who underwent a HSCT between 2000 and 2011 for ALL and who relapsed in the year following their transplant, were included in our study.

Our primary endpoint was 1-year overall survival. Secondary endpoints were complete remission (CR) and the following parameters related to clinical status at 6 months: Lansky score, time spent in hospital compared to the period of survival, school attendance and cumulative organ toxicity grade defined by the WHO. Cumulative organ toxicity was based on the maximum grade of toxicity, as defined by the WHO scale for cardiac, pulmonary, renal and neurological damage, for each patient during the first 6 months after relapse. We established a composite toxicity score represented by the sum of the maximum grade of these toxicities. The poorest possible score was 16.

Data collection

All patients were enrolled in the PROMISE transplant tracking registry and legal guardians, on behalf of the children, gave their informed consent in accordance with the Declaration of Helsinki for the anonymous registration of pre and post-transplant data. We completed the data using patient medical records provided by the participating centers after local medical

agreement. We collected clinical status at relapse as evaluated by Lansky score, residual toxicities graded according to WHO classification, characteristics of disease relapse and treatment provided for relapse. Children who only received supportive care (transfusion and nutrition) represented group A. Treatment groups were outpatient treatment (group B) and intensive inpatient treatment (group C). The number of days spent in hospital was collected from hospital administrative systems and reported as the percentage of total survival during the 6 months following post-transplant relapse.

Statistics

Quantitative variables were described by median and range or mean and standard deviation (SD). For categorical variables, number (N) and percentage (%) were presented for each category. Quantitative parameters were compared by Wilcoxon-Mann-Whitney or Kruskall-Wallis tests. We used exact Fisher test to compare categorical variables. Kaplan-Meier analyses were performed for survival estimates and the log-rank test for comparison of survival functions. All reported p-values were two-sided and were considered significant when <0.05. SAS Version 9.3 software was used for statistical analyses. Our analyses and comparisons are exclusively made between groups B and C (only 2 patients in group A).

RESULTS

Patient Characteristics

A total of 21 children having relapsed within 12 months after transplant were listed. Two patients who had a second transplant during the study period (respectively, 9 and 23 months after the first transplant) were excluded from the analysis. Finally 19 transplants were included in our study. Five girls (26%) and 14 boys (74%), aged between 3 months and 16

years old at ALL diagnosis were enrolled, with a median age at transplantation of 7.5 years [0.7-18.2]. Of the 19 relapses, 11 (58%) occurred within the first 6 months after transplantation. The median delay between first transplant and relapse was 122 days [18–354 days]. Relapses were medullary for 13/19 cases, combined for 3/19 cases and extra-medullary for 3/19 cases.

Eighteen of the 19 transplants (91.3%) were performed in complete morphologic remission, of which 10 (52.6%) were in first remission. Eight transplants (42.1%) occurred after two or more previous treatment lines. Median Lansky score at relapse was 70 % [60%–100%]. One month pre-transplant Ig/TCR MRD was greater than 10^{-3} for 6 of the 19 transplants (32%).

One patient (5.3%) presented with engraftment failure. Briefly, 12/19 (63.2%) patients developed acute graft versus host disease (aGVHD), 7/19 (36.8%) developed cGVHD, 2/19 (10.5%) developed veno-occlusive disease and 2/19 (10.5%) hemorrhagic cystitis. Immunosuppressive therapy was still in place for 7/19 (36.8%) patients at relapse. Details are listed in supplemental Table 1.

Treatment decisions

When relapse was diagnosed, immunosuppression therapy was immediately stopped for each patient.

