Acute leukaemia in children : aspects of diagnosis and treatment

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HLA-identical haematopoietic stem cell transplantation for acute leukaemia in children – less relapse with higher biologically effective dose of TBI

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Summary:

To examine relapse, survival and transplant-related complications in relationship to disease- and pre-treatment-related characteristics, we evaluated 132 children, who consecutively received an allogeneic HLA-identical SCT for acute leukaemia in our centre: ALL in 1st remission (n=24), ALL in 2nd remission (n=53) and AML in 1st remission (n=55). The source of the stem cells was bone marrow in all but three cases. Most patients (89%) were pre-treated with cyclophosphamide and an age-related dose of TBI. Initially, GVHD prophylaxis consisted of long-course MTX only (n=24), later short-course MTX and CsA (n=102) was given. All patients were nursed in strictly protective isolation and received total gut decontamination to suppress their potentially pathogenic enteric microflora. The 5-year probability of overall survival was 63%, 53% and 74% for ALL1, ALL2 and AML1, respectively (median follow-up 10.6 yrs). The overall transplant-related mortality was 6%. The incidence of acute GVHD was 17%; 6% was grade II-IV. A higher total biologically effective TBI dose (BED) resulted in a decreased relapse frequency (p=0.034) and increased overall survival. AML patients with acute GVHD got no relapse (p=0.02); this was not the case in ALL patients. Fractionated TBI regimens with higher BED should be evaluated in prospective studies.

Introduction

The prognosis in terms of cure and survival of children with acute leukaemia has improved impressively over the last four decades, following protocolized chemotherapy regimens applied in large prospective studies. Currently, 80-90% of children diagnosed with ALL and AML achieve a first complete remission (CR) and up to 60% and 80% for AML and ALL, respectively, reach a sustained CR and long-term survival with chemotherapy alone(1-5). In "high risk" ALL sustained first CR is obtained in only 30 to 60% of the patients according to different studies(6;7). Outcomes after relapse remain poor. Reported event-free survival rates are between 14 and 50% in ALL patients, depending on their risk profile and treatment modality(8-11), and 2-year overall survival rates are around 20% in retreated AML patients(12). For high-risk leukaemia patients an allogeneic stem cell transplantation (SCT) is still the preferable alternative treatment to reach cure(13). The major cause of failure after haematopoietic SCT in childhood leukaemia is relapse of the disease, followed by transplant-related mortality (TRM) as a result of graft-versus-host disease (GVHD), drug toxicity and infections.

For patients undergoing allogeneic SCT for leukaemia, total body irradiation (TBI) was and still is, despite a number of adverse late effects, a major component of the conditioning regimen. A randomised study in adults with CML on the dose of TBI delivered before SCT confirmed that a higher total dose of TBI (15.75 Gy vs. 12 Gy) resulted in a lower probability of relapse(14). This is, however, at the cost of greater transplant-related mortality. A similar TBI-dose related effect on relapse was seen for adults with AML in CR1 (15;16) and with ALL (17). Another possibly important variable with respect to the occurrence of relapse is the so-called graft-versus-leukaemia (GVL) effect. This effect is thought to be mediated by alloreactive T cells and/or NK cells from the donor(18;19). Retrospective evaluation of large numbers of patients clearly showed that GVHD, as equivalent for a reaction of donor T cells towards recipient's histocompatibility antigens, suppresses leukaemia recurrence after SCT. Donor lymphocyte infusions (DLI), however, seem to be much more effective in cytogenetic relapses of CML than in AML, and are barely effective in ALL(20).

Here, we summarize the results of 132 children with acute leukaemia who consecutively

received transplants from HLA-identical sibling donors (matched sibling donor (MSD)). We retrospectively analysed potentially relevant risk factors for the occurrence of relapse of the disease, development of GvHD, TRM and overall survival after SCT.

Patients and methods

Patients

From September 1980 to September 2002 a total number of 132 children received an allogeneic haematopoietic SCT with a MSD for the treatment of acute leukaemia in the paediatric SCT-unit of the Leiden University Medical Centre, the Netherlands. The characteristics of these patients are given in Table 1. Seventy-seven children suffered from ALL and 55 from AML.

