Outcome for Children and Young Adults with T-cell Acute Lymphoblastic Leukemia and Induction Failure in Contemporary Trials

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ABSTRACT

Purpose: Historically, patients with T-cell acute lymphoblastic leukemia (T-ALL) who fail to achieve remission at the end of induction (EOI) have had poor long-term survival. The goal of this study was to examine the efficacy of contemporary therapy, including allogeneic hematopoietic stem cell transplantation (HSCT) in first remission (CR1).

Methods: Induction failure (IF) was defined as the persistence of at least 5% bone marrow lymphoblasts and/or extramedullary disease after 4-6 weeks of induction chemotherapy. Disease features and clinical outcomes were reported in 325 of 6167 (5%) patients ≤21 years of age treated in 14 cooperative study groups between 2000 and 2018.

Results: With a median follow-up period of 6.4 years (range, 0.3 to 17.9 years), the 10-year overall survival (OS) was 54.7% (SE=2.9), which is significantly higher than the 27.6% (SE=2.9) observed in the historical cohort from 1985-2000. There was no significant impact of sex, age, white blood cell count, central nervous system disease status, T-cell maturity or bone marrow disease burden at EOI on OS. Post-induction complete remission (CR) was achieved in 93% of patients with 10-year OS of 59.6% (SE=3.1%) and DFS of 56.3% (SE=3.1%). Among the patients who achieved CR, 72% underwent HSCT and their 10-year DFS (with a 190 day landmark) was significantly better than non-transplanted patients [63.8% (SE=3.6) versus 45.5% (SE=7.1), *P*=0.005], with OS of 66.2% (SE=3.6) versus 50.8% (SE=6.8), *P*=0.10, respectively.

Conclusion: Outcomes for patients ≤21 years with T-ALL and IF have improved in the contemporary treatment era with a DFS benefit among those undergoing HSCT in CR1. However, outcomes still lag considerably behind those who achieve remission at end of induction, warranting investigation of new treatment approaches.

CONTEXT SUMMARY

Key Objective

What are the outcomes for children with T-cell ALL (T-ALL) who fail induction therapy (≥5% marrow blasts) in a contemporary treatment era?

Knowledge Generated

The vast majority of children with T-ALL induction failure achieve a complete remission (CR) with post-induction chemotherapy and their 10-year overall survival (OS) rates have nearly doubled over the past 20 years and now approach 60%. Among children who achieve a CR, disease-free survival (DFS) was superior with hematopoietic stem cell transplantation (HSCT) in first remission compared to chemotherapy alone in this retrospective analysis from 14 treating consortia.

INTRODUCTION

T-cell acute lymphoblastic leukemia (T-ALL) comprises about 10% of ALL in young children and 25-30% in adolescents and young adults with a historically worse prognosis than B-cell acute lymphoblastic leukemia (B-ALL).[1,2] Outcomes have improved in recent trials using risk adapted intensive therapy, however, resistant and recurrent disease remain a challenge, not least in young adults.[3–24] Central nervous system (CNS) involvement at diagnosis is more common in T-ALL[25] and the kinetics of bone marrow disease response in T-ALL is slower than B-ALL with a higher proportion showing prednisone poor response (34.7% versus 6.3% B-ALL), induction failure (IF) (8% versus 1.5%)[26–28] and persistence of high minimal residual disease (MRD) levels at the end of consolidation therapy (≥$5x10^{-4}$ in 20.9% versus 5.9%) in AIEOP-BFM trials.[6, 29]

Patients with T-ALL and IF had a very poor outcome (10-year overall survival 28%) in a previous inter-group Ponte di Legno (PDL) study.[28] As some studies have shown higher cure rates with allogeneic hematopoietic stem cell transplant (HSCT),[30,31] this treatment approach has been pursued in first remission (CR1) in many groups. To determine if greater application of CR1 HSCT and the use of nelarabine may have improved outcomes in this high-risk subgroup, we, as inter-group PDL, analyzed a cohort of IF T-ALL cases diagnosed between 2000 and 2018, who failed to achieve complete remission (CR) at the end of induction (EOI) therapy. Our primary aim was to assess long-term outcome with contemporary therapy, including the role of HSCT.