Only 2 patients with relapse received exclusively supportive care (group A); 11 received outpatient chemotherapy (group B); and 6 received intensive therapy (Group C). Intensive therapy included various combinations of chemotherapy (treatment according to the protocol COOPRALL 97 with a VANDA course including a combination of dexamethasone, aracytine, mitoxantrone, VP16, Peg Asparaginase and triple intratecal - or another combination of cyclophosphamide, vincristine and prednisone or a combination of methotrexate and asparaginase), followed by another transplantation for 1 child. Details of these treatment groups are summarized in Figure 1. The characteristics of the transplantation

(number of pre-transplant treatment lines, source of the graft, conditioning regimen, type of donor and pre-transplant hematological status) were not significantly different between treatment groups (B or C). However in group B, there was significantly fewer preparative regimens using total body irradiation (TBI) (p = 0.01) and more transplants performed with a pre-transplant MRD $<10^{-3}$ (p = 0.05) than in group C. The delay between transplant and relapse, the type of relapse or the Lansky score at relapse were not significantly different between treatment groups (Table 1).

Overall outcome

Overall survival at 12 months was 31.5%. The 6 patients alive at 1 year presented with an extramedullary relapse (2 patients), a combined relapse (2 patients) and an isolated medullary relapse (2 patients). Median survival [range] in this study was 222 days [4-3544] (Suppl figure 1).

We observed a trend in overall survival associated with the delay between transplant and relapse (p = 0.09). Overall survival at 1 year after relapse was 27% for relapses occurring within 6 months post-transplant (median survival 132 days [4-2991]) and 50% for relapses occurring between 6 and 12 months after transplant (median survival 279 days [185-3544]). Delay between transplant and relapse was significantly longer for patients with aGVHD (p = 0.04), regardless of stage (152 days versus 98 days). However aGVHD did not affect overall survival (p = 0.76).

At 6 months post-relapse, 5 patients (26.3%) achieved a CR. One-year overall survival rate was 80 % for those who experienced CR following relapse and 20% for those who did not (p <0,01) (Suppl figure 2). Whether a patient experienced CR within 6 months after relapse did not depend on the type of leukemia (p = 1.00), the time period between transplant and relapse

(p = 1.00), the type of transplant (p = 0.25), the site of relapse (p = 1.00), or the occurrence of aGVHD (p = 1.00).

Impact of treatment

The likelihood of a patient being in CR at 6 months post-relapse did not differ between treatment groups B and C (p = 0.60) (n = 4 [36.3%] in group B; n=1 [16.5%] in group C). Nor was there any significant difference but a trend in 12-month survival between the two treatment groups with a OS rate of 45.5% for patients in group B and 16.5% for those in group C (p = 0.24) (Figure 2). Patients in group B had a median survival of 222 days [104-3544] versus 259.5 days [18-486] for group C.

Quality of life 6 months post-relapse

The Lansky score, time spent in hospital relative to the period of survival, school attendance and cumulative organ toxicity according to WHO grade were evaluated according to patient characteristics and post-relapse treatment.

The median composite toxicity score, as defined in methods, was 4.5 [3–6] for group A, 2.8 [0–7] for group B and 5 [0–9] for group C (p = 0.74). Grade 3-4 complications were mainly neurological toxicities, reported for 7 (63%) patients in group B and 4 (66%) patients in group C (Figure 3). No neurotoxicity risk factors have been demonstrated.

None of the patient or disease characteristics tested significantly affected school attendance in our study. However, we observed a trend for the delay between transplant and relapse (p = 0.18): only 3 children whose relapses had occurred within 6 months post-transplant (27 %) attended school while 5 (62 %) who relapsed between 6 and 12 months after transplantation attended school. School attendance did not differ between treatment groups (p = 0.61).

The Lansky score differed significantly (p = 0.04) between children relapsing within the first 6 months following transplant (45.4% [0%–100%]) and those who relapsed between 6 and 12

months post-transplant (76.2% [60%–90%]). The Lansky score was not significantly different ($p = 0.71$) between treatment groups.

Time spent in hospital (overall days, for antileukemic treatments or management of complications) relative to the number of days of survival was evaluated for the first 6 months post-relapse and significantly differed between treatment group: 21.7% ± 13.0 for group B and 59.1% ± 32.8 for group C ($p=0.03$).