Table 1. Patient and disease characteristics

Data				No
Total number				132
Patient age in yrs, range (median)				1.1 – 17.3 (8.5)
Patient sex, M / F				77 / 55
Diagnosis				
	ALL1			24
		Slow remission or insufficient response to steroids		11
		t (11q23) and/or MLL rearrangement		2
		t (4;11)		2
		t (9;22)		3
		T-ALL		2
		Extramedullary leukaemia		3
		Data not available		1
	ALL2			53
		Early relapse after first CR (<24 months)		14
		Late relapse after first CR (≥24 months)		39
	AML1			55
		Trisomy 21		
		FAB classification M3 (no t(15;17))		3
		Specific cytogenetic translocations or inversions (t(8;21), inv(16))		10
		Standard risk		40

Table 2: Donor and transplant characteristics

Data				No
Donor age in yrs, range (median)			0.3 – 25.6 (8.5)	
Donor sex, M / F			72/60	
Relationship				
	Matched sibling donor			130
	Syngeneic twin			2
Source of stem cells				
	Marrow			129
	Cord blood			3
Cell dose, nucleated cells x10^8/ kg, range (median)				
	Marrow			0.5 – 6.8 (2.8)
	Cord blood			0.25 – 0.3 (0.26)
Conditioning regimen[1]				
	TBI-based			122
		≤ 8 Gy	93	
		12 Gy	29	
	TBI-CY			38
	TBI-CY-VP16			53
	TBI-CY-AraC			25
	TBI-CY-Melph[2]			1
	TBI-AraC-Dauno[3]-Vincr[4]			3
	TBI-VP16			1
	TBI-Melph[2]			1
	no TBI			10
	BU-CY			3
	BU-CY-VP16			3
	BU-CY-AraC			3
	AraC-Melph[2]			1
GVHD prophylaxis[1]				
	CyA + MTX			102
	MTX			24
	CyA			4
	No (syngeneic donor)			2
CMV status, patient / donor				
	+ / +			25
	+ / -			16
	- / +			6
	- / -			82
	Unknown			3

[1]See text for exact doses
[2]Melphalan (total dose: 140 mg/m^2)
[3]Daunorubicine (total dose: 80 mg/m^2)
[4]Vincristin (total dose: 1.5 mg/m^2)

Patients with a secondary AML and patients in either partial first remission, second (for AML) or third remission were excluded from this analysis. All but 9 patients were treated according to the treatment protocols of the Dutch Childhood Leukaemia Study Group (DCLSG); also the indication for MSD-SCT was according to the successive DCLSG-protocols. The number of patients at increased risk for relapse according to recent criteria (3;7;21-24) is given in Table 1. The median age at time at SCT was 8.5 years (range 1.1 – 17.3 years). The median follow-up time after SCT was 10.6 years (range 1.3 to 23.3 years), the cut-off point for the evaluation being 1st of January 2004.

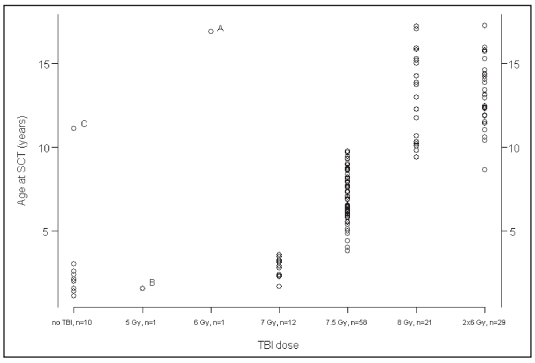
Graft characteristics and transplant procedures

