Reports of Practical Oncology and Radiotherapy 25 (2020) 436–441

Available online at www.sciencedirect.com

Reports of Practical Oncology and Radiotherapy

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Once-a-day fractionated total-body irradiation: A regimen tailored to local logistics in allogeneic stem cell transplantation for acute lymphoblastic leukemia

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ARTICLE INFO

Article history:
Received 14 September 2018
Accepted 20 March 2020
Available online 28 April 2020

ABSTRACT

The objective of the study was to estimate the cumulative incidence (CI) of relapse, relapse-free survival (RFS) and overall survival (OS) in ALL patients after a once-a-day fractionated TBI (F-TBI) regimen with 9.9 Gy. The secondary objectives were evaluation of short and long-term toxicity and non-relapse mortality (NRM).

Background: Total body irradiation (TBI), as a part of the conditioning regimen before allogeneic stem cell transplantation (ASCT) for acute lymphoblastic leukemia (ALL), allows disease control by eradicating residual blast cells in the transplant recipient.

Materials and methods: Retrospective study conducted in patients with ALL who received between March 2003 and December 2013 a conditioning regimen with F-TBI and chemotherapy. Irradiation was delivered with 3.3 Gy once-a-day for three consecutive days.

Results: Eighty-seven patients were included. The median age was 19 years (range: 5–49 years). The 3-year CI of relapse was 30%. The estimated 3-year RFS and OS were 54% and 58%, respectively. Cumulative incidence of acute graft-versus-host disease (aGVHD) grade II–IV and chronic GVHD (cGVHD) was 31% and 40%, respectively. Interstitial pneumonitis was observed in 2 patients. The 3-year CI of NRM was 16%. In multivariate analysis, cGVHD was associated with a lower CI of relapse (RR = 0.26, 95% CI: 0.07–0.95, $p = 0.04$). High-risk cytogenetics was associated with a lower RFS (RR = 2, 95 CI: 1.04–3.84, $p = 0.03$). Grade II-IV aGVHD was an independent predictor of higher CI of NRM (RR = 6.7, 95% CI: 1.4–31.7, $p = 0.02$).

Conclusions: Once-a-day F-TBI regimen is effective, safe and practical in patients who underwent ASCT for ALL.

1. Background

Total body irradiation (TBI) is a part of the preparative regimen in allogeneic stem cell transplantation (ASCT) for acute lymphoblastic leukemia (ALL). However, high doses of TBI result in acute and late toxicities. The most commonly used F-TBI schedule is 12 Gy in six fractions, delivered twice daily over 3 days. For logistical reasons, this schedule could not be applied in our center. To circumvent these conditions, we have used once-a-day F-TBI with a total of 9.9 Gy in three fractions delivered over 3 days as reported by others.[1,2] In a previous study, we reported a high early relapse rate in 24 patients transplanted for acute and chronic leukemia who have received this regimen of F-TBI. The heterogeneity and the small size of that series precluded any conclusion to be drawn.[3]

1.1. Aims

The aim of the current study was to evaluate cumulative incidence of relapse, relapse-free survival (RFS), overall survival (OS) in patients who underwent ASCT from an HLA-identical sibling donor for ALL after a once-a-day F-TBI associated to chemotherapy conditioning and to report the short and long-term toxicity and non-relapse mortality (NRM) induced by this regimen.

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https://doi.org/10.1016/j.rpor.2020.03.023
1507-1367/

2. Materials and Methods

2.1. Patients

Between March 2003 and December 2013, patients with ALL underwent ASCT from HLA-identical sibling donors after once-a-day F-TBI and chemotherapy-based conditioning regimen. Clinical and biological data were collected retrospectively. TBI data, dose delivered to the lung, dose rate and types of machine were obtained from the individual case records in the radiotherapy department.

ALL with high-risk cytogenetics include leukemia with *t*(9;22), *t*(4;11) in both adults and children; *t*(1;19), near-haploidy, near-triploidy in adults, and hypodiploidy in children.

Informed consent was obtained from all the patients or legal guardian and the study approved by the local committee.

