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ORIGINAL ARTICLE

In haematopoietic SCT for acute leukemia TBI impacts on relapse but not survival: results of a multicentre observational study

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The aim of this study was to determine whether parameters related to TBI impacted upon OS and relapse in patients with acute leukemia in CR who underwent haematopoietic SCT (HSCT) in 11 Italian Radiation Oncology Centres. Data were analysed from 507 patients (313 males; 194 females; median age 15 years; 318 with ALL; 188 with AML; 1 case not recorded). Besides 128 autologous transplants, donors included 192 matched siblings, 74 mismatched family members and 113 unrelated individuals. Autologous and allogeneic transplants were analysed separately. Median follow-up was 40.1 months. TBI schedules and HSCT type were closely related. Uni- and multi-variate analyses showed no parameter was significant for OS or relapse in autologous transplantation. Multivariate analysis showed type of transplant and disease impacted significantly on OS in allogeneic transplantation. Disease, GVHD and TBI dose were risk factors for relapse. This analysis illustrates that Italian Transplant Centre use of TBI is in line with international practice. Most Centres adopted a hyperfractionated schedule that is used worldwide (12 Gy in six fractions over 3 days), which appears to have become standard. TBI doses impacted significantly upon relapse rates.

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INTRODUCTION

In conditioning regimens for haematopoietic SCT (HSCT), TBI is used in combination with high-dose chemotherapy for two main reasons: to ensure engraftment by weakening immunological competition between donor and recipient and to prevent relapse by reducing the tumor burden. Although anti-cancer drugs have a major role in reducing the leukemic burden before HSCT, TBI provides greater tissue penetration, does not need to be carried in the bloodstream, is not affected by pleiotropism or cross resistance and reaches sanctuary organs like the testicle and central nervous system, which anti-leukemic agents penetrate with difficulty. Furthermore, the radiation dose can be modulated by shielding radiosensitive organs and giving boost doses to more resistant areas.[1–4] To strengthen TBI-related immunosuppression and its anti-leukemic efficacy and reduce toxicity, parameters such as fractionation, single and/or total-dose values, have been modified over the years.[4–6] Although several studies suggested that TBI modalities and parameters could impact upon outcomes,[5,6] results of very few randomized studies are available and consequently the optimal TBI schedule has not been identified.[7]

Following a survey on the use of TBI among Italian Radiation Oncology Centres, this multi-centre study was designed to determine whether diverse TBI schedules impacted upon OS and relapse in a series of over 500 consecutive patients with acute leukemia in CR.

MATERIALS AND METHODS

Patient data came, after appropriate authorization, from the Italian Bone Marrow Transplantation Group (Gruppo Italiano Trapianto di Midollo Osseo, GITMO) and Pediatric Oncology and Hematology Association (Associazione Italiana di Ematologia e Oncologia Pediatrica, AIEOP), and from the 11 Italian Radiation Oncology Centres that were involved in the study and provided full information about their patients.

The cohort consisted of 518 patients, with acute leukemia in CR who were treated with TBI-based conditioning regimens in preparation for HSCT. As 11 patients did not engraft, 507 were evaluable for analysis. There were 313 males (61.7%) and 194 females (38.3%); median age was 15 years (with first quartile 8 years and third quartile 30.25, range 0–61). Three hundred and eighteen (62.8%) patients had ALL and 188 (37.1%) had AML; in one case the type of acute leukemia was not recorded. Two hundred and twenty-three patients in first CR (CR1) were analysed as one group; 275 patients in second or third remission were analysed together (CR$>$1) because only 45 were in third remission. Disease status was not recorded in nine cases.

Haematopoietic stem cell grafts derived from different sources: autologous transplants accounted for 25.2%, HLA-matched sibling transplants for 37.9%, three loci mismatched-related transplant (haploidentical) for 14.6% and unrelated transplants for 22.3%, with 16.2% (82 patients) matched and 6.1% mismatched at 1 locus (31 patients). Table 1 reports patient distribution and disease features for each HSCT type.

