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ORIGINAL ARTICLE

Outcome after failure of allogeneic hematopoietic stem cell transplantation in children with acute leukemia: a study by the société Francophone de greffe de moelle et de thérapie cellulaire (SFGM-TC)

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Allogeneic hematopoietic stem cell transplantation (SCT) contributes to improved outcome in childhood acute leukemia (AL). However, therapeutic options are poorly defined in the case of post-transplantation relapse. We aimed to compare treatment strategies in 334 consecutive children with acute leukemia relapse or progression after SCT in a recent 10-year period. Data could be analyzed in 288 patients (157 ALL, 123 AML and 8 biphenotypic AL) with a median age of 8.16 years at transplantation. The median delay from first SCT to relapse or progression was 182 days. The treatment consisted of chemotherapy alone ($n = 108$), chemotherapy followed by second SCT ($n = 70$), supportive/palliative care ($n = 67$), combination of chemotherapy and donor lymphocyte infusion (DLI; $n = 30$), or isolated reinfusion of donor lymphocytes (DLI; $n = 13$). The median OS duration after relapse was 164 days and differed according to therapy: DLI after chemotherapy = 385 days, second allograft = 391 days, chemotherapy = 174 days, DLI alone = 140 days, palliative care = 43 days. A second SCT or a combination of chemotherapy and DLI yielded similar outcome (hazard ratio (HR) = 0.85, $P = 0.53$) unlike chemotherapy alone (HR = 1.43 $P = 0.04$), palliative care (HR = 4.24, $P < 0.0001$) or isolated DLI (HR = 1,94, $P < 0.04$). Despite limitations in this retrospective setting, strategies including immunointervention appear superior to other approaches, mostly in AML.

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INTRODUCTION

Hematopoietic stem cell transplantation (SCT) has contributed to improved outcome for pediatric patients with acute leukemia (AL). However, post-transplantation relapse is still associated with a dismal prognosis and its optimal treatment remains unclear. Therapeutic treatments for patients who relapse after first SCT are limited. Treatment options include supportive care, chemotherapy,[1,2] second SCT using the same or an alternative donor[3–8] and more recently donor lymphocyte infusion (DLI).[9–13] So far, no standard approach to this difficult clinical problem has been established. Therapeutic strategies may vary according to the delay between transplant and relapse, as well as centers and child's specific requirements.

We aimed to compare survival according to different treatment strategies, in case of relapse or progression post allogeneic SCT in children with acute leukemia in a recent 10-year period.

MATERIALS AND METHODS

Data collection

We analyzed all consecutive children (< 18 years), who received a first allogeneic SCT for ALL or AML from January 2000 to December 2009 and experienced a relapse or progression thereafter. Clinical data were prospectively collected using ProMISe (Project Manager Internet Server), an internet-based data registry system shared by the 33 centers of the SFGM-TC (French Society of Bone Marrow Transplantation and Cell Therapies) who participated in this study.

The study was designed by the SFGM-TC. The study was approved by the ethics committee at each participating institution and was conducted in accordance with the consent of patients.

The primary end point was overall survival (OS) after diagnosis of relapse or progression post first SCT whatever the treatment post relapse was. Failure was defined as hematological relapse (defined by recurrence of blasts in peripheral blood, or infiltration of bone marrow by more than 5% blasts) or progression of the initial leukemia. Secondary tumors were

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excluded. Secondary end points included OS after (i) second SCT, (ii) chemotherapy alone, (iii) DLI, (iv) chemotherapy followed by DLI or (v) supportive and palliative care. We also assessed the prognostic risk factors for survival after failure post SCT.

Eligibility criteria

Inclusion was based on the following criteria: age <18 years at first allogeneic transplant, diagnosis of acute leukemia (lymphoid acute leukemia or myeloid acute leukemia), relapse or progression after first SCT, available follow-up data, first allogeneic SCT for ALL or AML from January 2000 to December 2009.

