:medac

TREOSULFAN IN HSCT

Abstracts

EBMT
50th Annual Meeting
14-17 April 2024
Glasgow, UK

Dear Reader,

We are pleased to present you a compilation of selected clinical results focusing on Treosulfan-based conditioning treatment prior to stem cell transplantation in children and adults presented at the 50th Annual Meeting of the EBMT in Glasgow.

A wide variety of studies on the use of Treosulfan was shared, both as oral and poster presentations, in the fields of adult and pediatric transplantation for malignant and non-malignant diseases.

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

Best regards from Wedel,

Yours

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Contents

Abbreviations

a/cGvHD	Acute/chronic Graft-versus-Host-Disease
AE	Adverse event
ALL	Acute lymphoblastic leukaemia
allo	Allogeneic
AML	Acute myeloid leukaemia
ATG	Anti-thymocyte globulin
auto	Autologous
AYA	Adolescents and young adults
BMF	Bone marrow failure
BSA	Body surface area
Bu	Busulfan
CEAM	Lomustine/Etoposide/Cytarabine/Melphalan
CHO(E)P	Cyclophosphamide/Hydroxydaunorubicine/ Vincrstine/(Etoposide/)Predniso[lo]ne
CIR	Cumulative incidence of relapse
CLL	Chronic lymphocytic leukemia
CML	Chronic myelogenous leukemia
CMML	Chronic myelomonocytic leukemia
CNS	Central nervous system
CR	Complete response/remission
CRFS	cGvHD and relapse-free survival
CT	Chemotherapy
Cy	Cyclophosphamide
d	Day(s)
DBA	Diamond Blackfan anaemia
DFS	Disease-free survival
DLBCL	Diffuse large B-cell lymphoma
ECOG Group	Eastern Cooperative Oncology
EFS	Event-free survival
EWS	Ewing sarcoma
FBT	Fludarabine/Busulfan/TBI
FHLH	Familial hemophagocytic lymphohistiocytosis
Flu	Fludarabine
FT	Fludarabine/Treosulfan
FTA	Fludarabine/Treosulfan/ATG
FTT	Fludarabine/Treosulfan/Thiotepa
f-up	Follow-up
GF	Graft failure
GRFS	GvHD- and relapse-free survival
haplo	Haploidentical
HBP	Hemoglobinopathy
HD	High dose
HR	High risk
HSCT	Hematopoietic stem cell transplantation
HSOS	Hepatic sinusoidal obstruction syndrome
IEM	Inborn errors of metabolism
LD	Low dose
LFS	Leukemia-free survival
MAC	Myeloablative conditioning
MCL	Mantle-cell lymphoma
MDS	Myelodysplastic syndrome
MDS/MPN-RS-T	MDS/MPN with ring sideroblasts and thrombocytosis
MDS/MPN-U	MDS/MPN, unclassifiable
Mel	Melphalan
MF	Myelofibrosis
MFD	Matched family donor
MLD	Metachromatic leukodystrophy
mo	Month(s)
MPN	Myeloproliferative neoplasia
MRD	Minimal residual diease
MSD	Matched sibling donor
MTX	Methotrexate
MUD	Matched unrelated donor
n.m.	not mentioned
NB	Neuroblastoma
NHL	Non-Hodgkin lymphoma
NMD	Non-malignant disease
NRM	Non-relapse mortality
OS	Overall survival
PFS	Progression-free survival
PID	Primary immunodeficiencies
PMBCL	Primary mediastinal large B-cell lymphoma
pOS	Probability of OS
PRES	Posterior reversible encephalopathy syndrome
PS	Performance score
PSM	Propensity score matching
PTCy	Post-transplantation Cyclophosphamide
pts	Patients
QoL	Quality of life
RFS	Relapse-free survival
RI	Relapse incidence
RTC	Reduced toxicity conditioning
SAA	Severe aplastic anemia
sAML	Secondary AML
SCD	Sickle-cell disease
SCID	Severe combined immunodeficiency
Sir	Sirolimus
SOS	Sinusoidal obstruction syndrome
TBI	Total body irradiation
TDT	Transfusion dependent thalassemia
TM	Thalassemia major
Treo	Treosulfan
TRM	Transplant-related mortality
TT	Thiotepa
VOD	Veno-occlusive disease
WAS	Wiskott-Aldrich Syndrome
y	Year(s)

Adult Patients

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Fludarabine Plus Treosulfan or TBI as a Conditioning Therapy Before Allogeneic HSCT in Acute Lymphoblastic Leukemia. A Matched-Pair Analysis From the ALWP of the EBMT

OS12-06
Oral presentation

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Study design	Retrospective registry analysis	**Aim**	Comparison of Flu/Treo vs. Flu/TBI conditioning in adult pts with ALL
Outcome parameters	GF, a/cGvHD, RI, NRM, LFS, OS, GRFS		
Patients	584	**Median age (range)**	56.5 y (18.1 – 74.3) Flu/Treo 54.1 y (18.1 – 74.4) Flu/TBI
Disease	ALL		
Conditioning regimen	**Flu/Treo (n=153)** [ΣTreo 30 – 42 g/m²]	**Flu/TBI (n=431)** [ΣTBI 8-12 Gy]	p
Results*			
GF	3.5%	1.7%	n.m.
aGvHD (grade II-IV / III-IV)	26.6% / 13.7%	30% / 9.3%	0.431 / 0.132
2 y cGvHD (overall / extensive)	33.5% / 18.8%	40.7% / 20.2%	0.226 / 0.87
2 y RI	28.1%	25.6%	0.154
2 y NRM	25.6%	20.4%	0.382
2 y LFS	46.2%	54.5%	0.095
2 y OS	55%	61.3%	0.223
2 y GRFS	33.7%	40.8%	0.063
Conclusion	• Comparable outcomes between Flu/Treo and Flu/TBI. ➪ Flu/Treo is a valuable alternative for ALL patients with contraindications for irradiation.		

*Numbers differing from abstracts were based on final presentation at conference

Abstract

Background

Total body irradiation (TBI)-based conditioning is considered as a standard therapy before allogeneic hematopoietic stem cell transplantation (alloHSCT) in patients with acute lymphoblastic leukemia (ALL). Although treosulfan (Treo) is a frequently used component of TBI-free conditioning in patients with acute myeloid leukemia, there are very limited data on Treo-based conditioning before alloHSCT in ALL patients. As Treo is commonly used in combination with fludarabine (Flu), we aimed to compare Flu/Treo with Flu/TBI as a conditioning therapy before alloHSCT in ALL patients.

Methods

Based on EBMT registry we retrospectively analyzed data of 2055 adult patients with ALL who met inclusion criteria: 1) first alloHSCT in first or second complete remission (CR1, CR2) between years 2006 and 2022; 2) matched sibling (MS), unrelated (UD) or haploidentical donor; 3) Flu/Treo (30-42g/m^2) or Flu/TBI (8-12 Gy) as a conditioning therapy. 153 patients in Flu/Treo group and 431 patients in Flu/TBI group were included in a final matched-pair analysis.

Results

The median patients age was 54.1 and 56.5 years in Flu/TBI and Flu/Treo group, respectively. Male to female proportion was 52%/48% in both groups. Philadelphia negative (Ph-), Ph positive (Ph+) B-ALL and T-ALL were diagnosed in 61 (39.9%), 42 (27.5%), 22 (14.4%) patients in Flu/Treo group and in 168 (39%), 111 (25.8%), 70 (16.2%) patients in Flu/TBI group. CR1/CR2 proportion was 75%/25% in both groups. The allograft was derived from UD (54.2% in Flu/Treo and 52% Flu/TBI group), MS (30.7% and 32.5%) and haploidentical donor (15% and 15.5%).

Graft failure was diagnosed in 5 (3.5%) and 7 (1.7%) patients in Flu/Treo and Flu/TBI group, respectively. The incidence of acute graft versus host disease (GVHD) grade II-IV and III-IV was 26.6% and 13.7% in Flu/Treo and 30% and 9.3% in Flu/TBI group (HR 0.87 (95% CI 0.6-1.24), p=0.43, and HR 1.5 (0.89-2.54), p=0.13, respectively). The 2-year incidence of overall and extensive chronic GVHD was 33.5% and 18.8% in Flu/Treo while 40.7% and 20.2% in Flu/TBI group (HR 0.81 (0.57-1.14), p=0.23, and HR 1.04 (0.65-1.68), p=0.87). The 2-year incidence of relapse and non-relapse mortality was 28.1% and 25.6% in Flu/Treo and 25.1% and 20.4% in Flu/TBI group (HR 1.31 (0.91-1.88), p=0.15 and HR 1.19 (0.8-1.77), p=0.38, respectively). Leukemia-free survival and overall survival was 46.2% and 55% in Flu/Treo and 54.5 and 61.3 in Flu/TBI group (HR 1.25 (0.96-1.63), p=0.1 and HR 1.19 (0.9-1.59), p=0.22, respectively). GVHD and relapse-free survival was 33.7% and 40.8%, respectively in Flu/Treo and Flu/TBI group (HR 1.25 (0.99-1.57), p=0.06).