TBI schedules

Fractionated or hyper-fractionated TBI schedules were used, with different single and total doses, in 86.4% of cases. Eighty-four patients (16.6%)

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Table 1. Patient distribution and disease features vs haematopoietic SCT

	Autologous	*HLA-matched sibling*	*Haploidentical*	*Unrelated*	*Total*	P-*value*
No. of patients	128	192	74	113	507	
Median age (range)	12.8 (2–61)	19.8 (0–59)	24.9 (3–53)	10.5 (2–51)	15.5 (0–61)	<0.000
Gender						
Male	70	114	47	82	313	<0.037
Female	58	78	27	31	194	
Disease						
ALL	61	124	41	92	318	<0.000
AML	67	67	33	21	188	
Not recorded		1			1	
Disease status						
CR 1	76	107	15	25	223	<0.000
CR>1	52	81	55	87	275	
Not recorded	0	4	4	1	9	

Table 2. TBI parameters according to haematopoietic SCT

	Autologous (128 patients)	*HLA-matched sibling (192 patients)*	*Haploidentical (74 patients)*	*Unrelated (113 patients)*	P-*value*
Total dose					
7, 7.5, 8, 10 Gy[a]	0	11	51	6	<0.000
9.9 Gy	13	54	1	16	
12 Gy, 14.4 Gy	115	126	22	91	
Not recorded		1			
Lung dose					
3.8 Gy–7.5 Gy	1	11	46	4	<0.000
8 Gy–9.81 Gy	31	81	6	29	
9.82 Gy–13 Gy	73	90	14	76	
Not recorded	23	10	8	4	
Testis irradiation[b]					
Yes	23	33	7	24	0.056
No	13	42	17	39	
Not recorded	0	2	0	3	

[a]Administered in single dose. [b]Administered to male patients with ALL.

received 3.3 Gy daily for 3 days (total 9.9 Gy); 321 patients (63.3%) received 2 Gy twice a day for 3 days (total 12 Gy); 33 patients (6.5%), received 1.2 Gy 3 times a day for 4 days (total 14.4 Gy). Single-dose TBI (STBI) was administered at doses of 7, 7.5 or 8 Gy to 65 patients (12.8%) and at 10 Gy to 3. In one case the TBI schedule was not recorded.

Table 2 indicates the TBI parameters (total dose, dose to the lungs, testis irradiation) that were used in each HSCT type. In fractionated and hyper-fractionated schedules, each fraction dose was not analysed as a TBI parameter, as it correlated strongly with the total dose.

Statistical analysis

Prognostic factors (age, disease, disease status and gender) and TBI-related parameters (total and lung doses and testis irradiation) were analysed according to the different types of transplantation. Differences in age were tested by ANOVA. Disease, disease status, gender and TBI-related parameters were analysed by the χ^2-test applied to contingency tables.

OS was estimated by the Kaplan–Meier method; the log-rank test was used to test significance. Probability of relapse was assessed by cumulative incidence analysis, with death as a competitive event; the Gray test was used to test significance.[8,9]

Prognostic factors and TBI parameters, except for testicular irradiation, were tested as risk factors for OS and relapse in univariate and/or multivariate analyses. Although reported to reduce the risk of relapse,[10] testicular irradiation was not analysed because only a minority of patients received it. Autologous and allogeneic transplants were analysed separately because GVHD, which was considered a time-dependent variable, is found only in allogeneic transplantation. Multivariate analysis was performed by Cox proportional hazard models.[11] All *P*-values were two-sided with the type I error rate fixed at 0.05.

Statistical analyses were performed with SPSS 17 (SPSS Inc. Chicago, IL, USA) and R (freely available at www.r-project.org) software packages.

RESULTS

Median follow-up was 40.1 months (range 0.5–121 months)

Prognostic factors and TBI-related parameters were not uniformly distributed in the four HSCT types (Tables 1 and 2). GVHD occurred in 258/379 allogeneic transplant recipients with 74% of cases being Grade I–II. It developed in 140 matched recipients, 24 haploidentical recipients and 94 unrelated recipients.