METHODS

Study design and patients

Data from 14 cooperative study groups (Table 1 in the Supplementary Appendix) in Europe, North America, and Asia were collected on patients registered on clinical trials conducted from 2000 to 2018 (included). All the clinical trials from which data were used in this analysis had received approval from the relevant institutional review boards or ethics committees and written informed consent had been obtained from patients or guardians.

Each study group was asked to identify all patients 21 years of age and younger with T- ALL who had induction failure defined as persistence of at least 5% bone marrow lymphoblasts by morphology and/or persistence of extramedullary disease (EMD) at EOI, which was scheduled according to protocol, between days 28 and 43. Medullary induction failure was confirmed by MRD analysis ($\geq 10^{-2}$) in 211 of the 220 patients with available data (96%), using a more contemporary MRD-based definition of treatment failure.[32] A predefined set of data was collected for each patient: clinical, biologic, and genetic characteristics; treatment protocol, including treatment arm and HSCT; early treatment responses, including minimal residual disease (MRD) level at EOI and end of consolidation (EOC) where available; and clinical outcomes, including the achievement of CR with post-induction treatment (defined as a blast percentage by morphology less than 5% and no EMD), relapse, second malignant neoplasm (SMN) and death. All data were centrally reviewed for consistency and completeness before analyses.

Follow-up extended through May 2021 with a median of 6.4 years (range, 0.3 to 17.9); in particular, 70% of patients without a first relapse or death in CR were followed for more than five years. Treatment strategies for patients with EOI failure differed among the study groups. Most common post-induction schedules consisted of protocol IB (Consolidation), augmented IB, nelarabine followed by augmented IB or intensive chemotherapy blocks.[3,6,9,10,14,15,18–20,22,24] Frequently, there was a protocol indication to proceed to CR1 HSCT in patients who obtained CR with post-induction treatment.

Statistical analysis

Baseline characteristics are reported as percentages. The main endpoints were overall survival and disease-free survival. Overall survival (OS) was calculated from diagnosis to death of any cause or date of last contact, if alive. Disease-free survival (DFS) was computed only for subjects who achieved CR with post-induction therapy and was defined as the time from diagnosis until relapse, death in CR, development of a second malignant neoplasm or date of last contact, if disease-free. Date of diagnosis was used as time of origin since date of CR differed among study groups and was not uniformly available. The

Kaplan-Meier estimator was used for OS and DFS, with associated standard errors (SEs) calculated by Greenwood and the log-rank test was used for comparisons.

We further analyzed the T-ALL cohort described in the historical cohort reported by Schrappe et al.[28] for assessment of OS and achievement of remission with post-induction treatment in order to be able to compare their outcome data with those of the more recent cohort reported here. To minimize potential bias in the comparison of outcome between patients treated with chemotherapy followed by transplantation and with intensive chemotherapy only, the Kaplan-Meier curves were adjusted to account for the waiting time to transplantation: the curves originated at a landmark (median time to transplantation) and did not include patients who experienced events or whose data were censored before that time; the curves were also adjusted to account for the delayed entry of patients into the transplantation group, when transplantation occurred after the landmark. [33]

To deal with the lack of proportional hazards, as seen by graphical check, between the two treatment cohorts (HSCT vs. no HSCT) and to model the profile of the hazard ratio in time, we applied a piecewise Poisson model on DFS (in intervals of 30 days*)*.[33] In the model, transplantation was treated as a time-dependent variable (a transplanted patient was included in the chemotherapy group until HSCT). The time since diagnosis was modelled by a flexible B-spline function (6 degrees of freedom), whereas the time dependence of the treatment effect (i.e., non-proportional hazards) was accommodated by including a term for interaction between treatment and time since transplantation (modelled as B-spline with one knot at 180 days). The model was adjusted for age, sex, white blood cell count, bone marrow (BM) at the EOI and period of diagnosis. Survival after different types of transplant (from date of HSCT) was also estimated and compared. Analyses were carried out using R and

SAS 9.4 (SAS Institute, Cary, NC) software programs. *P*-values < 0.05 were considered statistically significant.