Conclusions

The combination of Flu with Treo as a conditioning therapy before alloHSCT in ALL patients results in comparable transplant outcomes as Flu combined with TBI. Therefore Flu/Treo appears a valuable alternative for ALL patients with contraindications for irradiation. Our findings require confirmation in prospective trials.

Treosulfan- Versus Busulfan-Based Conditioning in Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndrome: A Single-Centre Retrospective Propensity Score-Matched Cohort Study

OS12-08
Oral presentation

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Study design	Single-centre retrospective PSM cohort study	**Aim**	Comparison of Treo-based vs. Bu-based conditioning for MAC-ineligible pts with MDS
Outcome parameters	OS, RFS, GRFS, NRM, EFS, a/cGvHD		
Patients	138	**Median age (range)**	66 y (55 - 74) FT 65 y (50 - 74) FBT200
Disease	MDS, CMML		
Conditioning regimen	Treo-based (n=46) FT	Bu-based (n=92) FBT200	p
Results*			
2 y OS	66.9%	44.5%	0.013
2 y RFS	63.1%	39.1%	0.008
2 y GRFS	57.4%	35.1%	0.009
2 y RI	15.6%	27.6%	0.22
1 y NRM	9.9%	29.7%	0.04
1 y EFS	40.3%	9.2%	<0.001
aGvHD d+100 (grade II-IV / III-IV)	28.3% / 4.3%	22.8% /7.6%	0.46 / 0.75
2 y cGvHD (all / moderate-severe)	13.8% / 10.9%	30.2% / 21.0%	0.07 / 0.22
Conclusion	• Treo-based conditioning is associated with improved OS, NRM, EFS, RFS and GRFS compared to Bu-based conditioning in MAC-ineligible patients with MDS. • The main effect of Treo-based conditioning is likely through a reduction of TRM; whether it is also associated with lower relapse remains unclear and may depend on the dose used (30 g/m^2 vs. 42 g/m^2).		

*Additional info and info different from abstract based on talk at conference

Abstract

Background

Treosulfan has shown promise in allogeneic hematopoietic cell transplantation (HCT) for its myeloablative properties and low toxicity. However, existing retrospective studies lack data from well-matched cohorts whereas phase III data failed to define optimal treosulfan dosing. In this single-centre retrospective propensity score-matched cohort study we compared treosulfan- and busulfan-based conditioning in allogeneic HCT for myeloablative conditioning-ineligible patients with myelodysplastic syndrome (MDS).

Methods

This study included 138 adults who underwent allogeneic HCT for MDS or chronic myelomonocytic leukemia (CMML) at Princess Margaret Hospital, Toronto 2015-2022. Using propensity score matching, we compared transplant outcomes between two well-matched cohorts who received conditioning with either fludarabine-treosulfan (FT) (n=46) or fludarabine-busulfan with total body irradiation (FBT200) (n=92).

Results

Patient characteristics are shown in **Table 1**. A scoring system based on patient age, Karnofsky performance score and hematopoietic cell transplant comorbidity index was used to assign patients based on fitness to low-dose (30 g/m^2) or high-dose (42 g/m^2) treosulfan: 32 (69.6%) received high-dose treosulfan. Primary outcomes were analyzed at a median follow-up of 747 days.

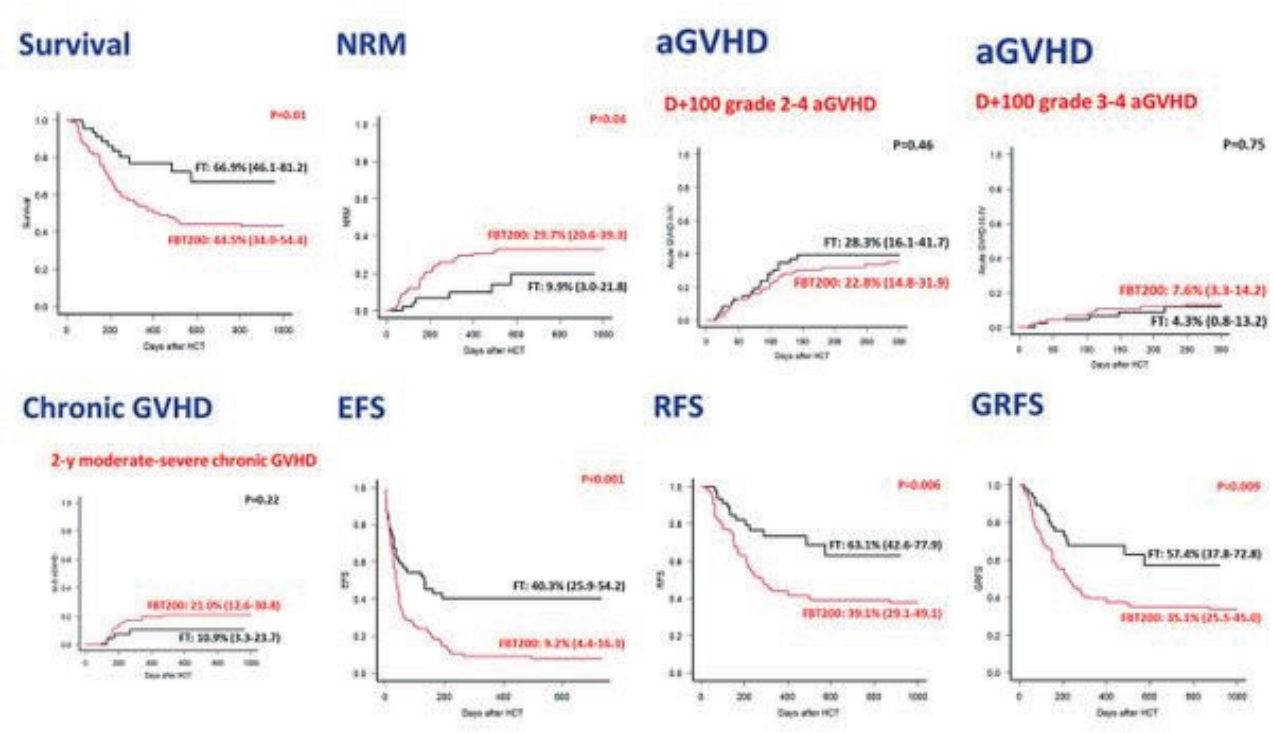
Outcomes are shown in **Figure 1**. Patients who received FT had a superior 2-y overall survival (OS) compared to those who received FBT200: 66.9% (95% confidence interval (CI): 46.1-81.2) vs. 44.5% (95% CI: 34-54.4), hazards ratio (HR): 0.43, 95% CI: 0.22-0.84 (P=0.013). In multivariate analysis (MVA), only the use of fresh grafts (P=0.02) and FT (P=0.01) were associated with improved OS.

FT was associated with superior 2-y relapse-free survival (RFS) compared FBT200: 63.1% (95% CI: 42.6-77.9) vs. 39.1% (95% CI: 29.1-49.1), HR: 0.44 (95% CI: 0.24-0.81), P=0.008. In MVA, the use of fresh grafts (P=0.03) and FT (P=0.009) were associated with improved RFS.

Recipients of FT demonstrated superior 2-y graft versus host disease relapse-free survival (GRFS) compared to those who received FBT200: 57.4% (95% CI: 37.8-72.8) vs. 35.1% (95% CI: 25.5-45). In MVA, only FT was associated with superior GRFS (P=0.02).

FT was associated with lower 1-y non-relapse mortality (NRM) compared to FBT200 in univariate analysis (9.9% (95% CI: 3.0-21.8) vs. 29.7% (95% CI: 20.6-39.3), HR: 0.41 (95% CI: 0.17-0.96), P=0.04) and MVA (P=0.04).

FT recipients exhibited markedly superior 1-y event-free survival (EFS) compared to recipients of FBT200 in univariate analysis (40.3% (95% CI: 25.9-54.2) vs. 9.2% (95% CI: 4.4-16.3), HR: 0.47 (95%CI: 0.30-0.72), P<0.001) and MVA (P=0.004).