Median OS was not reached for autologous transplant recipients and HLA-matched sibling donors. Median OS was 7.56 months for haploidentical transplant recipients and 23.16 months for unrelated transplant recipients. The 5-year probability of OS was 61% for autologous transplant recipients, 60% for

HLA-matched sibling transplant recipients, 25% for the haploidentical group and 42% for the unrelated group (Figure 1). Significant differences emerged in probability of OS when matched sibling transplants were compared with haploidentical ($P<0.000$) and unrelated ($P<0.01$) transplants. No significant difference emerged in matched sibling and autologous transplant recipients ($P=0.69$).

The 5-year probability of relapse was 37% (95% CI: 28–46%) after autologous transplantation, 25% (95% CI: 19–31%) after matched sibling transplantation, 13% (95% CI: 7–23%) after the haploidentical and 16% (95% CI: 9–23%) after the unrelated transplants (Figure 2). Autologous transplantation had a significantly higher risk of relapse than matched sibling transplants ($P=0.017$). No significant differences were found between unrelated and haploidentical transplant vs matched sibling transplant.

In autologous transplant, none of the prognostic factors or TBI parameters was significant for OS or relapse in uni- and multivariate analyses. Results of univariate analysis for OS are shown in Table 3.

In the allogeneic transplant setting univariate analysis showed type of transplant, disease, disease status, total dose and lung dose had a significant effect on OS (Table 4). In multivariate analysis, only type of transplant and disease impacted significantly on OS while GVHD reached borderline significance (Table 5, Figure 3). Figure 3 also shows the TBI-related parameters (total dose and lung dose) did not impact significantly on OS.

GVHD, disease and TBI total dose were significant factors for relapse (Table 6). The 5-year probability of relapse was 15% with STBI, 18% with hyperfractionated schemes (2 Gy twice a day for 3 days and 1.2 Gy three times a day for 4 days) and 31% with the fractionated schedule of 3.3 Gy a day for 3 days ($P=0.03$) (Figure 4).

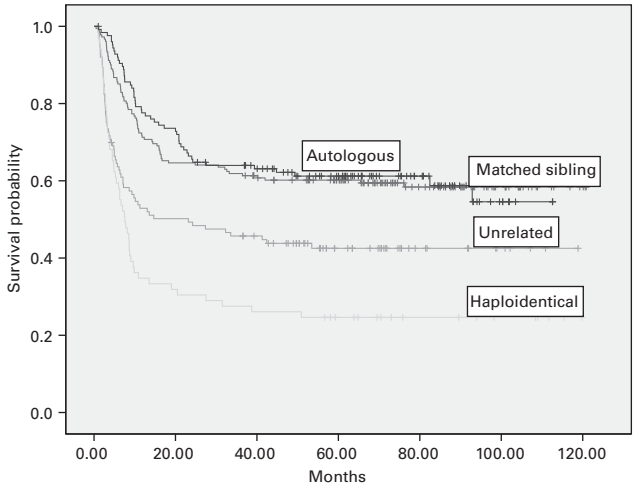

Figure 1. OS according to haematopoietic SCT.

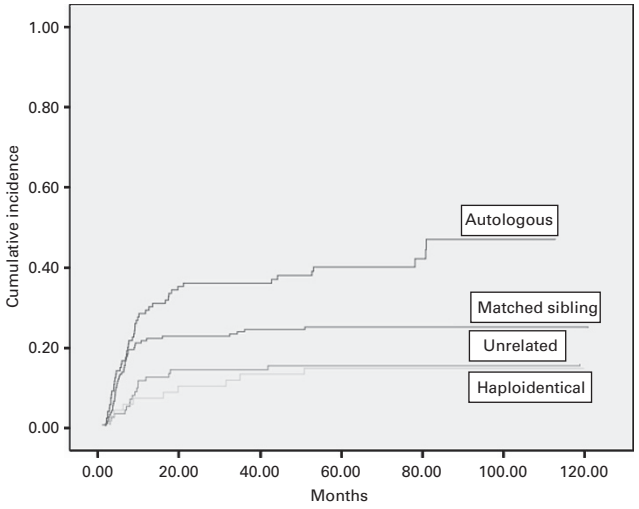

Figure 2. Probability of relapse according to haematopoietic SCT.

