: medac

TREOSULFAN IN HSCT

Abstracts

HIGHLIGHTS PRESENTED AT ASH 2023

Dear Reader,

We are pleased to share with you some selected abstracts on the use of Treosulfan-based conditioning treatment prior to stem cell transplantation presented at the 65th Annual Meeting of the American Society of Hematology 2023 in San Diego.

Besides three oral presentations, a variety of posters was presented, showing the use of Treosulfan in conditioning for different diseases in both children and adults up to elderly patients over 65 years of age.

We hope you will enjoy reading this overview on the most recent results on Treosulfan-based conditioning and we are looking forward to meeting you in person at further interesting conferences.

Best regards from Wedel,

Yours,
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Contents

ABBREVIATIONS

a/cGvHD	Acute/chronic Graft-versus-Host-Disease
ALL	Acute Lyphoblastic Leukemia
allo	Allogeneic
AML	Acute myeloid leukemia
ATG	Anti-thymocyte globulin
AYA	Adolescent and young adult
BCP	B-cell precursor
BCR/ABL	Philadelphia chromosome
BM	Bone marrow
Bu	Busulfan
CI	Confidence interval / cumulative incidence
CIR	Cumulative incidence of relapse
CMML	Chronic myelomonocytic leukemia
CMV	Cytomegalovirus
CR	Complete remission/response
Cy	Cyclophosphamide
DCC	Donor chimerism
DFS	Disease-free survival
EFS	Event-free survival
ELN	European Leukemia Net
FB	Fludarabine/Busulfan
FBT	Fludarabine/Busulfan/Thiotepa
FLAMSA	Fludarabine/Amsacrine/Cytarabine
Flu	Fludarabine
FSH	Follicle stimulating hormone
FT	Fludarabine/Treosulfan
FTT	Fludarabine/Treosulfan/Thiotepa
GRFS	GvHD and relapse free survival
haplo	Haploidentical
HCT-CI	Hematopoietic cell transplant comorbidity index
HR	High risk / Hazard ratio
HSCT	Hematopoietic stem cell transplantation
HYPO	Hypodiploidy
LFS	Leukemia-free survival
MAC	Myeloablative conditioning
MD	Matched donor
MDS	Myelodysplastic syndrome
Mel	Melphalan
MF	Myelofibrosis
mo	Months
MPN	Myeloproliferative neoplasia
MRD	Minimal residual disease
MSD	Matched sibling donor
MVA	Multivariate analysis
NRM	Non-relapse mortality
n.s.	not significant
OS	Overall survival
Pts	Patients
PFS	Progression-free survival
PSM	Propensity score matching
PTCy	Post-transplantation cyclophosphamide
r/r	Relapsed/refractory
RCT	Randomized controlled trial
RFS	Relapse-free survival
RIC	Reduced-intensity conditioning
RTC	Reduced-toxicity conditioning
RWD	Real-world data
SCD	Sickle-cell disease
SM	Secondary malignancy
SOS	Sinusoidal obstruction syndrome
TB	Thiotepa / Busulfan
TBI	Total body irradiation
TCD	T-cell depletion
TDT	Transfusion dependent thalassemia
TFS	Thalassemia-free survival
TGFS	Thalassemia GVHD free survival
TKI	Tyrosine kinase inhibitor
TPLL	T-cell prolymphocytic leukemia
Treo	Treosulfan
TRM	Transplant-related mortality
TT	Thiotepa
TV	Testicular volume
VP16	Etoposide
VOD	Veno-occlusive disease
XIAP	X-linked inhibitor of apoptosis
y	Years

TREOSULFAN RELATED PRESENTATIONS – ADULT PATIENTS

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Treosulfan Compared to Busulfan in Allogeneic Haematopoietic Stem Cell Transplantation for Myelofibrosis: A Registry-Based Study from the Chronic Malignancies Working Party of the EBMT

#473
Oral presentation

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Study design	Retrospective registry analysis	**Aim**	Compare outcomes of MF HSCT following TREO and BU based MAC or RIC regimens
Patients	530	**Median age**	63 y (39 - 76)
Disease	MF		
Conditioning regimen	Treo + (mostly) Flu (n=73) or Bu + (mostly) Flu ± other (n=457)		
Results 3 y OS	62%, Treo significantly better than BuMAC (HR 0.61) and trend to better OS than BuRIC (HR 0.92)		
3 y PFS	49%, Treo significantly better than BuMAC (HR 0.57) and BuRIC (HR 0.60)		
3 y CIR	26%, Relapse risk similar between regimens		
3 y NRM	25%, Treo significantly better than BuMAC (HR 0.44) and trend to better NRM than BuRIC (HR 0.54)		
Conclusion	• Better PFS with Treo-based regimens compared to Bu-based conditioning in patients with MF receiving HSCT. • Compared to MAC Bu-based conditioning, Treo-based regimen was also associated with better OS and NRM. • Prospective studies are needed.		

Abstract

Background

The optimal conditioning prior to allogeneic stem cell transplantation (HSCT) for myelofibrosis (MF) remains an ongoing matter of debate. There is a paucity of randomized trials robustly showing superiority of one over another. Registry studies comparing reduced intensity conditioning (RIC) versus myeloablative conditioning (MAC) regimens did not show significant differences in overall survival (OS). Recently, a multi-center phase 3 trial in MDS-AML reported an advantage of fludarabine-treosulfan (TREO) over fludarabine-busuflan (BU) RIC (Lancet Haematol Beelen et al 2020). The role of this large EBMT registry study was to compare outcomes of MF HSCT following TREO and BU based MAC or RIC regimens.

Methods

Patients with MF transplanted from a T-cell replete graft between 2010-2018 following BUMAC, BURIC or TREO were identified in the EBMT registry. Patients who were transformed into AML were excluded. Centers were contacted to participate in additional data collection. 63 centers included a total of 536 patients of whom 6 patients were excluded due to missing data for major endpoints (relapse or regimen). The role of TREO was tested in multi-variable models adjusted on major prognostic factors especially those who were not well balanced between groups and using multiple imputation for missing values.

Results

Most TREO (n=73) patients received it in combination with FLUDARABINE (95%) and most BU (n=457) received FLUDARABINE +/- other (93%). Median total dose received of TREO was 42 g/m^2 and median dose of BU was 8mg/kg. Main differences between the 3 groups were: 1) Recipient age; patients were the oldest in the RIC group (median age 61 years, (IQR: 55-65), the youngest in BUMAC (56 years, (IQR: 51-62)), and intermediate in the TREO group (59 years, (IQR: 54-64); 2) Performance status; Karnofsky score was < 80 in 20%, 30%, 42% in the TREO, BUMAC and BURIC groups, respectively; 3) Comorbidity score (HCT-CI) was lowest in the MAC group (HCT-CT 'low' in 56%, 45% and 37% of BUMAC, BURIC and TREO groups); 4) Disease status; patients in the TREO group were more often transplanted with progressive disease (58% vs 30% in BUMAC and 34% in BURIC); 5) JAK inhibitor prior to HSCT; a higher proportion of patients in the TREO group were treated with a JAK inhibitor before HSCT (61% vs 50% in BUMAC and 42% in BURIC); 6) Cytomegalovirus (CMV) donor/ recipient status; CMV combinations were more frequently donor recipient -/- in the TREO cohort (41% vs 28% in MAC and 36% in RIC); 7) an HLA matched sibling donor was less frequently used in TREO group (18% vs. 28% in BURIC and 36% in BUMAC). The 3 groups were well balanced regarding period of transplantation, MF classification (primary versus secondary), splenomegaly at time of transplantation, chromosome abnormalities, MF related symptoms, DIPSS score, GVHD prophylaxis and use of ATG. Median time to neutrophil recovery was 17 days (range: 6-54), with no differences between the 3 groups. Cumulative incidence of engraftment at day 30 was 91.5% (95%CI: 89.1-93.9), with no differences between the 3 groups. Cumulative incidence of grade 2-4 acute GVHD at 120 days for the entire cohort was 23% (95%CI: 19-26%); similar in the 3 groups. Three-year OS was 62% (95% CI 58 -66), 3-year PFS was 49% (45-53). At 3 years, cumulative incidence of relapse was 26% (22-29) and NRM was 25% (21-29). Figure 1 shows OS, PFS, NRM and cumulative incidence of relapse (CIR) according to regimen. Multiple variables Cox models after selection are shown in Table 1. TREO group had a significantly better OS than BUMAC (HR: 0.61, 95%CI: 0.39-0.93), BURIC had similar OS to BUMAC (HR: 0.92, 95%CI: 0.68-1.26) and there was a trend for a better OS with TREO over BURIC (HR: 0.66, 95%CI: 0.41-1.05). The same trend was also observed for PFS with a significant advantage of TREO over BUMAC (HR: 0.57, 95%CI: 0.38-0.84) and BURIC (HR: 0.60, 95%CI: 0.39-0.91) while BURIC had a similar risk to BUMAC (HR: 1.05, 95%CI: 0.80-1.39). The improvement of OS and PFS was related to a lower NRM (HR: 0.44, 95%CI: 0.24-0.80 TREO vs BUMAC; HR: 0.54, 95%CI: 0.28-1.04 TREO vs BURIC) and same relapse risk with TREO over BU (TREO vs BUMAC, HR: 0.71, 95%CI: 0.42-1.20; TREO vs BURIC, HR: 0.63, 95%CI: 0.36-1.11).

Conclusion

TREO based regimens compared to BU based shows better PFS in MF HSCT. This advantage was also confirmed for OS and NRM when compared to BUMAC. More specific prospective studies are needed to confirm findings from this registry based study.

	Overall survival	P-value	PFS	P-value	NRM	P-value
BURIC vs BUMAC	0.92 (0.67-1.26)	0.599	0.97 (0.73-1.27)	0.808	0.82 (0.55-1.22)	0.324
Treosulfan vs BUMAC	0.61 (0.39-0.93)	0.023	0.59 (0.40-0.86)	0.007	0.45 (0.25-0.81)	0.008
Treosuflan vs BURIC	0.66 (0.41-1.05)	0.079	0.61 (0.40-0.92)	0.02	0.55 (0.28-1.05)	0.067
Age	1.02 (1.00-1.03)	0.066				
Disease stage						
Partial response	1		1		1	
Stable	1.31 (0.79-2.18)	0.288	1.16 (0.76-1.77)	0.488	1.20 (0.67-2.14)	0.545
Progressive	1.85 (1.10-3.11)	0.021	1.54 (0.99-2.38)	0.054	1.79 (0.99-3.26)	0.056
CALR mutated	0.65 (0.40-1.03)	0.069	0.57 (0.38-0.86)	0.008	0.59 (0.33-1.06)	0.076
DIPSS						
Low	1		1			
Int-1	2.70 (0.84-8.66)	0.094	2.16 (0.90-5.19)	0.085		
Int-2	3.04 (0.98-9.39)	0.054	2.72 (1.15-6.41)	0.022		
High	3.19 (1.02-9.93)	0.045	2.64 (1.12-6.19)	0.026		

Table 1. Multiple Cox model after selection

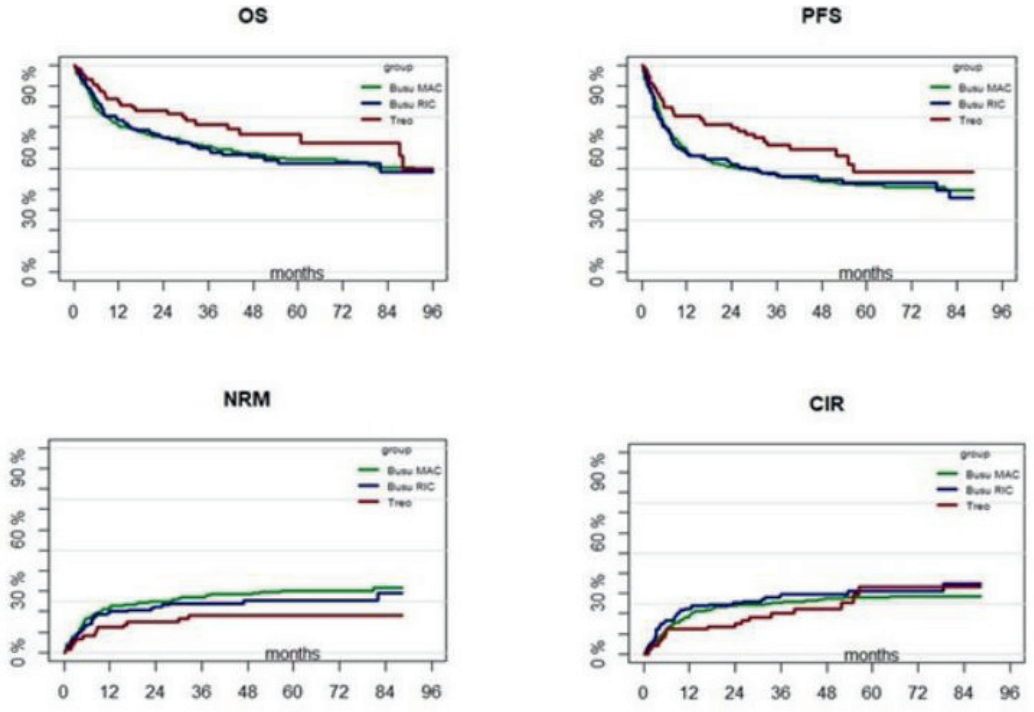

Figure 1. Outcome according to conditioning regimen

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Sequential Conditioning Does Not Improve Outcomes of Allogeneic Stemcell Transplantation in CMML Patients

#2156
Poster presentation

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Study design	Retrospective study	**Aim**	Comparison of TB with FLAMSA-FB and FT12 in CMML	
Parameters assessed	OS, PFS, NRM, CIR, a/cGvHD			
Patients	69	**Median age (range)***	63 y (50 - 69) TB 59 y (30 - 75) FLAMSA-FB 69 y (52 - 79) TB	
Disease	CMML			
Conditioning regimen	**TB** TT (Σ 10 mg/kg) Bu (Σ 6.4 or 9.6 mg/kg)	**FLAMSA-FB** Amsa (Σ 400 mg/m²) Flu (Σ 120 mg/m²) AraC (Σ 4 g/m²) after 3 d interval: Bu (Σ 6.4 mg/kg) Flu (Σ 60 mg/m²)	**FT12** Treo (Σ 36 mg/m²) Flu (Σ 150 mg/m²)	p
Results				
n	22	27	20	
3 y OS	84%	37%	49%	0.07
3 y PFS	79%	30%	30%	0.03
3 y NRM	17%	30%	26%	0.07
3 y CIR	0%	41%	43%	0.02
aGvHD grade II-IV	41%	35%	30%	0.75
cGvHD	50%	65%	40%	0.35
Conclusion	• Sequential conditioning with FLAMSA-FB does not improve transplant outcomes in patients undergoing alloHSCT for CMML.			

*Numbers different from abstract were taken from presentation.