All patients were transplanted with genotypically HLA-identical grafts, donated by siblings. Donor and transplant characteristics are summarized in Table 2. Most patients, 118 out of 132, were conditioned using a TBI-cyclophosphamide (total dose: 120 mg/kg)-based therapy. Nine patients were conditioned with a busulphan (total dose: 20 mg/kg)-cyclophosphamide -based regimen, for 8 of them because of their young age (mean 1.8 years; range 1.1-2.6 years) and for 1 because of a personalized conditioning regimen, due to earlier toxicity of treatment. In addition to the basic conditioning, 56 ALL patients also received VP-16 (total dose: 350 mg/m^2), and 28 AML patients also received ARA-C (total dose: 2000 mg/m^2) in their pre-treatment. This was a time-related change of the protocol, in accordance with the treatment protocols of the DCLSG. Individualized conditioning regimens were used in 7 patients because of previous toxicity of chemotherapy on vital organs or earlier allergic reactions to certain chemotherapeuticals. TBI was given with a linear accelerator (4 or 6 MV), applying mean instantaneous dose rates of 25 cGy/min, and mean overall dose rates of 18 cGy/min. TBI doses and the number of fractions varied, according to the age of the child, and sometimes as a consequence of earlier treatment (Figure 1). In general: children between 2 and 4 years received 1x 7 Gy, those between 4 and 10 years received 1x 7.5 Gy, and children older than 10 years received 1x 8 Gy, before 1990, and 2x 6 Gy (total dose: 12 Gy) on two consecutive days, after 1990.

Post-SCT immunosuppression and supportive care

Up to 1986, GVHD prophylaxis consisted of a long-course MTX only, later on a short-course MTX combined with CsA prophylaxis was used(25). The long-course of MTX

Figure 1. Distribution of TBI dose depends on patient age.



A, B, C: personalized conditioning regimen, due to Fanconi anemia, trisomy 21, and earlier toxicity of treatment, respectively

consisted of 15 mg/m^2 at day +1, and 10 mg/m^2 at days +3, +6, +11 and weekly thereafter until day +102. Short-course MTX was given at a dose of 10 mg/m^2 i.v. at days +1, +3, and +6 (and in some, +11), and was combined with CsA 2 mg/kg/day i.v. from day –1 until oral medication was tolerated at a dose of 6 mg/kg/day, using dose adjustment for upper levels (potential toxicity level ≥200 µg/L) according to the results of weekly blood sampling. This was continued for 180 days, tapered thereafter and finally stopped. All patients were nursed in strict protective isolation using positive-pressure laminar-air flow cubicles or rooms, and got total gut decontamination with non-absorbable antimicrobials to suppress the potentially pathogenic intestinal microflora; before discharge they were recontaminated with strictly anaerobic faecal flora plus Biogarde^R (26). All blood products for infusion were leukocyte depleted and irradiated with a dose of 25 Gy.

Diagnosis and treatment of GVHD

Acute and chronic GvHD were diagnosed and graded according to standard criteria (27;28). Acute GvHD was treated with methylprednisolone 2 mg/kg/day i.v., followed by tapering on improvement; exceptionally another drug e.g. ATG, Campath-monoclonals (anti-CD52) or thalidomide was used.

Criteria for engraftment and response

The day of leukocyte engraftment was defined as the first day at which blood granulocyte counts rose to 0.5 × 10^9/L (for two consecutive determinations) and of platelet engraftment as the first day at which blood platelets rose to 50 x 10^9/L (untransfused). Engraftment of

different donor cell lineages was documented by XY-FISH analysis in patients with opposite sex donor(29) or by analysis of variable number of tandem repeats (VNTR)(30) and later on of CA-repeats(31) with PCR technology.

Statistical analysis

The Kaplan-Meier method was used to estimate the distribution of overall survival and time to relapse. For the distribution of time to relapse, children were censored when they experienced TRM. Hence, TRM was not modelled as a competing risk, but children with TRM were assumed to have the same potential time-to-relapse distribution as the ones without TRM. Logistic regression analysis was used for evaluation of potential risk factors for development of acute GVHD. Patients who did not survive beyond d+50 or received grafts from either cord blood donors or syngeneic donors were excluded from this analysis. Evaluation for chronic GVHD was contingent upon survival to d+100. All statistical analyses were performed with the S-PLUS 2000 statistical package. P-values < 0.05 were considered as statistically significant and refer to the overall best for difference between the curves (log-rank best).