DISCUSSION

Deriving from a survey on TBI use among Italian Radiation Oncology Centres, the present study determined whether TBI-related parameters impacted upon the probability of OS and relapse in a series of 507 acute leukemia patients in CR who were irradiated before HSCT at 11 Italian Radiation Oncology Institutions. Prognostic factors such as age, gender, disease and disease status at transplant were unevenly distributed across the diverse forms of HSCT. For example, matched siblings or autologous HSCT were usually given at an earlier disease stage, while transplants from the other HSC sources were generally administered to patients with more advanced stage disease.

What clearly emerged was that TBI schedules and type of HSCT were closely related. As elsewhere, a hyper-fractionated TBI schedule (2 Gy twice a day for 3 consecutive days until a total dose of 12 Gy) was the most common schedule. It accounted for 64% of cases in this series, almost always preceded autologous HSCT, was used in conditioning for 80.5% of unrelated transplants and in 51% of the matched sibling transplant procedures. Hyperfractionated TBI schemes (two or more fractions a day) were developed with the aims of shortening duration of the conditioning regimen and BM aplasia[4,10,12] compared with the original fractionated schedule (12 Gy administered in six fractions over 6 days) that demonstrated a significant survival advantage over STBI (10 Gy at 5c Gy/min) in patients with AML who were transplanted in first remission.[13]

Table 3. Univariate analysis for OS in autologous transplant

Factors	*No. of patients*	*Probability at 5 years*	*s.e.*	*Median time of survival in months*	*P-value*
Age					
⩽18 years	81	0.67	0.053	Not reached	0.061
>18 years	45	0.50	0.075	82	
Disease					
ALL	61	0.55	0.066	92.86	0.23
AML	65	0.66	0.059	Not reached	
Disease status					
CR I	74	0.61	0.057	Not reached	0.88
CR>I	52	0.52	0.10	Not reached	
TBI total dose[a]					
1	0				
2	13	0.75	0.12	Not reached	0.27
3	113	0.59	0.047	Not reached	
Lung dose[b]					
1	1				
2	31	0.63	0.08	Not reached	2 vs 3: 0.86
3	73	0.64	0.057	Not reached	

[a]Total dose: 1 = 7, 7.5, 8 and 10 Gy administered in single dose; 2 = 3.3 Gy a day until 9.9 Gy; 3 = 2 Gy twice a day for 3 days until 12 Gy and 1.2 Gy three times a day for 4 days until 14.4 Gy. [b]Lung dose 1 = from 3.8 Gy to 7.5 Gy; 2 = from 8 Gy to 9.81 Gy; 3 = from 9.82 Gy to 13 Gy.

Table 4. Univariate analysis for OS in allogeneic transplants

Factors	*No. of patients*	*Probability at 5 years*	*s.e.*	*Median time of survival in months*	P-*value*
Age					
≤18 years	197	0.492	0.036	41.3	0.85
>18 years	165	0.469	0.039	38.7	
Type of transplant					
Matched sibling	182	0.60	0.036	Not reached	Matched sibling vs unrelated 0.001
Haploidentical	69	0.24	0.053	7.56	Matched sibling vs haploidentical 0.000
Unrelated	113	0.42	0.047	23.16	Unrelated vs haploidentical 0.027
Disease					
ALL	257	0.439	0.031	18.3	0.010
AML	121	0.576	0.047	Not reached	
Disease phase					
CR I	147	0.55	0.042	Not reached	0.010
CR>I	223	0.44	0.034	19	
TBI total dose[a]					
1	68	0.288	0.061	8.16	1 vs 2: 0.000
2	71	0.57	0.0059	Not reached	2 vs 3: 0.145
3	239	0.494	0.0033	40.13	3 vs 1: 0.003
Lung dose[b]					
1	61	0.24	0.062	8.16	2 vs 3:0.52
2	116	0.54	0.047	Not reached	1 vs 2: 0.000
3	180	0.50	0.0037	76.13	1 vs 3 0.000