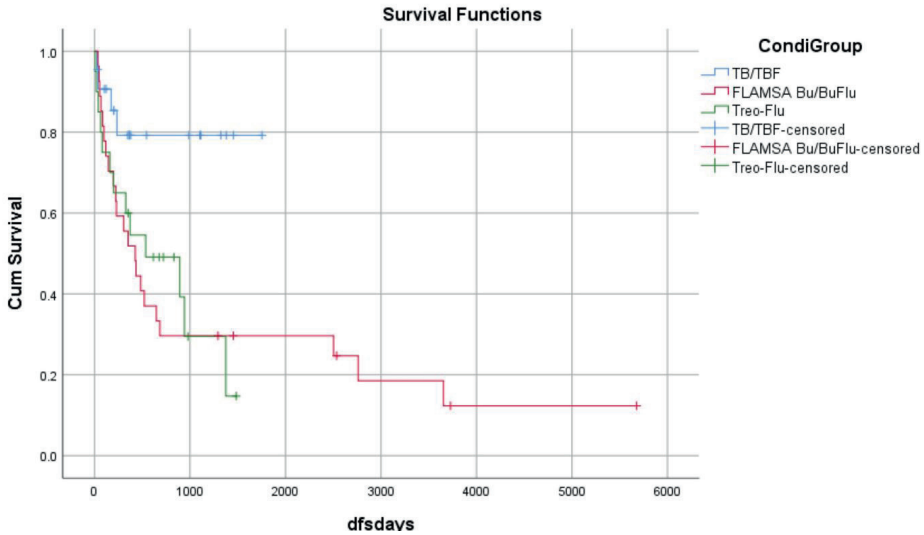
Abstract

Background
Allogeneic stem cell transplantation (SCT) is potentially curative therapy for patients with CMML. Data on optimal allo-SCT conditioning in CMML Patients is scarce.

Methods
This retrospective study from the Department of Stem Cell Transplantation at the University Medical Center Hamburg, Germany, compared allo-SCT outcomes in CMML patients across three conditioning regimes: Thiotepa-Busulfan (TB), Sequential FLAMSA-Busulfan Fludarabine (FLAMSA-FB), and Treosulfan-Fludarabine (Treo-Flu). TB consisted of Thiotapa (5mg/Kg; a total dose of 10mg/Kg) on day -6 and -5 and Busulfan (3.2mg/Kg; total dose 6.4mg/Kg or 9.6mg/Kg) on days -4 and -3 or -4 to -2. FLAMSA-FB regimen consists of fludarabine (30 mg/m^2 ; total dose 120 mg/m^2), amsacrine (100 mg/m^2 ; total dose 400 mg/m^2), and cytarabine (1 g/m^2 ; total dose 4 g/m^2) therapy from days -11 to minus -8, followed by a three-day interval without therapy and Busulfan from day -4 to -2 with a total dose of 6.4mg/Kg and Fludarabine on day -4 and -3 (30 mg/m^2, total dose 60mg/m 2).Treo-Flu regimen consisted of Treosulfan (12 g/m^2 , total dose 36 mg/m^2) on days-6 to -4 and fludarabine (30 mg/m^2 ; total dose 150 mg/m^2) on days -6 to -2.

Results
Sixty-nine consecutive patients with CMML who underwent allo-SCT between the years 2006-2022. Twenty-two received TB, 27 received FLAMSA-FB, and 20 received Treo-Flu conditioning. Transplant sources included matched related donors (MRD, 8 patients), mismatched related donors (MMRD, 8 from TB), matched unrelated donors (MUD, 31), and mismatched unrelated donors (MMUD, 23) with significant group variations (p<0.001). Most Patients received ATLG for GVHD prophylaxis (TB 68%, FLAMSA-FB 93%, Treo-Flu 85%, p=0.08). Regarding CPSS-mol scores, the TB group exhibited a significantly higher proportion of high (46%) and intermediate-2 scores (32%) than FLAMSA-FB (11% high, 7% intermediate-2) and Treo-Flu (40% high, 20% intermediate-2) (p=0.001). One TB patient experienced primary graft failure, but engraftment times were comparable across groups. Although not statistically significant (p=0.07), the TB group showed a trend towards improved 3-year OS rates (84%) compared to FLAMSA-FB (37%) and Treo-Flu (49%). The TB group also displayed significantly higher 3-year PFS rates (79%) compared to FLAMSA-FB and Treo-Flu (both 30%), (p=0.03). (Figure 1) No significant differences were observed in 3-year non-relapse mortality (NRM) across the TB (17%), FLAMSA-FB (30%), and Treo-Flu (26%) groups (p=0.7). Interestingly, no TB patients relapsed at 3 years, contrasting with the FLAMSA-FB (41%) and Treo-Flu groups (43%, p=0.02). Lastly, cumulative incidences of acute GVHD grade II-IV (TB 41%, FLAMSA-FB 35%, Treo-Flu 30%, p=0.75) and all-grade chronic GVHD (TB 50%, FLAMSA-FB 65%, Treo-Flu 40%, p=0.35) were similar across groups.

Conclusion
Our study suggests that sequential conditioning with FLAMSA-FB does not improve Transplant outcomes in patients undergoing allo-SCT for CMML.



Allogeneic Hematopoietic Stem Cell Transplantation with Treosulfan -Fludarabine and Busulfan-Fludarabine Conditioning Have Similar Efficacy in Patients ≥65 Years Old or Those with Comorbidities

#2166
Poster presentation

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Study design	Single center retrospective analysis	**Aim**	Efficacy of FT vs FB4 in older or comorbid adults
Parameters assessed	OS, CIR, TRM, a/cGvHD, GRFS		
Patients	190	**Median age**	65 y (FT and FB4 older) 58 y (FB4 younger)
Disease	AML, MDS, MPN, ALL, other		

Conditioning regimen	**FT**	**FB4 younger** (pts <65 y and HCT-CI ≤2)	**FB4 older** (pts ≥65 y and HCT-CI >2)
Results			
n	57	61	72
OS	40.4%	52.5%	44.4%
CIR	24.6%	16.4%	18.1%
TRM	36.8%	32.8%	36.1%
aGvHD	38.6%	50.8%	40.3%
cGvHD	15.8%	34.4%	25.0%
GRFS	26.3%	32.8%	37.5%

Conclusion

- In older patients or in those with comorbidities, FT appears to be as efficient as FB4 conditioning.
- Outcomes are comparable to those observed in younger patients conditioned with FB4.

Abstract

Background

Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for hematological malignancies. Myeloablative conditioning (MAC) results in a better disease-free survival (DFS) compared to reduced-intensity conditioning (RIC). However, the use of MAC in older adults or in those with comorbidities is limited due to a high rate of non-relapse mortality (NRM). Treosulfan-based conditioning regimens were found to result in superior DFS compared to RIC, without increased NRM. However, patients over the age of 65 were less represented in trials assessing the safety and efficacy of treosulfan-based conditioning relative to MAC. In recent years, fludarabine-treosulfan (FT) conditioning was used at Rambam for patients ≥65 years old, or for those with an HCT – comorbidity index (HCT-CI) score >2. This study aimed to evaluate the efficacy of the FT conditioning protocol and fludarabine-busulfan for 4 days (FB4) in older adults or in those with comorbidities.

Methods

This single-center retrospective study included the following 3 groups: 1) patients who received the FT protocol; 2) patients aged <65 years with HCT-CI ≤2, who received the FB4 protocol; 3) patients aged ≥65 and/or with HCT-CI >2, who received the FB4 protocol. The results of patients included in group 2 were used as a reference. Data were retrieved from the electronic medical records. Baseline characteristics, transplant outcomes and complications were compared. Categorical variables and non-parametric variables were evaluated with the Fisher's exact test and Mann-Whitney U test, respectively.

Results

One hundred and ninety patients were analyzed. All underwent HSCT between January 2015 and December 2021 (table 1). The FT group, younger and older FB4 groups included 57, 61 and 72 patients, respectively. Patient median age was 65 years in both the FT and older FB4 groups, compared to 58 in the younger FB4 group ($p<0.05$). Patients in the FT group had significantly more comorbidities compared to younger FB4 ($p<0.001$) and older FB4 groups ($p=0.005$), with a median HCT-CI of 4, 0 and 3, respectively. During a median follow-up of 48.8 months, there were no significant differences between the groups in terms of the incidence of acute graft-versus-host disease (GVHD), disease relapse, NRM or overall survival (table 2). However, the chronic GVHD rate was 34.4% in the younger FB4 group and only 15.8% in the FT group ($p=0.035$). This rate was 25% in the older FB4 group (p=NS). Mucositis rate was significantly lower in the FT group, with 31.6% of patients being mucositis-free, compared to 6.6% and 13.9% in the younger and older FB4 groups, respectively. However, the rate of bacteremia events was significantly increased in the FT group (49.1%) relative to the younger FB4 (13.1%) and the older FB4 (23.6%) groups.

Conclusions

In older patients or in those with comorbidities, FT appears to be as efficient as FB4 conditioning. Furthermore, these outcomes are comparable to those observed in younger patients conditioned with FB4. Hence, both of the evaluated regimens could be considered in these patient populations. Prospective randomized studies are warranted to further evaluate these findings.

Table 1. Patients and transplant characteristics

Patients group	FT protocol (Group 1) n=57	FB4 protocol With age <65 and HCT- CI ≤2 (Group 2) n=61	FB4 protocol With age ≥65 Or HCT- CI >2 (Group 3) n=72	P value Group 1 Vs Group 2	P value Group 1 Vs Group 3	P value Group 2 Vs Group 3
Median age in years [range]	65 [19-74]	58 [19-64]	65 [22-72]	0.002	0.846	<0.001
Female gender, n (%)	22 (38.6%)	21 (34.4%)	31 (43.1%)	0.78	0.741	0.402
Diagnosis, n (%)				0.25	0.094	0.291
AML	35 (61.4%)	32 (52.5%)	44 (61.1%)			
MDS	12 (21%)	16 (26.2%)	12 (16.7%)			
MPN	5 (8.8%)	11 (18%)	12 (16.7)			
ALL	5 (8.8%)	2 (3.3%)	1 (1.4%)			
Other	0 (0%)	0 (0%)	3 (4.2%)			
*Disease status CR, n /N(%)	35/40 (82.5%)	33/34 (97%)	41/45 (91.1%)	0.538	0.741	0.878
Donor type, n (%)				0.532	0.264	0.021
Match Related Donor	20 (35.1%)	27 (44.3%)	19 (26.4%)			
Match Unrelated Donor	30 (52.6%)	26 (42.6%)	48 (66.7%)			
Mis- Matched Unrelated Donor or Mis- Matched Related Donor	7 (12.3%)	8 (13.1%)	5 (6.9%)			
Female donor to male recipient transplant, n (%)	8 (14%)	12 (19.7%)	8 (11.1%)	0.569	0.817	0.257
GVHD prophylaxis, n (%)				0.017	0.019	0.562
1. CSA/MTX	46 (80.7%)	60 (98.4%)	70 (97.2%)			
2. CSA/MMF	8 (14%)	1 (1.6%)	2 (2.8%)			
3. Tac/MTX	1 (1.8%)	0 (0%)	0 (0%)			
4. Tac/MMF	2 (3.5%)	0 (0%)	0 (0%)			
ATG use	42 (73.7%)	36 (59%)	53 (73.6%)	0.137	1	0.11
HCT- CI, Median [range]	4 [0-8]	0 [0-2]	3 [0-6]	<0.001	0.005	<0.001
Donor/recipient CMV status, n (%)				0.075	0.032	0.615
Positive/ positive	34 (60.7%)	40 (66.7%)	52 (73.2%)			
Negative/ negative	4 (7.1%)	6 (10%)	3 (4.2%)			
Positive/ negative	12 (21.4%)	14 (23.3%)	16 (22.5%)			
Negative/ positive	6 (10.7%)	0 (0%)	0 (0%)			
ABO mismatch type, n (%)				0.06	0.131	0.397
Matched	28 (50%)	23 (38.3%)	37 (52.1%)			
Major	17 (30.4%)	15 (25%)	16 (22.5%)			
Minor	11 (19.6%)	16 (26.7%)	12 (16.9%)			
Bi-directional	0 (0%)	6 (10%)	6 (8.5%)			

*CR status is relevant only for a diagnosis of AML or ALL. n= patients in CR, N= patients with AML or ALL. Diagnosis groups: AML: acute myeloid leukemia, MDS: myelodysplastic syndrome, MPN: Myeloproliferative neoplasms, ALL: Acute lymphoblastic leukemia, Other: T-cell prolymphocytic leukemia, Hemophagocytic lymphohistiocytosis or Chronic lymphocytic leukemia. CR: Complete response, ATG: anti thymocyte globulin, GVHD: graft versus host disease, CSA: cyclosporine A, MTX: Methotrexate, MMF: Mycophenolate mofetil, Tac: Tacrolimus, HCT- CI: Hematopoietic Cell Transplantation-specific Comorbidity Index.

Table 2. Transplant outcomes

Patients group	FT protocol (Group 1) n=57	FB4 protocol With age <65 and HCT- CI ≤2 (Group 2) n=61	FB4 protocol With age ≥65 Or HCT- CI >2 (Group 3) n=72	P value Group 1 Vs Group 2	P value Group 1 Vs Group 3	P value Group 2 Vs Group 3
ANC engraftment, days post transplant, median [range]	18 [10-42]	16 [10-25]	14 [8-20]	0.044	<0.001	0.022
PLT engraftment, days post transplant, median [range]	15 [9-153]	12.5 [8-48]	13 [8-168]	0.001	0.002	0.702
Length of stay	31 [12-92]	31 [24-76]	31 [19-56]	0.53	0.849	0.439
¥Overall survival, n alive (%)	23 (40.4%)	32 (52.5%)	32 (44.4%)	0.257	0.774	0.455
¥Relapse rate, n (%)	14 (24.6%)	10 (16.4%)	13 (18.1%)	0.383	0.494	0.982
¥Transplant related mortality rate, n (%)	21 (36.8%)	20 (32.8%)	26 (36.1%)	0.788	1	0.827
*‡Acute GVHD rate, n (%)	22 (38.6%)	31 (50.8%)	29 (40.3%)	0.251	0.99	0.297
‡Chronic GVHD rate, n (%)	9 (15.8%)	21 (34.4%)	18 (25%)	0.035	0.29	0.318
¥GRFS status, n (%)	15 (26.3%)	20 (32.8%)	27 (37.5%)	0.57	0.247	0.701

* Acute GVHD Grades 2-4. ‡ Acute and chronic GVHD rates by day 180 post transplant.

¥ Actual rates for the median follow up of 48.8 months [range, 1-94].

ANC: absolute neutrophil count, PLT: platelets, GVHD: graft versus host disease. GRFS: GVHD relapse free survival.

Treosulfan-Based Conditioning Prior to Allogeneic Hematopoietic Stem Cell Transplantation (alloHSCT) for Patients with Myelodysplastic Syndrome (MDS): Comparative Analysis of a Randomized Controlled Trial and Real-World Data

#3526
Poster presentation

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Study design	Retrospective analysis	**Aim**	Comparison of RCT results with RWD in pts with MDS receiving Treo-based conditioning
Parameters assessed	Baseline characteristics, OS, RFS, relapse/progression, engraftment, safety in whole cohort and propensity score matched analysis		
Patients	195 (of which n=53 each pair-matched pts)	**Median age (range)**	62 y (39 – 76)
Disease	MDS (n=84 from RCT, n=111 RWD)		
Conditioning regimen	FT10: Treo 30 g/m^2, Flu		

Results	**RCT**	**RWD**	**p**
2 y OS	73%	72%	n.s.
2 y RFS	68%	67%	n.s.
2 y CIR	11%	15%	n.s.
2 y NRM	21%	18%	n.s.
Engraftment @28d			
neutrophils	93%	94%	n.s.
platelets	89%	93%	n.s.
PSM sensitivity analysis	Comparable efficacy		

Conclusion

- Efficacy and safety of Treo-based conditioning therapy prior to alloHSCT in post-authorization real world setting are comparable with the results from RCT.
- BM blast count is not strong predictor for survival, making Treo-based conditioning promising even for pts with increased blasts.