Results

Transplant outcome

Of the 132 patients, 131 engrafted, and 1 patient died 15 days after SCT, due to an aspergilloma and was not evaluable for engraftment. The median time to engraftment was 27 days for granulocytes and 34 days for thrombocytes. At the end of follow-up, 77 (58 %) patients were alive without disease, 47 (36%) had experienced a relapse, and 8 patients (6%) had died of transplant-related causes (Table 3) of which 6 within 100 days after transplantation, and 2 between 100 days and 1 year after transplantation. The 5-year probability of survival was 63%, 53% and 74% for children with ALL1, ALL2, and AML1, respectively, while the 5-year probability of relapse was 35%, 49% and 26% for ALL1, ALL2, and AML1, respectively (Figure 2, no significant difference). The median time to relapse was 8 months (range 0.2-5.2 years). Of 47 relapses, 33 occurred within the first year post-SCT. Most relapsed patients

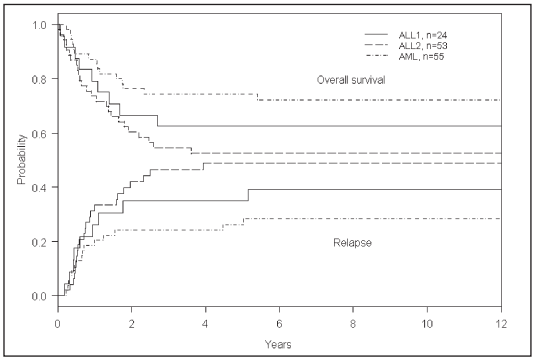
Table 3: Relapse and transplant-related mortality

Causes			No. of patients
Progressive disease/relapse			47 (36%)
Transplant-related mortality			8 (6%)
	GVHD		1
	ARDS		1
	Vascular Leak Syndrome		1
	Encephalopathy		1
	Infection		
		Systemic Candidiasis	1
		Invasive Aspergillosis	1
		Cerebral toxoplasmosis	1
	Hemorragic complications		1

died within two year after relapse (40 of 47 patients), but 2 patients survived with additional treatment for 2.7 and 10.4 years and then died due to relapse and pulmonary insufficiency, respectively; another 5 patients (all patients with ALL) are still alive after reinstitution of remission by chemotherapy following a relapse (time after relapse: median 4.7, range from 2.9 – 17.9 years).

The effect of acute GvHD on relapse was evaluated for children surviving more than 50 days. Patients who received cells from a syngeneic donor or cord blood were excluded from this evaluation. The incidence of acute GVHD Grade II to IV was 6% (7 of 124 evaluable patients).

Figure 2. Kaplan-Meier estimates of overall survival and cumulative incidence of relapse after HLA-identical SCT for AML1, ALL1 and ALL2.



In 14 patients acute GVHD grade I was suspected on clinical grounds. One patient died due to acute GVHD. Chronic GVHD occurred in 10 patients among 119 evaluable patients (8%); in 6 it was extensive, but not lethal so far.

Variables possibly related to relapse, overall survival and acute GvHD after stem cell transplantation

Table 4 summarizes the results on the probability to remain relapse-free for five years after SCT in our group of patients. Neither the duration of first remission for the ALL2 patients, nor the presence of factors potentially deferring a decreased chance of relapse for AML1 patients were significantly related to occurrence of relapse. Addition of VP16 in 53 ALL patients and AraC in 25 AML patients did not result in a difference in relapse-free survival. From the other variables evaluated, a younger age of the patient and a lower dose of TBI were significantly related with decreased post-transplantation survival (Figure 3). Patient age and TBI dose were, however, interrelated, since the TBI dose depended on the age of the patient (see Patients and Methods and Figure 1). Relatively more AML and less ALL cases were found in the (older) children receiving higher TBI dose (2x 6Gy), in accordance with the age distribution at presentation of acute leukaemia, but no differences were present in risk

Figure 3A and B. Kaplan-Meier estimates of relapse-free survival for patients conditioned for HLA-identical SCT for acute leukemia by chemotherapy and TBI.