Statistical analysis

Descriptive analyses were created for all study variables using means, SDs, medians, ranges and percentages where appropriate. Quantitative variable were categorized if needed using median, terciles or quartiles. Kaplan–Meier analysis was performed to report survival times and associations between progression and variables were tested with log-rank test.[14] Overall survival was defined as the time from the date of relapse after first transplantation or non-remission assessment date until the date of death.

We used a Cox proportional-hazards regression model to examine simultaneously the effects of multiple covariates on survival. We first performed univariate Cox analyses and covariates that achieved a significance level of $P \leqslant 0.2$ were taken to the multivariate model. Tests for interaction between pairs of variables in the final models were also performed. The effect of each variable in these models was assessed with the use of the Wald test and described by the hazard ratio (HR), with 95% confidence interval. Subjects with missing additional therapy after first relapse were excluded from the Cox models. The final models were developed by introducing all variables of interest in a stepwise backward multivariate analysis. We checked the adequacy of all models using graphical techniques. As the proportion of missing data for therapy variable was 13.8%, secondary analysis was performed using multiple imputation. Missing therapy data were imputed randomly 10 times from scores of similar patients with complete data, and the method of multiple imputation[15] was applied to the 10 full data sets so created. The outcome (overall survival) was included among the predictors of these missing data. We addressed the question of the relation between time to relapse and post-relapse treatment choice in two ways; first:we entered time to relapse as a covariate in the Cox models explaining overall survival of the population; second:we systematically tested for second-order interaction between time to relapse and post-relapse treatment. The *P*-values for interaction tests were not significant and around 0.90. So we did not find any interaction and did not include this interaction term in our models.

Statistical analyses were performed with PASW software version 18.0 (SPSS, Chicago, IL, USA).

Table 1. Characteristics of the 288 patients included in the retrospective study

Characteristics	*Number of patients and percentage*
Gender of the patient	
Male	174 (60.4%)
Female	114 (39.6%)
Leukemia type	
AML	123 (43.9%)
B ALL	127 (43.9%)
T ALL	30 (10.5%)
Biphenotypic	8 (2.8%)
Myeloablative regimen	
Yes	263 (91.3%)
No	25 (8.7%)
Interval first-transplant relapse (days)	
0–91	77 (26.7%)
92–182	67 (23.3%)
183–364	71 (24.7%)
$\geqslant 355$	73 (25.3%)

RESULTS

Between January 2000 and December 2009, 1307 children received a first SCT for acute leukemia. (ALL $n=761$, AML $n=501$, biphenotypic AL $n=45$). Of whom, 334 children (25.5%) relapsed or progressed thereafter. In 46 of them, the post failure data were not available and 288 patients were thus included in the analysis. The median overall survival of the 46 excluded children was 2.6 months versus 5.3 months for the 288 analyzed patients. We did not observe any significant difference in the median time from transplantation to relapse or progression between included and excluded population (182 days and 180 days, respectively). Analyzed patients had a better median follow-up (160 days and 80 days for excluded children). ALL was the most frequent type of leukemia ($n=157$) (B-cell phenotype, $n=127$; T-cell phenotype, $n=30$), followed by AML ($n=123$) and biphenotypic AL ($n=8$; Table 1). At transplantation, 236 (82%) patients were in CR (CR1, $n=122$, CR2 $n=98$, CR3 $n=16$), whereas 52 (18%) had a cytologically detectable disease. Donors were matched related siblings ($n=103$, 36%), mismatched unrelated ($n=70$, 24%), matched unrelated ($n=51$, 18%), unrelated without precision ($n=46$, 16%), mismatched related ($n=11$, 4%) or syngeneic ($n=5$, 2%). Stem cell source was bone marrow ($n=184$, 65%), umbilical cord blood ($n=67$, 23%) or peripheral stem cells ($n=34$, 12%) . Median time from diagnosis to first SCT was 245 days. Ninety-one percent ($n=263$) of the children received a myeloablative regimen and 9% ($n=25$) received reduced intensity conditioning regimen. TBI was performed in 159 children (55%). Acute GvHD after first SCT occurred in 161 patients (56%; grade I $n=62$ (38%), grade II to IV $n=99$ (62%)). The median time from first SCT to relapse/progression was 182 days. The treatments for relapse after first SCT consisted in reinduction chemotherapy alone aiming at obtaining a CR ($n=108$, 37%), chemotherapy followed by second SCT ($n=70$, 24%), best supportive care including palliative chemotherapy ($n=67$, 23%), combination of chemotherapy and DLI ($n=30$ 10%), or isolated DLI ($n=13$, 6%; Table 2). Analysis of the type of reinduction chemotherapy was hampered by the too large number of different regimens.