Further reading: Beelen DW, Stelljes M, Reményi P, et al. Treosulfan compared with reduced-intensity busulfan improves allogeneic hematopoietic cell transplantation outcomes of older acute myeloid leukemia and myelodysplastic syndrome patients: Final analysis of a prospective randomized trial. Am J Hematol. 2022;97(8):1023-1034. doi:10.1002/ajh.26620 *https://onlinelibrary.wiley.com/doi/10.1002/ajh.26620*
Stelljes et al. Favourable Outcome after Treosulfan Based Conditioning of Patients Receiving an Allogeneic Hematopoietic Cell Transplantation (AlloHCT) for the Treatment of a Myelodysplastic Syndrome (MDS) (TCT congress 2022)

Abstract

Introduction

MDS is a clonal myeloid disorder manifested by diverse genotypes and phenotypes, characterized by ineffective hematopoiesis. AlloHSCT is the only potential curative therapy for MDS. Myeloablative conditioning regimens are integral part of alloHSCT that allow engraftment and provide a therapeutic effect. Treosulfan has myeloablative and immunosuppressive properties and provides less transplantation related mortality than some of the traditionally used myeloablative conditioning regimens like busulfan-based treatments. In our analysis, we compared the results from the MDS subgroup of the randomized controlled trial (RCT) MC-FludT.14/L (NCT00822393) with real-world data (RWD) of patients treated at the University Hospital Münster and the University Hospital Dresden.

Methods

MDS patients conditioned with treosulfan (30 g/m^2) and fludarabine in the RCT (June 2013 to January 2018) and the data obtained from 2 hospitals (RWD) (August 2017 to February 2023) were compared. Baseline characteristics, overall survival, relapse-free survival, relapse (or progression), non-relapse mortality, time to engraftment, and safety profiles between the RCT and RWD were compared. A sensitivity analysis was conducted using propensity score matching (PSM). Additionally, subgroup analyses evaluated the clinical effectiveness of treosulfan by baseline morphologic blast count and the revised International Prognostic Scoring System (IPSS-R).

Results

Overall, 195 MDS patients (RCT 84, RWD 111) with at least 12 months follow-up were analyzed. Median age was 62 years (range 39-76 years). Baseline characteristics only differed between the RCT and RWD with respect to age, IPSS-R categories, Hematopoietic Cell Transplantation Co-Morbidity Index total score (HCT-CI), and neutrophil count, indicating some heterogeneity between the RCT and RWD patients. In the PSM analysis, 106 (RCT 53, RWD 53) patients were matched to address the heterogeneity.

The Kaplan-Meier estimates for overall survival (OS) at 2 years were 73% (95% CI 62 81%) and 72% (95% CI 62-81%) for the RCT and RWD (Figure 1), and for relapse free survival (RFS) at 2 years were 68% (95% CI 57-77%) and 67% (95% CI 56-76%), respectively. Cumulative incidence of relapse at 2 years was 11% (95% CI 4-18%) and 15% (95% CI 7-23%), and for non relapse mortality (NRM) was 21% (95% CI 12-30%) and 18% (95% CI 10 26%) for the RCT and RWD, respectively. In addition, cumulative incidence of neutrophil engraftment at 28 days was 93% (95% CI 87-98%) and 94% (95% CI 89 98%) for the RCT and RWD, while the median engraftment time was later in the RCT (19 days vs 15 days). Cumulative incidence of platelet engraftment at 28 days was 89% (95% CI 83-96%) and 93% (95% CI 88-98%) for the RCT and RWD, with the same median time 14 days. Further, the PSM sensitivity analysis showed comparable efficacy between the RCT and RWD. Interestingly, bone marrow blast count prior to conditioning and IPSS-R subgroups only had minor, statistically not significant impact on survival endpoints (Table 1).

The number of deaths were 27 (32%) and 28 (25%) in the RCT and RWD, respectively. The most frequent cause of death was transplantation related (20% vs 14%). One patient experienced primary graft failure in the RCT and none in the RWD. More patients had acute GVHD with at least grade 2 in the RCT (27%) than in RWD (18%).

Conclusion

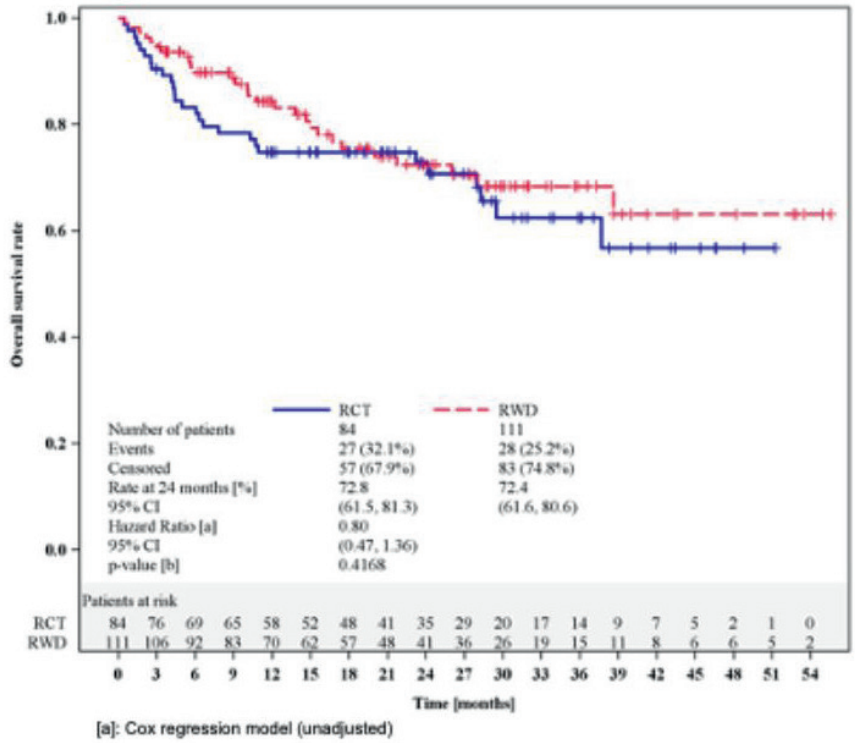
The efficacy and safety of treosulfan-based conditioning therapy prior to alloHSCT in post-authorization real world setting was comparable with the results obtained from the RCT. Our data suggest that bone marrow blast count is no strong predictor for survival after alloHSCT. Therefore, we conclude that the approved treosulfan-based conditioning therapy for patients with MDS, including those with increased blasts, has promising outcomes after alloHSCT.

Survival outcomes	Blast Count			IPSS-R				
	Blasts <5%	Blasts 5-10%	Blasts >10%	Very low risk	Low risk	Intermediate risk	High risk	Very high risk
	N = 84	N = 77	N = 33	N = 6	N = 20	N = 39	N = 55	N = 75
Overall survival probability at 24 months [a] [%] (95% CI)	74.0 (62.4, 82.4)	65.0 (51.4, 75.6)	86.6 (68.0, 94.8)	66.7 (19.5, 90.4)	69.6 (44.5, 85.1)	82.4 (64.4, 91.8)	83.0 (68.5, 91.2)	61.3 (47.8, 72.2)
Relapse-free survival probability at 24 months [a] [%] (95% CI)	68.3 (56.3, 77.7)	60.0 (46.5, 71.2)	82.6 (62.5, 92.5)	66.7 (19.5, 90.4)	54.3 (27.3, 75.0)	79.2 (60.6, 89.7)	78.8 (63.7, 88.2)	56.9 (43.7, 68.0)
Cumulative incidence of relapse at 24 months [%] (95% CI)	12.8 (4.9, 20.7)	13.6 (5.7, 21.5)	10.7 (0.0, 22.5)	0.0 (0.0, 0.0)	15.4 (0.0, 35.2)	6.8 (0.0, 15.9)	8.5 (0.4, 16.7)	20.2 (10.6, 29.7)
Cumulative incidence of non-relapse mortality at 12 months [%] (95% CI)	15.9 (8.0, 23.9)	17.3 (8.8, 25.9)	6.7 (0.0, 15.6)	33.3 (0.0, 71.1)	30.4 (10.0, 50.7)	10.3 (0.7, 19.8)	7.4 (0.4, 14.4)	17.1 (8.2, 25.9)
Cumulative incidence of non-relapse mortality at 24 months [%] (95% CI)	18.9 (10.2, 27.5)	26.4 (15.0, 37.8)	6.7 (0.0, 15.6)	33.3 (0.0, 71.1)	30.4 (10.0, 50.7)	14.0 (2.4, 25.7)	12.7 (3.0, 22.4)	23.0 (12.5, 33.4)

a: Based on Kaplan-Meier estimates.

Abbreviations: CI = Confidence interval; IPSS-R = Revised International Prognostic Scoring System.

Table 1



[a]: Cox regression model (unadjusted)

[b]: Log-rank test

Abbreviations: CI = Confidence interval; RCT = Randomized controlled trial; RWD = Real-world data.

Figure 1

medac

Comparable Survival for Fludarabine and Treosulfan Vs. Fludarabine and TBI as Conditioning Regimens in Patients with AML and MDS Undergoing Allogeneic Stem Cell Transplantation

#3535
Poster presentation

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Study design	Retrospective analysis	**Aim**	Comparison of Flu/TBI with FT10 in AML and MDS	
Parameters assessed	OS, LFS, CIR, NRM, a/cGvHD in whole cohort and propensity score matched			
Patients*	311 (of which 53 pair-matched pts)	**Median age**	64 y (FT10); 47 y (Flu/TBI) for non-pair-matched pts	
Disease	AML in CR (n=215), MDS (n=96)			
Conditioning regimen	**FT10** Treo (Σ 30 mg/m²), Flu (Σ 150 mg/m²)		**Flu/TBI** TBI (Σ 4x2Gy), Flu (Σ 120 mg/m²)	p
Results				
3 y OS unmatched	71%		79%	0.06
matched	80%		71%	0.54
LFS unmatched	59%		66%	0.42
matched	70%		59%	0.42
3 y CIR unmatched	25%		25%	0.8
matched	28%		28%	0.7
1 y NRM unmatched	8%		5%	0.07
matched	9%		2%	0.03
d+100 aGvHD grade II-IV	No significant differences			
3 y cGvHD matched	32%		43%	0.4
Conclusion	• Dose-reduced conditioning with either FT10 or FluTBI has favorable and comparable survival rates of >70%. • CIR and NRM were low for both regimens. • MRD prior to alloHSCT seemed to have no significant impact on survival rates in AML pts receiving FT10 and should be further evaluated.			

*Numbers different from abstract were taken from presentation.

Abstract

Introduction

Allogeneic stem cell transplantation (alloSCT) is a standard treatment option for patients (pts) with acute myeloid leukemia (AML) and myelodysplastic neoplasia (MDS) with relapse remaining the main cause of treatment failure. For AML pts transplanted in complete remission (CR) or MDS pts, the combination of fludarabin with fractionated total body irradiation (8 GyTBI, "FluTBI") is an established conditioning regimen. Based on the favorable outcome data reported for fludarabine/treosulfan ("FluTreo"), especially for older and/or comorbid pts, this regimen has become a reliable dose reduced conditioning therapy prior to alloSCT and a valuable alternative to other TBI or chemotherapy-based regimens.

Methods

We conducted a retrospective analysis of 215 pts with AML in CR and 96 pts with MDS who underwent first alloSCT between 2010 and 2022 with a median follow-up (FU) of survivors of 34 months (range: 1 – 124 months). After conditioning therapy with FluTreo (150mg/m² fludarabin, 30g/m² treosulfan) or FluTBI (120mg/m² fludarabin, 4x2Gy TBI) pts were allografted from matched related (MRD; n=65), 10/10 human leukocyte antigen (HLA)-matched unrelated (MUD; n=200), or 9/10 HLA-matched unrelated donors (MMUD; n=46). For AML pts, any detectable molecular/cytogenetic alteration prior to alloSCT was classified as potentially measurable residual disease. Propensity score matching allowed us to identify 55 pair-matched FluTBI and FluTreo pts (nearest matching for age at alloSCT, sex, disease, HCT-CI score, ECOG, with a caliper distance of 0.5).

Results

Before matching, pts characteristics differed significantly between FluTreo and FluTBI in terms of age at alloSCT (median 64 vs. 47 yr), underlying disease (AML: 59% vs. 88%), ECOG (≥2 15% vs. 6%) and HCT-CI-Score (≥3 50% vs. 25%). In the AML subgroup, pts with measurable residual disease prior to alloSCT were significantly more frequent in the FluTreo group (68% vs. 48%, p<.001). GvHD prophylaxis consisted of calcineurin inhibitor and methotrexate/MMF in all pts. In addition, pts transplanted from unrelated donors received ATLG (Neovii). In the FluTreo group, more patients were transplanted from MRDs (24% vs. 14%, p.013). After matching, patient characteristics were well balanced with respect to age (median 57 vs. 55 yr, p.11), disease (AML/MDS) (p .8), HCT-CI score (p .24), sex (p .85), donor types (MRD: 25.5% vs. 14.5%, MUD: 58.2% vs. 67.3%, MMUD: 16.4% vs. 18.2%, p .36) and measurable residual disease prior to alloSCT (p .58). Risk groups for AML and MDS pts at diagnosis were comparable across both groups (ELN for AML and IPSS-R for MDS).

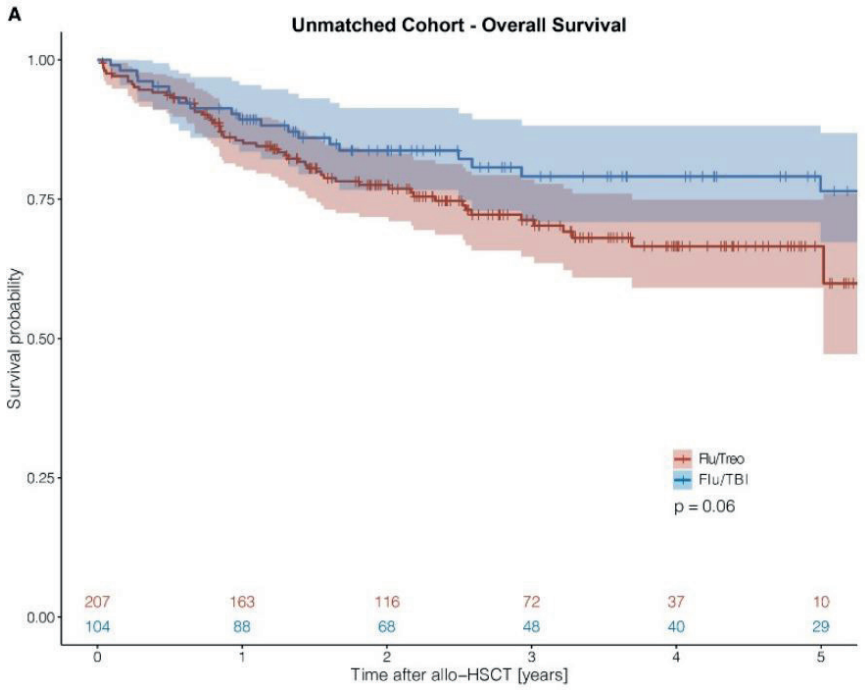
Relapse incidences (RI) at 3 yrs were similar for FluTreo and FluTBI pts in the unmatched (25% vs. 25%, p.8) and matched cohorts (28% vs. 28% p .7). The non-relapse mortality (NRM) rate was <10% trending towards a lower NRM rate for the FluTBI group in the unmatched cohorts (at 1 yr: 8% vs. 5%, p .07) and a significant difference after matching (at 1 year 2% vs. 9% p .03). Overall survival (OS) for the whole cohort showed a trend towards an inferior outcome for FluTreo (3 yr: 71% vs. 79% p .06), after matching, no difference could be observed (3 yr: 80% vs. 71% p .54). Leukemia-free survival (LFS) was comparable across conditionings in the unmatched (59% vs. 66% p .42) and the matched cohorts (70% vs. 59% p .42).