Variable	FT (N=46)	FBT200 (N=92)	P-value
Age (median, range)	66 (55-74)	65 (50-74)	0.15
≥65 (N, %)	25 (54.3)	45 (48.9)	0.59
Female gender (N, %)	13 (28.2)	38 (41.3)	0.19
Diagnosis (N, %)			0.82
CMML	10 (21.7)	18 (19.6)	
MDS	36 (78.3)	74 (80.4)	
therapy-related	10 (21.7)	9 (9.8)	0.07
Donor			0.90
MSD	9 (19.6)	20 (21.7)	
MUD	27 (58.7)	50 (54.3)	
MMUD	7 (15.2)	10 (10.9)	
HID	3 (6.5)	12 (13.0)	
Donor age (median, range)	34 (18-69)	32 (18-67)	0.26
Female -> male (N, %)	10 (21.7)	16 (17.4)	0.64
GVHD-P (N, %)			0.22
Dual TCD (ATG+PTCy)	36 (78.3)	80 (87.0)	
Other	10 (21.7)	12 (13.0)	
DRI (N, %)			0.92
Low-intermediate	31 (67.4)	63 (68.5)	
High	15 (32.6)	29 (31.5)	

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Variable	FT (N=46)	FBT200 (N=92)	P-value
IPSS (N, %)			0.85
Low	0	2 (2.2)	
Intermediate	13 (28.3)	26 (28.3)	
High	7 (15.2)	19 (20.7)	
Missing	26 (56.5)	45 (48.9)	
HCT-CI (N, %)			0.86
<3	22 (47.8)	46 (50.0)	
≥3	24 (52.2)	45 (48.9)	
Missing	0	1 (1.1)	
KPS (N, %)			0.83
<90	12 (26.1)	21 (22.8)	
≥90	34 (73.9)	70 (76.1)	
Missing	0	1 (1.1)	
CD34 dose (median, range)	6.2 (1.7-8.3)	8.2 (3.5-48.1)	<0.001
Stem cell source			1.00
PBSC	46 (100.0)	91 (98.9)	
BMSC	0	1 (1.1)	
Graft manipulation			0.55
Fresh	35 (76.1)	64 (69.6)	
Frozen	11 (23.9)	28 (30.4)	
Follow-up in days (median, range)	365 (100-959)	1106 (169-2734)	<0.001
Treosulfan dose			
30 g/m^2	14 (30.4)		
42 g/m^2	32 (69.6)		

Abbreviations: M (male), F (female), MDS (myelodysplastic syndrome), CMML (chronic myelomonocytic leukemia), MSD (matched sibling donor), MUD (matched unrelated donor), haplo (haploidentical donor), MMURD (mismatched unrelated donor), FtM (female donor to male recipient), GVHD (graft versus host disease), PTCy (post transplantation cyclophosphamide), ATG (antithymocyte globulin), DRI (disease risk index), HCT CI (hematopoietic cell transplantation specific comorbidity index), KPS (Karnofsky performance status), F-U (follow up), IPSS (international prognostic scoring system), SC (stem cell), BM (bone marrow), PBSC (peripheral blood stem cell).

Conclusions

This study is the first to utilize propensity score matching in assessing the role of treosulfan in stem cell transplantation of MAC ineligible patients with MDS and contributes to the increasing body of evidence supporting the antileukemic properties of the drug while underscoring its safety, even at the dose of 42 g/m^2. Randomized controlled trials comparing treosulfan given at 30 g/m^2 and 42 g/m^2 are warranted.

Treosulfan Plus Fludarabine "Reduced Intensity Conditioning" With Posttransplant Cyclophosphamide in Patients With Acute Myeloid Leukemia Older Than 65 Years

A131
Poster presentation

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Study design	Retrospective multicenter study	**Aim**	Outcome of AML pts >65 y with Treo-based conditioning before haploHSCT
Endpoints	Survival, CIR, engraftment, GvHD		
Patients	30	**Median age (range)**	69 y (65 – 74)
Disease	AML		
Conditioning regimen	FT10: Treo 30 g/m^2, Flu 150 mg/m^2, followed by PTCy		
Results Engraftment [median (range)] OS [d100 / 1 y] Chimerism [Full donor / mixed] aGvHD [grade I-II / III-IV] 2 y cGvHD [grade I-II / III-IV] TRM [d100 / 1 y] CIR [d100 / 1 y]	 neutrophil 14 d (13 -21), platelets 22 d (13 – 48) 76% / 65% 92% / 3.7% 10% / 15% 20% / 15% 17% / 26% 4% / 13%		
Conclusion	• RIC with FT10 before haploHSCT in combination with PTCy should be considered in patients over 65 y who do not have a MRD or MUD. • FT10 seems to limit relapse and GvHD without increasing TRM.		

Abstract

Background

Allogenic stem cell transplantation (allo-HSCT) is the only curative option for intermediate and high-risk adult acute myeloid leukemia (AML). The majority of patients (pts) older than 65y had been excluded from this potentially curative option for decreasing allo-HSCT tolerance, for toxicity related to myeloablative conditioning and for a low probability of finding a HLA-identical donor. We report here the outcome of AML pts with older than 65y who underwent unmanipulated haploidentical transplantation (aplo-HSC) received a reduced intensity conditioning with intravenous 10 g/m^2 treosulfan daily, for 3 days plus 30 mg/m^2 intravenous fludarabine daily for 5 days (T10F) and post-transplant cyclophosphamide (PT-CY) as prevention of gvhd, with encouraging results in terms of survival and relapse incidence, engraftment and graft-versus-host disase (GvHD) incidence.