RESULTS

Of the 344 patients assessed, 19 were found not eligible and thus 325 are included in the cohort analyzed (Supplementary Figure 1). The 5 and 10-year OS were 58.0% (SE=2.8) and 54.7% (SE=2.9), and significantly higher than the 28.5% (SE=2.9) and 27.6% (SE=2.9) observed in the historical cohort (N=241; Figure 1).[28] Of note, within the recent cohort, the OS improved even more for patients diagnosed in the period 2009-2018 (N=183) compared to those diagnosed from 2000-2008 (N=142; OS=62.2%, SE=4.0%, versus 45.4%, SE=4.3%, *P*=0.0044; Table 1). No significant impact on OS was seen for sex, age, white blood cell count at diagnosis nor for T-cell immunophenotype maturity (Table 1 and Supplementary Figure 2). The early thymocyte precursor (ETP) subtype, which represents approximately 15% of T-ALL in children and adolescents, was diagnosed in 58 (29%) of 200 patients with adequate immunophenotypic data, using definitions established at each participating consortium; their 10-year survival was however similar to the non-ETP patients (51.3%, SE=6.9% versus 58.6%, SE=4.2%, respectively; Supplementary Figure 2). Information on *NOTCH* and *PTEN* mutations were reported for a minority of patients: *NOTCH* mutation was detected in 29/86 patients (34%), which is a lower frequency than in unbiased cohorts,[34] with no significant difference in survival compared with those with the wild type; *PTEN* mutation was present in 9/63 patients (14%) with only three patients surviving (Table 1). Among 294 patients with CNS status data at diagnosis, 227 were CNS1, 48 CNS2 and 19 CNS3 and their survival was not significantly different (Table 1 and Supplementary Figure 2, *P*=0.098).

At EOI, 14 patients with complete remission bone marrow (BM <5% blasts) had IF because of persistent isolated EMD (1 CNS, 5 mediastinal mass, 3 lymph nodes, 4 thymus/liver/ spleen/lymph nodes, 1 unknown), seven of whom survived. The 10-year OS for the 156 patients with M2 (5-25% blasts) and the 139 with M3 ($\geq$ 25% blasts) marrows was 60.4% (SE=4.1%) versus 49.2% (SE=4.6%, *P*=0.09), respectively. The 211 patients with MRD at EOI $\geq 10^{-2}$ had 10-year OS for survival (58.4%, SE=3.6%) similar to that of the whole cohort (54.7%, SE=2.9, Table 1). Of the 313 patients evaluable for CR, 290 patients (93%) achieved a CR (Supplementary Figure 1) and they had 10-year OS and DFS of 59.6% (SE=3.1%) and 56.3% (SE=3.1%), respectively (Figure 2). Among the 290 who achieved CR, 232 had information on the time of remission, reported at a median time of 84 days from diagnosis (interquartile range 63-102 days). There was no significant difference in survival, with a 10-year OS of 57.8% (SE=4.8) in patients who achieved CR by day 84 after diagnosis (n=118) vs. 59.5% (SE=4.9) in those (n=114) who obtained CR later (*P*=0.7). Of the 23 patients who did not achieve CR, 22 died at a median of 5 months from diagnosis and one was lost to follow-up (Supplementary Figure 3 and Table 1).

As mentioned in the methods section, we also re-analyzed the historical cohort, which was published in 2012 (period 1985-2000)[28] for the data on achievement of CR. Of the 206 with available information on post-induction treatment outcome, 143 (69%) achieved CR, a rate significantly lower than that of the current cohort (*P*<0.001). For those that did achieve CR in the historical cohort the 10-year OS was 40.1% (SE=4.1%).