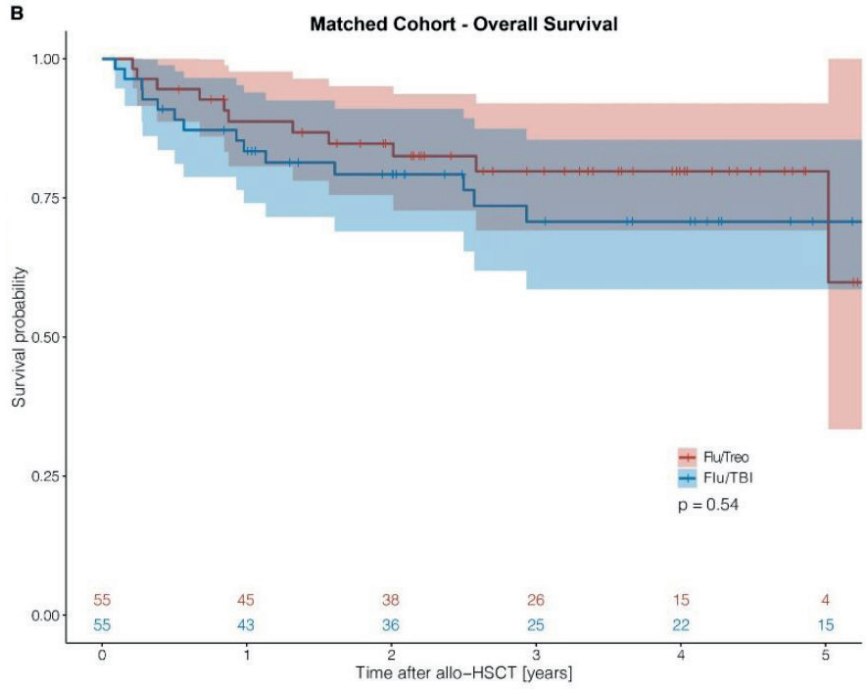
Irrespective of conditioning therapy, pts with measurable residual disease prior to alloSCT had comparable OS and LFS. However, for the matched cohort, pts with measurable disease treated with FluTreo showed a trend towards an inferior OS and LFS after 3 yr in contrast to FluTBI pts (OS: 66% vs. 80%, p .13; PFS: 58% vs. 67%, p .3).

No significant differences could be observed in the incidence of acute onset graft versus host disease (GvHD) grade 2-4 at day 100 after alloSCT. Similarly, occurrence of chronic GvHD at 3 yr did not differ in the matched cohorts (32% vs. 43%, p .4).

Conclusion

With a meaningful median follow up of 34 months, our data for dose-reduced conditioning with either FluTreo or FluTBI highlight favorable and comparable survival rates of >70%. RI and NRM were low for both regimens. For pts with AML, who received FluTBI, measurable residual disease prior to alloSCT seemed to have no effect on outcome, while for the FluTreo cohort measurable residual disease prior to alloSCT showed a trend towards lower survival rates. This finding should be evaluated in a prospective trial comparing TBI and treosulfan based conditioning.


A
Unmatched Cohort - Overall Survival
Survival probability
1.00
0.75
0.50
0.25
0.00
Flu/Treo
Flu/TBI
p = 0.06
207 163 116 72 37 10
104 88 68 48 40 29
0 1 2 3 4 5
Time after allo−HSCT [years]


B
Matched Cohort - Overall Survival
Survival probability
1.00
0.75
0.50
0.25
0.00
Flu/Treo
Flu/TBI
p = 0.54
55 45 38 26 15 4
55 43 36 25 22 15
0 1 2 3 4 5
Time after allo−HSCT [years]

Outcomes of Allogeneic HSCT in Elderly Patients (70 years old and above) -a Canadian Experience

#3733
Poster presentation

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Study design	Retrospective analysis	**Aim**	HSCT outcomes in pts ≥ 70 y, compare an earlier vs. more recent HSCT cohort
Parameters assessed	OS, EFS, NRM, CIR, a/cGvHD, hospitalization and readmission		
Patients	84	**Median age (range)**	71 y (70 – 76)
Disease	AML, MDS, MPN, CMML, ALL, TPLL		
Conditioning regimen*	Flu4/Bu2/TBI200 (n=73), Flu4/Treo30 (n=7), or Flu/Treo42 (n=3), Mel140 (n=1)		

Results	Cohort A (HSCT 2015 - 2019)	Cohort A (HSCT 2020 - 2022)	p
n	44	40	
1 y OS	45%	62%	0.1
1 y EFS	37%	58%	0.07
1 y NRM	45%	23%	0.04
1 y CIR	~18%		n.s.
Hospitalization	Median 33.5 d (range 16 – 166)		
aGvHD	32% (grade I-II), 9.5% (grade III-IV)		n.s.
cGvHD	14% (mild-moderate), 2% (severe)		n.s.

Conclusion

- There was a statistically significant improvements in NRM and trend to improvement in OS and EFS in more recent cohort.
- Improvement might be due to:
  - Introduction of frailty testing.
  - Capping the CD34 cell dose in grafts.
  - Introduction of Treo for selected indications (MDS/CMML).
  - Letermovir for CMV prophylaxis.
  - Reduced ATG dose for GvHD prophylaxis.
  - Focus on diet, nutrition, exercise.

*Numbers different from abstract were taken from presentation.

Abstract

Introduction

Allogeneic hematopoietic cell transplant (alloHCT) in elderly patients is a challenge, as with increasing age, there is higher incidence of co-morbidities and pre-frail status. In our recent study on alloHCT in patients 60 years (y) or older, those who were 70y or more had worse outcome and high 2-y non-relapse mortality (NRM) of 53% (Al-Shaibani E et al. Ann Hematol, 2023, 102: 917-926). We therefore implemented a number of changes to improve outcomes in elderly patients undergoing alloHCT. In this study, we analyze transplant outcomes in patients ≥ 70 y, and compare the earlier cohort with the more recent cohort.

Methods

This is a retrospective analysis of all consecutive patients 70y or older, who had an alloHCT from Jan 2015 to Dec 2022. We compared those who underwent an alloHCT from 2015-2019 (Cohort A, n=44) with those who had a transplant from 2020-2022 (Cohort B, n=40).

The median age of the patients was 71y (range 70-76). The underlying diagnosis was mainly a myeloid malignancy (AML, MDS, MPN, CMML, n=82; lymphoid (ALL, TPLL, n=2). There were 54 males. Stages of disease at transplant were in CR1 (n=51), CR2 (n=4) or stable disease (n=15, MDS, MPN or CMML pts). All patients received RIC regimens for conditioning including Flu4/Bu2/TBI200 (n=73), Flu4/Treo30 (n=7) and Flu/Treo42 (n=3). The GVHD prophylaxis regimens used included ATG2/PTCy/CSA (n=32), ATG4.5/PTCy/CSA (n=35), ATG4.5/CSA/MTX (n=7), ATG2/CSA/MTX (n=3). The donors were either matched related (n=10), matched unrelated (including minor mismatch) (n=57) or haploidentical (n=16). Graft source was peripheral blood in all except one who received bone marrow. (Details in Table).

The overall survival (OS), event free survival (EFS), NRM, cumulative incidence of relapse (CIR), incidence of acute and chronic GVHD, length of transplant hospitalization and the number of hospital re-admissions in first 6 months were assessed. The Kaplan Meier curves were plotted for OS and EFS for the overall sample, as well as stratified by the two eras (cohort A and B) and the differences assessed using log-rank tests. Cumulative incidence curves for NRM and CIR were generated, and differences assessed using Gray's K-sample

Results

For all patients transplanted in 2015-2022, the 1-year OS was 53%, the 1-year EFS was 45% and the 1-year NRM was 35%. The median number of days of transplant hospitalization for the whole population was 33.5 days (range 16 - 116). The incidence of grade I-II aGVHD was 32%, and grade III-IV aGVHD was 9.5%; mild to moderate cGVHD was 14% and severe cGVHD was 2%. The 1-year CIR was approximately 18%.

Comparing the two cohorts A and B, the 1y OS was 45% vs 62% (p=0.10) respectively; the 1-year EFS was 37% vs 58% (p=0.07) respectively and the 1-year NRM was 45% vs 23% (p=0.04) respectively (Figures attached). The incidence of GVHD and CIR were similar in both cohorts, despite reducing the ATG dose in cohort B.

Conclusions

Our study shows that there were statistically significant improvements in NRM and a trend towards improvement in the OS and EFS in the patients transplanted during 2020-2022 compared to patients undergoing alloHCT from 2015-2019. This improvement may be due to one or more changes implemented in recent years, although it is not possible to identify a single factor. These changes were (a) introduction of Frailty testing in all patients (Salas MQ et al. BMT. 2021; 56:60-69). (b) capping the CD34 cell dose in grafts (c) introduction of Treosulfan for selected indications (MDS/CMML) (Pasic I et al. Leuk Res 2023, 128: 107131). (d) Letermovir for CMV prophylaxis (e) reducing ATG dose for GVHD prophylaxis and (f) focus on diet, nutrition, exercise. While alloHCT should be offered to medically eligible elderly patients, there is a special need to minimize the risks that are part of age related vulnerabilities.

	Total (N=84)	Cohort A (2015-2019) (N=44)	Cohort B (2020-2022) (N=40)	P value
Age at BMT				
Median (range)	71 (70 – 76)	71 (70 – 76)	71 (70 – 75)	0.47
Gender, *N (%)*				
Female	30 (35.71%)	14 (31.82%)	16 (40%)	
Male	54 (64.29%)	30 (68.18%)	24 (60%)	
Diagnosis, *N (%)*				
AML	46 (54.76%)	28 (63.64%)	18 (45.00%)	
MDS/MDS-MPN/CMML	27 (32.14%)	12 (27.27%)	15 (37.50%)	
MF/ET/MPN-unclassifiable	7 (8.33%)	3 (6.82%)	4 (10.00%)	
t-ALL/TPALL	2 (2.38%)	1 (2.27%)	1 (2.50%)	
Others	2 (2.38%)	0 (0.00%)	2 (5.00%)	
CD34 cell count/kg, *N (%)*				
Median (range)	6.9 (2.2 – 20.1)	7.4 (2.2 – 20.1)	6.6 (3.6 – 10.2)	**0.026**
Conditioning regimen, *N (%)*				
Flu(4)-Bu(2)-TBI(200)	73 (86.90%)	44 (100%)	29(72.5%)	**<0.001**
Flu-Treo	10	0	10 (25%)	
Melphalan 140mg/m2	1	0	1 (2.5%)	
GVHD prophylaxis, *N (%)*				
ATG(2)-PTCy-CSA	32 (38.55%)	12 (27.27%)	20 (51.28%)	**0.002**
ATG(4.5)-PTCy-CSA	35 (42.17%)	24 (54.55%)	11 (28.21%)	
ATG(2)-CSA-MTX	3 (3.61%)	0 (0%)	3 (7.69%)	
ATG(4.5)-CSA-MTX	7 (8.43%)	6 (13.64%)	1 (2.56%)	
Other	6 (7.22%)	2 (4.54%)	4 (10.25)	
KPS, *N (%)*				
70-80	17 (20.24%)	10 (22.73%)	7 (17.50%)	0.55
90-100	67 (79.76%)	34 (77.2%)	33 (82.50 %)	
Primary Cause of death, *N (%)*				
Relapse	16 (34.04%)	9 (28.13%)	7 (46.67%%)	
Infection	18 (38.30%)	15 (46.88%)	3 (20%)	
GVHD	6 (12.77%)	6 (18.75%)	0 (0.00%)	
Other	7 (14.89%)	2 (6.25%)	5 (33.33%)	
OS, *(%)*				
1-year	53%	45%	62%	0.10
EFS, *(%)*				
1-year	45%	37%	58%	0.07
NRM, *(%)*				
1-year	35%	45%	23%	**0.04**

Abbreviations: Flu=fludarabine, Bu= Busulfan, Treo=treosulfan, PTCy= post-transplant cyclophosphamide, CSA= cyclosporine, MTX=methotrexate

Table 1. Patients and transport variables. Outcomes at 1-years.

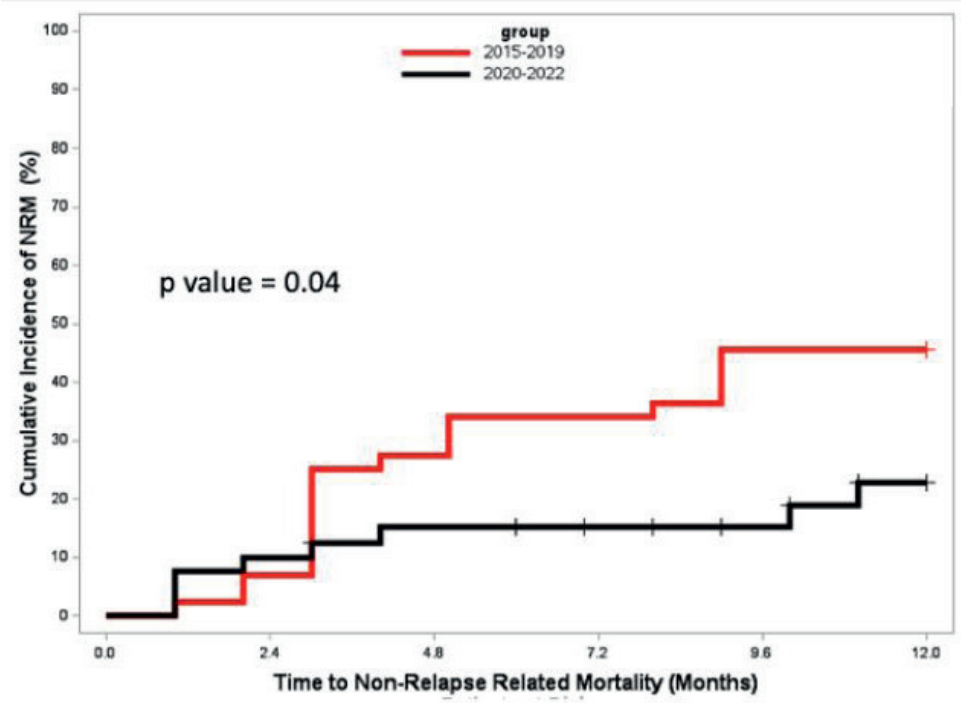

Figure 1. NRM patients 70 years or older, who received an Allogeneic HCT in 2015-2019 vs 2020-2022

Blast Clearance after High Dose-Melphalan Conditioning for Allogeneic Stem Cell Transplantation in Relapsed and Refractory Acute Myeloid Leukemia

#4911
Poster presentation

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Study design	Retrospective analysis	**Aim**	Prognostic factors for long-term survival in r/r AML pts with active disease
Parameters assessed	OS, EFS, relapse		
Patients*	197	**Median age (range)**	Non-TBI: 67 y (45 – 76) TBI: 51 y (19 – 71)
Disease	r/rAML		
Conditioning regimen*	HD-Mel d-11 followed from d-6 by 8 Gy TBI (n=70) or non-TBI regimens (Bu n=102 or Treo n=25) with Flu		
Results*	• 3 y OS 51% (HR 0.75 for pts with/without blast clearance, p=0.15). • 3 y RFS 48% (HR 0.76 for pts with/without blast clearance, p=0.17). • 3 y CIR 23% (HR 1.27 for pts with/without blast clearance, p=0.42). • 3 y NRM 26%; pts without blast clearance after Mel had significantly increased NRM. • MVA: age, HCT-CI scores >3 points, adverse risk (acc. to ELN 2017), donor mismatch <10/10 => adverse prognosis.		
Conclusion	• Sequential conditioning regimens before alloHSCT offer long-term survival for >50% of pts with active r/rAML. • Trend to higher relapse risk but not inferior survival for pts not achieving complete blast clearance. => close monitoring and early interventions important after HSCT.		

