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Outcome of Single Fraction Total Body Irradiation-Conditioned Stem Cell Transplantation in Younger Children with Malignant Disease

Comparison with a Busulphan-Cyclophosphamide Regimen

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The logistic difficulties of using fractionated total body irradiation (TBI) in the youngest children often limit the choice to single fraction TBI (sfTBI) or non-TBI-based regimens. We retrospectively evaluated 44 such children (< 7 years) conditioned with either sfTBI (n = 26) or busulphan-cyclophosphamide (Bu-Cy) (n = 18), transplanted for hematological malignancies between 1988 and 2001. Both neutrophil and platelet engraftment were faster in the sfTBI group with a similar incidence of graft failure (6.8%). Acute GVHD (graft versus host disease) grade 2–4 occurred in 38.4% and 38.8% and chronic GVHD in 20% and 15.4% of the patients in the sfTBI and Bu-Cy groups, respectively. Grade 2–4 GVHD was associated with reduced risk of relapse (p = 0.03). This finding was more pronounced in high-risk patients with 2/10 relapses in patients with GVHD grade 2–4, compared with 13/18 relapses among those with GVHD 0–1 (p = 0.05). The probability of overall survival was 43.3% in the sfTBI group and 33.3% in the Bu-Cy group (p = 0.6). However, the outcomes for high-risk patients and those with acute lymphoblastic leukemia were better in the sfTBI group. While hypothyroidism, growth hormone deficiency, learning problems and cataract formation were observed only in the sfTBI group, early cardiac toxicity, behavioral problems and seizures were more common in the Bu-Cy group. Thus, where fractionated TBI is not feasible, sfTBI offers improved survival in high-risk children with acute lymphoblastic leukemia compared with Bu-Cy, without an unacceptable increase in early or late toxicity.

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Allogeneic bone marrow transplantation (BMT) still provides the best chance of disease-free survival in children with advanced leukemias (1–4). However, the ideal conditioning regimen for children undergoing BMT remains elusive. Traditional conditioning regimens administered before stem-cell transplantation include total body irradiation (TBI) together with cyclophosphamide (Cy) (1). Attempts have been made to optimize chemotherapy-based regimens in order to reduce toxicity but maintaining the antileukemic potential (5).

It is known that radiation to the central nervous system (CNS) may cause tissue damage, such as necrotizing leucoencephalopathy and mineralizing microangiopathy with dystrophic calcification, which have been correlated with memory deficits and lower intelligence quotients (6, 7). Owing to the less abundant vascularization of the white matter and subcortical nuclei, these regions are likely to be in a position of particular vulnerability to vascular insufficiency. Evidence of leucoencephalopathy and calcification of the basal ganglia are consistent with a vascular etiology underlying the neuropsychological effects of cranial irradiation. The youngest children (especially those below 3 years of age) are the most sensitive to CNS late effects (6, 7).

The long-term effects of TBI in older children are well documented, growth impairment, cataracts, infertility and hypothyroidism (8–12) being particularly common. On the other hand, these late effects are rare following conditioning with busulphan (Bu) and cyclophosphamide (Cy) (5, 8, 12, 13). Acute side effects of busulphan-containing regimens such as veno-occlusive disease of the liver (VOD) and hemorrhagic cystitis are less common with TBI-based regimens (14). In addition, excessive incidence of obstructive bronchiolitis, partial alopecia and chronic graft versus host disease (GVHD) has been reported in patients condi-

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tioned with Bu-Cy (15). There is also concern that the Bu-Cy regimen might be less effective against acute lymphoblastic leukemia (ALL) and in more advanced leukemias (16, 17).

Controversy also exists regarding the mode of delivering TBI. While there has been a shift in practice over the past decade in the use of fractionated TBI in an attempt to reduce toxicity, this is not entirely evidence based (18–20). Few studies have addressed this issue in a controlled randomized manner (18). Moreover, there are still situations where it is logistically difficult to organize fractionated TBI for those children who need anesthesia for accomplishing the treatment. There is also a question about whether it is safe to anesthetize a small child twice a day for several consecutive days. Thus, single fraction TBI might at times be the only option in this age group if TBI-based conditioning is deemed necessary.