2.2. Conditioning regimen

Conditioning consisted of once-a-day F-TBI with a total dose of 9.9 Gy (3.3 Gy per day) in three fractions for 3 consecutive days (d-7 until d-5 of the graft infusion), followed by either Etoposide (60 mg/kg per day in d-3), or Cyclophosphamide (60 mg/kg per day for two days: d-3 and d-2).

2.3. TBI technique

TBI was performed by a linear accelerator. The total dose delivered was 10 Gy to the whole body to the mid-plane of the abdomen at an instantaneous dose rate of 4.5 cGy/mn and ranged from 2.8 to 3.94 cGy/mn (mean 3.43 cGy/mn). The dose delivered to the lungs was 9 Gy with protection by a custom cache cerrobend during the second session of irradiation.

2.4. Graft-versus-host disease prophylaxis

All patients received cyclosporin (CsA) at a dose of 3 mg/kg from day −1 until at least day +120 and a short course of Methotrexate (MTX) at a dose of 15 mg/m^2 on day +1 and 10 mg/m^2 on days +3, +6. MTX was withheld in children with advanced disease and who received a bone marrow graft.

2.5. Antifungal and cytomegalovirus prophylaxis

All patients received Fluconazole from day −7 to day +75 and Acyclovir from day +1 to day +180. They were monitored once-a-week from engraftment to day +100 for cytomegalovirus (CMV) by pp 65 antigenemia test.

2.6. Graft sources

All patients received either bone marrow (BM) or peripheral blood stem cells (PBSC) as a graft source from an HLA-identical sibling donor.

2.7. Statistical analysis

Student's *t*-test was used for comparisons of continuous variables. Qualitative variables were analyzed by chi-2 test. For analysis of acute complications, data were censored at day 100 post transplant. Survival curves were estimated by the Kaplan–Meier method and comparisons were made using the log-rank test. Univariate analysis was performed to evaluate predictor factors of RFS, OS, cumulative incidence of NRM and relapse using log-rank test for survival analysis and competing risks approach for cumulative incidence of relapse, NRM, aGVHD and cGVHD.[4,5] Variables with $p < 0.2$ on univariate analysis were entered in a multivariate Cox-regression model to determine their independent contributions to outcome. All tests were performed using SPSS statistical analysis software version 20. The cumulative incidence of relapse and NRM were calculated using the XLSTAT software. All *p*-values were 2-sided and a $p < 0.05$ was considered statistically significant.

Table 1
Patient's characteristics (ad = adults, ch = children, MNC = mononuclear cells, WBC = white blood cell count).

Characteristics	*N* = 87
Children (<18 years)	42 (48.3%)
Adults	45 (51.7%)
Sex-ratio	2.1
Age (years)	19 (5–49)
Median (range)	11 (5–17)
Children	30 (18–49)
Adults	
Phenotype	
B-ALL	50 (57.5%)
T-ALL	37 (42.5%)
WBC at diagnosis ($\times 10^9$/l)	35 (0.7–600)
Median (range)	
Cytogenetic risk	
Standard-risk	51 (58.6%)
High-risk	28 (32.2%)
Not available	8 (9.2%)
Prior chemotherapy	
EORTC 58951	57 (65.5%)
GRAALL 2005	13 (15%)
Others	17 (19.5%)
Time diagnosis-transplant (months)	5 (3–132)
Median (range)	
Disease status at transplant	
CR1	65 (74.7%)
CR2/CR3	16 (18.4%)
Blastic phase	6 (6.9%)
EBMT score ≥ 2	47 (54%)
Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) score	
0	71(81.6%)
≥1	16 (18.4%)
Conditioning regimen	
F-TBI + etoposide	79 (90.8%)
F-TBI + cyclophosphamide	8 (9.2%)
Parameters of TBI dose	
Median dose rate (range)	3.43 cGy/mn (2.8–3.94)
Median dose in abdomen (range)	9.98 Gy (9.49–10.43)
Median dose in mediastinum (range)	10.22 Gy (8.85–11.03)
Median dose in lung (range)	9.03 Gy (8.5–10.11)
<9.4 Gy	*n* = 52 (59.8%)
≥9.4 Gy	*n* = 7 (8%)
Not indicated	*n* = 28 (32.2%)
Stem cell source	
Bone marrow (BM)	63 [28ad/35ch] (72.4%)
Peripheral blood (PB)	24 [17ad/7ch] (27.6%)
GVHD prophylaxis	
Cyclosporin + methotrexate	52 (59.8%)
Cyclosporin	35 (40.2%)
Median CMN $\times 10^8$/kg (range)	2.15 (0.8–4.8)
Median CD34 $\times 10^6$/kg (range)	4.6 (2.28–7.65)

3. Results

3.1. Patient's characteristics

The characteristics of the patients are detailed in Table 1.