At the time of analysis in December 2014, 12% of children were alive with a median follow-up of 1315 days (ranges 58–4182). The median OS duration after relapse was 164 days among the 288 patients (Figure 1). ALL was associated with a better outcome as compared with AML ($P=0.006$; Figure 2).

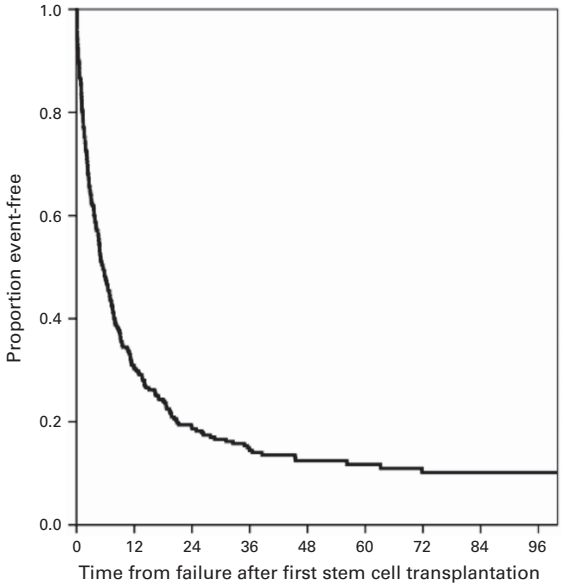
Prognostic factors

The following variables impacted the outcome: age at first transplant between 5 and 9 (HR = 0.64, $P<0.002$) and GvHD occurrence after

Table 2. Survival according to treatments after failure of first stem cell transplantation

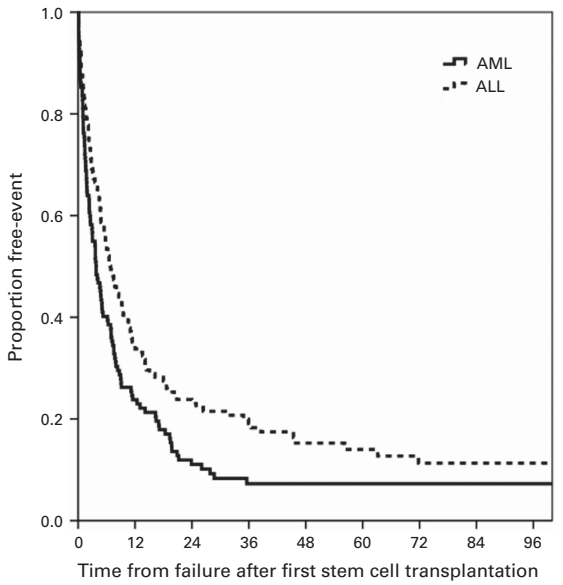
Additional treatment (includes cell therapy)	*Number of patients*	*1-Year survival %*	*Median survival (days)*		
			Estimation	*95% CI*	
				Inferior range	*Superior range*
Chemotherapy	100	27.9	174	118.7	229.4
Second SCT	70	51.0	391	264.3	517.7
Palliative care	73	4.5	43	32.7	53.3
Chemotherapy and DLI	30	53.3	385	293.7	476.2
DLI	13	15.4	140	9.6	270.3
Global	288	30.2	164	127.7	200.2

Abbreviations: CI = confidence interval; DLI = donor lymphocyte infusion; SCT = stem cell transplantation. Log-rank test: $P<10^{-5}$.