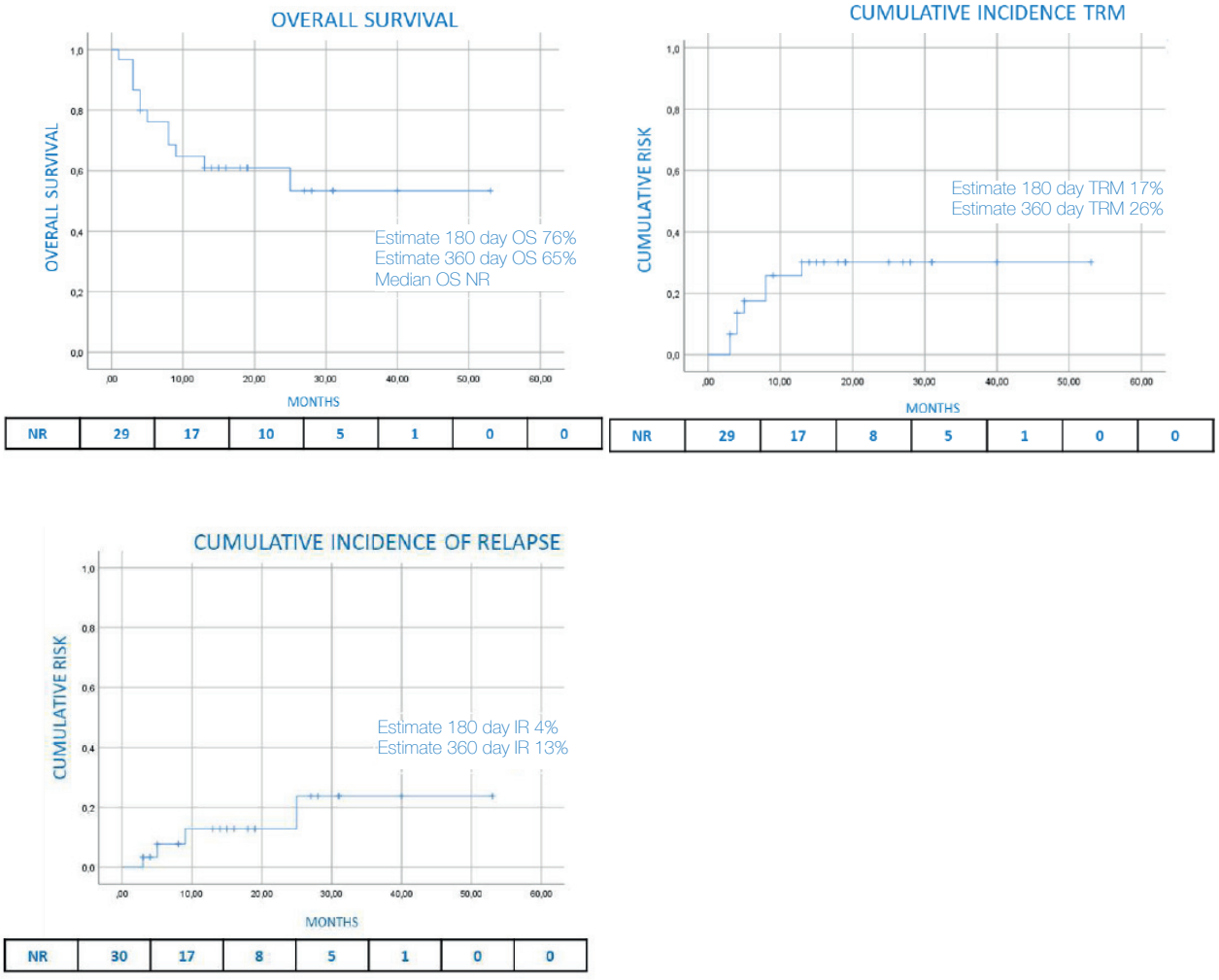
Methods

Between Jun 2019 and June 2023, 30 consecutive adult pts aged ≥65y received an aplo-HSCT for AML in four Hematology Transplant Unit. Patients' median age was 69y (range 65–74). Twenty-four pts (80%) and 6 (20%) experienced this in 1° complete remission (CR) and in ≥ 2° CR respectively. GvHD prophylaxis consisted of post-transplant cyclophosphamide (PT-CY), mycophenolate mofetile and ciclosporin. All patients received peripheral blood stem cells as sours of graft (PBSC) TAB1

Transplant characteristics	
KPS ≥ 90%	30 (100%)
Cell dose CD34+:	
Mean ^{X} 10^6/Kg (range)	6.2 (4.6-9.5)
Donor Kinship:	
Brother/sister	8 (27%)
Child	10 (33%)
Parent	11 (37%)
Niece	1 (3%)
Time diagnosis to HAPLO-PT-CY months (range)	11 (5-77)
Extrahematological toxicity Grade3-4):	
Nausea	8 (26%)
Vomit	6 (20%)
Diarrhea	5 (16%)
Mucositis	8 (26%)
Sepsis	8 (26%)
Invasive Micosys	2 (6%)
PT-Cy (GVHD prophylaxis):	
PT-Cy; 50 mg/m2 day+3+4	14 (47%)
PT-Cy; 50 mg/m2 day+3+5	12 (40%)
PT-Cy; 40 mg/m2 day+3+4	4 (13%)

Results

The median time to neutrophil engraftment>0.5x10^9/l and platelet>20x10^9/l was 14 days (range 13-21) and 22 days (range 13-48) respectively. All pts except one (3%) achieved full engraftment at day 30. One (3%) patient in CR2 had autologous reconstitution at day 90. Among the 27 (90%) pts alive at day 100, chimerism was full donor in 25 pts (92%), one patient for mixed chimerism received donor lymphocyte infusion. The cumulative incidence of acute GvHD was 25% (grade I-II and III-IV was 10% and 15% respectively) and cumulative incidence chronic GvHD (evaluated in 27 patients) was 35% (grade I-II and III-IV was 20% and 15% respectively). After a median follow-up of 15 months (range 3-50); 18 (60%) pts are alive and sustained leukemia remission with minimal residual desease negativity and 12 (40%) pts died. Only 4 (13%) pts died of progressive disease, while 8 (26%) pts died from transplant related causes (4 pts die for infections, 3 pts from GvHD, and 1 pts from cachesia). The estimate day 100 and 1-year respectively overall survival were 76% and 65% respectively. The TRM was 17% and 26% at day 100 and 1-year respectively. The estimate day 100 and 1-year cumulative incidence of relapse were 4% and 13% respectively (Fig1).



Conclusions

Our results confirm that reduced intensity conditioning with treosulfan plus fludarabine beafore Aplo-HCT with posttransplant cyclophosphamide should be considered in AML patients older than 65y in absence of related or unrelated matching donor. This reduced intensity conditioning (T10F) would seem to limit relapse and GvHD without increasing TRM. Multicentric and larger studies with similar platforms are needed to confirm our results.

Improving Outcomes in MDS/MPN: Treosulfan-Based Conditioning for Allogeneic Hematopoietic Stem Cell Transplantation

A278
Poster presentation

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Study design	Single center analysis	**Aim**	Assessing Flu/Treo conditioning in patients with MDS/MPN
Outcome parameters	Engraftment, OS, PFS, GRFS, RI, TRM, a/cGvHD		
Patients	21	**Median age (range)**	61 y (35 – 71)
Disease	CMML (n=13), aCML (n=4), MDS/MPN-U (n=3), MDS/MPN-RS-T (n=1)		
Conditioning regimen	FT14: Treo 42 g/m^2, Flu 150 mg/m^2; in n=2 only 30 g/m^2 Treo due to age ≥70y; in n=10 intensification by second alkylator or TBI		
Results			
Engraftment	95%; median 22 d [14 – 59] / 32 d [13 – 188] (neutrophil / platelet)		
2 y OS	80.4%		
2 y PFS	80.7%		
2 y GRFS	60.5%		
2 y RI	9.8%		
TRM	9.5%		
d100 aGvHD (grade II-IV / III-IV)	19.4% / 4.8%		
2 y cGvHD (overall / moderate/severe)	30.1% / 15.3%		
Conclusion	• AlloHSCT with Treo-based conditioning seems effective and well-tolerated in pts with MDS/MPN and is associated with low risk of relapse and TRM.		

Abstract

Background
MDS/MPN is a rare group of diseases mostly affecting elderly patients. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is nowadays the only potentially curative treatment for MDS/MPN, unfortunately with contradictory and disappointing results in terms of relapse and treatment related mortality (TRM). Moreover, transplant strategies across EBMT centers are highly heterogeneous and the best conditioning strategy is unknown in this difficult setting.

Methods
We conducted a single-center analysis on consecutive adult patients with MDS/MPN who underwent a first allo-HSCT for this indication at our institution between March 2009 and November 2022 and received a treosulfan-based conditioning. We collected data of 21 patients (13 CMML, 4 aCML, 3 MDS/MPN-U, 1 MDS/MPN-RS-T, according to WHO-2016). Conditioning regimen included treosulfan 14 g/m^2 from day -6 to -4 and fludarabine 30 mg/m^2 from day -6 to -2; two patients received a reduced dose of treosulfan of 10 g/m^2 because of age at transplant ≥70 years. Conditioning was intensified with alkylating agents (melphalan, thiotepa) or radiotherapy (TBI 2-4 Gy or splenic irradiation in case of splenomegaly) in 10 patients. GvHD prophylaxis consisted in post-transplant cyclophosphamide, sirolimus and mycophenolate (MMF) in 15 patients, as our institution standard policy, while others received a combination of ATG based regimens with sirolimus or cyclosporine. Twenty patients received PBSC. Median numbers of infused CD34+ cells/Kg and CD3+ cells/Kg were 6.83 x 106 (range 2.10-10.87) and 2.34 x 108 (range 0.28-3.80), respectively.

Results
Median age at allo-HSCT was 61 years (range 35-71 y). Seventeen patients receive allo-HSCT in presence of active disease (15 upfront, 2 after failed induction treatment), while four patients were in first complete remission (CR1) after induction with hypomethylating agents (HMAs) or intensive chemoterapy. Comorbidity index was evaluable for 18 patients, 10 had a score ≥ 3. Two patients underwent allo-HSCT from a matched-related donor, 15 patients from a matched-unrelated donor and 4 patients from a haploidentical donor. Twenty patients (95%) engrafted. Median time to neutrophil ≥0.5x109/L was 22 days (range 14-59), to platelet ≥20x109/L was 32 days (range 13-188). Median follow-up was 28 months (range 1-141). Overall survival (OS), progression free survival (PFS) and GvHD/relapse free survival (GRFS) were 80.4%, 80.7% and 60.5% at 2-years. Relapse incidence was 9.8% at 2-years. Transplant related mortality (TRM) was 9.5% at 100 days and at last follow-up. Notably, no cases of veno occlusive disease were observed. The 100-day Cumulative Incidence (CI) of aGvHD grade 2-4 and 3-4 was 19.4% and 4.8%. CI of all grades cGvHD and moderate/severe cGvHD at 2 years was 30.1% and 15.3%. We found no significant differences in OS and PFS stratifying by diagnosis, disease status at transplant, conditioning intensity and donor type.

Conclusions
Treosulfan-based conditioning seems to be effective and well-tolerated in patients with MDS/MPN undergoing allo-HSCT, for both low risk of relapse and low TRM. Further studies on larger cohorts are necessary to confirm these findings and to clarify the role of pre-transplant induction treatment with HMAs or intensive chemotherapy in this disease setting.