3.2. Hematopoietic recovery

Engraftment occurred in all patients. Median time to neutrophil count >0.5 × 10^9/l, and platelet count >20 × 10^9/l were 15 days (range: 6–37 days) and 18 days (range 9–52 days), respectively.

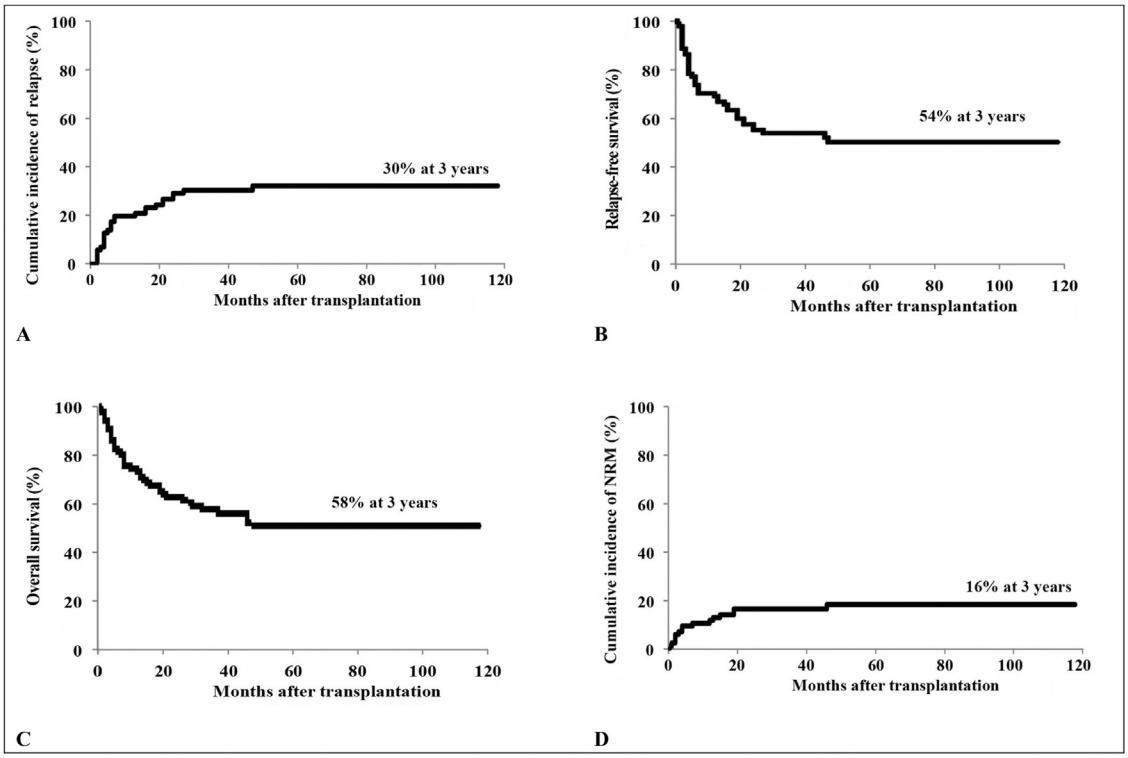

Fig. 1. (A) Cumulative incidence of relapse. (B) Kaplan–Meier estimate of relapse-free survival (RFS). (C) Kaplan–Meier estimate of overall survival (OS). (D) Cumulative incidence of non-relapse mortality (NRM).