DISCUSSION

We reported the results of a retrospective study on the management of relapses occurring early after HSCT performed in children with ALL in GOCE centers between 2000 and 2011. We raised the question of an impact of post relapse treatment in addition to survival and quality of life.

We found no significant differences in overall survival or the occurrence of complete remission, after relapse between the treatment groups tested. However we observed a significant difference in the proportion of time spent in hospital during the first 6 months post-relapse. We chose this period because previous findings have shown a median overall survival for such patients of 6 months, with less than 5% of children surviving at 1 year [12] . In our study, children had a median overall survival of 7.2 months.

Despite 10 years of observation, the sample size of our study remains small. Indeed these relapses are uncommon due to improved treatment for children with ALL and thus the less frequent need for transplantation. The understanding of the risk factors for relapse post-transplant has also improved, reducing the number of early relapses. To the best of our knowledge, this is nevertheless the first study to evaluate precisely clinical status parameters for ALL children who relapsed within 1 year after transplant.

Because of the retrospective design and absence of recommendations for treatment of post-transplant early relapses of ALL in childhood, we could not identify reasons why clinicians chose a particular therapeutic strategy. However, the high MRD level (evaluated by IgH/T-cell receptor) and the use of TBI are likely explanations for the choice of a multichemotherapy regimen for children in group C probably due to the thinking that a such MRD $>10^3$ reflected a more aggressive disease.

Our population was in-line with previous reports of post-transplantation relapse, with 60% of patients with high pre-transplant MRD [9,13] and a low proportion with cGVHD [6]. One-year overall survival in our study was a little higher (31.5%) than previous observations [12], but very early deaths could have not been identified as relapses. Moreover, we observed a large proportion of patients with extramedullary or combined relapses, whose prognosis is better than isolated medullary relapses [14,15] .

We have shown that the intensity of relapse treatment does not positively impact overall survival or median survival in early post-transplant relapse of ALL. Additionally, the likelihood of achieving complete remission following relapse was similar, regardless of treatment group. The impact of our results could be limited by the size of our population despite a long period of multicenter survey but in this context, the analysis of children's clinical status may be important factors to guide the clinicians' decisions about the most appropriate therapeutic strategy. Our study thus provides the first objective evaluation of school attendance, Lansky score, proportion of time spent in the hospital and cumulative organ toxicity during the first 6 months after relapse.

The amount of time spent in hospital depended significantly on the treatment received; a child receiving intensive treatment stayed more than twice as long at hospital than children receiving a less intensive treatment. This could thus represent an important factor to consider when choosing the appropriate treatment for these children. We could not demonstrate

whether school attendance was significantly better for children receiving outpatient treatment, but we observed better school attendance for children with a longer time to relapse (beyond 6 months after transplant).

To compare organ toxicity between treatment groups, we calculated a composite toxicity score. Our study did not reveal any significant differences in this toxicity score in our analyses. Our findings did show however that neurological complications were the most frequent toxicity event in these patients.

In conclusion, our study showed in a pre targeted-therapies era, that the combination of corticosteroid / vincristine may be offered to children with early post-transplant relapse without jeopardizing the potential for cure, and decreasing the proportion of time spent in hospital. New immunotherapeutics such as CD19 CAR-T and blinatumomab could become a more appropriate option in the future all the more since many of these patients could be managed on an outpatient setting after the immediate toxicity period. Nevertheless, the prognosis of these post-transplant relapses nowadays remains very poor regardless of treatment. Finally future studies in this patient population should also incorporate validated quality of life measurements.

This preliminary retrospective study encourages the development of recommendations for early post-transplant relapse of pediatric ALL and highlights the need for national prospective studies to guide the development of new therapeutic strategies, such as targeted therapies for high-risk patients.

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FIGURE LEGENDS

Figure 1: Definition of treatment groups. Group A, supportive care; group B, outpatient treatment; and C, intensive inpatient treatment. TKI: tyrosine kinase inhibitor; IT MTX: intrathecal methotrexate; HSCT: hematopoietic stem cell transplantation.