To our knowledge, there are no published reports about single fraction TBI conditioned stem cell transplants (SCT) in younger children. The aim of this retrospective, single institution study was to analyze the outcome of young children treated with either single fraction TBI and Cy- or Bu-Cy-containing regimens before SCT for malignant hematological diseases, in cases where fractionated TBI could not be organized.

MATERIAL AND METHODS

All children below 7 years of age treated with single fraction TBI (sfTBI) or Bu-Cy conditioning before stem cell transplantation in Bristol Royal Hospital for Children between October 1988 and September 2001 were identified from the registry. A total of 26 patients with malignant diseases received treatment with sfTBI and 18 received Bu-Cy. The detailed characteristics of these study patients are presented in Table 1. The risk grouping of the patients was according to standard risk (SR) and high risk (HR). HR patients were defined as having failed to reach remission, having relapse on treatment or early after treatment, age below 1 year, having unfavorable cytogenetics, and secondary leukemia.

Preparative regimens

In the sfTBI group, patients received 60 mg/kg cyclophosphamide, i.v. on two consecutive days, and 10 Gy sfTBI at a low dose rate (0.05 to 0.08 Gy/min) either on day 1 or day 0. Shielding was not used on any part of the body. The patients with an unrelated donor or mismatched graft also received intravenous CAMPATH-1G on 5 consecutive days with doses 5 mg/day for patients below 20 kg, and 10 mg/day for those between 20 and 50 kg, or antithymocyte globulin (rabbit-ATG) 5 mg/kg/day for 5 days. Patients with central nervous system (CNS) relapse received 6 Gy irradiation in four fractions to whole brain in the week before TBI. No prophylactic testicular boosts were used. In the Bu-Cy group, oral busulphan was given at a dose of 4 mg/kg/day in divided doses for 4 days, and Cy at 200 mg/kg

Table 1

Patient characteristics

	sfTBI (n = 26)	Bu-Cy (n = 18)	p-value
Age at transplant (years)			0.012
Median	3.05	1.55	
Range	0.99–7.0	1.0–6.4	
Gender			0.63
Female	12	7	
Male	14	11	
Diagnostic group			0.047
ALL	15	4	
AML	8	8	
JMML	3	6	
Risk grouping			0.054
Standard	6	10	
High	20	8	
CNS radiation			0.068
No	21	18	
Yes	5	0	
Status at transplant			0.11
CR1/CP	14	14	
CR2	12	4	
Type of transplant			0.22
Related	5	7	
mmrelated	3	2	
Vud	10	8	
mmvud	8	1	
Graft source			0.48
BM	21	17	
pbsc	2	1	
Both	1	0	
Cord	2	0	
CMV status of recipient			0.57
Negative	23	14	
Positive	3	3	
Unreported	0	1	
CMV status of donor			0.23
Negative	17	14	
Positive	9	3	
Unreported	0	1	
Graft manipulation			0.031
No	8	12	
Yes	18	6	
Recipient T-cell antibodies			0.045
Not used	4	8	
Used	22	10	
GVHD prophylaxis			0.39
None	1	1	
CyA	14	7	
CyA + mtx	11	10	

Categorical variables have been tested by Fisher exact tests and numerical variables by non-parametric Kruskall–Wallis tests.
Abbreviations: BM = bone marrow, pbsc = peripheral blood stem cells, CMV = cytomegalovirus, CyA = cyclosporin A, mtx = methotrexate, VUD = voluntary unrelated donor.

over 4 days. Hydration and MESNA uroprotection were used (20 mg/kg with cyclophosphamide over 1 h, and then 76 mg/kg infused over 23 h). The patients treated with busulphan received a prophylactic anticonvulsant agent (either clonazepam or carbamazepine) over the administration time of busulphan.

GVHD prophylaxis

In all cases of mismatch between donor and recipient, the graft was T-cell depleted either by monoclonal purge or selection of CD34 positive cells as described earlier (2), and the recipient received T-cell antibodies (either Campath-1G or ATG). In transplants from matched unrelated donor, T-cell antibody in vivo was administered to obtain T-cell depletion of the graft. Cyclosporin A (CyA) was given to all patients either alone or in combination with a short course of methotrexate (MTX), if the graft was not T-cell depleted. CyA was given from day 1 to 6 months post-transplant, and then tapered over 3 months in the absence of GVHD. Levels were measured twice weekly and dosage modified to maintain therapeutic levels (125–225 ng/L).