*Numbers different from abstract were taken from presentation.

Abstract

Introduction

For patients (pts) with relapsed or refractory acute myeloid leukemia (r/r AML) allogeneic stem cell transplantation (ASCT) has become an established highly effective and potential curative treatment option. Even for pts with active disease, direct ASCT using sequential conditioning regimens has shown promising outcomes. In this retrospective study, we examined prognostic factors for long-term survival in r/r AML pts with active disease with special focus to the prognostic value of blast clearance during condition therapy.

Patients and Methods

186 r/r AML pts treated with sequential conditioning regimens at our center between 2014-2023 were included in our analysis. Patients underwent high-dose melphalan (100 - 140 mg/m², day -11 prior ASCT) followed by either fractionated total body irradiation with 8 Gy (TBI, n = 71) or non-TBI regimens (busulfan, n = 101, or treosulfan, n = 14) in combination with fludarabin (120 - 150 mg/m²) from day -6 before ASCT. TBI-based conditioning was applied almost exclusively in patients aged < 60 years. Graft versus host-disease (GvHD) prophylaxis consisted of calcineurin inhibitors, mycophenolate and anti-T-lymphocyte globulin. In 180 out of 186 patients, blast clearance was assessed by cytologic and flow cytometric blast count via bone marrow (BM) aspirate in median 5 days after Melphalan and prior to continuation of the sequential conditioning therapy. Blast clearance was defined as cytologic BM blast count < 5% and < 0.1% BM cells with leukemia-associated immunophenotype in flow cytometry.

Results

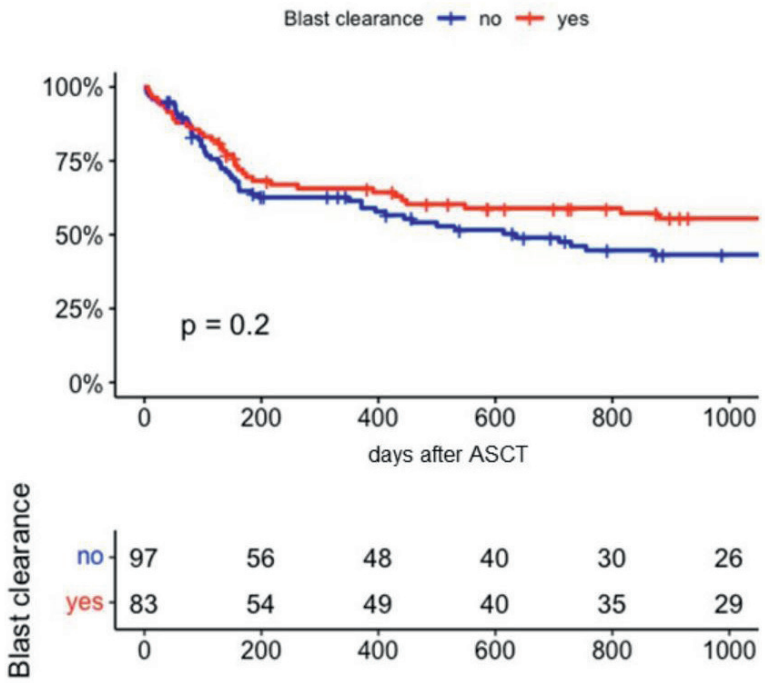
Median pts age was 67 years (range 45 - 76 years) in the non-TBI group and 51 years (range 19 - 71 years) in the TBI group, respectively. Median follow up of surviving patients was 46 months. As expected, comorbidities and disease-specific factors varied between these groups. HCTCI scores > 3 points were observed in 14% of TBI pts compared to 32% in non-TBI pts (p .01) and 45% versus 54% harbored adverse risk genetics according to European Leukemia Net (ELN) 2017 classification (p .41), respectively. In the non-TBI group, 38% of the pts had a secondary or therapy-related AML compared to 20% of pts in the TBI group (p .03). HLA-mismatched (<10/10 matched) donor grafts were transplanted in 21% (TBI) vs. 20% (non-TBI) of the pts. 185 of 188 pts received GCS-F mobilized stem cell grafts; 3 pts received a bone marrow graft.

Kaplan-Meier estimates for overall survival (OS) with and without blast clearance at 2 years were 69.6% (95% CI 60.1-80.6%) vs. 58% (95% CI 48.8-69.1%, p .33), for event free survival (EFS, event defined as death or overt relapse) 58.9% (95% CI 49-70.8%) vs. 46.1% (95% CI 36.7-58.1%, p .2), respectively. We included the re-occurrence / persistence of defined molecular and cytogenetic markers or decreasing CD34+ bone marrow chimerism (< 95%) after transplant as measures for impending relapse as a modified EFS. The EFS including impending relapse was 49.8% (95% CI 40-62%) vs. 36.4% (27.7-47.8%) after 2 years. A non-significant trend with reduced relapse risk for those patients who achieved blast clearance after Melphalan (p .1, HR 0.73) was observed. Most patients with impending relapse showed similar survival as patients without evidence of relapse after ASCT. In multivariate cox regression, age, HCTCI scores > 3 points, adverse risk according to ELN 2017 definitions and donor mismatch < 10/10 resulted in adverse prognosis. Especially, patients with mismatched donors displayed highly significant inferior outcomes. Both leukemic burden prior to ASCT as well as blast clearance after melphalan showed no significant correlation with clinical outcome parameters.

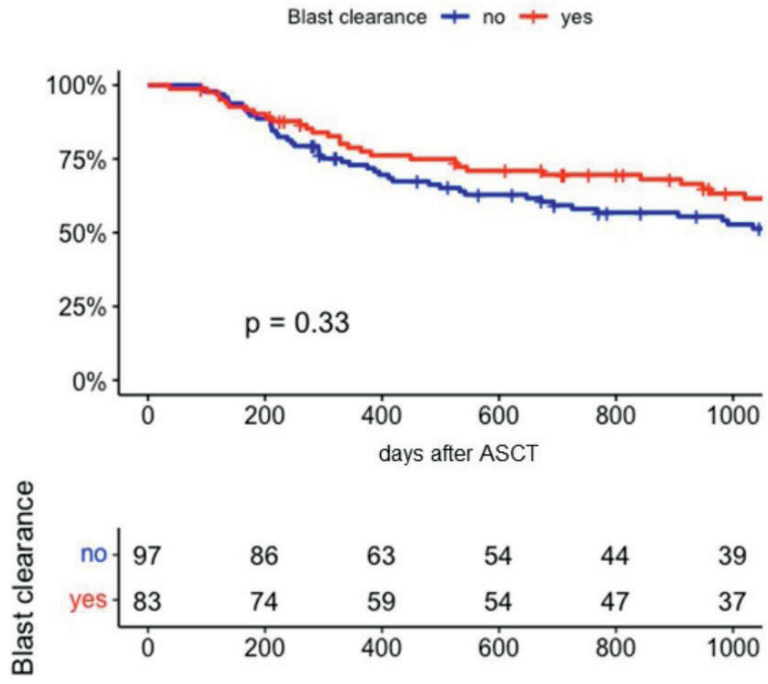
Conclusions

Sequential conditioning regimens followed by ASCT offer long-term survival for more than 50% of pts with active relapsed or refractory AML. Patients who did not achieve complete blast clearance during conditioning therapy showed a trend towards higher relapse risk after ASCT which did not result in inferior survival. This underscores the importance of close monitoring and early interventions such as accelerated immunosuppression tapering, preemptive donor lymphocyte infusions and targeted therapies in case of impending relapse after ASCT.

A) Event Free Survival after ASCT



B) Overall Survival after ASCT



TREOSULFAN RELATED PRESENTATIONS – PEDIATRIC PATIENTS

Moderate Incidence but Striking Correlation with TBI of Secondary Malignancies after HSCT in Children with ALL: Long-Term Follow-up from the Prospective International BFM- and Forum-Trials

#110
Oral presentation

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Study design	Retrospective analysis of two prospective multinational trials	**Aim**	Secondary malignancies in patients enrolled in BFM 2003 and FORUM trials
Parameters assessed	Secondary malignancies		
Patients	2151 (n=668 BFM 2003, n=1483 FORUM)	**Median age (range)**	9.2 y (0.5 - 23)
Disease	ALL		
Conditioning	TBI/VP16 (n=1429) or chemo-conditioning (Bu- or Treo-based, n=722)		
Results	• Median follow-up 3.29 y (range 0.1-16.4). • 46 SM (33 in BFM 2003, 13 in FORUM) diagnosed at a median of 5.12 y (range 0.4-13.4) post HSCT, all but one in the TBI group. • CI of SM: 5 y 0.02 (±0.01), 8 y 0.06 (±0.01), 10 y 0.13 (±0.03). • 8y CI of SM: 0.08±0.02 (TBI group) vs. 0.04±0.04 (chemo-conditioning), p=0.004.		
Conclusion	• TBI conditioning is a risk factor for SM in pediatric ALL. • Further analysis is ongoing regarding the association with immune phenotype of ALL and details of genetic risk factors.		

Further reading: Peters C, Dalle JH, Locatelli F, et al. Total Body Irradiation or Chemotherapy Conditioning in Childhood ALL: A Multinational, Randomized, Noninferiority Phase III Study. J Clin Oncol. 2021;39(4):295-307. doi:10.1200/JCO.20.02529 *https://ascopubs.org/doi/pdfdirect/10.1200/JCO.20.02529*

Abstract

Introduction

Total body irradiation (TBI)-based conditioning was found to be associated with superior leukemia-free survival when compared to chemo-based conditioning for children with ALL undergoing allogeneic hematopoietic stem cell transplantation (HSCT) in the prospective, international, randomized FORUM trial (Peters et al, JCO 2021). Nevertheless, TBI is considered as the major risk factor for developing secondary malignancies (SM). We and others have previously reported the incidence, risk factors, and outcomes of SM after HSCT in children with ALL (Eichinger et al, Leukemia 2022), but prospective studies of SM after HSCT in children are limited. Therefore, we analyzed the results of 2151 patients enrolled in the prospective BFM 2003 and the FORUM trial from 2003-2022.

Patients and Methods

We included data from all 668 patients (pts) treated in the BFM 2003 trial and from all 1483 patients treated in the FORUM trial with HSCT from HLA-identical family donors (MFD, 26% of patients), matched unrelated donors (MUD, 65%), and either related or unrelated mismatched donors (MMD, 9%).

In the BFM 2003 trial pts >2 years (y) of age years were offered TBI/VP-16 (12 Gy TBI in 6 fractions of 2 Gy each, given as 2 fractions per day for 3 days; VP-16 60 mg/kg, maximum total dose 3600 mg) as conditioning. Only pts with contraindications for TBI received chemo-conditioning, which consisted of i.v. busulfan, cyclophosphamide and etoposide.

In the FORUM trial pts >4y of age were randomized to receive either TBI- or chemo-based conditioning regimens; pts <4y were allocated to the chemo-conditioning arm consisting of fludarabine/thiotepa and either busulfan or treosulfan. Details on the transplant procedure have been previously described (C. Peters, et al. JCO 2015 /2021).

Results

Centres from 31 countries on 5 continents contributed to the two studies. The median age was 9.2 (range 0.5-23) y. The majority were male (63%, 1356/2151) and >2 y of age at HSCT (94%, n=2024). TBI-based conditioning was applied in 64% (n=1429), while 34% (n=722) of pts received chemo-conditioning. TBI/VP16 was given in 27% (43/159) of age group 2-4y, and in 76% (1269/1672) of age group >4y.

With a median follow-up of 3.29 (range 0.1-16.4) y, a total of 46 SM (33 in BFM 2003, 13 in FORUM) were diagnosed at a median of 5.12 (range 0.4-13.4) y post HSCT, all but one in the TBI group. Four pts experienced ALL relapse prior to the occurrence of the SM leaving 42/2151 cases for further analysis. The 5-, 8-, and 10-y cumulative incidence (CI) of SM, with relapse and non-relapse mortality being competing events, were 0.02 (±0.01), 0.06 (±0.01), and 0.13 (±0.03), respectively. Details of the SM are described in Table 1. Regarding age at HSCT, no SM was observed in the very young age group (<2 years) (0/127), 4 SM in the 2-4 years group (2.2%, 4/181), 20 SM in the 4-10 years group (2.3%, 20/867), and 22 SM in the >10 years group (2.25%, 22/976) (p=n.s.). Six patients developed an additional SM: these were MDS (n=2), and glioblastoma, breast cancer, basal cell carcinoma, and squamous cell carcinoma (one each). The first SM occurred at a median of 5.12 (range 0.4-13.4) y, and the additional SM at 10.7 (range 4.3-12.1) y after HSCT.

The probability of OS after SM diagnosis was 0.65 (±0.008) at 5y and 0.32 (±0.17) at 10y. Causes of death were SM in 12/14 cases and 2/14 ALL relapse-associated. All 3 glioblastoma-pts died within 8 months after diagnosis. 17/18 pts (94%) with thyroid cancer were alive at last follow-up (0-10 y after SM diagnosis). As shown in Figure 1, the 8-y CI of SM differed significantly between TBI- and chemo-conditioning (0.08[±0.02] versus 0.04[±0.04], p=0.004) in both age groups (2-4 y and >4 y). No significant correlation was observed with patient characteristics such as age, gender and ALL remission status.

In addition, we did not identify other statistically significant transplant-specific risk factors including donor type, stem cell source, grade II-IV and III-IV aGVHD and cGVHD.

Conclusions

Updated data from two prospective studies using uniform regimens confirmed TBI-based conditioning as a risk factor for SM in pediatric ALL. Further analysis is ongoing regarding the association with immune phenotype of ALL and details of genetic risk factors (e.g. TP53 mutations). Rigorous long-term FU of TBI patients is mandatory.