Multichemotherapy: COOPRALL97 (VANDA course: dexamethasone 20mg/m2/d, aracytine 4g/m2/d, mitoxantrone 8mg/m2/d, VP16 150mg/m2/d, Peg Asparaginase 2500UI/m2/d and triple intrathecal) or another combination of cyclophosphamide, vincristine and prednisone or a combination of methotrexate and asparaginase); [16]

Suppl figure 1: Patient survival. Overall median survival was 222 days.

Figure 2: Overall survival according to post-transplant treatment

Suppl figure 2: Overall survival according to complete remission. Median post-transplant survival was 756 days for patients achieving complete remission after relapse, and 185.5 days for patients who did not. CI: Confidence interval

Figure 3: Toxicity evaluation. Mean (bars) and standard deviation for each toxicity according to treatment B and C are represented. “B” represents out-patient treatment and “C” intensive chemotherapy. Four main toxicities according to the World Health Organization scale (WHO) were considered: heart, lung, kidney and neurology. For each toxicity, the number of patients is reported. WHO 4 pulmonary toxicities were dyspnea at rest (n=4). WHO 3 nephrotoxicity was severe hematuria (n=1). WHO 3 neurologic toxicities were pain interfering with activities of daily living (n=8), moderate ataxia (n=1), somnolence > 50% of day (n=1) and WHO 4 neurologic toxicity was disabling pain (n=1).

Table 1: Patient and disease characteristics according to treatment group

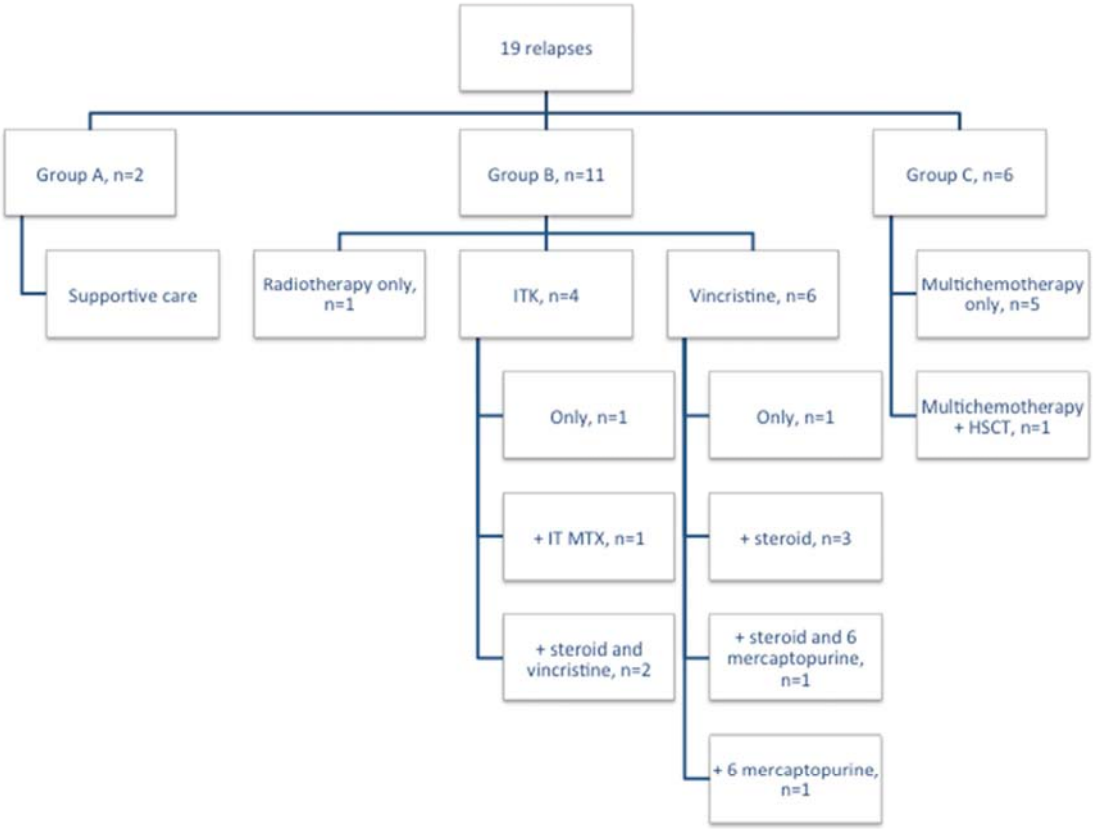
	Group B (N=11) n(%)	**Group C (N=6) n(%)**	***p***
Disease status			*0.54* **
CR1	6 (54.5%)	3 (50%)	
CR2+	5 (45.5%)	3 (33%)	
No CR	0	1 (17%)	
MRD			*0.05* **
< 10-3	6 (54.5%)	0	
> 10-3	3 (27.3%)	5 (83.3%)	
Preparative regimens			
Non myeloablative	0	0	
Myeloablative	11	6	
TBI			*0.01* **
Without	10 (81%)	2 (33%)	
HSC Donor			*0.58* **
Matched related	2 (18.2%)	2 (33%)	
Matched unrelated	9 (81.8%)	4 (67%)	
Source of transplant			*0.55* **
UCB	4 (36.4%)	1 (16.7%)	
BM	7 (63.6%)	4 (66.7%)	
PSC	0	1 (16.7%)	
Lansky score at relapse (mean ± SD)	75.5 ± 11.3	84 ± 16.3	*0.31* *
Site of relapse			*0.29* **
Medullary	7 (64%)	4 (67%)	
Extra medullary	3 (27%)	0	
Combined	1 (9%)	2 (33%)	
Delay between transplant and relapse (mean ± SD, days)	165 ± 97	184± 106	*0.88* *
Number of patients according to delay between transplant and relapse			*1.00* **
6-12 months	5 (45.5%)	3 (50%)	
< 6 months	6 (54.5%)	3 (50%)	