3.3. Relapse

Twenty-seven patients relapsed. The 3-year cumulative incidence of relapse was 30% (Fig. 1A). The median time from transplantation to relapse was 27 months (range: 2.3–136 months). The 3-year cumulative incidence of relapse was not different between children and adults (35.7% and 29.9%, respectively, $p = 0.25$). The relapse rate was not significantly different between patients transplanted in CR1 and those transplanted beyond CR1 (30.8% and vs. 45.7%, respectively, $p = 0.28$).

3.4. Relapse-free survival

The estimated 3-year RFS was 54% (Fig.1B). RFS was not statistically different between patients transplanted in CR1 and those transplanted with advanced disease (56.6% vs. 45.5%, respectively, $p = 0.59$). Similarly, no significant difference was found between adults and children recipients ($p = 0.82$).

3.5. Overall survival

After a median follow-up of 36 months (range: 15 days–144 months), the estimated 3-year OS was 58% (Fig.1C). The OS did not differ between children and adults (58.1% vs. 59.3%, respectively, $p = 0.65$).

3.6. Regimen-related toxicities

The frequencies of acute complications are detailed in Table 2.

Pulmonary complications occurred in 17 (21.3%) patients (pneumonia infection in 8 patients, bronchiolitis obliterans in 7 patients and interstitial pneumonitis in 2 patients). Seven patients received a lung dose ≥9.4 Gy.

Ten of 39 patients (25.6%) who had had thyroid-stimulating hormone (TSH) test, developed peripheral hypothyroidism. Among them, 6 patients had clinical hypothyroidism and required treatment.

Table 2
Acute complications.

Complication	No. of patients (%)
Anorexia	72 (82.7%)
Vomiting	58 (66.7%)
Diarrhea	51 (58.6%)
Asthenia	40 (46%)
Parotiditis	39 (44.8%)
Headache	21 (24.1%)
Erythema	5 (5.8%)
Fever	4 (4.6%)
Mucositis	80 (92%)
Clinically documented infections	24 (27.6%)
Microbiologically documented infections	30 (34.5%)
CMV infection	22 (25.3%)
Pulmonary aspergillosis	8 (9.2%)
Sinusoidal obstruction syndrome (SOS)	3 (3.4%)
Macrophage activation syndrome (MAS)	3 (3.4%)
Acute renal failure	9 (10.3%)

Serum concentrations of sex hormones were assessed in only 21 adults and 13 children (older than 13 years for males and 12 years for girls). Peripheral hypogonadism was observed in 12 adults (57.1%) and 6 children (46.2%).

Ocular complications occurred in 10 patients (12.5%): dry eye syndrome in 7 patients and cataracts in 3 patients.

At last follow-up, no patient developed a secondary cancer.

3.7. Acute GVHD

Twenty-seven patients (31%) developed aGVHD grade II-IV (21 BM and 6 PBSC) at a median time of 20 days post transplant (range: 10–50 days). The cumulative incidence of aGVHD grade II–IV was 31%, with 19 grade II (22%), 7 grade III (8%) and 1 grade IV GVHD

Table 3
Univariate analysis.