Month	0	12	24	36	48	60	72	84	96
Number at risk	288	85	48	33	21	16	12	6	5

Figure 1. Overall survival after failure of first stem cell transplantation (all treatments considered).



Month		0	12	24	36	48	60	72	84	96
Number at risk	AML	123	29	13	7	6	4	4	1	1
	ALL	153	50	31	23	14	11	7	4	3

Figure 2. Overall survival for leukemia subtype. There is a statistically significant difference between acute myeloid leukemia and acute lymphoid leukemia ($p < 0.006$).

the first transplant (HR = 0.60 $P < 0.002$) were associated with a better outcome. Relapse rather than progression was also associated with a better prognosis with a HR of 0.42 ($P < 0.0001$; Table 3). There was no impact on outcome from the following variables: gender, conditioning with TBI, stem cell source (Table 3).

After univariate analysis, a Cox model multivariate analysis on 288 patients showed the impact of the following factors on survival: CR before relapse (HR = 0.60, $P < 0.004$). The time interval

Table 3. Cox model univariate analysis

Characteristics	*HR*	*95% CI*		P-*value*
Age (years)				**0.016**
0–4	1			
5–9	0.64	0.46	0.90	**0.01**
10–14	0.94	0.68	1.30	0.72
>14	1.08	0.79	1.48	0.61
Gender				
Female	1.24	0.98	1.57	0.07
TBI				
Yes	0.86	0.68	1.09	0.21
Stem cell source				0.21
BM	1			
PB	1.39	0.96	2.02	0.08
CB	1.07	0.81	1.40	0.64
Leukemia type				0.04
AML	1			
B ALL	0.72	0.56	0.93	**0.01**
T ALL	0.81	0.54	1.21	0.30
Biphenotypic	0.48	0.19	1.18	0.11
GvHD				
Yes	0.60	0.43	0.83	**0.002**
Complete response				
Yes	0.42	0.31	0.56	$< \mathbf{10^{-5}}$
Myeloablative regimen				
Yes	0.62	0.42	0.93	**0.02**

Abbreviations: BM = bone marrow; CB = cord blood; CI = confidence interval; HR = hazard ratio; PB = peripheral blood. The bold values indicate the significant difference.

from transplantation to relapse was also associated with prognosis: when comparing with relapses occurring within the first 90 days, days 90–182, days 183–364 and $\geqslant$365 days yielded HRs of 0.62, 0.45 and 0.29 ($P \leqslant 0.0001$), respectively.

The median time from first SCT to relapse/progression was 182 days. Relapse before 182 days was associated with a statistically significant higher rate of failure ($P \leqslant 0.003$) than late relapse (Table 4).