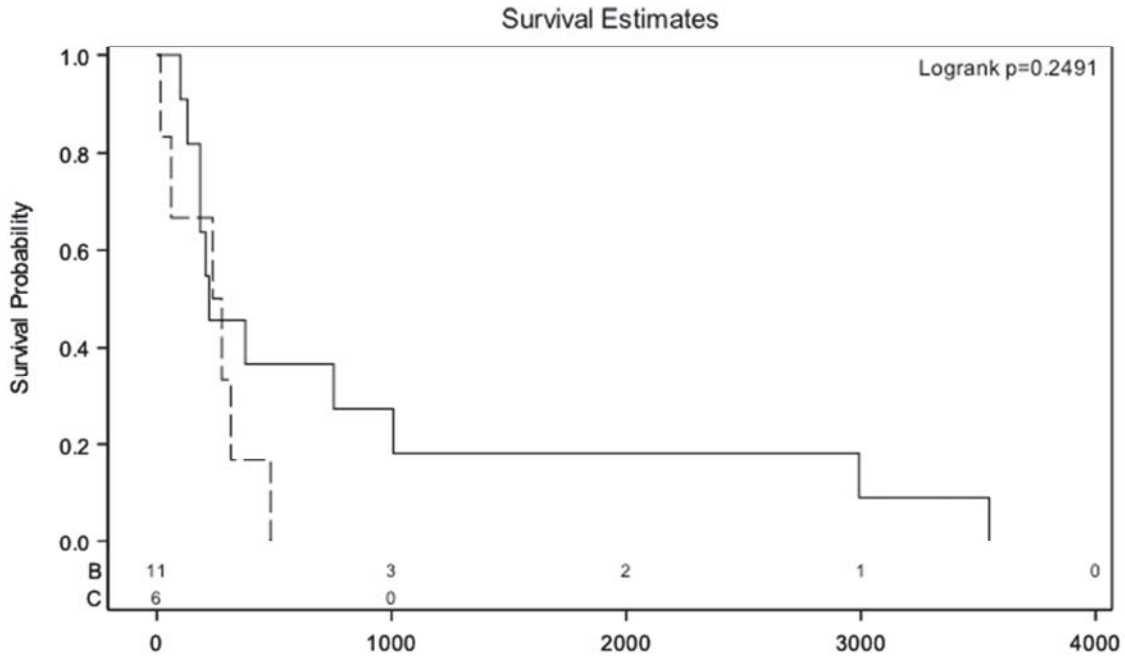
CR1, first complete remission; CR2+, second and more complete remission; MRD, minimal residual disease ; TBI, total body irradiation ;
HSC, hematopoietic stem cells; matched, 10/10 for BM and PSC and ≥ 5/6 for UCB, umbilical cord blood; BM, bone marrow;
PSC, peripheral stem cells; ** Fisher test; * Wilcoxon test; SD, standard deviation