Fludarabine/Treosulfan vs. Fludarabine/TBI Conditioning for AlloSCT for AML and MDS: Comparable Survival Rates but Divergent Immune Reconstitution

B094
Poster presentation

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Study design	Retrospective analysis	**Aim**	Comparison of Flu/Treo vs. Flu/TBI conditioning in adult pts with AML and MDS
Outcome parameters	GF, a/cGvHD, RI, NRM, LFS, OS, GRFS		
Patients	106 pair-matched pts from 215 total	**Median age (range)**	56.5 y Flu/Treo 54.1 y Flu/TBI
Disease	AML (n=215), MDS (n=96)		

Conditioning regimen	**Flu/Treo (n=53)** [ΣTreo 30 g/m² ΣFlu 120 – 150 mg/m²]	**Flu/TBI** (n=53) [ΣTBI 8 Gy ΣFlu 120 mg/m²]	p
Results			
3 y OS	80%	69%	n.s.
3 y RFS	73%	63%	n.s.
3 y RI	23%	23%	n.s.
3 y NRM	3.8%	14%	0.08
d100 aGvHD (grade III-IV)	7.5%	5.7%	n.s.
3 y cGvHD (all grades)	29%	32%	n.s.
Mucositis ≥CTC (grade 2)	23%	51%	0.005
Median ECOG PS @1y	0.77	1.14	0.01

Conclusion

- Comparable and favorable survival rates for Flu/Treo and Flu/TBI.
- Partially earlier immune reconstitution and less restriction regarding ECOG PS with Flu/Treo

➪ Flu/Treo is a compelling alternative to Flu/TBI.

Abstract

Background

Allogeneic stem cell transplantation (alloSCT) is a standard treatment option for patients (pts) with acute myeloid leukemia (AML) or myelodysplastic neoplasms (MDS). Dose-reduced conditioning regimens, such as ‚FluTBI' (fludarabine and 8 Gy fractionated total body irradiation) or ‚FluTreo' (fludarabine and treosulfan) are employed for pts with AML in complete remission (CR) and MDS pts. FluTreo is preferred in older and/or comorbid patients, potentially offering lower toxicities compared to FluTBI.

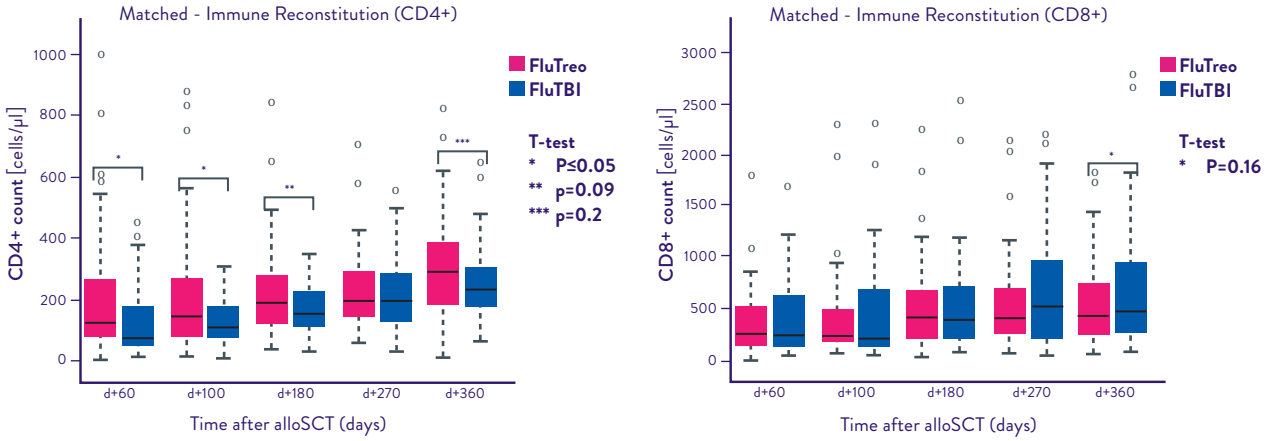
Methods

In this retrospective study, we analyzed 215 pts with AML in CR and 96 MDS pts who received a first alloSCT between 2010 and 2022. Pts were conditioned with FluTreo (120-150mg/m² fludarabine, 30g/m² treosulfan) or FluTBI (120mg/m² fludarabine, 4x2Gy TBI) prior to alloSCT. Median follow-up of survivors was 34 months. Using propensity score matching, we identified 53 pair-matched pts from both groups (nearest matching for disease, sex, age at alloSCT and ECOG; caliper distance of 0.3 standard deviations).

Results

Following propensity score matching, differences in age at alloSCT (FluTreo 56 y vs. FluTBI 54 y), disease (AML: 83% vs. 81.1%), sex and ECOG were balanced. Both groups (FluTreo vs. FluTBI) were also equilibrated for ELN2017 risk categories for AML (adverse 40.9% vs. 27.9%) and IPSS-R risk categories for MDS (very high/high 66.7% vs. 70%). In terms of transplant characteristics, both groups demonstrated comparable rates of measurable residual disease (MRD) positivity before start of conditioning (59.1% vs. 51.2%) and similar distributions of donor types.

For the matched cohorts, we found comparable overall (OS) and relapse free survival (RFS) (3-yr OS: 80% vs. 69%; 3-yr RFS: 73% vs. 63%). Relapse incidences were comparable (3-yr RI: 23% vs 23%). Notably, a trend towards lower non-relapse mortality (NRM) was observed in the FluTreo cohort (3-yr NRM: 3.8% vs. 14%, p=0.08). The incidence of acute/chronic graft-versus-host disease (GvHD) was comparable between the matched groups (aGvHD grade III-IV) 100d: 7.5% vs. 5.7%; cGvHD (all grades) 3-yr: 29% vs. 32%). For pts with MRD prior to alloSCT RFS and OS did not significantly differ between both groups. Analysis of toxicities revealed higher frequency of mucositis in the FluTBI cohort (mucositis ≥CTC grade 2: 23% vs. 51%, p=0.005). Over the first three years after alloSCT, matched FluTreo pts displayed significant better ECOG performance status (PS) than FluTBI pts (median ECOG PS at 1-yr: 0.77 vs. 1.14, p=0.01). A subset of immune reconstitution represented by normalization of CD4 pos. lymphocytes (>300/µl) in the peripheral blood trended to be faster in the FluTreo group (100d: 19% vs. 2%, p=0.03), while normalization of CD8 pos. and B-lymphocytes did not display significant differences. Normalization of immunoglobulin G trended to be slightly faster in the FluTreo group, without reaching significance.



Conclusions

Our data revealed comparable and favorable survival rates for both conditioning regimens. FluTreo conditioning exhibited partially earlier immune reconstitution and less restriction regarding the ECOG performance status, emphasizing FluTreo as a compelling alternative to FluTBI. This warrants further evaluation in a comparative prospective trial.

5-Year Transplant Success After Treosulfan Conditioning

B096
Poster presentation

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Study design	Retrospective single center analysis	**Aim**	Long-term outcomes of patients treated with Treo-based conditioning
Parameters assessed	OS, RFS, RI, NRM, GRFS, CRFS, return to work		
Patients	345	**Median age (range)**	50.2 y (0.7 – 70.5)
Disease	AML (n=186), MDS (n=106), ALL (n=36), other (n=17)		
Conditioning regimen	FT: Treo 30 – 42 g/m^2, Flu 150 - 200 mg/m^2; in n=255 additional 2 Gy TBI		
Results			
5 y OS	56%		
5 y RFS	51%		
5 y RI	27%		
5 y NRM	21%		
5 y GRFS	38%		
5 y CRFS	42%		
Return to work or school	54% (1 y)	60% (3 y)	58% (5 y)
Unemployed or home	10% (1 y)	10% (3 y)	8% (5 y)
Limited by health	34% (1 y)	30% (3 y)	32% (5 y)
None of the above	3% (1 y)	1% (3 y)	2% (5 y)
Conclusion	• Treo-based regimens yield encouraging long-term outcomes. • The return-to-work status in this population is consistent with reports from the registry studies while GRFS and CRFS appear to be superior to what has been reported in large registry studies with other regimens.		

Abstract

Background

New regimens including Treosulfan (TREO) have been increasingly used in allogeneic hematopoietic cell transplantation (HCT), frequently in combination with fludarabine (FLU), where it has been effective in establishing engraftment with low toxicity and non-relapse mortality (NRM). Herein, we report long-term outcomes of patients treated with TREO-based regimens, which have not been described yet.