Supportive care

All patients were treated in rooms with high-efficiency air particle filtration. The patients being either cytomegalovirus (CMV) seropositive or receiving a graft from a CMV-positive donor were considered at high risk of developing CMV disease. For these CMV high-risk patients, prophylaxis was given in the form of 3-weekly intravenous immunoglobulin (200 mg/kg) for 3 months and high-dose aciclovir (500 mg/m^2/dose three times a day.) until day +30. All patients received prophylactic ciprofloxacin, aciclovir and itraconazole (since 1996) in the immediate post-graft period. G-CSF was administered to all patients from day 10 and was discontinued after 3 days of neutrophil counts exceeding 1×10^9/L. Co-trimoxazole was given as prophylaxis for Pneumocystis carinii until 6 months post-transplant. Thereafter, penicillin-V was started as life-long prophylaxis against infection.

Assessment of early toxicities and infections

During the isolation, blood pressure, heart rate and oxygen saturation were measured every four hours unless otherwise clinically indicated. Mucosal membranes, and skin were checked daily. Oral intake of food and fluids were recorded, as well as intravenous drug and fluid input and all output (urine, stools, vomit). The state and volume of stools was monitored and recorded, as well as urinalysis of each urine sample. Full blood count and chemistry were checked daily, cyclosporin levels and colonization samples for mycology were taken twice a week, as well as blood samples for Epstein-Barr virus (EBV), CMV, and adenovirus detection. If loose stools/diarrhea occurred, samples were sent for microbiology (culture and sensitivity), virology (viral search by electron microscopy, adeno- and CMV-PCR, and culture) and *Clostridium difficile* toxin detection. If urinanalysis was positive to blood and/or protein, samples for microbiology and virology were sent. If the patient was pyrexial $> 38^\circ$C, blood cultures and complete infection screen were taken (urine, stools, nose and throat swabs, line swabs). Positive samples were followed up until three negative samples were obtained (with the exception of blood cultures). Mucositis was graded: no mucositis if the membranes were not broken and/or the patient did not need painkillers and was able to eat; mucositis present, if the patient needed regular treatment with painkillers because of painful swallowing. Diarrhea was graded using standard GVHD assessment criteria (21).

Assessment of engraftment and GVHD

The day of engraftment was defined as the first of three consecutive days with an absolute neutrophil count 0.5×10^9/L or more. Acute GVHD was graded using standard criteria (21). Chronic GVHD was defined as none, limited or extensive. Patients were considered evaluable for chronic GVHD if they engrafted and survived for 100 days. The results were analyzed up to June 2002, which allowed at least 9 months' follow-up for all patients.

Long-term follow-up

After discharge from the transplant unit, the patients were usually taken care of by their local hospitals but returned to our unit for regular reviews at 3, 6, 9, 12, 18 and 24 months post-transplant. Thereafter, the appointments take place annually (or more frequently if needed) at the late-effect clinic led by an endocrinologist and a transplant physician. The follow-up protocol includes: full blood count, electrolytes, calcium status, liver and kidney function, cyclosporin levels until medication finished, PCR tests for EBV, (CMV) and adenoviruses, antigen detection for CMV (these virus tests are stopped after immunosuppression is finished). Bone marrow aspirate and trephine are taken 1, 3, 6, 12, 18 and 24 months post-transplant. A yearly check is carried out on immunoglobulin levels, blood glucose, cortisol, thyroid function tests, gonadotrophin levels (starts near puberty, usually after 9 years of age in girls and 10 y in boys). At each visit, patients are checked for symptoms of chronic GVHD (skin, eyes, diarrhea), growth (chart is completed), pubertal stage (according to Tanner), blood pressure, heart rhythm by auscultation, symptoms of a second malignancy, neurological symptoms, and possible psychosocial symptoms. Neuropsychological testing is recommended after 12 months post-transplant, and especially before school age. An ophthalmologist is seen at 3, 6 and 12 months, and yearly thereafter. Dental check-ups are recommended at 3, 6, 12, 18, 24 and 36 months, and every 6 months thereafter. Cardiac ultrasound examination is recommended at 6, 12 and 24 months, then once a year.

The same recommendations hold for lung function testing (spirometry and diffusion capacity) but children are usually cooperative just after 5 years of age. However, there are always some patients who develop their symptoms between those scheduled visits. In this study population, those patients with neurological late effects were all diagnosed early by symptoms.