[a]Total dose: 1 = 7, 7.5, 8 and 10 Gy administered in single dose; 2 = 3.3 Gy a day until 9.9 Gy; 3 = 2 Gy twice a day for 3 days until 12 Gy and 1.2 Gy three times a day for 4 days until 14.4 Gy. [b]Lung dose 1 = from 3.8 Gy to 7.5 Gy; 2 = from 8 Gy to 9.81 Gy; 3 = from 9.82 Gy to 13 Gy.

Table 5. Multivariate analysis for OS in allogeneic transplants

	HR	*95% CI*	P-*value*
GVHD yes vs no	0.73	0.534–1.008	0.056
AML vs ALL	0.568	0.403–0.799	0.001
Referent transplant: HLA matched sibling	1		
Haploidentical vs matched sibling	2.698	1.834–3.970	0.000
Unrelated vs matched sibling	1.698	1.211–2.381	0.002

Abbreviations: CI = confidence interval; HR = hazard ratio.

Another hyper-fractionated TBI schedule (1.2 Gy three times daily for 4 days until 14.4 Gy) was used for 28 matched sibling transplants who received T cell depleted HSCT to prevent GVHD. It was derived from the 13.2 Gy fractionated into 1.2 Gy thrice daily schedule, which was designed by Shank *et al.*[10] at Memorial Sloan Kettering Cancer Center, New York. The team postulated that small irradiation doses would increase the total dose and showed that hyper-fractionation exerted an effect on the cell cycle with a build-up of cells in the more radiosensitive phases.[10,14] Both factors exerted a greater anti-leukemic effect.[10] The extra dose was added in Perugia with the aim of overcoming the high risks of rejection and relapse that are associated with extensive T cell depletion of the graft. Clinical outcomes confirmed the efficacy of this TBI schedule which was, however, combined with ATG, thiotepa, and CY or, more recently, fludarabine[15–17] to increase the myeloablative power of the conditioning regimen.

In the present study, a fractionated TBI schedule (3.3 Gy until 9.9 Gy in 3 days) was given to 16.6% of cases overall: 13/128 (10%) autologous, 54/192 (28%) matched sibling, 1/74 (1%) haploidentical and 16/113 (14%) unrelated transplants. This regimen was developed in Genoa many years ago to overcome the disadvantages of 10 Gy STBI, which was associated with a high risk of secondary cancers[18] and a 30% transplant-related mortality.[19] The 9.9 Gy schedule was hypothesized to impair neither leukemia cell killing nor clinical outcome as the GVL effect has a major role in allogeneic transplantation.[19] Despite these premises and the good clinical outcomes, this schedule was associated with a higher leukemia relapse rate and a worse OS than 12 Gy (six fractions in 3 days) in unrelated transplant recipients.[19] In our allogeneic HSCT recipients, multivariate analysis showed probability of relapse was higher after conditioning with 9.9 Gy than with either of the two hyperfractionated schedules. Comparing results from Genoa and the present series is, however, difficult due to differences in disease and disease stage at transplant.

Finally, as STBI exerts more powerful immune suppression than fractionated schedules,[20–23] it was predominantly used in haploidentical transplants because of the high risk of rejection across the HLA incompatibility barrier in this setting. At doses ranging from 7 to 8 Gy, and a dose-rate of 0.16 ± 2 Gy/min per midplane, clinical outcomes were good without undue extra-haematological toxicity. Indeed, interstitial pneumonia was almost completely prevented once fludarabine was substituted for CY and the dose administered to the lungs was reduced to 4 Gy.[24–26]