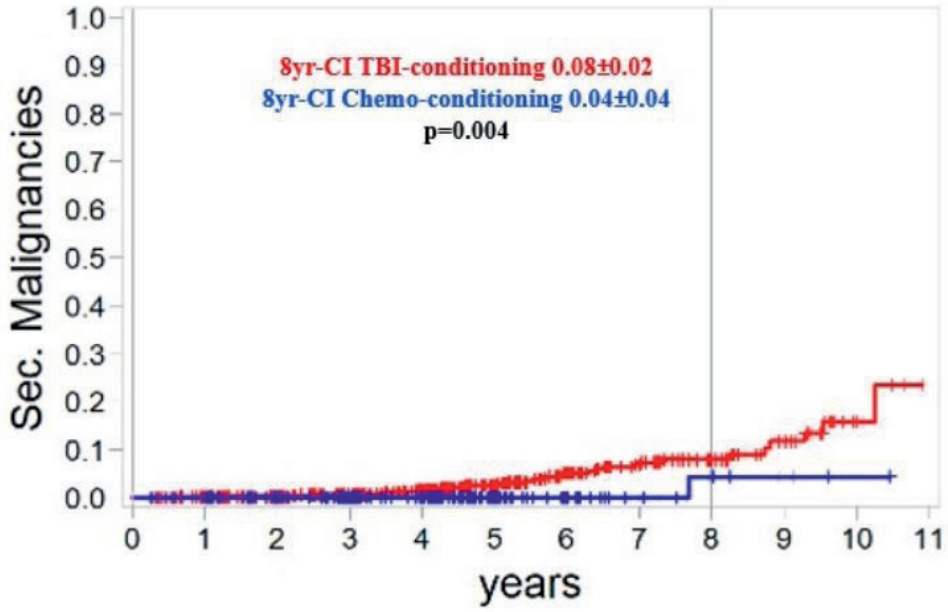

Figure 1. Cumulative Incidence (CI) of SM

Type of SM	Total		Study				Conditioning				Age							
			FORUM		ALL-SCT2003		TBI		CHEMO		<2 y		2-4 y		4-10 y		> 10 y	
	46	%	13	%	33	%	45	%	1	%	0		4	%	20	%	22	%
thyroid cancer	18	39 %	4	31 %	14	42 %	18	40 %					3	75 %	11	55 %	4	18 %
MDS	4	9%	1	8%	3	9%	4	9%					0	0%	1	5%	3	14 %
osteosarcoma	4	9%	1	8%	3	9%	3	7%	1	100 %			1	25 %	1	5%	2	9%
basal cell carcinoma	3	7%	0	0%	3	9%	3	7%							1	5%	2	9%
glioblastoma	3	7%	0	0%	3	9%	3	7%							1	5%	2	9%
melanoma	3	7%	3	23 %	0	0%	3	7%							1	5%	2	9%
breast cancer	2	4%	1	8%	1	3%	2	4%							0	0%	2	9%
colon cancer	2	4%	0	0%	2	6%	2	4%							2	10 %	0	0%
AML	1	2%	1	8%	0	0%	1	2%							0	0%	1	5%
Ewing sarcoma	1	2%	0	0%	1	3%	1	2%							0	0%	1	5%
Hodgkin lymphoma	1	2%	1	8%	0	0%	1	2%							0	0%	1	5%
inflammatory myofibroblastic tumor	1	2%	1	8%	0	0%	1	2%							1	5%	0	0%
parotid carcinoma	1	2%	0	0%	1	3%	1	2%							1	5%	0	0%
rhabdomyosarcoma	1	2%	0	0%	1	3%	1	2%							0	0%	1	5%
squamous cell carcinoma	1	2%	0	0%	1	3%	1	2%							0	0%	1	5%

Table 1. Type of Secondary Malgnancies (SM)

Comparable Outcome after Busulfan- or Treosulfan-Based Conditioning Regimen in Children Above 4 Years of Age with ALL Undergoing Allogeneic HSCT. Results from the Prospective International Forum-Trial

#232
Oral presentation

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Study design	Subgroup analysis of prospective randomised multinational trial	**Aim**	Comparison of FTT and FBT within FORUM trial in children >4 y	
Parameters assessed	OS, EFS, NRM, CIR, a/cGvHD, GRFS			
Patients	308	**Median age**	9.9 y (4 – 19.5)	
Disease	ALL			
Conditioning	FTT* (n=128)		FBT* (n=180)	p
Results				
3 y OS	0.72±0.04		0.71±0.03	n.s.
3 y EFS	0.55±0.04		0.61±0.04	n.s.
3 y CIR	0.36±0.04		0.31±0.03	n.s.
3 y NRM	0.09±0.03		0.08±0.02	n.s.
aGvHD/cGvHD	Comparable between treatment groups			n.s.
3 y GRFS	0.43±0.04		0.42±0.04	n.s.
Conclusion	• OS, EFS, CIR, NRM comparable between Bu and Treo. • Either of the two regimens can be effectively and safely used in pts over 4 y of age, who can't be treated with TBI due to contraindications or location specific constraints.			

*Treosulfan dose 42 g/m^2; Busulfan was dosed once, twice, or four times a day according to local guidelines, age, and body weight, commonly with therapeutic drug monitoring and pharmacokinetic dose adjustment (Peters et al. 2021 JCO)

Further reading: Peters C, Dalle JH, Locatelli F, et al. Total Body Irradiation or Chemotherapy Conditioning in Childhood ALL: A Multinational, Randomized, Noninferiority Phase III Study. J Clin Oncol. 2021;39(4):295-307. doi:10.1200/JCO.20.02529

https://ascopubs.org/doi/pdfdirect/10.1200/JCO.20.02529

Abstract

Purpose

Total body irradiation (TBI) has proved to be the "gold standard" as part of the conditioning regimen before allogeneic hematopoietic stem cell transplantation (HSCT) in pediatric patients with acute lymphoblastic leukemia (ALL). Its superiority over chemo-based conditioning was recently demonstrated in the prospective, international, randomized phase III study, which enrolled 417 patients beyond the age of 4 years transplanted for ALL in complete morphological remission (CR) from either matched sibling (MSD) or matched unrelated donor (MD) (Peters et al, JCO 2021, FORUM study; EudraCT: 2012-003032-22;ClinicalTrials.gov: NCT01949129). The use of either of the two protocol-prespecified chemo-conditioning regimens resulted in significantly worse EFS. Given the unavailability of TBI in some regions/centres and contraindications to TBI in individual patients, we here compare the outcomes of patients who received busulfan (BU) - based regimen vs of those who were given a treosulfan (TREO) - based conditioning in FORUM centres in both randomizing and non-randomizing countries in the years 2013-2018.

Patients and Methods

Patients ≤ 18 years at diagnosis (median age at HSCT 9.9 years, range 4-19.5), in CR pre-HSCT and with an MSD or MUD were assigned to myeloablative conditioning with fludarabine (FLU), thiotepa (THIO) and either BU or TREO according to country preference. Children transplanted from MSDs received cyclosporine A only as graft-versus-host disease (GvHD) prophylaxis, whereas recipients of MUD HSCT also received short-term methotrexate and anti-thymocyte globulin (ATG). Further details of the transplant procedure have been previously described (Peters C, et al. J Clin Oncol 2021).

Results

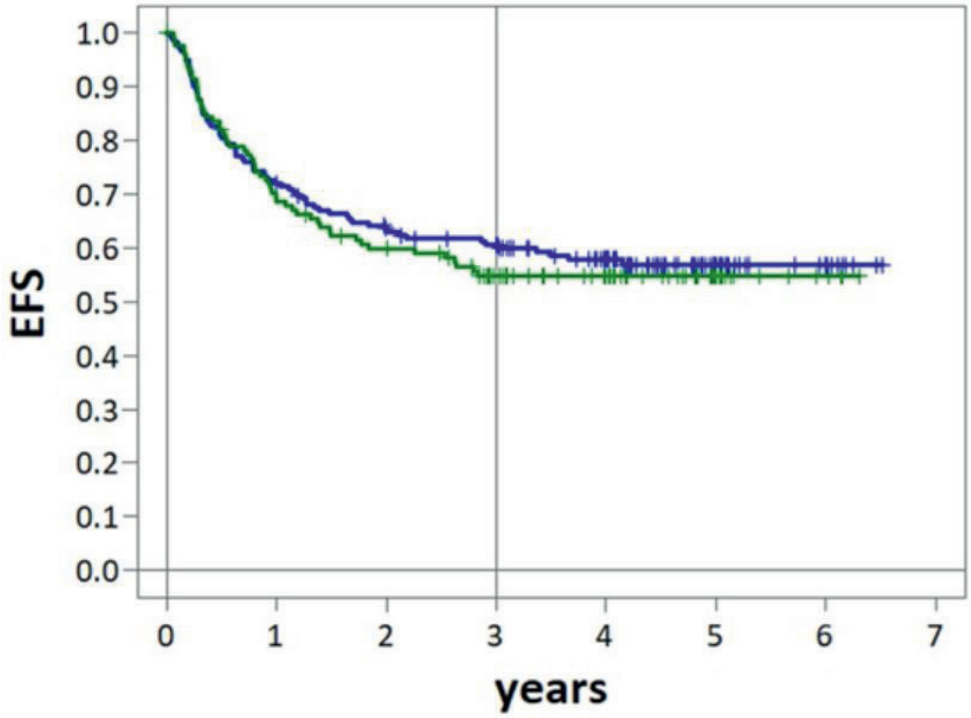
In addition to the 193 patients from the randomizing countries, the FORUM trial included 115 additional children enrolled in countries where randomization could not occur (for legal or technical reasons). Overall, 180 vs. 128 patients received BU/THIO/FLU vs TREO/THIO/FLU, respectively. There were no differences about the patients' gender, age, and remission status and slight differences regarding donor, stem cell source and MRD status pre-transplant between the two cohorts of patients (see Table 1 for details). Patient's outcomes were updated as of February 20th, 2023, and median follow-up was 4.2 years (range 0.3 – 9.1). There were neither differences between the 3-year overall survival (OS) (0.71±0.03 for BU/THIO/FLU vs 0.72±0.04 for TREO/THIO/FLU) nor event-free survival (EFS) (0.61±0.04 for BU/THIO/FLU vs 0.55±0.04 for TREO/THIO/FLU, p=NS). Three-year cumulative incidence of relapse (CIR) and non-relapse mortality (NRM) were 0.31±0.03 and 0.08±0.02 following BU/THIO/FLU and 0.36±0.04 and 0.09±0.03 following TREO/THIO/FLU, respectively (p=NS). Only one case of secondary malignancy was observed in the TREO cohort and one case of fatal liver veno-occlusive disease (VOD) in the BU group. No statistical differences were observed regarding the cumulative incidence of both aGvHD and cGvHD between the two groups; 3-year GFRS was almost identical (0.42± 0.04 in the BU/THIO/FLU group and 0.43±0.04 in the TREO/THIO/FLU cohort). There were no differences in OS, EFS, CIR, NRM and GFRS in either CR1 or CR2 patients between the two conditioning regimens. Furthermore, there were no differences in outcomes between countries. Patients given BU/THIO/FLU had a faster leucocyte, neutrophil and platelet recovery as compared to those prepared with TREO/THIO/FLU.

Conclusion

Comparable long-term outcomes were observed after BU/THIO/FLU or TREO/THIO/FLU in children with ALL undergoing allogeneic HSCT included in the FORUM trial. Therefore, either of the 2 regimens may be effectively and safely used worldwide in patients > 4 years having a contraindication to or treated in centres/countries unable to deliver TBI.

		Total		Conditioning				p-value
				FLU/THIO/BU		FLU/THIO/TREO		
		n	%	n	%	n	%	
Total		**308**	**100%**	**180**	**100%**	**128**	**100%**	
Sex	Male	194	63%	114	63%	80	63%	0.881
	Female	114	37%	66	37%	48	38%	
Age	4-6	39	13%	22	12%	17	13%	0.123
	6-10	120	39%	79	44%	41	32%	
	10-14	73	24%	42	23%	31	24%	
	>14	76	25%	37	21%	39	30%	
Remission	CR1	157	51%	85	47%	72	56%	0.169
	CR2	131	43%	81	45%	50	39%	
	CR3	19	6%	14	8%	5	4%	
	>CR3	1	0%	0	0%	1	1%	
Donor	MSD	87	28%	59	33%	28	22%	0.036
	MD	221	72%	121	67%	100	78%	
Source	BM	237	77%	130	72%	107	84%	0.043
	pB	62	20%	42	23%	20	16%	
	CB	6	2%	6	3%	0	0%	
	BM+CB	1	0%	1	1%	0	0%	
	BM+pB	1	0%	0	0%	1	1%	
	ukn	1	0%	1	1%	0	0%	
MRD	<10-4	168	75%	113	81%	55	66%	0.012
	>10-4	54	24%	26	19%	28	34%	

Table 1. Patient and donor characteristics at HSCT



regimen	Patients	eval patients	Events	3-yrs EFS	5-yrs. EFS	p-value
FLU/THIO/BU	180	179	75	0.61±0.04	0.57±0.04	0.578.
FLU/THIO/TREO	128	128	58	0.55±0.04	0.55±0.04	.

Figure 1. EFS after conditioning with BU-based (blue) or TREO-based regimen (green)

Haploidentical αβ- T Cell Depleted HSCT Represents a Curative Alternative in Pediatric and Adult Patients with Transfusion Dependent Thalassaemia

#2169
Poster presentation

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Study design	Retrospective analysis	**Aim**	Explore haplo-identical transplant in patients with TDT
Patients	n=20	**Median age (range)**	11 y (2 – 23) (TCD-haplo) 10 y (4 – 12) (MSD)*
Disease	TDT		
Donor*	TCD-haplo (n=13), MSD (n=7)		
Conditioning regimen*	FTT: Treo 42 g/m², Flu 160 mg/m², TT 10 mg/kg, ATG		
Results*	**MSD**		**T-Haplo**
OS	100%		100%
DFS	100%		93%
Chimerism, median (range)	91% (27.7% - 99.6%)		99% (34.6% - 100%)
Transfusion independency	100%		92%
VOD/SOS	0		0
a/cGvHD	0		4 grade I-II aGvHD, 1 mild cGvHD
Conclusion	• Treosulfan is an excellent alternative to busulfan in this setting, reflected in the safety and efficacy data. • Outcomes are encouraging, with a competitive OS. • HSCT in pediatric and AYA TDT patients lacking a MD is feasible.		

*Numbers different from abstract were taken from presentation.

Abstract

Background
Quality of life remains severely compromised in patients suffering from Transfusion Dependent Thalassemia (TDT) despite optimal supportive care. HSCT with a MSD, the current curative option, achieving a 92.1% 2y-OS in children and 84.4% in adults (EBMT registry). Unfortunately, availability of MDs is limited, so that haploidentical HSCT is increasingly explored.

Methods
13 TDT patients (median age: 11 years; range: 2-23) received either a CD3+/CD19+ (n=4; all class II/III) or αß/CD19+ (n=10; 7 class II, II/III) T-haplo-HSCT and were compared with 8 TDT-patients (7 class II, II/III, III) receiving a BM graft from a MSD (median age: 11 years; range: 4-22). Indication for T-haplo HSCT patients was severe iron overload/ transfusion-associated complications. All patients received an identical conditioning regimen consisting of treosulfan, thiotepa, fludarabine (FTT) and ATG-Grafalon, with the only difference in the timing of ATG (upfront in T-haplo-HSCT, prior to d0 in MSD-HSCT). Immunosuppression (IST) was maintained for a minimum of 180 days consisting of calcineurin inhibitors (mainly tacrolimus) and MMF.