Statistical analyses

Categorical variables were compared using the Fisher exact test and the Kruskall–Wallis non-parametric method was used for the continuous variables. All the outcome variables were analyzed also against the following factors: diagnostic group, gender, transplant type, risk grouping, source of the graft, CMV status of recipient and donor, use of graft manipulation, use of T-cell antibodies, mode of GVHD prophylaxis, and possible CNS radiation. A multiple logistic regression model was fitted to the data by a stepwise approach using the statistical SPSS program (SPSS version 9 for Windows, Woking, UK) for risk factor analysis if more than one variable had a significant p-value (< 0.05). The probability of various events was examined by the Kaplan–Meier method and the groups were compared using the log-rank test.

RESULTS

Engraftment

The sfTBI group achieved neutrophil engraftment in a median of 14.5 days, compared with 17 days for the Bu-Cy group ($p = 0.07$). Platelet engraftment was also faster in the sfTBI group, occurring in a median of 22 days (34 days for Bu-Cy group, $p = 0.04$). Neither neutrophil nor platelet engraftments were influenced by graft manipulation, CMV sero status, use of T-cell antibodies or use of post-transplant methotrexate.

Graft rejection was observed in only one patient in the sfTBI group and two in the BU-CY group.

GVHD

The incidence of acute GVHD was 57.6% (15/26) in the sfTBI group and 55.5% (10/18) in the Bu-Cy group ($p = 0.9$). Grade 2–4 acute GVHD occurred in 38.4% in the former and 38.8% in the latter group ($p = 0.9$). Chronic GVHD occurred in 20% (4/20) and 15.3% (2/13) of the sfTBI and Bu-Cy groups, respectively. Neither acute nor chronic GVHD was related to age, gender, graft manipulation, CMV sero status, use of T-cell antibodies or donor type.

Relapse

Eleven patients suffered relapse in the sfTBI group and 7 in the Bu-Cy group ($p = 0.8$). Patients with grade 2–4 GVHD had a lower risk of relapse (3/16, probability 35.4, 95% CI 57–100, versus 15/27 with grade 0–1 GVHD, probability 79.4, 95% CI 1–69.8; log rank $p = 0.03$, Fig. 1). This effect was more pronounced in HR patients, with 2/10 relapses in patients with GVHD grade 2–4, compared with 13/18 relapsing amongst those with GVHD 0–1 (log rank $p = 0.05$). In addition, 13 out of 24 patients receiving a manipulated graft relapsed, compared with 5/20 patients transplanted with an unmanipulated graft ($p = 0.06$). In a multivariate analysis, grade 2–4 GVHD was the only variable associated with a lower risk of relapse (RR 0.2, 95% CI 0.04–0.8, $p = 0.04$).

Survival

There was no difference in the overall survival between the two groups. The actuarial survival at 5 years was 43.3% (95% CI 23.3–63.3) in the sfTBI group compared with 33.3% (95% CI 7.9–58.7) in the Bu-Cy group (log-rank $p = 0.6$). However, when stratified according to risk category, sfTBI was associated with a trend towards improved survival in the HR group (cumulative survival 48.4%, 95% CI 25.9–70.9 versus 25%, 95% CI 0–54; log-rank $p = 0.07$, Fig. 2).

The impact of the conditioning regimens seemed to be disease related. In patients with ALL, sfTBI was associated with significantly improved survival with a cumulative survival of 64.6% (95% CI 39.6–89.6), compared to no long-term survivors in the Bu-Cy group (log-rank $p = 0.03$). On the other hand, in the patients with myeloid malignancies, Bu-Cy was associated with a cumulative survival of 50% (95% CI 24–76) and this was 18.2% (95% CI 0–40.9) in the sfTBI group (log-rank $p = 0.2$).

The cause of death was relapsed disease in 18 cases, bacterial sepsis in 4 cases, disseminated adenovirus infection, intracranial hemorrhage, and severe acute GVHD with gastrointestinal bleeding in one case each.