The most commonly used post-induction therapies (in 274 patients with data) were protocol IB (Consolidation) (n=143), high-dose chemotherapy blocks (n=50), nelarabine containing regimens (n=48) and Augmented IB (n=29). No significant difference in survival was observed according to treatment received (Supplementary Figure 4). Of the 290 patients who achieved CR, 209 (72%) received a transplant and 70 received only chemotherapy (33 relapsed, 7 of whom were transplanted in second CR); no data on HSCT were available for 11 patients. In a 190-day landmark analysis (Figure 3), 10-year DFS was significantly better for transplanted patients [63.8% (SE=3.6) versus 45.5% (SE=7.1), *P*=0.005], which translated into a non-significantly better OS of 66.2% (SE=3.6) versus 50.8% (SE=6.8), *P*=0.10. The most frequent adverse event following HSCT was relapse (n=44) followed by death in CR (n=25) (Table 2). As shown in Supplementary Figure 5 (panel A), there was an improvement in survival in transplanted patients diagnosed in the period 2009-2018 (5-year OS of 74.4%, SE=4%) compared to those diagnosed in 2000-2008 (5-year OS of 59.4%, SE=5.4%), albeit the difference was not statistically significant (*P*=0.08). Small decreases both in the rate of transplant related mortality (9.5% versus 16%) and of post-transplant relapse (19% vs 24%) were observed. Of note, compared to patients treated in the early period, those treated in the latter period were more likely to have undergone transplant in CR (78% versus 71%) and included more matched unrelated donor HSCTs (33% versus 24% of transplanted patients). Survival in transplanted patients by type of donor was higher and similar for sibling (5 years since HSCT 79.8%, SE=5.5) and matched unrelated (72%, SE=5.8) donors (*P*=0.3) compared to other types of donors (58.4%, SE=5.3, *P*=0.03 for the 3-way comparison, Supplementary Figure 5, panel B).

The Poisson model on DFS (Table 3) shows that prognosis was favorably associated with HSCT in CR1 versus no HSCT (*P*=0.007), with a time-dependent effect reporting a significant protection after one year since HSCT (hazard ratio at 2 years since HSCT=0.24, 95% CI, 0.11-0.52) after adjusting for age, white blood cell count, sex, marrow status at end of induction and period of diagnosis (for this latter variable, the estimated hazard ratio for death was 0.63, 95%CI: 0.58-4.42, P=0.0171, 2009-2018 versus 2000-2008). While data on MRD level prior to HSCT were not available, data on MRD at the end of Consolidation were available in a subset of patients. Of the 290 patients who achieved CR, 140 had available MRD data at EOC, and there were 47 with EOC MRD $<10^{-4}$, including 12 patients with PCR MRD that was positive but not quantifiable. The OS of patients with EOC MRD $<10^{-4}$ was 67.1% (SE=7%) compared to 51.2% (SE=5.5%) for $\geq 10^{-4}$, (P=0.1, Supplementary Figure 6). An exploratory analysis comparing DFS and OS in patients undergoing HSCT or chemotherapy alone showed an advantage for HSCT within both EOC MRD-based subgroups (Supplementary Figure 7).

DISCUSSION

T-ALL with IF occurs in approximately 8% of patients,[9,35] representing about 1% of all cases of childhood ALL. While survival rates for pediatric patients with newly diagnosed T-ALL without induction failure have steadily improved and now tend to approximate those achieved in B-ALL, T-ALL with IF remains challenging to treat.[13] Such an uncommon subgroup can best be investigated in a large intergroup collaboration, such as that of the PDL Group. A previous PDL study of IF reported a 10-year OS of 27.6% (SE=2.9%) in 241 T-ALL patients with IF diagnosed between 1985-2000.[28] Seventy-seven (54%) of the 143 patients who achieved CR underwent HSCT and the 10-year OS was 40% in patients who received a matched related donor and 45.8% in the 55% patients who received HSCT from other donors.[28]

We report an improvement in 10-year OS to 54.7% (SE=2.9%) (P<0.0001) for 325 patients with T-ALL and IF treated in a subsequent era from 2000-2018. The improved outcome might be attributable to a higher proportion of patients achieving CR after subsequent treatment (93% versus 69%, $P<0.0001$) and proceeding to CR1 HSCT (72% versus 54%), including increased use of unrelated and haploidentical donors. A variety of post-induction treatments were used to achieve CR but most included standard/augmented IB with (17%) or without nelarabine. CR was achieved in 97.2% (139 out of 143) after IB based therapy, 89.6% (26 out 29) after augmented IB and 85.4% after nelarabine followed by augmented IB (41 out of 48). There was no significant difference in outcome based on post-induction treatment given, and EOC MRD was only available in 30% of subjects reported here. Thus, no recommendation can be made on the optimal regimen based on our data. Attainment of an MRD negative remission prior to HSCT could have impacted outcomes as well; however, these data were not routinely available and/or reported in this study. As expected, all patients who did not achieve CR had a fatal outcome.