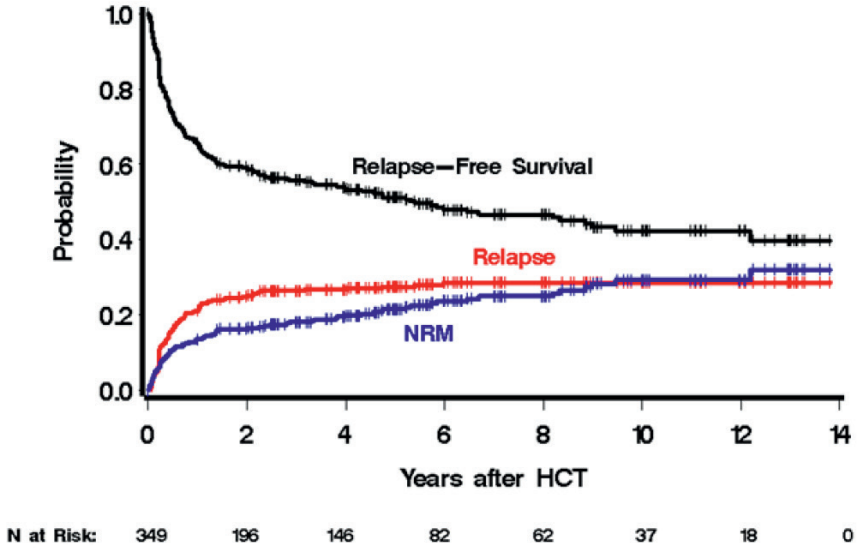
Methods

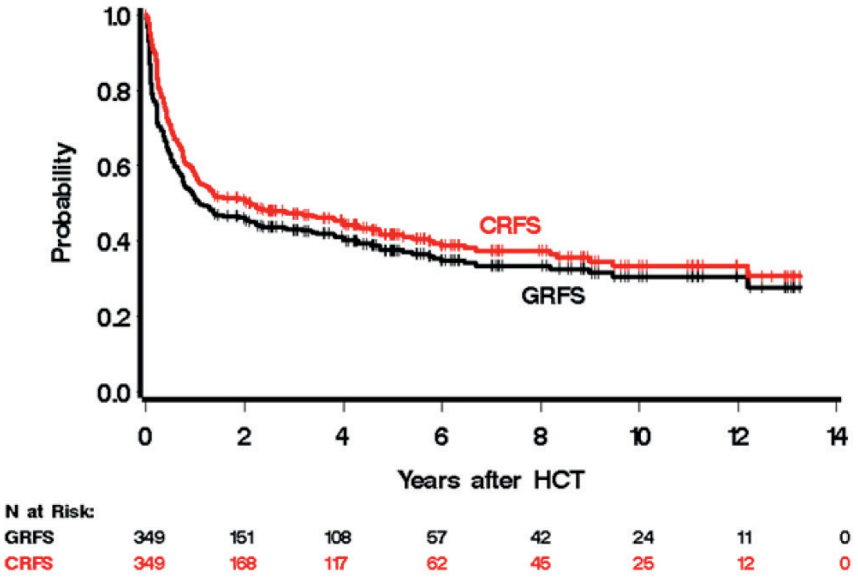
Retrospective analysis of all patients (n=345) who received TREO-based conditioning for HCT at the Fred Hutchinson Cancer Center (FHCC) between 2005-2019. Donors were matched related (RD), unrelated (URD) or cord blood (CB). Patients received TREO on days −6 to −4 at 10 or 14 g/m²/day (total 30 or 42 g/m²) and FLU IV on days −6 to −2 at 30 or 40 mg/m²/day (total 150-200 mg/m²). Most patients (n=255) also received 2Gy total body irradiation on day 0, followed by infusion of donor cells. Graft-versus-host disease (GVHD) prophylaxis included tacrolimus/methotrexate in the RD/URD cohort and cyclosporine/MMF for CB. The FHCC Long-Term Follow-Up questionnaire was used to analyze the return-to-work status information of patients who were alive 1 year post transplant (n=259).

Results

Median patient age at HCT was 50.2 years (range, 0.7-70.5), 50% were males, 199 (58%) received peripheral blood grafts, 120 (35%) received CB, and 26 bone marrow. Most had acute myeloid leukemia (54%) or myelodysplastic neoplasm (31%). The median follow-up among survivors was 65 months (range, 12-165.7) [Table]. Estimated overall survival (OS) at 5 years was 56% (95% confidence interval (CI) 51-61), relapse-free survival was 51% (46-56), relapse was 27% (23-32), NRM was 21% (17-26). The composite endpoint of immunosuppression-requiring chronic GVHD-free relapse-free survival (CRFS) was 42% (36-47) and GVHD-free relapse-free survival (GRFS: grade 3-4 acute GVHD, immunosuppression-requiring chronic GVHD, relapse, or death) was 38% (32-43) [Figure]. With respect to the return-to-work status, 196/259, 91/185 and 62/124 patients responded at 1-year, 3-years and 5-years post-HCT, respectively. The distribution at respective timepoints was: back to work (43%, 53%, 52%), school (11%, 7%, 6%), unemployed (3%, 3%, 6%), home (7%, 7%, 2%), limited by health (34%, 30%, 32%), and none of the above (3%, 1%, 2%).

BASELINE CHARACTERISTICS	**N=345**	**%**
Donor type (n, %)		
HLA-matched unrelated	128	37
HLA-matched related	85	25
Cord blood	120	34
HLA-mismatched unrelated	12	3
Disease (n, %)		
Acute myeloid leukemia	186	54
Myelodysplastic neoplasm	106	31
Acute lymphoblastic leukemia	36	10
Others	17	5
Cytomegalovirus (n, %)		
Patient CMV +	225	67
Patient CMV -	113	33
Donor CMV +	90	35
Donor CMV -	166	65
Female-to-Male **Donor-recipient sex** (n, %)	62	27
Follow-up among survivors; median (range); in months	**64.6** (12-165.7)	





Conclusions

TREO-based regimens yield encouraging long-term outcomes. The return-to-work status in our population is consistent with reports from the registry studies [Bhatt et al. JTCT 2021;27(8):679.e1-679.e8], while GRFS and CRFS appear to be superior to what has been reported in large registry studies with other regimens [Mehta et al. JCO 2020;38(18):2062-2076, and Holtan et al. Blood 2015; 125(8): 1333–1338].

Impact Of Pretransplant MRD in Patients Allografted for AML After Treosulfan-Based Conditioning

B102
Poster presentation

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Study design	Retrospective single center analysis	**Aim**	Can FT conditioning modifiy the prognostic impact of preHSCT MRD on postHSCT outcome?
Endpoints	OS, RFS, CIR, NRM		
Patients	200	**Median age (range)**	58 y (21 – 77)
Disease preHSCT MRD	AML in CR1 (n=154) or CR2 (n=46) positive (n=103), negative (n=97)		
Conditioning regimen	FT		
Results 2 y OS 2 y RFS 2 y CIR 2 y NRM	 72% 59% 32% 11% MRD-positivity preHSCT, sAML vs *de novo* AML, absence of cGVHD were prognostic factors for poor RFS.		
Conclusion	• Flu/Treo conditioning cannot eliminate the negative impact of pretransplant MRD positivity on RFS. • MRD positivity did not have an impact on OS in this analysis, which may be explained in part by graft-derived alloreactivity implied by cGvHD.		

Abstract

Background

Allo-SCT represents the only curative treatment option for a majority of AML patients but was traditionally reserved for young and fit patients (pts) due to related toxicities. However, the introduction of Treosulfan (Treo) as "toxicity-reduced" conditioning expanded the access of elderly and/or patients with comorbidities to allo-SCT due to a relevant reduction of treatment-related mortality, while preserving sufficient anti-leukemic effect. However, even in pts allografted in complete remission relapse represents the main cause of treatment failure after allo-SCT. It is unclear so far whether a specific condition regimen or intensity may be able to modifiy the prognostic impact of pretransplant measurable residual disease on posttransplant outcome.

Methods

We conducted a retrospective single center analysis over a 12-year-period (2010-2022) in patients with AML in first or second complete remission (CR) who were allografted after Fludarabine/Treo conditioning. OS and RFS were estimated by Kaplan-Meier method and logrank tests were applied for univariable comparisons, while multiple Cox-regression models were used for multivariable analysis. MRD was evaluated within 4 weeks prior allo-SCT either by flow-cytometry, qRT-PCR or NGS to detect disease-specific markers. The study was approved by the ethics committee of the University Hospital Essen (approval number: 22-10708-BO) and all patients gave written informed consent for scientific use of their data.