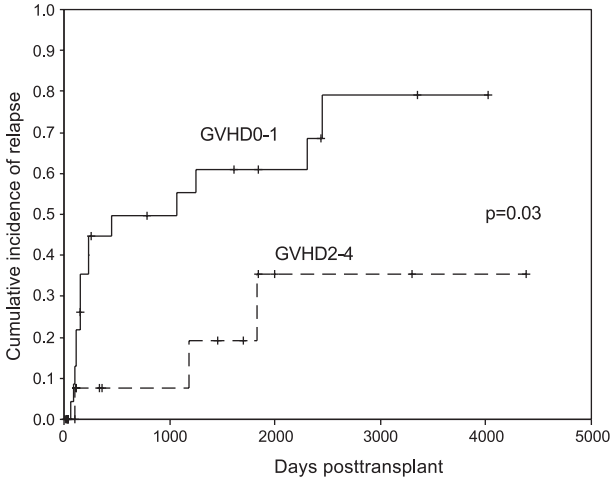

Fig. 1. Graft versus host disease (GVHD) and relapse. The broken line represents patients with grade 2–4 GVHD and the solid line represents those with grade 0–1 GVHD.

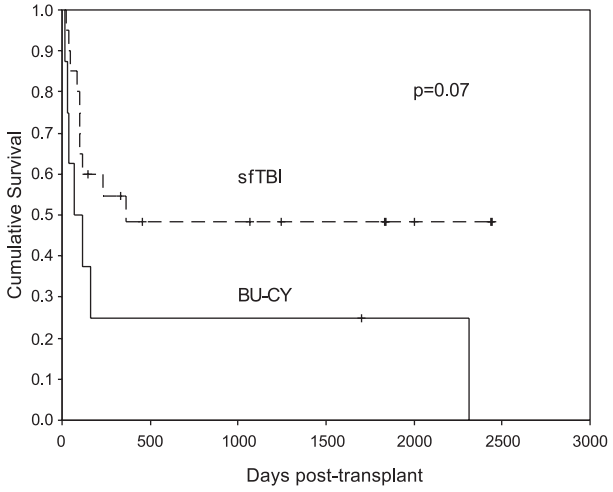

Fig. 2. The effect of a conditioning regimen on survival in high-risk patients. The broken line represents those receiving single fraction total body irradiation (sfTBI) and the solid line represents those receiving busulphan-cyclophosphamide (Bu-Cy).

Non-relapse mortality (NRM) was lower in the sfTBI group (7.7%, 95% CI 0–17.8), compared to the Bu-Cy group (28.7%, 95% CI 7.4–50) [log-rank p = 0.08, Fig. 3]). There was no impact of any other variable on overall survival or NRM.

Regimen-related toxicities

Early post-transplant (within 100 days). No difference was found between the two groups in terms of early mucositis, diarrhea or infections. There was also no difference in terms of early CNS or pulmonary toxicities. However, cardiovascular toxicities (such as cardiac failure and hypertension) within the first 9 months were noticed only in the Bu-Cy group (4/18 vs. 0/26, p = 0.02) (Table 2).

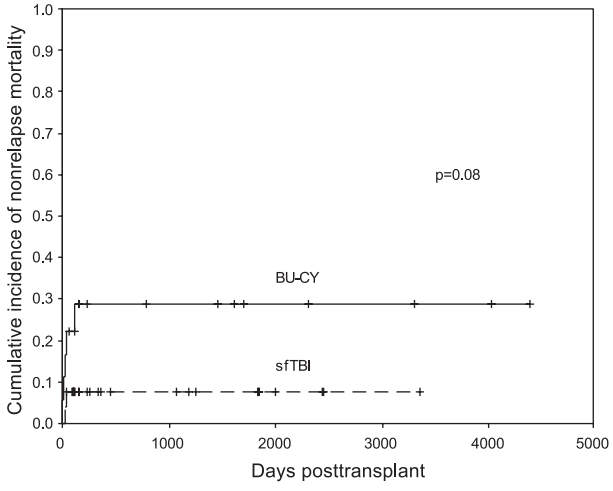

Fig. 3. Non-relapse mortality. The broken line represents patients receiving single fraction total body irradiation (sfTBI) and the solid line represents those receiving busulphan-cyclophosphamide (Bu-Cy).

Late post-transplant (after 9 months). Late effects were analyzed in the group of patients who were alive at least 9 months post-transplantation (n = 21). In this group of patients, there were two patients who encountered a late relapse (3 and 6 years post-transplant). In the single fraction TBI group, the median (range) follow-up time of survivors was 4.7 (0.75–9.2) years, and in the Bu-Cy group 8.9 (3.5–12) years. The follow-up was more than 3 years in 16 out of 21 survivors (Table 3).