As expected, the probability of OS was higher in autologous and matched sibling transplantation than in the other two allogeneic transplant groups and the probability of relapse was highest in the autologous group. Our results compare well with similar series of autologous transplantation in patients with ALL or AML.[27–32] Unfortunately, despite analysing 128 autologous transplants, we were unable to identify any risk factors that impacted on OS and relapse. Unlike diverse TBI schedules that were used in conditioning to autologous transplantation,[27–29,31] ours were strongly skewed in favor of hyperfractionated schemes. For this reason, it was hardly surprising that neither total nor lung dose emerged as significant risk factors. Age was the only factor that tended towards significance for OS in univariate analysis

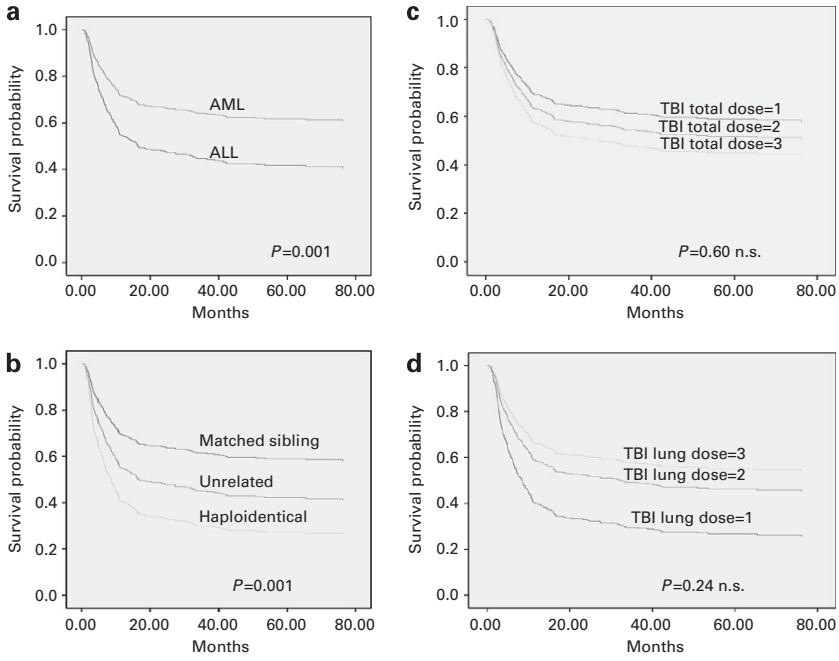

Figure 3. Cox model. OS adjusted curves according to: disease (**a**); type of transplant (**b**); TBI total dose (**c**); TBI lung dose (**d**).

Table 6. Multivariate analysis for relapse in allogeneic transplants

	HR	*95% CI*	P-*value*
GVHD yes vs no	0.482	0.289–0.806	0.005
AML vs ALL	0.526	0.303–0.913	0.022
TBI total dose[a]			
1 (single fraction <10 Gy) vs 3 (fractionated $\geqslant 12$ Gy)	0.947	0.422–2.12	0.896
2 (fractionated <12 Gy) vs 3 (fractionated $\geqslant 12$ Gy)	2.313	1.337–4.003	0.003

Abbreviations: CI = confidence interval; HR = hazard ratio. [a]TBI total dose: 1 = 7, 7.5, 8 and 10 Gy administered in single dose; 2 = 3.3 Gy a day until 9.9 Gy; 3 = 2 Gy twice a day for 3 days until 12 Gy and 1.2 Gy three times a day for 4 days until 14.4 Gy.

(67% $\leqslant$ 18 years vs 50% for age $>$ 18 years, $P = 0.061$). Although the cutoff was usually higher in other series than in ours,[27,28,31,32] we chose 18 years so as to analyse adults and children separately and because 12 years was the median age in the entire cohort of autologous transplants. Despite this cutoff, the age distribution was still imbalanced as 2/3 of patients were 18 years old or younger.