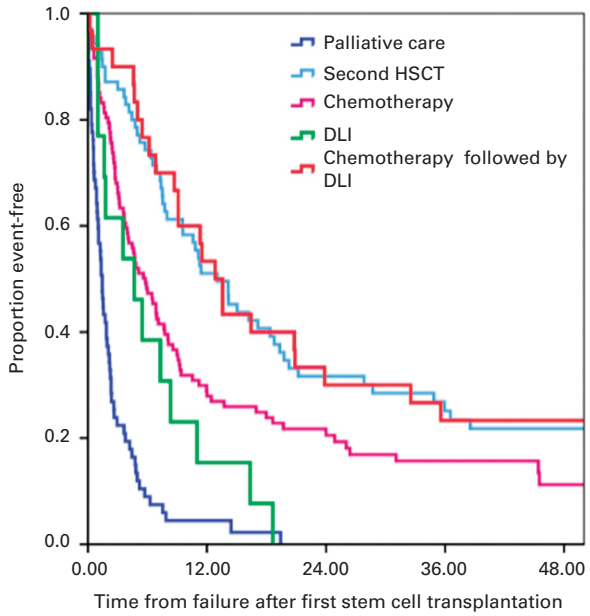
We then analyzed the impact of the therapeutic strategy on the survival of post-transplant relapsed patients: The patients treated by 'chemotherapy followed by a second allogenic stem cell transplantation', and the patients treated by 'chemotherapy and donor lymphocyte infusion' had a similar outcome (HR = 0.85, $P = 0.53$) with a respective 1-year survival rate of 51 and 53.3%. Treatment with chemotherapy alone (HR = 1.43, $P = 0.04$), palliative care (HR = 4.24, $P < 0.0001$) or DLI alone (HR = 1.94, $P < 0.04$) were associated with a lower survival (Table 4, Figure 3). When omitting the missing values, the statistical analysis yielded comparable results, except for the fact that the difference between the second SCT and chemotherapy alone became nonsignificant (Supplementary Table S1). Additional subgroup analyses show that, in AML patients, a second transplant and chemotherapy+DLI yielded similar results, superior to chemotherapy or palliative care. Conversely, patients with ALL fared better when treated either by second transplant, chemotherapy plus DLI or chemotherapy alone (see Supplementary File). This highlights the higher GVL effect in AML than in ALL.

We analyzed whether there was any interaction between late relapse and second hematopoietic SCT/DLI by including treatment strategy as a time-dependent covariate. Although there was an

Table 4. Cox model multivariate analysis including therapy strategy and time from transplant to failure

Characteristics	*HR*	*95% CI*		*P-value*
Post-transplant CR				
No	1			
Yes	0.60	0.43	0.85	0.004
Treatment				$<10^{-5}$
Second transplant	1			
Chemotherapy and DLI	0.85	0.52	1.40	0.53
Palliative care	4.24	2.84	6.34	$<10^{-5}$
Chemotherapy alone	1.43	1.01	2.03	0.04
DLI alone	1.94	1.03	3.64	0.04
Time from transplant to failure (days)				$<10^{-5}$
0–91	1			$<10^{-5}$
92–182	0.62	0.43	0.89	0.009
183–364	0.46	0.31	0.67	$<10^{-5}$
⩾365	0.30	0.20	0.44	$<10^{-5}$

Abbreviations: CI = confidence interval; DLI = donor lymphocyte infusion; HR = hazard ratio.



Month		0	12	24	36	48
Number at risk	Chemotherapy followed by DLI	30	16	9	7	5
	DLI	13	2	0	0	0
	Chemotherapy	108	29	18	11	5
	Second HSCT	70	35	21	15	11
	Palliative care	67	3	0	0	0

Figure 3. Overall survival according to therapy after post transplant relapse/progression.

imbalance between the therapeutic groups according to the interval between first SCT and failure, we found no significant relation between the delay of post-transplant relapse and the type of treatment received ($P=0.90$). Thus, we did not find any statistical relationship between time to relapse and post-relapse treatment that might have influenced the HR obtained in Cox models.

Table 5. Survival according to interval between first transplant and relapse/progression

Time to relapse after allogenic SCT	*Number of patients*	*1-Year survival (%)*	*Median survival (days)*		
			Estimation	*95% CI*	
				Inferior range	*Superior range*
0 to 6 months	144	11.9	81	63.1	98.9
7 to 12 months	71	40.1	242	133.5	350.5
More than 12 months	73	56.6	514	320.3	707.7
Global	288	30.2	164	127.7	200.2

Abbreviations: CI = confidence interval; SCT = stem cell transplantation.

DISCUSSION

Older strategies for post-relapse therapy mainly relied either on a 'heavy' approach consisting of reinduction therapy followed by allogeneic second transplant in remission, or on light care including outpatient leukemia chemotherapy or in several cases only support therapies. New treatment options including DLI emerged in the late nineties (11). This is why we aimed at investigating whether immunotherapeutic approaches can yield a prolonged survival without the cost and treatment burden of a second allogeneic transplant.