Hypothyroidism, growth hormone deficiency, learning problems (difficulties in reading and/or mathematics, and the need for special school in one case) and cataracts were noted only amongst sfTBI group. Cataract formation was associated with additional CNS radiation used in certain patients with ALL (a total of 5 patients). Three of the 7

Table 2

Early complications (before day 100)

	sfTBI (n = 26)	Bu-Cy (n = 18)	p-value
Mucositis			0.12
No	12	13	
Yes	14	5	
Diarrhea			0.32
No	15	13	
Yes	11	5	
Viral infection			0.98
No	16	11	
Yes	10	7	
Fungal infection			0.78
No	24	17	
Yes	2	1	
Bacterial infection			0.58
No	18	11	
Yes	8	7	
FUO only			0.72
No	20	13	
Yes	6	5	
Cardiovasc. toxicity			0.023
No	26	14	
Yes	0	4	
CNS toxicity			0.78
No	24	17	
Yes	2	1	

Statistical tests and abbreviations are as in Table 1. Viral infections: either reactivation (1) or new case (0) of CMV, 5 cases of adenovirus, 4 of them were from stools which may be reactivation, 1 RSV bronchiolitis, 5 rotavirus diarrhea, 2 influenza A bronchiolitis, 1 parainfluenza infection, 1 polyomavirus in urine, 1 case of shingles. Bacterial infections were either blood culture positive (7) or from skin, ear, or perianal infections. Fungal infections were 1 Candidemia, 1 Aspergillus antigenemia, and 1 skin infection.
Abbbreviation: FUO = fever of unknown origin, which means recurring fever without any positive viral, bacterial or fungal samples.

Table 3

Late-effects in patients surviving >9 months post-transplant

	sfTBI (n = 14)	Bu-Cy (n = 7)	p-value
Cataract			0.047
No		7	
Yes	7	0	
Thyroid hormone treatment			0.061
No	8	7	
Yes	6	0	
Growth hormone treatment			0.061
No	8	7	
Yes	6	0	
Learning problems			0.12
No	10	7	
Yes	4	0	
Behavioral problems			0.026
No	14	4	
Yes	0	3	
Cardiovascular problems			0.53
No	12	7	
Yes	2	0	
CNS symptoms			0.088
No	13	4	
Yes	1	3	
Pulmonary problems			0.33
No	14	6	
Yes	0	1	

patients with cataracts had received a CNS boost, whereas only 2 out of 14 survivors who had not developed cataracts received this form of therapy ($p = 0.08$). This effect of CNS radiation (boosts) was also evident in patients with growth hormone deficiency. Three of the six patients with growth hormone deficiency had received CNS radiation, compared with 2/15 not developing this complication ($p = 0.05$).

Behavioral problems (hyperactivity, depression) and CNS symptoms (seizures, developmental delays and deafness) were more common in the Bu-Cy group. Pulmonary toxicities were noted in one patient in the Bu-Cy group and in none of the sfTBI recipients.

DISCUSSION

In several studies the outcome of TBI-based conditioning regimens has been compared with Bu-Cy conditioning (16, 17). While several conclusions have been drawn from these studies, none of them have addressed the issue exclusively in a pediatric population. This is more relevant for the youngest children where there is greater concern regarding the use of TBI. Again, the use of fractionated TBI has become an accepted practice in most adult as well as pediatric transplants, in an attempt to reduce TBI-related side effects (18–20). This has been based largely on empiric or theoretical considerations, with little supporting evidence from randomized studies. Moreover, the use of fractionated TBI in small children (below school-age) is fraught with logistic difficulties, such as repeated anesthesia. Thus the only feasible way of delivering TBI to these younger children might be sfTBI. The choice is then between sfTBI and non-TBI regimens. There are currently no data comparing sfTBI and Bu-Cy regimens in younger children. Despite being retrospective and on small cohorts with substantial heterogeneity, our study is of importance from that point of view.