In allogeneic HSCT, multivariate analysis showed HSCT type was a significant prognostic factor for OS, which was significantly better in patients whose donors were HLA-identical siblings. One must bear in mind, however, that patients receiving transplants from unrelated donors or mismatched family members had more advanced-stage disease and had been heavily pretreated, often with several courses of chemotherapy while searching for an appropriate donor. Disease-stage did emerge as a significant factor for OS although only in our univariate analysis. Furthermore, OS was worse in ALL patients, while lack of the GVHD effect had a borderline impact. In multivariate analysis, risk factors for relapse were ALL, lack of the GVHD/GVL effect and total TBI dose. STBI and hyperfractionated schedules with higher biological effective dose values than 9.9 Gy administered in three fractions were associated with a lower risk of relapse, concurring with other reports.[33,34]

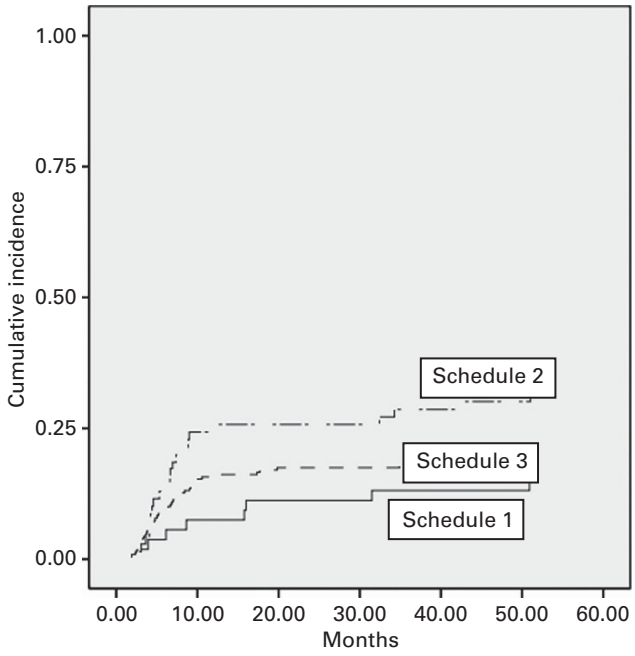

Figure 4. Probability of relapse according to TBI schedule. Schedule 1 = 7, 7.5, 8 and 10 Gy administered in single dose; schedule 2 = 3.3 Gy a day until 9.9 Gy; schedule 3 = 2 Gy twice a day for 3 days until 12 Gy and 1.2 Gy three times a day for 4 days until 14.4 Gy.

Lung dose did not impact upon OS or relapse in multivariate analyses. Even though shielding generally limits it to 75–80% of the total dose so as to reduce the risk of interstitial pneumonia and transplant-related mortality, in some series the ensuing reduced dose to rib BM was linked to a higher incidence of relapse.[35,36] In order to compensate for this lower dose, a boost with electrons was advocated[10] but was not clearly shown to be

advantageous. Indeed, our results with most patients shielded and only 41 patients receiving a boost, confirm that lung protection was not a risk factor for relapse.[34]

In conclusion, the present analysis illustrates that Italian Transplant Centre use of TBI is in line with international practice. Most Italian Centres adopted the same type of hyperfractionated schedule that is used worldwide (12 Gy in six fractions over 3 days), and which appears to have become standard. The only exceptions were the 9.9 Gy regimen in one center and the 14.4 Gy in another offering T cell depleted matched HSCT. The second centre, as its HSCT program focussed on haploidentical transplantation, also administered STBI to a majority of patients.

Biases in this study were its observational design and the close correlation between type of transplant and type of TBI schedule, with the consequent imbalance in patient distribution. Despite this, the study provides evidence to show that TBI total dose is a risk factor for relapse in allogeneic transplantation. Although arduous to perform, randomized multicentric studies are warranted and necessary because their lack hampers comparisons between treatment regimes.[7] In our view, however, any future advances in the use of TBI in HSCT will most probably may not come from variations in fractionation but rather from promising new administration modalities, which will increase the total dose to the marrow without any significant extra-haematological toxicity.[7,37–39]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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