Although we cannot exclude selection biases, the outcome of transplanted patients in CR1 (adjusted by landmark analysis at 190 days) was significantly better than those not transplanted, in regard to DFS (63.8%,SE=3.6, versus 45.5%,SE=7.1) with a tendency for improved OS (66.2%,SE=3.6, versus 50.8%,SE=6.8). Patients transplanted from sibling and unrelated donors had superior outcomes compared to alternative donor transplants. Patients diagnosed in the latter half of the study period had a better outcome (10-year survival estimate of 62.2% versus 45.4% in 2009-2018 and 2000-2008, respectively). While the proportion achieving CR1 was similar, a slightly higher proportion of patients were transplanted in the later period (78% versus 71%) which, along with better post-transplant outcomes, might partly explain the improved overall outcome.

We had limited data on immunophenotype, cytogenetic and molecular profiles. Several studies have reported a higher incidence of IF in the ETP subgroup[11,36] and our data confirms that observation with an enrichment of the ETP subtype (29%) compared with T-ALL at diagnosis (15%). Similar to the previous reports of patients with ETP ALL without IF,[11,26] ETP patients with IF had no worse outcome than other T-ALL patients with IF. In this study, IF was firmly established by MRD in 211 of 311 patients with M2/3 BM. Of the nine patients with MRD $<1x10^{-2}$, seven remain in continuous CR, of whom three received HSCT and four chemotherapy only. The relatively favorable outcome of these patients may suggest an incorrect morphological classification of the BM and emphasizes the importance of MRD in establishing IF in future cases.

Although our study is limited by its retrospective nature, heterogeneity of chemotherapy regimens used to achieve CR after IF and the use of different types of transplantation procedures, we can report a significant improvement in outcome compared to a historical cohort. The use of nelarabine as salvage therapy did not impact treatment outcomes in our study. Notably, attainment of a CR following IF is paramount as there were no survivors among patients with refractory disease, highlighting the need for effective salvage regimens. Our study suggests transplantation should be considered in T-ALL IF patients who subsequently attain a CR with conventional chemotherapy, regardless of MRD status at the EOC. Despite the reported improvement in this more recent treatment era, the outcome of T-ALL patients with IF remains considerably worse than those who achieve CR after induction therapy and they should be candidates for early phase studies of new T-cell targeted therapy including cellular approaches.

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FIGURE LEGENDS

Figure 1. Overall survival (OS) since diagnosis of T-ALL patients with Induction failure (IF) in the current study (n=325) and in the “historical cohort” (n=241) reported by Schrappe et. al.[28]

Figure 2: Overall survival (OS) and disease-free survival (DFS) of 290 T-ALL patients resistant to induction therapy who achieved complete remission with post-induction treatment. Date of relapse was not available for one patient, thus it was excluded from DFS analysis.

Figure 3: Disease-free survival (DFS, panel A) and overall survival (OS, panel B) of T-ALL patients who achieved remission with post-induction treatment according to whether they received HSCT or not in first CR – time since landmark at 190 days (median time from diagnosis to HSCT). DFS comparison: *P*-value=0.005 (unadjusted Poisson model, Likelihood ratio test with 5 degrees of freedom); OS comparison: *P*-value=0.1 (unadjusted Poisson model, Likelihood ratio test with 5 degrees of freedom).

Supplementary Figure 1: CONSORT 2010 Flow Diagram

Supplementary Figure 2: Kaplan-Meier overall survival (OS) estimate by baseline characteristics: A) by white blood cell count (WBC), B) by early thymocyte precursor (ETP) status, C) by age, D) by central nervous system (CNS) status at diagnosis, E) by marrow at end of induction (EOI) (M1 with isolated extramedullary disease; the test for comparison between M2 and M3 gives *P*=0.09).