Results

Overall 200 patients with a median age of 58 years (range, 21 to 77) were included and of these 154 (77%) were allografted in CR1, while 46 (23%) were in CR2. The median post-transplant follow-up was 42.5 months (range, 1-156). Overall, 103 pts (52%) had detectable MRD prior allo-SCT, while 97 pts (48%) were MRD-negative. Besides a higher amount of pts with adverse ELN genetic risk in the MRD-positive subgroup (MRD-pos: 44/59 (43%) vs. MRD-neg: 26/70 (27%), p=0.03) patient-, disease- and transplant related characteristics were evenly distributed between both groups. Posttransplant OS-, RFS-, CIR, and NRM-probability were 72%, 59%, 32% and 11% at 2 years for the entire cohort. In univariable analyses MRD-positivity prior to transplant, sAML compared to de novo AML and absence of cGVHD were associated with poor RFS and these parameters also retained their prognostic significance in multivariable analysis. Regarding OS sAML, absence of cGvHD and presence of cKT were identified as poor prognostic factors in univariable analysis, whereas MRD-positivity prior allo-SCT had no impact. Multivariable analysis revealed cKT and absence of cGvHD as independent parameters associated with poor OS.

Conclusions

Our analysis shows that Flu/Treo-based conditioning cannot eliminate the negative impact of pretransplant MRD positivity on RFS. However, MRD positivity did not have an impact on OS in our analysis, which may be explained in part by graft-derived alloreactivity implied by cGvHD.

Fludarabine Treosulfan Reduced-Intensity Conditioning Regimen Prior Haploidentical Hematopoietic Cell Transplantation with Post Transplantation Cyclophosphamide in Frail/Older AML Patients: Preliminary Results of a Single Center Experience

B103
Poster presentation

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Affiliation: [1]Institut Paoli Calmettes, Marseille, France

Study design	Single center study	**Aim**	Safety of FT10 prior to haploHSCT in AML pts unfit for MAC
Endpoint, primary	Safety		
Patients	20	**Median age (range)**	60 y (49 – 68)
Disease	AML		
Conditioning regimen	FT10: Treo 30 g/m^2, Flu 150 mg/m^2, followed by PTCy		
Results			
AEs	No hemorrhagic cystitis or hepatic SOS		
Mucositis	75% (n=10 grade 1, n=5 grade 2)		
Engraftment [median (range)]	100%: neutrophil 17 d (11 - 25), platelets 20 d (8 – 161)		
Full donor T-cell chimerism	100%		
aGvHD	n=3 (all grade II)		
cGvHD	n=6 (moderate to severe)		
1 y LFS	89%		
1 y OS	89%		
Conclusion	• FT10 regimen prior to haplo-SCT with PTCy provides rapid full engraftment and low early toxicity in AML patients who are unfit for MAC.		

Abstract

Background

Haploidentical transplantation (haplo-SCT) after non-myeloablative conditioning (NMAC) regimen and post-transplantation cyclophosphamide (PT-Cy) dramatically extended the feasibility of allo-HSCT in frail and/or older patients with AML who do not have a HLA identical donor (PMID:26261255). However, in this patient population who usually carries high risk AML, incidence of relapse remains high, approximately 40%. Different reduced intensity conditioning (RIC) regimens have been develop as an attempt to reduce the risk of relapse as compared to NMAC regimens but they failed to improved survival in older patients due to a higher NRM that counterbalances the benefit in antileukemic effect (PMID:35752739). Treosulfan was recently approved in association with fludarabine (FT30) in RIC regimen based on a phase III study showing a benefit in OS compared to fludarabine busulfan due to a lower toxicity and NRM in the context of older AML or MDS patients undergoing HLA identical allo-HSCT (PMID:31606445) . However, there is no reported data of the same FT30 RIC regimen in the context of haplo-SCT with PT-Cy. We thus started in 2022 a program with FT30 RIC regimen prior haplo-SCT in AML patients unfit for myeloablative regimen and report here the safety results of the first 20 patients.

Methods

We included 20 AML patients undergoing first peripheral blood haplo-SCT who were unfit for myeloablative regimen from March 2022 to September 2023. They received fludarabine (150mg/m^2) treosulfan (30g/m^2) and a standard GVHD prophylaxis based on PT-Cy, CSA and MMF.

Results

Median age was 60 years (range: 49-68). At diagnosis, ELN 2022 risk was favorable, intermediate and unfavorable for 3 (15%), 7 (35%) and 10 (50%) patients, respectively. All patients received intensive induction chemotherapy as initial treatment of AML. At the time of haplo-SCT, they were in CR1 except one in MLFS and one in CRi. 5/20 (25%) needed salvage therapy to reach CR1. MRD at the time of haplo-SCT was negative, positive and unknown for 12 (60%), 5 (25%) and 3 (15%) patients, respectively. HCT-CI was ≥ 3 in 11 patients (55%).

No hemorrhagic cystitis or hepatic SOS was observed. Grade 1 and 2 mucositis was observed in 15 (75%) 10 (50%) and 5 (25%) patients, without any grade 3 or 4. All patients achieved neutrophil (>0.5 G/L) and platelets (>20G/L) engraftment in a median time of 17 (range: 11-25) and 20 (range: 8-161) days, respectively. All patient achieved full donor blood T cell chimerism on day+30. 3 patients developed grade II acute GVHD, no grade III or IV was observed. With a median follow up of 385 days (range: 100-648), 6 (30%) patients developed moderate to severe chronic GVHD, 3 of them after prophylactic DLI.

One patients died from NRM on day+91 (acute pulmonary failure) and one patient relapse from AML on day+183 and subsequently died. Thus, both 1-year LFS and OS were 89%.

Conclusions

FT30 RIC regimen prior haplo-SCT with PT-Cy provides rapid full engraftment and low early toxicity in AML patients who are unfit for myeloablative regimens, with promising antileukemic effect that need to be evaluated in prospective comparison.

Treosulfan-Fludarabine Conditioning Regimen with Post-Transplant High-Dose Cyclophosphamide: A Retrospective Analysis

B115
Poster presentation

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Study design	Single center retrospective study	**Aim**	Safety and efficacy of FT10 combined with PTCy
Endpoints	OS, RFS, CIR, TRM, toxicities		
Patients	97	**Median age (range)**	62 y (17 – 75)
Disease	MDS (n=28), AML (n=26), ALL (n=3), MDS/MPN (n=7), MF (n=7), lymphoma (n=15), other (n=11)		
Conditioning regimen	FT: Treo 30 g/m^2, Flu 150 mg/m^2, followed by PTCy 50 mg/kg on days 3 and 4		
Results*			
OS	88% (1 y) 80% (2 y)		
RFS	74% (1 y) 67% (2 y)		
CIR	21% (1 y) 27% (2 y)		
TRM	5.3% (1 y) 6.6% (2 y); causes of death: relapse (n=17), GvHD (n=2), infection (n=3), organ failure/toxicity (n=1)		
	one PGF, one early rejection (both in MF pts, both rescued by 2nd allograft)		
GRFS	62% (1 y) 54% (2 y)		
Conclusion	• FT10 in combination with PTCy had low TRM with acceptable CIR, especially taking into account the rather unfavorable patient/disease characteristics.		

*Numbers differing from abstracts were based on final presentation at conference

Abstract

Background

In allogeneic hematopoietic stem cell transplantations (alloHSCT), toxicity related to conditioning regimen is a significant factor in transplantation-related mortality (TRM). Reduced intensity conditioning (RIC), on the other side, may increase the risk of relapse. Treosulfan is an alkylating agent used in conditioning, with myeloablative, immunosuppressive and antileukemic effects but minor non-hematological toxicity. Graft-versus-host disease (GVHD) prophylaxis with post-transplant cyclophosphamide (PTCy) is widely accepted in the setting of haploidentical donors, but the usage has also been extended to other donor types.

Methods

In this single center study, we evaluated retrospectively the safety and efficacy of treosulfan-based RIC regimen combined with PTCy. All our patients received treosulfan 10 mg/m² iv for three days and fludarabine 30 mg/m² iv for five days followed by PTCy 50 mg/kg on days 3 and 4 after alloHSCT. In combination with PTCy, short courses of tacrolimus or everolimus and mycophenolate mofetil (MMF) were used as GVHD prophylaxis.