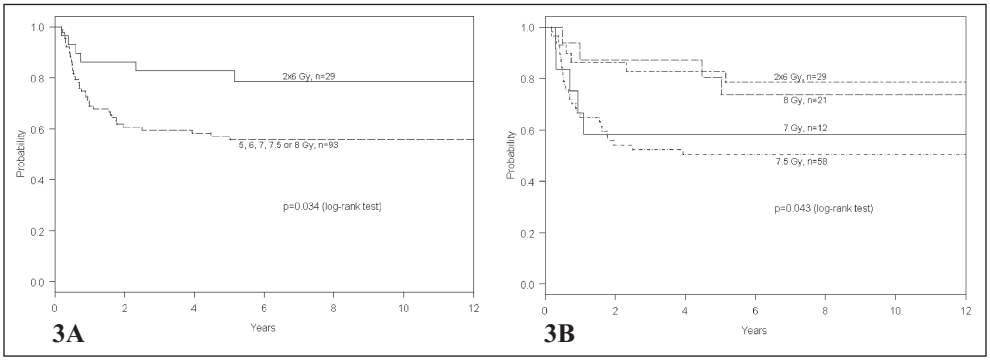


Table 4: Univariate analysis of variables possibly related to survival

Factor	5 years probability of relapse-free survival (TRM Censored)	95% CI	p[4]
ALL2, n=53			
early relapse, n=14	39%	19-77%	0.18
late relapse, n=39	56%	41-75%	
AML1, n=55			
good risk characteristics[1], n=15	73%	54-99%	0.75
others, n=40	74%	62-89%	
Cell dose[2]			
> 2.75 x 10^8/kg, n=64	67%	56-80%	0.54
≤ 2.75 x 10^8/kg, n=65	62%	51-75%	
TBI dose[3]			
≤ 8 Gy, n=93	57%	47-68%	0.034
12 Gy, n=29	83%	70-98%	
Age[3]			
< 8,7 years, n=61	53%	42-67%	0.03
≥ 8,7 years, n=61	75%	64-87%	
aGvHD, all cases			
grade 0, n=103	62%	54-73%	0.25
grade I-IV, n=21	72%	54-96%	
aGvHD, ALL1 and ALL2			
grade 0, n=58	57%	46-72%	0.89
grade I-IV, n=12	51%	27-93%	
aGvHD, AML1			
grade 0, n=45	69%	56-84%	0.08
grade I-IV, n=9	100%		
cGvHD, all cases			
None, n=109	63%	54-73%	0.26
Limited or extended, n=10	89%	71-100%	
Donor sex			
Male to male Tx, n=36	54%	39-74%	0.27
Female to male Tx, n=41	62%	49-79%	

[1]see Table 1

[2]CB excluded from analysis

[3]patients who did not receive any TBI were excluded from this analysis

[4]p-values reflect the differences between the whole survival curves

Table 5: Comparison of risk characteristics, according to TBI dose

TBI dose	5, 6, 7, 7.5 or 8 Gy	2x 6 Gy	p
Number of patients	93	29	
Age, median (range, in years)	7.38 (1.58-17.23)	13.15 (8.68-17.28)	
Diagnosis			
ALL1 and ALL2	60	14	0.03[4]
Standard risk[1]	33	7	0.97[4]
AML1	33	15	0.03[4]
Good risk[1]	9	3	0.73[5]
Transplant-related mortality[2]	7	0	0.20[5]
Acute GVHD, grade 1-4	15	6	0.58[5]
5 years probability of relapse-free survival (95% CI)[3]	57% (47-68%)	83% (70-98%)	0.034
Overall survival (95% CI)	52% (43-64%)	83% (70-98%)	0.01

[1] See Table 1, [2] See Table 3, [3] TRM Censored, [4] chi-square test for independence, [5]Fisher's exact test.

characteristics of the disease (Table 5). No significant difference in occurrence of relapse was found between children receiving 8Gy vs. 2x 6Gy. Acute GVHD was not significantly related with the occurrence of leukaemia relapse in our patient group as a whole, but, within the AML1 group none of the patients who experienced acute GVHD (n=9) developed a relapse in contrast to 15 relapse cases in 46 AML1 patients without acute GVHD (likelihood ratio test, including all AML1 patients, p=0.02).

To evaluate the univariate risk factors for the development of acute GVHD after SCT we excluded all patients transplanted with cells from syngeneic donors or cells derived from cord blood and patients that didn't survive beyond day 50 after SCT. The addition of CsA to the GVHD prophylaxis was not significantly associated with a lower incidence of acute GVHD (p=0.07), but when GVHD occurred, a clear shift in disease severity was noted; only 1 out of 13 acute GVHD patients treated with prophylactic MTX/CsA developed grade II or greater vs. 5 out of 6 acute GVHD patients with MTX alone (p=0.003). Sex mismatch and CMV status had no influence on the occurrence of acute GVHD in our study group (p=0.24 and 0.92, respectively). Both higher patient and higher donor age were (as continuous variables) significantly associated with the occurrence of acute GVHD (p=0.01 and 0.01, respectively, Table 6).