No difference was found in overall survival between the two groups, but sfTBI was associated with improved survival in the HR population, as reported in the Nordic study (3). The superiority of TBI in children with ALL was reported in that registry-based study and this was borne out in our study as well. The improved survival in HR patients following sfTBI was not only due to a reduced risk of relapse, but also to lower NRM in the sfTBI group. The lower NRM in the sfTBI group may have been partly due to the faster engraftment. This has also been reported by others, but this is the first time sfTBI has been shown to be associated with a more favorable outcome in this age group. On the other hand, Bu-Cy was equivalent if not superior in those with myeloid malignancies. A recent meta-analysis of myeloid leukemias has shown TBI and Bu-Cy to be equivalent in chronic myeloid leukemia (CML) but with TBI being slightly superior in acute myeloid leukemia (AML) (22).

There was a major impact of grade 2–4 GVHD on relapse. This was more evident in HR patients. The majority of patients receiving an unrelated donor or mismatched related donor grafts had graft manipulation and this tended to have an adverse impact on relapse. However, patients who developed significant GVHD had a lower probability of relapse irrespective of graft manipulation. The improved disease-free survival (DFS) in these patients was also because of the low mortality from GVHD. The age-dependent effect of GVHD on DFS was well demonstrated in a study, where patients receiving low-dose cyclosporine developed more GVHD and this was correlated with improved DFS, but only in younger patients (23). While the effect of GVHD on standard risk AML or ALL might be less apparent, GVHD and the resultant GVL effect undoubtedly play a role in the DFS of HR leukemias (24).

Compared to previous reports (15), no cases of VOD or hemorrhagic cystitis were detected in this study. Again, this might be related to the younger age group of these patients. However, a significant number of cardiac or vascular problems occurred in the Bu-Cy group (4 cases of high blood pressure needing treatment, and one of these in combination with cardiac insufficiency), which has not been reported previously. This may have been due to cyclosporine toxicity, rather than the conditioning treatment itself.

In terms of late effects, our data showed a clear tendency to increased numbers of cataracts, hypothyroidism and the need for growth hormone replacement among patients treated with sfTBI. These findings are in keeping with previous reports concerning the late effects of fractionated TBI (5, 8–12), although the frequency of cataract was lower than that reported in a French study (5), and we could not detect any cases of cataracts in the Bu-Cy group. Our finding differs from that of a Swedish report (13) suggesting that some cases of cataract also occur post-Bu-Cy treatment. However, the cases of cataract in chemotherapy groups may just reflect the use of steroids for chronic GVHD, which was less frequent in both the groups in our study. Cranial irradiation (boosts) was used in the sfTBI group alone and was associated with the need for growth hormone treatment and cataract formation.

Disturbances in pubertal development and gonadal function did not arise in this study population, as most of the patients are still prepubertal. The fairly short follow-up may also leave some cognitive late effects undetected. One might expect that any possible adverse effects on learning are likely to become apparent later on, when the demands on one's abilities increase. Thus, a long-term follow-up is necessary also in this field, and some formal neuropsychological testing should be routine. No symptoms of either radiation pneumonitis or pulmonary fibrosis were detected, though these could be a problem after sfTBI. Formal pulmonary function testing is technically possible for children above 5 years of age. In our unit, all the patients of suitable age are tested before SCT and routinely followed-up once a year. The follow-up is also too short for detecting any increased risk for second malignancy.

We did not find an excess of chronic GVHD or pulmonary late effects in the Bu-Cy group as reported by Ringden et al. (14). However, there was an increase in behavioral problems (hyperactivity, depression) and CNS symptoms (epilepsy, developmental delay, deafness) in the group treated with busulphan, which have not been mentioned in previous reports. Whether these effects were directly related to the conditioning regimen or secondary to subsequent treatments with, for example, cyclosporine or steroids cannot be determined with certainty. These findings could be because of the age group of the study population, warranting further investigation into the late CNS effects of Bu-Cy regimen in these very young children.

In conclusion, sfTBI was associated with a trend towards superior survival in patients with HR leukemias, particularly in those with ALL. Engraftment was faster and non-relapse mortality was lower in the sfTBI group. Grade 2–4 GVHD was associated with a trend towards improved disease-free survival, particularly in HR patients. There were differences in the pattern of late effects, with sfTBI being associated with ocular and hormonal abnormalities, whereas there were more behavioral- and seizure-related problems in the Bu-Cy group. Thus, if fractionated TBI cannot be delivered, sfTBI may be preferable to Bu-Cy in younger children with HR leukemias, particularly ALL, without an increase in early or late toxicities. Further randomized controlled studies are needed in this age group with regard to fractionation of TBI and comparisons between Bu-Cy and TBI.

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