In this study, at the time of analysis, 40 patients (12%) were alive with a median follow-up of 1315 days (range 58–4182). AL relapse after first allogeneic SCT still has a very poor prognosis as half of the children did not survive more than 150 days following their relapse or progression. Early relapse was associated with a statistically significantly lower outcome ($P\leqslant0.003$) than late relapse. When examining the patient's related factors influencing outcome, this delay is the most important point to consider. The 1-year survival rates after relapse/progression ranged from 12% for the patients having relapsed in the first 6 months, to 56% in those who relapsed more than 1 year after transplant (Table 5). A previous publication studied the outcome of 25 patients under 18 years with recurrent AML after an initial SCT conditioned with a busulfan and cyclophosphamide preparative regimen.[16] The Kaplan–Meier estimates of survival at 100 days, 1 year and 10 years were 88%, 56% and 48%, respectively. In addition, patients who received their second SCT <6 months after the first transplantation were at an increased risk of relapse ($P<0.03$).

We have then questioned whether the type of therapeutic approach might impact on the survival. Despite evident limitations due to the retrospective setting of our analysis, best treatment consisted of second transplantation or the combination of chemotherapy plus DLI, both yielded similar long-term results. These results must be taken with caution since the chemotherapy +DLI group is composed of only 30 patients. In a recent report of the Berlin/Frankfurt/Muenster Study Group, 93 children with relapsed ALL non-responsive to chemotherapy according to ALL relapse protocols (03/1990–2006/1999)[17] were investigated. They were retrospectively assigned to three therapeutic groups. The median survival after curative (intensive polychemotherapies, SCT), palliative chemotherapy or supportive care were 121, 89 and 42 days, respectively ($P<0.001$). Time point of relapse and treatment strategy after failure were independent predictors of survival duration.

We are aware that the therapeutic strategy is not independent from the time point of relapse after SCT. The earlier the relapse, the less the doctors and families are prone to aggressive treatments. This is highlighted in our study by the imbalance between the therapeutic groups according to the elapsed time

between first SCT and failure (Supplementary Table S2). Median time was shorter in the chemotherapy+DLI arm (211 days) than in the second transplant arm (308 days). The following guidelines could be proposed regarding the best results obtained by allogenic approaches in AML patients. For early (⩽6 months) relapses, taking into account the performance status of the child, the alternatives might lie between palliative/supportive care and a mild approach combining azacytidine plus DLI, as described successfully in adults.[18] For patients relapsing in the second semester after transplant, reinduction chemotherapy followed by DLI would be preferred and second transplant only proposed to those patients with persistent positive MRD. After 1 year, chemotherapy followed by a second transplant appears as the best strategy ensuring long-term survival hope.

In ALL patients, very early relapses would warrant innovative approaches with bi-specific antibodies or engineered T cells, or palliative care. For early (7–12 months) and late (>12 months) relapses, the preferred choice would be chemotherapy, either alone or followed by DLI. The benefit of a second transplant in patients with ALL appears questionable, even when the relapse occurs late. The high toxicity of the TBI-based conditioning usually used in the first transplant might contribute to explain the high mortality after second transplant in ALL patients. In all instances, a comprehensive information on treatment-related risks and an intense dialog should prevail, thus allowing the parents and the child to participate actively in the choice between several therapeutic options.

Specific genetic predictors and MRD strongly correlate with the treatment outcome[19–22] and may guide risk-stratified therapeutic decisions. The development of highly sensitive MRD techniques standardized for all patients, genetic profiling and identification of other predicting factors are required for better-individualized treatments. Emerging therapies like bi-specific antibodies[23,24] and CAR T cells[25,26] will profoundly modify the landscape of resistant ALLs, but these targeted therapies are still lacking for childhood AML.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies this paper on Bone Marrow Transplantation website (http://www.nature.com/bmt)