Table 6: Logistic regression analysis of risk factors for acute GvHD

Factor	Odds ratio	95% CI	p
GvHD prophylaxis (CsA+MTX vs. MTX)	0.35	0.11-1.09	0.07
Sex mismatch (Female to Male vs. Male to Male)	2.33	0.56-9.66	0.24
CMV (CMV positivity in either donor or recipient or both vs. CMV negativity in both)	1.05	0.40-2.77	0.92
Patient age	1.17	1.04-1.32	0.01
Donor age	1.11	1.02-1.22	0.01

Discussion

The aim of the present study was to evaluate the variables associated with transplant-related complications, leukaemia relapse and survival after MSD-haematopoietic SCT for acute leukaemia in a group of children, consecutively grafted in a single centre over a 20-year period. This population is characterized by a low incidence of severe GVHD, due to the gnotobiotic measures, regular microbiological surveillance and pre-emptive antimicrobial treatment used(26). This low frequency of severe GVHD and also of transplant-related mortality provided us the opportunity to study the effect of other variables, such as disease characteristics, age of donor and recipient, pretreatment and non-lethal GVHD on the relapse frequency and survival.

Remarkable progress in (conventional) medical anti-leukaemia treatment has been made over the past decades(2;5;24). Despite that, the prognosis of infants and children with ALL who have high-risk features (cytogenetic rearrangements, T-cell lineage, poor response to induction therapy, extramedullary disease)(3) is still poor and they may benefit from a SCT in first CR. Although the increasing intensity of chemotherapeutical therapy and advances in supportive care including nutrition and antibiotics/antifungals have improved survival for some of these subtypes of ALL and have made the option of SCT in CR1 sometimes controversial, it seems that the gap between the two treatment strategies increases as the risk profile of the patient worsens(3;32). For instance, in patients with the t(9;22) Philadelphia chromosome, the disease-free survival (DFS) was 65% and the overall survival (OS) 72% after SCT in CR1 compared with 25% DFS after chemotherapy alone(32). In our analysis the OS of children grafted in 1st CR of high-risk ALL was 63%, which is comparable to that in other centres(3;7;32).

There is evidence to suggest that SCT from HLA-identical donors may provide a superior outcome compared with chemotherapy alone for children in CR2, after relapse of ALL, especially in patients who have a short first remission duration (9;21;33). The 5-year OS for all ALL patients transplanted in CR2 was 53%. We observed a trend towards a better outcome for patients who relapsed after a ≥24 months interval from remission induction, but the difference was not significant, possibly due to small numbers (see Table 4).

Due, in part, to a higher risk of relapse among AML patients in CR1, in contrast to most cases of ALL, there appears to be a role for SCT in first-remission AML children. Many studies demonstrated significantly fewer relapses in patients who received (or were intended to receive) allogeneic SCT. Despite more TRM, the studies all show a superior disease-free survival in the group assigned to allogeneic SCT(34;35). For example, in the Children's Cancer Group study, the OS after allogeneic SCT was 60%, which was superior to survival after other strategies that included intensive chemotherapy (53%) and autologous SCT (48%) (4). In the MRC 12 trial, however, the 5 year OS was 66% with intensive chemotherapy only. While SCT decreased the risk of relapse, it did not translate into a significant improvement of OS(1;36). Our AML population, referred after remission induction, according to consecutive DCLSG protocols, and selected when they had a MSD, revealed an OS of 74% and a relapse rate of 26% after allogeneic SCT in CR1. These figures represent the outcome of patients, who were treated during a period of more than twenty years. The results suggest that patients with AML who have suitable sibling donors should be offered SCT in first remission. However, the probability of overall survival of patients with good risk features (based on resistance to therapy and karyotype) treated with chemotherapy alone improved considerably. For these patients an allogeneic SCT may not improve the outcome. Therefore, many AML study groups nowadays stratify therapy, considering SCT in the intermediate and poor risk groups(37-39).