Results
The OS and DFS for MSD and T-haplo-HSCT was 100%/100% and 100%/92%, respectively (Table 1). The median follow-up was 30 months for MSD (range 4-72) and 38 months for T-haplo-HSCT (range 4-86). Neutrophil engraftment was achieved after a median of 31 days for MSD patients and 17 days for T-haplo-HSCT with a median of 5 x 108 TNC/kg (range: 3.28–7.88) and 15 x 106 CD3+/CD19+ or αβ/CD19+ depleted CD34+ cells/kg (range: 9.2–24.2), respectively. One patient received two T-haplo HSCT, due to primary graft failure partly due to a major AB0 incompatibility. A mixed chimerism was observed in 3/7 MSD-HSCT (median 92%; range 27.5–100%) and in T-haplo-HSCT in 2/13 patients (median 99%; range: 45.3 -100%). Transfusion independence was achieved in all MSD and in all but one T-haplo patient. In MSD and in T-haplo-HSCT, IST was terminated after a median of 173 days and 226 days (range: 112-347), respectively. MSD patients reached CD4 counts >50/µl on day +43 (median; range: 25-125) and T-haplo-HSCT patients on day +114 (median; range: 33-173). The treosulfan-based conditioning regimen was well tolerated with no VOD/SOS observed in this high-risk population. No case of acute or chronic Graft-versus-Host disease (GvHD) was observed in the MSD population. In T-haplo-HSCT, 3 patients experienced grade I acute GvHD (skin) which resolved with prednisolone and in 2 cases with additional extracorporeal photopheresis. Only the oldest patient experienced mild chronic skin GvHD, which resolved by day +580. No severe infectious complications occurred despite a prolonged chimerism-triggered weaning of the IST.

Conclusion
Independent of donor availability, graft rejection and iron-overload related organ damage (VOD/SOS) are major pitfalls in transplanting advanced stage TDT patients. Treosulfan demonstrated to be an excellent alternative to busulfan in this setting reflected in the safety and efficacy data of this pilot series. Overall, outcomes of T-haplo-HSCT in TDT are very encouraging with a competitive OS, so that a transplant indication in pediatric and AYA TDT patients lacking a MD is feasible.

RESULTS		
	MSD	**T-haplo SCT**
OS/DFS (%)	100/100	100/92
Follow-Up (months) Median (range)	30 (4 - 72)	33 (4 - 86)
Engraftment (day) Median (range)	31 (20-45)	17 (12-37)
Chimerism Median (range)	91.75% (24.2% - 100%)	99.4% (45.3% - 100%)
Transfusion independency Median (range); days	100% 34 (9-469)	92% 85 (6-298)
Withdrawal IST (day) Median (range)	173 (107 - 227)	226 (112 – 347, 2 pts still under regular post-TX IST)
Immune-reconstitution >50 CD4+/µl (day) Median (range)	43 (25 – 125)	114 (33 – 173)
Viral reactivation	100%	100%
Treatment / Outcome	• No treatment 100 % resolved	• 33.3 % antiviral treatment • 8.3% VST 100% resolved

Table 1. Results. MSD = matched sibling donor; pt.= patient; IST= immunosuppressive treatment

Longitudinal Assessment of Pubertal Attainment and Testicular Function Following Pediatric Hematopoietic Stem Cell Transplantation: The Role of the Conditioning Regimen

#3584
Poster presentation

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Study design	Retrospective single center analysis	**Aim**	Pubertal attainment and testicular function in male pts <18 y at HSCT
Parameters assessed	Tanner stage, TV assessment, LH, FSH, total testosterone, laboratory data		
Patients	130	**Median age**	9 y at HSCT 21 y at last follow-up
Disease	Acute leukemia (65%), other malignancies (9%), non-malignant diseases (26%)		
Conditioning	TBI (45%), Bu (27%), Treo (14%), other chemo-conditioning (15%)		
Results*	• 43.8%: spontaneous progress into puberty, normal gonadal profile. • 56.2%: pubertal arrest (0.8%), increase of FSH (19.2%), overt or compensated hypergonadotropic hypogonadism (13.1% or 23.1%, respectively). • TV significantly lower in pts with endocrine disfunction. • Impact of conditioning regimen on a certain degree of gonadal dysfunction in 37% overall (85% of pts after TBI, 51% after Bu, 32% after Cy/Flu; no abnormal findings after Treo). • Conditioning regimen and pubertal status upon HSCT only variables significantly associated with testicular outcomes.		
Conclusion	• Halved risk of developing post-HSCT hypogonadism in prepubertal patients at HSCT. • Downwards trend in testosterone levels after achieving spontaneous puberty. • Gonadal-sparing profile of Treo compared to Bu-based regimens.		

*Numbers different from abstract were taken from presentation.

Further reading recommendations:
van der Stoep MYEC, Bense JE, de Kloet LC, et al. Effect of Busulfan and Treosulfan on Gonadal Function after Allogeneic Stem Cell Transplantation in Children and Adolescents with Nonmalignant Diseases Is Not Exposure-Dependent. Transplant Cell Ther. 2023;29(8):529.e1-529.e5. doi:10.1016/j.jtct.2023.05.003 *https://www.sciencedirect.com/science/article/pii/S2666636723012873/pdfft?md5=45f8421d0efe317697e671d90fa8d200&pid=1-s2.0-S2666636723012873-main.pdf*

Faraci M, Diesch T, Labopin M, et al. Gonadal Function after Busulfan Compared with Treosulfan in Children and Adolescents Undergoing Allogeneic Hematopoietic Stem Cell Transplant. Biol Blood Marrow Transplant. 2019;25(9):1786-1791. doi:10.1016/j.bbmt.2019.05.005 *https://www.bbmt.org/article/S1083-8791(19)30289-7/fulltext*

Abstract

Introduction
Endocrine disorders and impaired gonadal function are the most frequent sequelae after transplantation.

Methods
Male patients <18 years transplanted in the period 1992-2021 in the Pediatric Transplant Unit in Monza, surviving more than 2 years after HSCT, who either experienced spontaneous puberty (Tanner stage ≥2, testicular volume (TV) ≥4 mL or serum testosterone ≥0.2 ng/mL) or received pharmacological pubertal induction were included in this study.

Longitudinal endocrine evaluations were performed every 6-12-months, including Tanner stage and TV assessment and LH, FSH, total testosterone, among laboratory data.

Results
Of 130 patients (median age 9 years at HSCT, 21 years at last follow-up) fulfilling inclusion criteria, 65% were transplanted for acute leukemia, 9% for other malignancies and 26% for non malignant diseases after a TBI (45%), busulfan (27%), 14% treosulfan-based or 15% a different chemo-only conditioning. Upon HSCT 56% were prepubertal (PreP) and 44% where either peri- or postpubertal (PostP). The pubertal status upon the last endocrine evaluation was consistent with Tanner stage 3, 4 and 5 in 15%, 23% and 62% of the patients, respectively.

Overall, 44% had spontaneously progressed into puberty and had a normal gonadal profile (NOR) and 56% had experienced either pubertal arrest (1%), isolated increase of FSH (IIF 19%), compensated hypergonadotropic hypogonadism (cHH, 23%) or overt hypergonadotropic hypogonadism (oHH, 13%).

Gonadal outcome was not affected by pubertal status upon HSCT (p 0.298), even though, out of 81 patients who had achieved Tanner stage 5, TV was statistically greater in the PostP (12.2±5.1 ml) than in the PreP cohort (10.3±4.1 ml, p 0.049), whereas there were no significant differences in the last testosterone level recorded in the two cohorts, as well as in the hypogonadal versus the event-free patients (p 0.53), with events defined as any gonadal issue (IIF, cHH, oHH). TV was significantly lower in patients who developed any endocrine disfunction versus those who didn't.

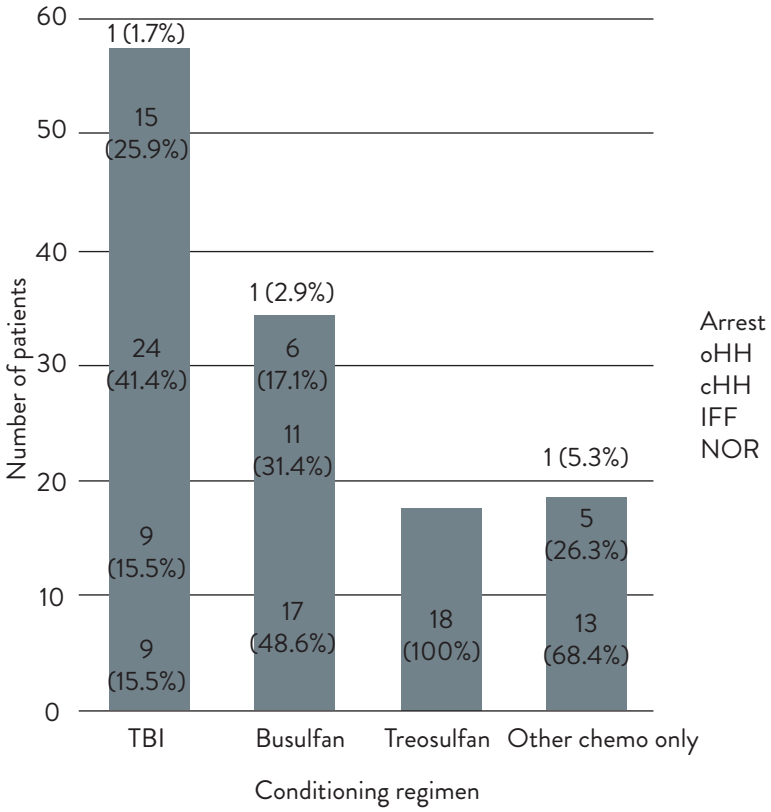
LH and testosterone levels showed a specular trend between 20 and 30 years, when a progressive decrease in sexual steroids was associated with a compensatory increase of the luteinizing hormone. Overall, adult LH (p 0.728) as well as FSH levels (p 0.318) were superimposable in the PreP and PostP cohorts.

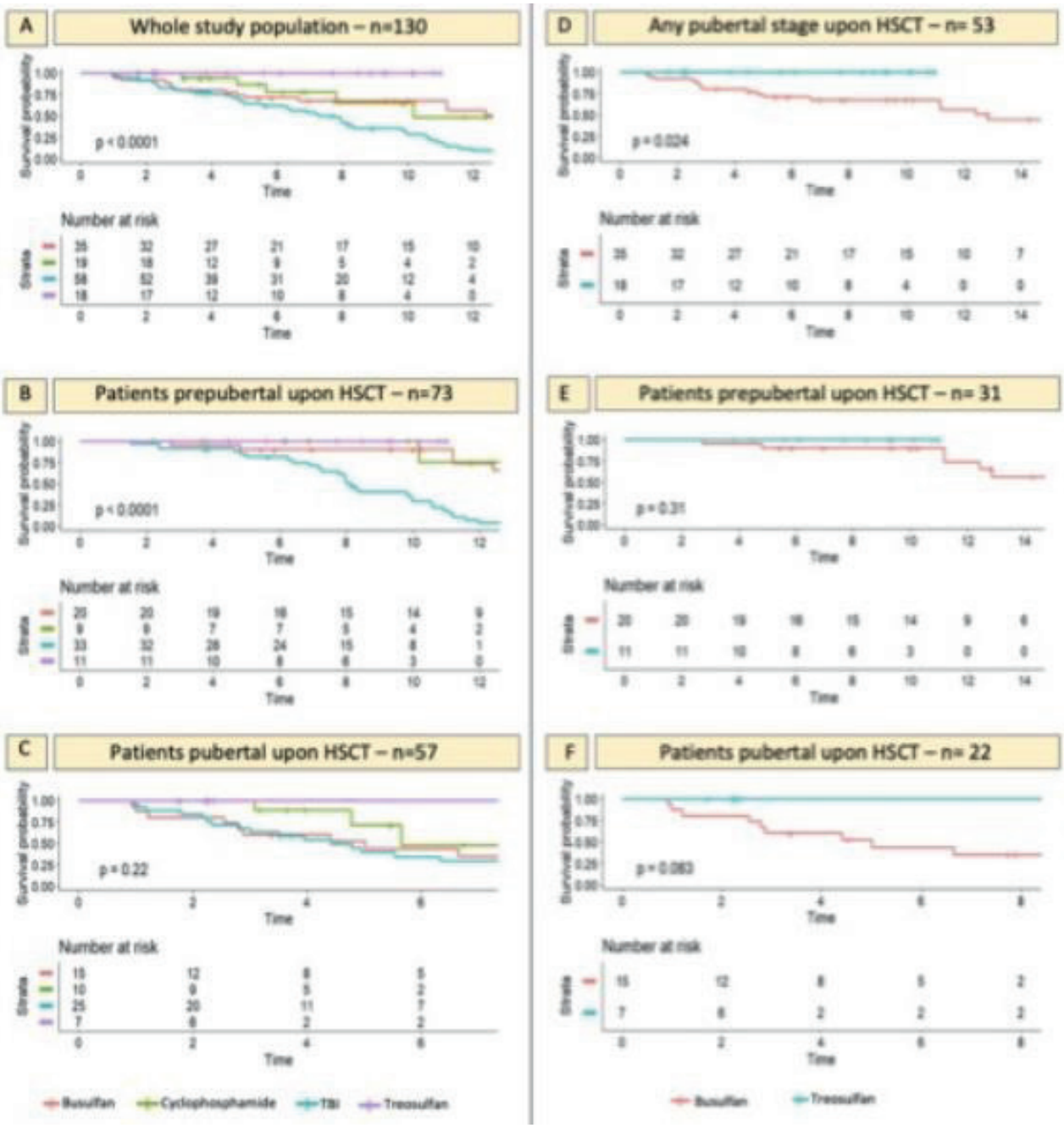
In terms of the impact of the conditioning regimen on gonadal outcomes, a certain degree of gonadal dysfunction (ranging from isolated increase of FSH to hypogonadism or pubertal arrest) was recorded in 37% of the patients overall, and in 85% of the patients after TBI, 51% after busulfan and 32% after cyclophoshamide/fludarabine, whereas no abnormal findings were found among the 18 patients exposed to treosulfan.

The likelihood of a gonadal event-free course was lowest for the TBI and busulfan cohorts, both overall (p<0.0001) and for PreP patients (p<0.0001), whereas it was 100% among the 18 patients conditioned with treosulfan-based schedules. A remarkably greater gonadotoxicity was detected in the busulfan compared with the treosulfan cohort (p 0.024), with a similar trend in the PreP and PostP subcohorts. Busulfan/cyclophosphamide-based conditioning regimens were associated with statistically larger median TV (p <0.001), higher testosterone levels (p 0.008) and lower LH/FSH levels (p <0.001) than those exposed to TBI.

Conditioning regimen (p 0.047) and pubertal status upon HSCT (p <0.0001) were the only variables significantly associated with testicular outcomes in the Cox model, with exposure to TBI being associated with a 2-fold increase in the risk of gonadal failure compared to busulfan (OR 1.93, CI 1.08-3.70), whereas being pre-pubertal upon HSCT was protective, as it was associated with a halved risk of developing any degree of testicular damage (OR 0.50, CI 0.26-0.70).

Conclusion
We demonstrated a i. halved risk of developing post-HSCT hypogonadism in prepubertal patients at HSCT, despite overall smaller final testicular volume; ii. downwards trend in testosterone levels after the achievement of full spontaneous puberty compensated by an inverse upwards trend in LH levels; iii gonadal-sparing profile of treosulfan compared to busulfan-based regimens, with a statistically lower occurrence of hypogonadism and a trend towards larger testicular volume, higher testosterone levels and lower gonadotropins.