Factors	No. of patients	CI of relapse at 3 years (%)		OS at 3 years (%)		RFS at 3 years (%)		CI of NRM at 3 years (%)	
		%	P	%	P	%	P	%	P
Recipient age									
Children	42	35.7	0.25	58.1	0.65	52.2	0.82	11.9	0.20
Adults	45	29.9		59.3		55.4		22.2	
Gender									
Female	28	15.8	**0.02***	82.2	**0.01***	78.4	**0.007***	7.1	0.08
Male	59	44.0		48.9		42.3		26.6	
WBC at diagnosis (10^9/l)									
≤30	41	32.3	0.30	57.4	0.84	53.1	0.95	25.5	0.30
>30	46	39.3		59.5		54.3		13.3	
Cytogenetic risk (79 evaluable)									
Standard-risk	51	32.2	0.52	62.0	0.35	58.4	0.07	17.2	0.32
High-risk	28	40.3		53.6		46.4		26.3	
Time diagnosis-transplant									
≤6 months	64	28.8	0.19	61.8	0.56	57.5	0.48	21.6	0.54
>6 months	23	47.8		52.2		43.5		16.3	
Disease status at transplant									
CR1	65	30.8	0.28	62.1	0.35	56.6	0.59	21.0	0.63
>CR1/failure	22	45.7		49.6		45.5		17.8	
Stem cell source									
BM	63	36.0	0.66	59.1	0.89	53.6	0.55	15.4	0.29
PB	24	29.2		58.3		54.2		32.2	
Donor recipient sex combination									
All other	61	26.2	0.25	63.5	0.22	58.9	0.22	14.8	0.53
Female donor, male recipient	26	38.5		47.7		42.3		23.1	
Donor age									
≤20 years	37	40.6	0.24	59.1	0.50	51.0	0.84	13.0	0.22
>20 years	50	29.1		60.6		55.9		24.6	
MTX for GVHD prophylaxis									
Yes	53	39.2	0.30	61.5	0.44	56.5	0.50	17.3	0.79
No	34	31.0		55.6		49.8		21.3	
CMV infection		0.17							
No	65	38.8	56.3		0,30	52.1	0.46	18.2	0,54
Yes	22	20.9	68.2			58.7		23.8	
Grade II-IV aGVHD									
No	60	39.4	0.16	61.2	0.61	54.9	0.43	12.8	0.007*
Yes	27	18.2		55.3		51.6		35.0	
cGVHD									
No	51	42.2	**<10^{-4}***	57.6	0.25	52.7	0.25	6.2	<10^{-4}*
Yes	29	16.2		72.4		68.8		24.6	

* $p \leq 0.05$.

(1%). The cumulative incidence of aGVHD grade II–IV was not significantly different between adults and children (24.4% vs. 38.1%, respectively, $p = 0.17$).

3.8. Chronic GVHD

Chronic GVHD occurred in 29 (36.2%) patients (10 limited, 19 extensive), with a cumulative incidence of 40% at 3 years. The median time to onset of cGVHD was 150 days (range: 109–450 days). Chronic GVHD occurred in 52.4% of adults and 18.4% of children with significant difference ($p = 0.002$), and was significantly more frequent in PBSC recipients than in BM (65% vs. 29%, respectively, $p = 0.002$).

3.9. Non-relapse mortality

Fifteen patients died of causes not related to relapse. The 3-year cumulative incidence of NRM was 16% (Fig.1D). Adult patients had the same probability of NRM as children ($p = 0.20$). The NRM was due to severe infection in 9 cases, GVHD in 5 cases (2 acute, 3 chronic) and to brain hemorrhage in one case.

3.10. Factors affecting relapse, survival and non-relapse mortality

In univariate analysis, gender and cGVHD significantly affected relapse. Gender significantly influenced OS and RFS. Grade II-IV aGVHD and cGVHD significantly increased NRM. There was a statistically significant tendency toward high-risk cytogenetics and shorter RFS (Table 3).

In multivariate analysis, only cGVHD was associated with a lower cumulative incidence of relapse. Patients with high-risk cytogenetics and male patients had lower RFS. Grade II-IV aGVHD was the only significant factor for cumulative incidence of NRM (Table 4).

4. Discussion

For several years, the single-dose TBI remained the standard conditioning regimen for ALL.[6] Then, doses became fractionated because of the high-risk of short and long-term toxicity of the single dose schedule.[7] The most used F-TBI regimen is 12 Gy in 6 sessions over 3 days (2 Gy per session).[6] For logistical reasons, this schedule could not be applied in the radiotherapy department located in another hospital which faced a very high activity that could not be interrupted twice a day for 3 consecutive days for TBI. To overcome this difficulty, we opted for once-a-day F-TBI. To our knowledge, our study is the largest series using a once-a-day 9.9 Gy F-TBI in ALL patients. Only a few groups have used this F-TBI regimen in ALL[1] and AML patients.[2]

4.1. Relapse

In our study, we found a cumulative incidence of relapse of 30% at 3 years. Better outcomes have been reported in series using

Table 4
Multivariate analysis.