Supplementary Figure 3: Kaplan-Meier overall survival (OS) estimate by remission status.

Supplementary Figure 4: Kaplan-Meier overall survival (OS) estimate by post-induction treatment.

Supplementary Figure 5: Overall survival (OS) after hematopoietic stem cell transplant (HSCT in 207 patients) by period of diagnosis (panel A) and by type of donor (panel B). Two HSCT patients were excluded as date of transplant was missing.

Supplementary Figure 6: Overall survival (OS) according to MRD status at the end of Consolidation (EOC).

Supplementary Figure 7: Disease-free survival (DFS, panel A) and overall survival (OS, panel B) of T-ALL patients who achieved remission with post-induction treatment according to whether they received HSCT or not in first CR according to MRD status at the end of Consolidation (EOC). Time originates at landmark (190 days, median time from diagnosis to HSCT).

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Table 1: Characteristics and early response on 325 patients, with Kaplan-Meier 10-year survival estimate (standard error, SE) and univariate survival comparisons.

CHARACTERISTICS	LEVEL	N.OF PATIENTS (%)	N.OF DEATHS	10-YRS SURVIVAL (SE)%	LOG-RANK P -VALUE
TOTAL		325(100)	139	54.7(2.9)	-
PERIOD OF DIAGNOSIS	2000-2008	142 (44)	75	45.4(4.3)	0.0044
	2009-2018	183 (56)	64	62.2(4.0)	
SEX N=324	Females	140 (43)	57	57.7(4.3)	0.6943
	Males	184 (57)	81	52.6(4)	
AGE (years)	<10	175 (54)	77	52.7(4.1)	0.5556
	10-14	105 (32)	40	60.5(4.9)	
	≥15	45 (14)	22	49.6(7.6)	
WBC (x1000 cells/mm³)	≤100	190 (59)	85	52.9(3.8)	0.8283
N=322	>100	132 (41)	54	56.7(4.6)	
IMMUNOPHENOTYPE	Cortical T	29 (16)	14	44.6(11.3)	0.5676
N=182	Early-T	112 (62)	45	56.9(5.1)	
	Mature T	41 (23)	17	58.1(7.8)	
ETP N=200	Yes	58 (29)	27	51.3(6.9)	0.6974
	No	142 (71)	57	58.6(4.2)	
NOTCH MUTATION N=86	Yes	29 (34)	10	61.9(9.8)	0.1022
	No	57 (66)	27	51.9(6.7)	
PTEN MUTATION N=63	Yes	9 (14)*	6	-	-
	No	54 (86)	20	59.8(7.3)	
CNS AT DIAGNOSIS N=294	CNS1	227 (77)	92	57.1(3.5)	0.098
	CNS2	48 (16)	25	39.1(9.1)	
	CNS3	19 (6)	11	42.1(11.3)	
EARLY RESPONSE (EOI)					
BM N=309 $	M1:<5%#	14 (5)	7	50.0(13.4)	-
	M2:5-24%	156 (50)	59	60.4(4.1)	0.09^
	M3:≥25%	139 (45)	66	49.2(4.6)	
MRD N=220	$<10^{-2}$	9 (4)*	2	-	-
	$\geq10^{-2}$	211 (96)	83	58.4(3.6)	
LATE RESPONSE**					
N=313	No remission	23 (7)	22	0	<0.0001
	Complete remission	290 (93)	110	59.6(3.1)	

BM=bone marrow; CNS1= including traumatic lumbar puncture without blasts; CNS2 = (<5 WBC in CSF with blasts); CNS3 = (≥5 WBC with blasts); CR=complete remission; EOI=end of induction; EMD=extra-medullary disease; MRD=Minimal residual disease; WBC=white blood cell count.