Table 2: Quality of life Assessment 6 months after relapse

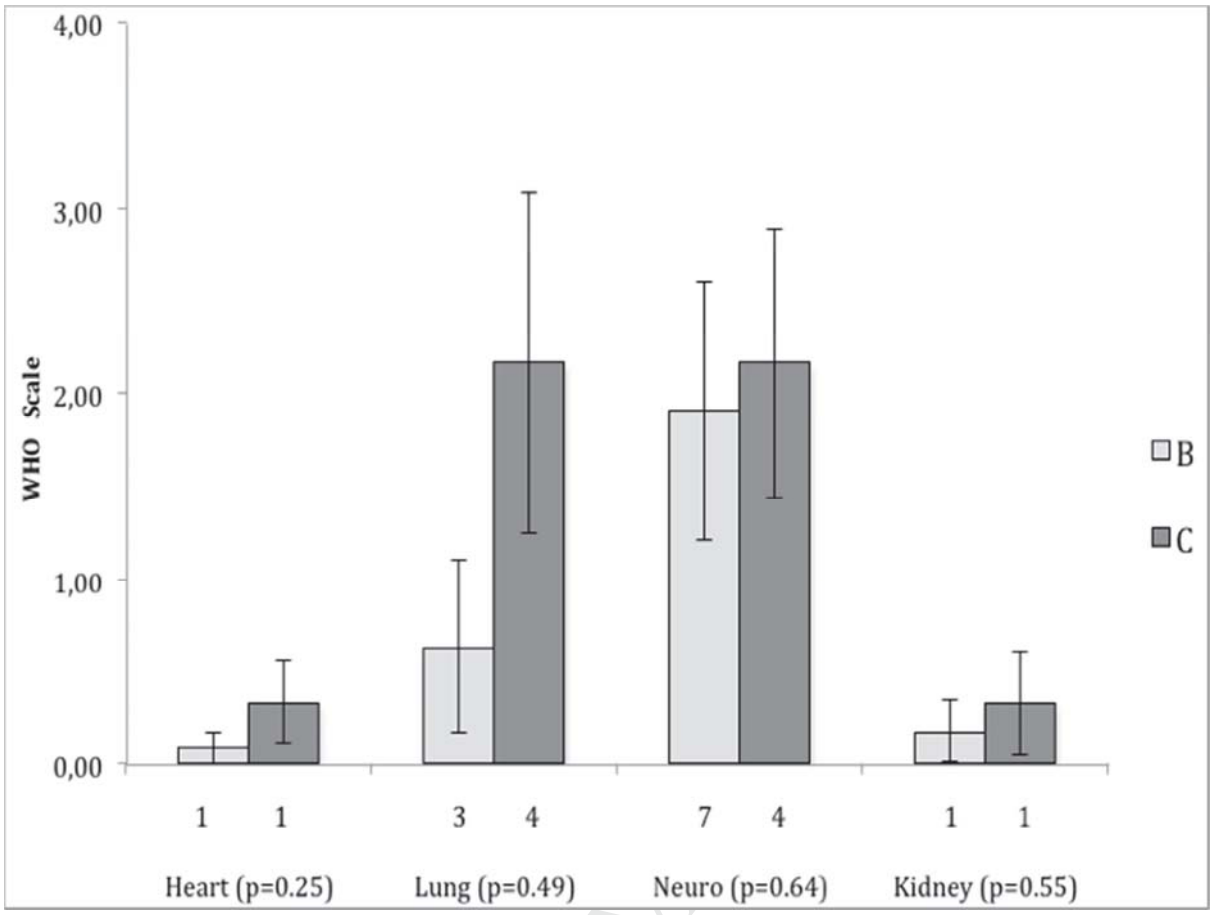
	Toxicity Score (mean±SD)	P	School Attendance (% of patients)	P	Lansky score	P	Hospitalization (% time±SD)	P
Group of treatment								
B	2.8 ± 2.1	0.15 *	54.5	0.62 **	72.7 ± 14.2	0.71 *	20.8 ± 13,0	**0.03 ***
C	5 ± 3.3		33		51.7 ± 40.2		59.1 ± 32.9	
ALL								
B	3.5 ± 2.7	0.53 *	47	0.47 **	65.2 ±27.1	0.05 *	40.4 ± 45.6	0.05 *
T	5 ± 2.8		0		0		100	
CR after transplantion								
< 6 months	4 ± 3.1	0.79 *	27	0.18 **	45.4 ±38.0	**0.04** *	63.3 ± 59.2	0.26 *
6 – 12 months	3.4 ± 1.9		62		76.2 ± 9.2		27.1 ± 15.4	
HSC Donor								
Related	2.4 ± 1.3	0.15 *	40	1.00 **	58.0 ± 33.4	0.96 *	45.5 ± 47.7	0.74*
Unrelated	4.1 ± 2.9		43		58.6 ±33.9		48.9 ± 50.8	
Source of transplant								
BM	3.7 ± 2.7	0.89 ***	33	0.45 **	53.3 ±32.8	0.38 ***	44.4 ± 40.9	0.82 ***
PSC	4		100		80		31.1	
UCB	3.5 ± 3.0		50		65.0 ±36.2		58.2 ± 68.3	
Site of relapse								
Medullary	3.8 ± 2.9	0.70 ***	31	0.13 **	55.4 ±33.6	0.56 ***	52.5 ± 54.5	0.27 ***
ExtraMedullary	2.3 ± 2.1		100		73.3 ±11.5		16.9 ± 18.5	
Combined	4.3 ± 2.3		33		56.8 ±49.3		59.8 ± 37.5	
Acute GVHD								
Yes	3 ± 2.7	0.33 *	28	0.63 **	62.5 ±31.0	0.57 *	39.7 ± 36.7	0.47 *
No	4 ± 2.5		50		51.4 ± 37.1		62.4 ± 65.5	
Disease status at transplantation								
CR1	3.6 ± 2.5	0.32 ***	40	0.61 **	68 ± 24.9	0.19 ***	45.2 ± 54.6	0.53 ***
CR2+	4.2 ± 2.7		47.5		43.7 ± 39.2		54.9 ± 46.0	
No CR	0		100		80		22.1	

Living conditions were analyzed according to diagnosis, duration of complete remission after HSCT, source of transplant, site of relapse, acute GVHD, disease status at transplantation and treatment group B or C. The results were described with mean and standard deviation.
School attendance was the percentage of children who attended school during the 6 months after relapse.
Composite toxicity score is sum of the maximum grade of the heart, lung, neurology and kidney toxicities.
Significant “p” values are written in bold
* Wilcoxon Test ; ** Fisher Test ; *** Kuskall Test





	Subjects	Event	Censored	Median Survival	95% CI	
B	11	11	0	222	132	1007
C	6	6	0	259.5	18	486



Intensity of relapse treatment does not impact overall survival or median survival

The likelihood of achieving complete remission following relapse was similar

Less time spent in hospital for chidren reveiving a less intensive treatment

The combination of corticosteroid / vincristine may be offered to these children