Many factors determine the outcome of SCT. Firstly, the GVL effect, mediated by donor alloreactive T cells and associated with the occurrence of acute GVHD, is an important contribution to the control of leukaemia. Its effect is considerably less for cases with acute leukaemia than in CML(40); AML seems more susceptible to GVL than ALL(20). In our

study, acute GvHD was not significantly associated with the occurrence of leukaemia relapse in the patient group as a whole, but within the AML1 group none of the cases who got acute GvHD developed a relapse, confirming a GVL effect after allogeneic SCT for AML. Withdrawal of CsA in combination with pre-emptive donor lymphocyte infusions (DLIs)(41) or the use of a lower dose of CsA(42) may add to an advantage in leukaemia-free survival of patients with increased risk of relapse, however, at the risk of an increased frequency of severe GvHD.

A second important factor, determining the transplant outcome, is the leukaemia reducing effect of the conditioning regimen. We found that a higher total dose of TBI was associated with a significantly lower risk of relapse and a higher overall survival. The total dose of TBI in our centre depends on the age of the patient at SCT (see Patients & Methods); these variables were confounding in the statistical analysis. For ALL, the influence of age on outcome is very important, as was studied in one clinical trial, in which children and adults were treated with chemotherapy and TBI, according to similar protocols. When corrected for all possible influencing factors, a 20-year-old had a two-fold higher risk of treatment failure than a 10-year-old patient (43). Studies on the influence of age on outcome of allogeneic SCT for ALL and AML report conflicting data. Some reports find that survival is better in younger patients and some find no influence of age on survival. Up to now, no studies have found an association of the risk of leukaemic relapse post transplant with age(44). In contrast, in this study we report a better DFS in the older children that received a higher dose of TBI (Table 5). No significant difference in occurrence of relapse was found between children receiving 8Gy vs. 2x 6Gy, possibly due to low numbers. A higher total dose of TBI may eliminate remaining malignant cells more effectively which could have been monitored with MRD determination post-SCT, not done in this study group. Alternatively, the result of a higher total TBI dose might have been that more cases became complete chimeras, a possible advantage for the control of remnant blast cells after SCT for acute leukaemia(45). A significant relationship between higher TBI doses and lower relapse incidence and increased overall survival was recently confirmed by a review of literature comparing various TBI regimens(46). Conversion of our TBI schedules into single biologically effective doses (BED)

for leukaemic cell kill, according to the linear-quadratic concept, leads to the following BED values: 1x7 Gy: BED=10.7 Gy; 1x7.5 Gy: BED=11.7 Gy; 1x8 Gy: BED=12.7 Gy; and 2x6 Gy: BED=17.6 Gy. Taking into account the calculated BED of different TBI schedules for leukaemic cell kill, the BED of our 2x6 Gy regimen is about 25% higher than the BED of the frequently used 6x2 Gy scheme (46) and 38% higher that the 1x 8Gy scheme. In the young children, however, a possible decreased relapse rate, following higher BED-TBI will need to be weighed against the increased susceptibility for neurodevelopmental and endocrinological adverse effects (18;47-49) and secondary cancer(50). To overcome these side effects, a fractionated TBI dose with higher biologically effective leukaemic cell kill may give superior suppression of malignant disease while limiting adverse effects on other tissues (46;51;52). Data supplied by the acute leukaemia working party (ALWP) of the EBMT confirm the superiority of fractionated TBI for children with ALL in CR2 (n= 525, median dose: 12 Gy, divided into two or more fractions, DFS: 56 +/-2%) versus single fraction TBI (n=245, median dose: 10 Gy, DFS 44 +/-3%; p=0.0008). In the same database this was not observed for children with AML in CR1. It should be noticed that the ALWP data might contain some bias, as they were not yet adjusted for other possible prognostic factors. Prospective trials comparing TBI schemes with multiple fractions with schemes with a low number of fractions should take the BED for leukaemic cell kill into account. In conclusion, optimization of TBI, total dose and fractionation (especially for ALL), and application of a GVL-effect (especially for AML) may further improve the outcome following SCT of children with high risk acute leukaemia.

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