*Due to the small number of patients in this subgroup, the reported survival estimate is omitted as well as the log-rank test
With isolated extra medullary disease
$ For 16 patients induction failure was defined as BM blasts ≥5% with no distinction between M2 and M3
** Response status after post-induction treatment
^ Test comparison between M2 and M3

Table 2: Events after achievement of remission according to whether patients underwent hematopoietic stem cell transplant (HSCT) in first remission (1st CR) or not.

	HSCT in 1st CR	
	NO (N=70)	**YES (N=209)**
EVENTS:		
RELAPSE	33	44
SITE OF RELAPSE		
BM ISOLATED	22	32
BM COMBINED	5	2
CNS	3	0
LYMPH.+MEDIASTINUM	0	1
MEDIASTINUM	1	2
ORBIT	0	1
TESTICULAR	1	0
UNKNOWN	1	6
SMN	1	4
DEATH IN CR	10*	25*
TYPE OF HSCT		
SIBLING	-	56
UNRELATED MATCHED	-	62
OTHERS	-	91**

* Deaths in CR in patients surviving at least 190 days (median time to HSCT) were 2/54 in the chemotherapy arm (3.6%) and 22/204 (11%) in the HSCT arm showing that raw numbers, with early mortality "assigned by default" to those patients who were not able to undergo transplant, give an apparent advantage to HSCT (immortal time bias).

**2 patients do not have time at HSCTHSCT = hematopoietic stem cell transplant

Table 3: Poisson model on disease-free survival (270 patients who achieved final remission with 113 events).

	TIME SINCE HSCT	HAZARD RATIO(95%CI)	P
HSCT VS NO HSCT			0.007
	6 months	1.15(0.65-2.01)	
	1 year	0.59(0.34-1.02)	
	2 years	0.24(0.11-0.52)	
AGE (YEARS)	≥10 vs <10	0.91 (0.63-1.33)	0.6278
WBC (1000/mm^3)	>100 vs ≤100	1.01 (0.68-1.5)	0.9487
SEX	Male vs Female	1.25 (0.85-1.83)	0.2533
BM EOI	M1 vs M3	0.92 (0.41-2.06)	0.8310
	M2 vs M3	0.75 (0.51-1.09)	0.1320
PERIOD	2009-2018 vs 1999-2008	0.63 (0.43-0.92)	0.0171

BM=bone marrow; EOI=end of induction; WBC=white blood cell count; HSCT = hematopoietic stem cell transplant

Supplementary Table 1*

GROUP	PROTOCOL	N. of T-ALL patients ≤21 years	N. Of T-ALL and IF	Day of planned BM
AIEOP- BFM	AIEOP-BFM ALL 2000^	1120	83	33
AIEOP- BFM - CPH-INS	AIEOP-BFM ALL 2009	903	49	33
CoALL	COALL03	110	14	29
	COALL09	100	19	29
COG	AALL0434	1536	41	28
CPH	ALLIC 2002	45	1	33
DFCI	00-001	49	5	28
	05-001	97	7	32
	11-001	26	4	32
DCOG	DCOG-ALL10	116	8	33
	DCOG-ALL11	116	6	33
EORTC	58081	140	13	35
	58951	296	6	35
INS	INS 2003 (BFM 2002)	60	1	33
	INS 2007 (mod BFM 2002)	53	3	33
JPLSG	CCLSG ALL2004	37	1	35
	CCLSG ALL2000	30	1	28
	JACLS ALL-T02	107	9	33
	JACLS ALL-T97	72	4	28
	KYCCSG ALL-02	21	1	29
	KYCCSG ALL-96	21	1	29
	TCCSG L04-16	117	3	43
	TCCSG L99-15	90	3	43
NOPHO	NOPHO ALL2008	304	19	NA
Ma-Spore	Ma-Spore ALL 2003	69	3	33
	Ma-Spore ALL 2010	27	1	33
SJCRH	Total XV	75	1	46
	Total XVI	104	3	42
UK	UKALL2003	371	15	28

* 8 IF T-ALL patients were diagnosed in 1999 and belonged to a pilot study before the beginning of AIEOP-ALL2000 (n=5), to JACLS ALL-T97 (n=2) and to 58951 (n=1)

^Also includes patients not enrolled in the randomized study but treated with the same protocol

NA=Not available