	Factors	CI of relapse at 3 years			RFS at 3 years			CI of NRM at 3 years		
	RR	95% CI	*p*	RR	95% CI	*P*	RR	95% CI	*p*	
cGVHD	No	1	0.07 × 0.95	**0.04**	-			×		
	Yes	0.26								
Gender	Female	×			1	1.15-6.04	0.02	×		
	Male				2.64					
Cytogenetic risk	Standard				1	1.04-3.84	0.03			
	High-risk				2					
	Yes									
Grade II-IV aGVHD	No	×			-			1	1.4–31.7	**0.02**
	Yes							6.7		

once-a-day F-TBI with a total dose of 9.9 Gy, with relapse incidence between 7.6% and 20%.[1,2] Nonetheless, Vitale et al.[1], included a few patients with ALL, mostly transplanted in CR1 (12/13).

Compared to hyperfractionated-TBI, our regimen was not inferior in terms of relapse. Indeed, Granados et al.[8] and Eroglu et al.[9] reported more relapses in ALL patients: 47% and 51.1%, respectively. Granados et al.[8] transplanted a small number of patients in CR1, whereas, Eroglu et al.,[9] reported a low incidence of GVHD which could explain the differences with our results. The lower cumulative incidence of relapse in our study may be related to the large use of Etoposide (90.8% of our patients). Etoposide and TBI was reported to be better than Cyclophosphamide and TBI in terms of incidence of relapse and overall survival.[10] In another study including ALL adult patients in CR1 after hyperfractionated-TBI and Cyclophosphamide, Sutton et al.[11] reported similar incidence of relapse. The cumulative incidence of relapse was statistically not different between children and adults, a finding reported by other studies.[8,10] Several reports showed that disease status at transplant was the most independent factor for predicting relapse.[8,10,12] This factor did not seem to be relevant in our study, probably because the small number of patients transplanted with advanced disease. However, we have not studied minimal residual disease for all patients. The use of high doses TBI in order to reduce the relapse risk post transplant is controversial. Hyperfractionated-TBI (≥12 Gy) was associated with a low incidence of relapse[13], especially in patients with ALL transplanted in second remission. Indeed, Corvo et al.[14] reported that 12 Gy hyperfractionated-TBI yields lower relapse rates than 9.9 Gy once-a-day F-TBI in patients with advanced disease (33% vs. 83%, respectively). However, high-dose TBI has been reported by many authors to impact negatively both OS and NRM.[13,15]We did not find such a high incidence of relapse in patients transplanted beyond CR1 but we acknowledge that they constituted a small group.

4.2. Relapse free survival

The estimated 3-year RFS was 54%. In multivariate analysis, a lower RFS was associated with high-risk cytogenetics (RR = 2, 95% CI: 1.04–3.84, $p = 0.03$). Male patients had lower RFS despite no differences in characteristics with female patients (RR = 2.64, 95% CI: 1.15-6.04, $p = 0.02$). We have no explanation to this finding. Jamieson et al.[12] reported a comparable RFS between CR1 (64%) and CR2 (61%) patients after hyperfractionated-TBI (13.2 Gy) and Etoposide. However, they reported a significantly higher rate of cGVHD in non-relapsed patients

4.3. Overall survival

With a median follow-up of 36 months, the estimated 3-year OS was 58%, with no difference between adults and children, and patients transplanted in CR1 and those transplanted beyond CR1. In univariate analysis, a significantly better outcome was observed for female patients. We have no explanation to this finding. Corvo et al.[16] found that the dose of TBI and cGVHD were independent factors affecting OS. Patients with ALL, who had received F-TBI conditioning regimen, had lower OS compared to the hyperfractionated-TBI group, particularly in patients in CR2 (23% vs. 60%, respectively).[14] In our study, the presence of cGVHD did not impact NRM and the OS, probably because it reduced significantly the cumulative incidence of relapse.

4.4. Toxicity

Analysis of toxicity showed that once-a-day F-TBI was generally well tolerated with manageable acute toxicity. Vitale et al.[1] in 18 patients with leukemia conditioned with the same once-a-day F-TBI combined with cyclophosphamide found that the most early complications were grade III gastrointestinal toxicity (50%) and parotiditis (11%). A high rate of SOS was reported in patients with ALL conditioned with 12 Gy (6 fractions) hyperfractionated-TBI.[8,17] In our study, the overall low rate of acute toxicities could be attributed to the selection bias of the patients who were relatively young and transplanted in first complete remission for the most.