60
50
40
30
20
10
0
Number of patients
1 (1.7%)
15
(25.9%)
24
(41.4%)
9
(15.5%)
9
(15.5%)
1 (2.9%)
6
(17.1%)
11
(31.4%)
17
(48.6%)
18
(100%)
1 (5.3%)
5
(26.3%)
13
(68.4%)
TBI
Busulfan
Treosulfan
Other chemo only
Conditioning regimen
Arrest
oHH
cHH
IFF
NOR


A
Whole study population – n=130
p < 0.0001
Number at risk
B
Patients prepubertal upon HSCT – n=73
p < 0.0001
Number at risk
C
Patients pubertal upon HSCT – n=57
p = 0.22
Number at risk
Busulfan
Cyclophosphamide
TBI
Treosulfan
D
Any pubertal stage upon HSCT – n= 53
p = 0.024
Number at risk
E
Patients prepubertal upon HSCT – n= 31
p = 0.31
Number at risk
F
Patients pubertal upon HSCT – n= 22
p = 0.083
Number at risk
Busulfan
Treosulfan

medac

Successful Treatment Outcomes of Hematopoietic Stem Cell Transplantation with Reduced-Toxicity Conditioning Regimen Incorporating Treosulfan in Pediatric Patients with XIAP Deficiency

#3922
Poster presentation

Jin Kyung Suh, MD, PhD[1]*, Ho Joon Im, MD, PhD[2]*, Sung Han Kang, MD[2]*, Hyery Kim, MD[2], Eun Seok Choi[2]* and Kyung-Nam Koh, MD, PhD[2]*

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Study design	Retrospective analysis	**Aim**	Outcomes of HSCT for patients with XIAP deficiency
Parameters assessed	Secondary malignancies		
Patients	4	**Median age (range)**	13.7 y (12.8 – 15.3)
Disease	XIAP deficiency		
Conditioning	Treo (42 g/m^2), Flu (150–180 mg/m^2), TT (10 mg/kg), ATG (5–7.5 mg/kg)		
Results*	• Engraftment and complete DCC 100%. • n=2 aGvHD grade III and VOD (recovered), no other acute regimen related toxicity ≥ CTCAE grade III. • n=1 limited, n=1 extensive cGvHD. • 100% DFS at median 43 mo (range 33.1 – 63.0) follow-up.		
Conclusion	• HSCT with treosulfan based RTC regimen is a promising treatment option for pediatric patients with XIAP deficiency, with successful engraftment and low treatment-related toxicity.		

*Numbers different from abstract were taken from presentation.

Abstract

Background

X-linked inhibitor of apoptosis (XIAP) defciency is an inherited primary immunodefciency characterized by chronic infammasome overactivity and associated with hemophagocytic lymphohistiocytosis (HLH) and infammatory bowel disease (IBD). Although hematopoietic stem celltransplantation (HSCT) is the only curative therapy, the outcomes of HSCT for XIAP deficiency remain unsatisfactory.

Methods

We have performed HSCT with treosulfan based RTC regimen for pediatric patients with non-malignant disorders since January 2016, and reviewed the medical records of patients with XIAP deficiency who underwent treosulfan based HSCT to investigate outcomes of HSCT for patients with XIAP deficiency.

Results

Since January 2016, 4 patients with XIAP deficiency had undergone HSCT using RTC regimen consisted of fludarabine (150–180 mg/m^2), treosulfan (42 g/m^2), rabbit ATG (5–7.5 mg/kg), and thiotepa (10 mg/kg). All patients were male and received HSCT (2 from URD and 2 from HFD) at median 13.7 years old (range, 12.8-15.3), median 2 years (range, 0.5-3.9) after diagnosis of XIAP. They all achieved engraftment and complete donor chimerism at the time of last evaluation. One patient who received HFD HSCT developed acute GI GVHD grade 3 and VOD within 1 month from HSCT, which was recovered after treatment with systemic steroid and defibrotide. Except the patient, there was no fatal acute regimen related toxicity ≥ CTCAE grade 3. Two patients developed chronic GVHD: one had limited disease which was resolved after systemic steroid therapy and the other had extensive disease. During the median 43 months (range, 33.1-63.0) follow-up, all survived without disease recurrence.

Conclusion

HSCT with treosulfan based RTC regimen is promising treatment option for pediatric patients with XIAP deficiency, with successful engraftment and low treatment-related toxicity. However, further studies including a larger multicenter trial and measures to refine the regimen are mandate to verify efficacy and safety of this regimen.

Haploidentical αβ- T Cell Depleted HSCT Represents an Alternative Treatment Option in Pediatric and Adult Patients with Sickle Cell Disease (SCD)

#4915
Poster presentation

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Study design	Single center study	**Aim**	Update on *in vitro* TCD depleted haplo-identical transplant in patients with SCD
Patients	n=49	**Median age (range)**	18 y (2 – 32) (T-haplo) 23 y (9 – 39) (MSD)
Disease	SCD or SCD-β Thal		
Donor	T-haplo (n=29), MSD (n=20)		
Conditioning regimen	FTT: Treo 42 g/m², Flu 160 mg/m², TT 10 mg/kg, ATG		
Results	**MSD**		**T-Haplo**
OS/DFS	95%		83%
Chimerism, median (range)	94.9% (40.5% - 100%)		97.8% (35.7% - 100%)
Viral Reactivation (outcome)	45% (100% resolved)		69% (3% kidney failure, 14% died)
aGvHD > grade III	0		0
Conclusion	• T-haploSCT in advanced stage pediatric and adult SCD patients lacking a MSD is feasible. • Viral monitoring and early treatment of viral reactivation essential.		

Abstract

Background
Sickle cell disease (SCD) is the most prevalent inherited hemoglobinopathy worldwide, which is associated with considerable morbidity and early mortality. Although HSCT with a MD offers a curative treatment option with an excellent 2-y OS of 95%, availability of MDs is limited and therefore haploidentical HSCT is increasingly explored. Here we update our in vitro T-depleted haploidentical HSCT approach, which is currently explored in a multicenter international trial (NCT04201210)..

Methods
29 pts with SCD or SCD-ß Thal (median age: 18 years; range: 2-32) received either a CD3+/CD19+ (n=9) or aß/CD19+ (n=20) T-haplo-HSCT and were compared with 20 SCD-pts receiving a BM graft from a MSD (median age: 23 years; range: 9-39) at our center. Indication for T-haplo HSCT pts included severe or moderate SCD related complications such as recurrent pain crisis (>5/year), acute chest syndrome, neurological events, osteonecrosis or nephropathy, transfusion-refractory allo-immunization. After exchange transfusion, almost identical conditioning regimens consisting of treosulfan, thiotepa, fludarabine (FTT) and ATG-Grafalon were applied in almost all pts, with the only difference in the timing of ATG (upfront in T-haplo-HSCT, prior to day 0 in MSD-HSCT). Immunosuppression (IST) was maintained for a minimum of 180 days consisting of calcineurin inhibitors (mainly tacrolimus) and MMF.y.

Results
The OS and DFS for MSD and T-haplo-HSCT was 95% and 83%, respectively (Table 1). The median follow-up was 49 months for MSD (range 5-118) and 67 months for T-haplo-HSCT (range 0.5-135). Neutrophil engraftment was achieved after a median of 29 days for MSD pts and 17 days for T-haplo-HSCT with a median of 2.8 x 108 TNC/kg (range: 0.65–4.11) and 12 x 106 CD3+/CD19+ or ab/CD19+ depleted CD34+ cells/kg (range: 4.8–49.2), respectively. One pt received two T-haplo HSCT due to primary graft failure after HHV6 infection with effective engraftment after the second transplantation. One pt required a stem cell boost of the same donor with slow subsequent engraftment and one pt died of infectious complications after the fourth T-haplo HSCT. A mixed chimerism <80% was observed in 1/20 MSD-HSCT (median 94.9%; range 40.5–100%) and in 2/29 T-haplo-HSCT pts (median 97.8%; range: 35.7 -100%). No severe cases of >°III aGVD was observed in both populations. MSD pts reached T cell counts >200/µl on day +62 (median; range: 24-293) and T-haplo-HSCT pts on day +136 (median; range: 25-758). Viral reactivation occurred both in T-haplo HSCT (20/29) and in MSD-BMT (9/20). However, one pt in the T-haplo group developed kidney failure after prolonged BKV infection and four of the T-haplo pts died of complications associated with severe CMV or HHV6 infections that were accompanied by hyperinflammation, macrophage activation and acute respiratory distress despite antiviral and anti-inflammatory treatment. One pt of the MSD group died of late treatment related toxicity in combination with preexisting SCD comorbidity. The last fatality occurred in 2020 with now 16 additional pts being transplanted safely, not least also because of a consistent letermovir prophylaxis. Overall, the treosulfan-based conditioning regimen was well tolerated with only one VOD/SOS and one CNS infarction being observed in this high-risk population. 4/20 pts in the MSD group and none in the T-haplo group developed PRES early after conditioning.

Conclusion
The safety and efficacy data of this pilot series of T-haplo-HSCT in SCD reveal that T-haplo-HSCT in advanced stage pediatric and adult SCD patients lacking a MSD is feasible. However, diligent viral monitoring and early treatment of viral reactivation, in particular HHV6 is mandatory as otherwise fatal infections may develop.

RESULTS		
	MSD	**T-haplo SCT**
OS/DSF (%)	95	83
Follow-Up (months) Median (range)	49 (range 5-118)	67 (range 0.5-135)
Engraftment (day) Median (range)	29 (17-41)	17 (11-35)
Chimerism Median (range)	94.9% (40.5-100%)	97.8% (35.7-100%)
Immune reconstitution >200 CD3+/µl (day) Median (range)	62 (24-293)	136 (25-758)
Viral reactivation	45%	69%
Outcome	100 % resolved	3% kidney failure (BKV) 14% fatal CMV/HHV6 infections

Table 1. Results. MSD = matched sibling donor; T-haplo SCT= t-cell depleted, haploidentical stem call transplantation, pt.= patient; IST= immunosuppressive treatment

Trecondi® 1 g / 5 g powder for solution for infusion

Qualitative and quantitative composition: One vial Trecondi 1 g (5 g) powder for solution for infusion contains 1 g (5 g) of treosulfan. When reconstituted, 1 mL of the solution for infusion contains 50 mg treosulfan. **Therapeutic indications:** Treosulfan in combination with fludarabine is indicated as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in adult patients and in paediatric patients older than one month with malignant and non-malignant diseases. **Posology and method of administration:** Administration should be supervised by a physician experienced in conditioning treatment followed by alloHSCT. *Adults with malignant disease:* Treosulfan is given in combination with fludarabine. Treosulfan 10 g/m² body surface area (BSA) per day as a two-hour intravenous infusion, given on three consecutive days (day -4, -3, -2) before stem cell infusion (day 0). The total treosulfan dose is 30 g/m²; Treosulfan should be administered before fludarabine. *Adults with non malignant disease*: Treosulfan is given in combination with fludarabine with or without thiotepa. Treosulfan 14 g/m² body surface area (BSA) per day as a two-hour intravenous infusion, given on three consecutive days (day -6, -5, -4) before stem cell infusion (day 0). The total treosulfan dose is 42 g/m²; Treosulfan should be administered before fludarabine. *Paediatric population:* Treosulfan is given in combination with fludarabine, with or without thiotepa. **Contraindications:** Hypersensitivity to the active substance; active non-controlled infectious disease; severe concomitant cardiac, lung, liver, and renal impairment; Fanconi anaemia and other DNA breakage repair disorders; pregnancy; administration of live vaccine. **Undesirable effects:** *Infections, infestations:* Very commonly infections (bacterial, viral, fungal). Commonly **s**epsis. Septic shock. *Neoplasms:* Treatment related second malignancy. *Blood, lymphatic system:* Very commonly myelosuppression, pancytopenia, febrile neutropenia. *Immune system:* Commonly hypersensitivity. *Metabolism and nutrition:* Commonly decreased appetite. Uncommonly glucose tolerance impaired including hyperglycaemia and hypoglycaemia. Acidosis, alkalosis, electrolyte imbalance, hypomagnesaemia. *Psychiatric:* Commonly insomnia. Uncommonly confusional state. *Nervous system:* Commonly headache, dizziness. Uncommonly intracranial haemorrhage, peripheral sensory neuropathy. Encephalopathy, intracranial haemorrhage, extrapyramidal disorder, syncope, paraesthesia, seizure. *Eye:* Dry eye, conjunctival haemorrhage. *Ear:* Uncommonly vertigo. *Cardiac:* Commonly cardiac arrhythmias (e.g. atrial fibrillation, sinus arrhythmia). Cardiac arrest, cardiac failure, myocardial infarction, pericardial effusion. *Vascular:* Commonly hypertension, hypotension, flushing. Uncommon haematoma. Embolism, capillary leak syndrome. *Respiratory, thoracic, mediastinal:* Commonly dyspnoea, epistaxis, oropharyngeal pain. Uncommonly pneumonitis, pleural effusion, pharyngeal or laryngeal inflammation, hiccups. Laryngeal pain, cough, dysphonia, hypoxia. *Gastrointestinal:* Very commonly stomatitis/mucositis, diarrhoea, nausea, vomiting, abdominal pain. Commonly oral pain, gastritis, dyspepsia, constipation, dysphagia, oesophageal or gastrointestinal pain, anal inflammation. Uncommonly mouth haemorrhage, abdominal distension, dry mouth. Gastric haemorrhage, neutropenic colitis, oesophagitis, proctitis, gingival pain. *Hepatobiliary:* Very commonly hepatotoxicity. Uncommonly veno-occlusive liver disease. Hepatomegaly. *Skin, subcutaneous tissue:* Very commonly pruritus, alopecia. Commonly (maculo-papular) rash, purpura, erythema, urticaria, palmar plantar erythrodysaesthesia syndrome, dermatitis exfoliative, pain of skin, skin hyperpigmentation. Uncommonly erythema multiforme, dermatitis acneiform, dry skin. Skin necrosis or ulcer, dermatitis, dermatitis bullous, dermatitis diaper. *Musculoskeletal and connective tissue:* Commonly pain in extremity, back pain, bone pain, arthralgia. Uncommonly myalgia. *Renal, urinary:* Commonly acute kidney injury, haematuria. Uncommonly urinary tract pain. Renal failure, haemorrhagic or noninfective cystitis, dysuria. *Reproductive system:* Scrotal erythema, penile pain. *General, administration site:* Very commonly asthenic conditions (fatigue, asthenia, lethargy), pyrexia. Commonly oedema, chills. Uncommonly non cardiac chest pain, pain, face oedema. *Investigations:* Very commonly blood bilirubin increased, ALT increased. Commonly AST increased, γGT increased, C**-**reactive protein increased, weight decreased, weight increased. Uncommonly blood alkaline phosphatase increased. Blood lactate dehydrogenase (LDH) increased. **Legal classification**: POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH Theaterstraße 6; 22880 Wedel, Germany. **Date of revision of text**: 11/2023

Trecondi has been authorised in all countries of the EU as well as in Belarus, Iceland, Kazakhstan, Norway, Liechtenstein, Russia, Switzerland (Ideogen AG), United Kingdom, Ukraine

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