4.5. Pulmonary complications

Seventeen patients (21.3%) developed pulmonary complications (pneumonia infection in 8 patients, bronchiolitis obliterans in 7 patients and interstitial pneumonitis in 2 patients). The median dose rate of once-a-day F-TBI was 3.43 cGy/mn. In our study, seven patients received a lung dose ≥9.4 Gy. Volpe et al.[18] found that pulmonary involvement was higher among patients who received a lung dose ≥9.4 Gy, whereas Beyzadeoglu et al.[19] reported that a dose rate >4 cGy/mn was significantly associated with a higher risk of interstitial pneumonitis.

4.6. Secondary cancers

With a median follow-up of 36 months, we found no secondary cancers in our series. Longer follow-up is needed. After hyperfractionated-TBI and cyclophosphamide, Omori et al.[20] reported a cumulative incidence rate of secondary cancers of 2.15% and 6.46% at 5 and 10 years, respectively. Curtis et al.[21] showed that patients who had received 13 Gy or more hyperfractionated-TBI, had an increased risk for secondary cancers.

4.7. GVHD

Cumulative incidence of aGVHD grade II–IV and cGVHD in our series was 31% and 40%, respectively. Lower rates of aGVHD were reported in studies using the same[1] or the hyperfractionated regimen[9], 36% and 22.2%, respectively. Authors who had used the hyperfractionated regimen[9] reported a lower rate of cGVHD (31.1%). In our study and as expected, cGVHD was more frequent

in adults compared to children (52.4% vs. 18.4 %, respectively, $p = 0.002$). Differences may also be explained by the wider use of PB as a stem cell source in adults (37.7%) and bone marrow as a source of stem cell in pediatric population (83.3%).

4.8. Non-relapse mortality

The 3-year NRM in our study was 16%, with no differences among patients with EBMT score risk ≥2 and <2 (21.3% vs. 10%, respectively, $p = 0.15$). Vitale et al.[1] reported a higher NRM (27.7%), knowing that the prevention of GVHD was not homogenous, since MTX according the Seattle protocol was used first and CsA later.

With hyperfractionated-TBI (12 Gy), the incidence of NRM was between 18% and 22%.[8,11] Granados et al.[8] included ALL patients who had undergone autologous SCT, which would probably produce a lower mortality rate related to transplant. The low NRM in our series could be explained by the young age of transplant recipients (median 19 years) even in adults (median 30 years), the use of geno-identical sibling donor for all patients and the small number of patients transplanted with an advanced disease. In multivariate analysis, the occurrence of grade II–IV aGVHD was significantly associated with a higher cumulative incidence of NRM (RR = 6.7, 95% IC: 1.4–31.7, $p = 0.02$). Belkacemi et al.[22] reported a five-year NRM of 37% with hyperfractionated-TBI (12 Gy), significantly higher in patients who had experienced GVHD.

In practical terms, once-a-day conditioning permitted us to use once-a-day F-TBI with fewer resources and less inconvenience for the patients. With this regimen, the radiotherapy department highly solicited, was spared supplementary sessions.

However, our study has some limitations. It is retrospective including a relatively heterogeneous population regarding the type of chemotherapy regimens received before transplant, and it included both adults and children. However, it included only ALL patients, mostly transplanted in CR1 and who had mostly received the same conditioning, the same total dose of TBI and the same dose rate.

Our study showed encouraging results in terms of OS and RFS, which were not inferior to those, reported by other teams who used the same or the hyperfractionated regimen in ALL patients. We have also found that such once-day F-TBI schedule was associated with low NRM. The overall outcome was not statistically different between pediatric and adult patients, which could be explained by the young age of the whole group.

5. Conclusions

Once-a-day F-TBI is a viable alternative to hyperfractionated-TBI in ASCT for ALL with satisfactory OS, RFS and a low NRM. It can be safely proposed to ALL patients in centers that face logistic difficulties to perform hyperfractionated-TBI.

Conflict of interest

None declared.

Financial disclosures

None declared.

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