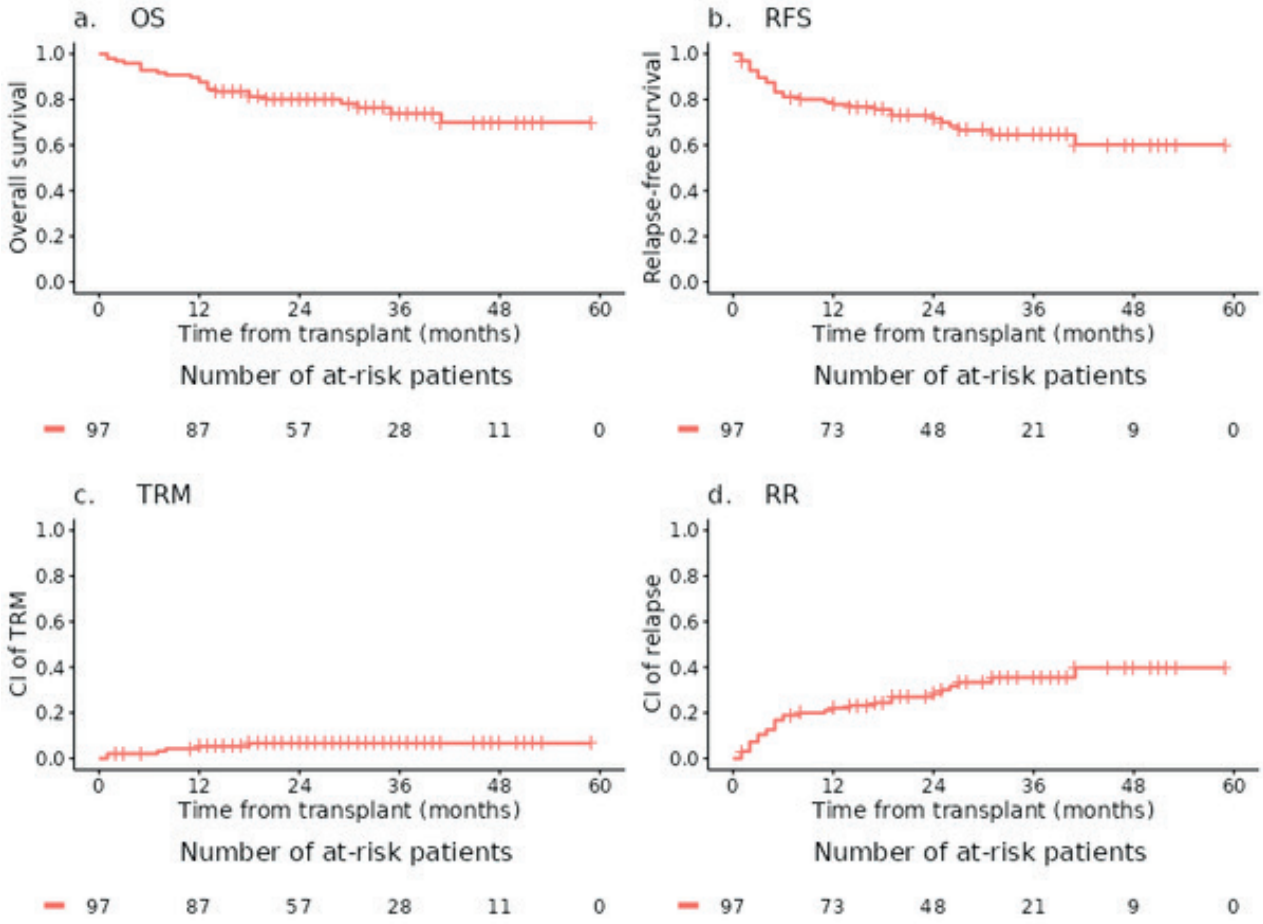
Results

Between April 2018 and July 2022, 97 patients received treosulfan-fludarabine conditioning regimen combined with PTCy. Median follow-up time was 27 (range 1-59) months. Patient, disease, and transplantation characteristics are presented in Table 1. Median age of the patients was 62 (range 17-75) years. MDS and AML were the most common diagnoses (28.9 % and 26.8 %, respectively). Almost half of the patients were not in complete remission (CR) at transplant, and the disease risk index (DRI) was high or very high in 52.6 % of patients. Stem cell source was peripheral blood in all patients. The 1-year and 2-year OS was 88 % and 80 %, respectively, and relapse-free survival (RFS) 78 % and 72 %, respectively, while the cumulative incidence of relapse was 22 % and 28 %, respectively. Transplantation-related mortality (TRM) at one and two years was 5.3 % and 6.6 %, respectively. Causes of death were relapse (n = 17), GVHD (n = 2), infection (n = 3) and organ failure/toxicity (n = 1). There was one primary graft failure and one early rejection, both occurring in patients with myelofibrosis, and both having been rescued by the second allograft.

Table 1. Patient, disease and transplantation characteristics

Characteristic	N=345	All patients (n = 97)
Median age, years (range)		62 (17-75)
Median time from diagnosis to alloHSCT, months (range)		8 (2-215)
Diagnosis, n (%)	MDS	28 (28.9)
	AML	26 (26.8)
	ALL	3 (3.1)
	MDS/MPN	7 (7.2)
	MF	7 (7.2)
	Lymphoma	15 (15.5)
	Other	11 (11.3)
Disease status before alloHSCT, n (%)	Active disease	45 (46.4)
	CR	52 (53.6)
Minimal residual disease (MRD) status before alloHSCT, n (%)	Positive	53 (54.6)
	Negative	19 (19.6)
	Not applicable	25 (25.8)
Donor type, n (%)	MUD	25 (25.8)
	MRD	7 (7.2)
	MMUD	2 (2.1)
	Haploidentical	63 (64.9)
Median follow-up time, months (range)		27 (1-59)

Figure 1. Main outcomes. **a** Overall survival
b Relapse-free survival
c Transplantation-related mortality
d Relapse rate



Conclusions

Treosulfan-fludarabine conditioning regimen combined with PTCy had low transplantation-related mortality and acceptable relapse rate, especially taking into account the relatively high age of the patients, high or very high DRI in more than half of the patients, and the high proportion of patients with active disease and/or positive MRD at transplant.

Comparison Of Fludarabine-Melphalan and Fludarabine-Treosulfan as Conditioning Regimens Prior to Allogeneic Hematopoietic Stem Cell Transplantation

B120
Poster presentation

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Study design	Single center retrospective analysis	**Aim**	Comparison of Flu/Treo vs. Flu/Mel conditioning in adults	
Primary objectives	TRM, OS			
Patients treated	59	**Median age (range)**	52 y (18 - 72) Flu/Treo 47 y (20 - 72) Flu/Mel	
Disease	AML (n=38), MDS (n=13), NHL (n=4), B-ALL (n=1), other (n=2)			
Conditioning regimen	**Flu/Treo (n=23)** ΣTreo 30 - 42 g/m²		**Flu/Mel (n=36)** ΣMel 110 - 140 mg/m²	p
Results				
GF	n=1		n=2	
TRM	8.7%		31.4%	0.052
RI	17.4%		25.7%	0.042
OS [days (range)]	154 d (6 – 896)		292 d (12 – 2054)	0.55
Alive / Deceased	18 / 5		15 / 20	0.004
Conclusion	• Better toxicity profile of FluTreo vs FluMel without affecting relapse incidence. • FluTreo is an appropriate RTC regimen in frail pts.			

Abstract

Background

The optimal counterpart in fludarabine-based (Flu) reduced intesity conditioning regimens in allogeneic hematopoietic cell transplantation (allo-HCT) is not defined yet. The combination of fludarabin-melphalan (FluMel) has shown efficacy but also toxicity. More recently treosulfan (Treo) has been introduced as a drug with potent immunosuppressive and antileukemic effect and a low toxicity profile. Thus, herein we compared the outocomes of patients receiving FluMel or FluTreo.

Methods

In this sinlge center analysis, we retrospectively analysed outcomes of patients who were selected to receive a fludarabin-based regimen combined with Mel 110 – 140 mg/m² (FluMel) or Treo 30-42 gr/m² (FluTreo), eg reduced toxicity regimens with a low or intermediate TCI score, from October 2005. Comaprison was done by univariate analysis using x^2 (categorical parameters), Mann-Whitney (continuous parameters) or log-rank (for OS) setting the statistical significance at $p< 0.05$.

Results

In total, 36 patients have recieved FluMel and 23 patients FluTreo. FluTreo patients were treated more recently (since April 2021) and thus the median follow up differed between these two groups. Detailed characteristics are listed in Table 1. There were no differences between age, HCT-CI, disease, disease status at allo-HCT and type of donor between the two groups. No difference in time to leukocyte and platelet engraftment was seen between the two groups. Transplant realted mortality was higher in the FluMel group (p=0.042) while relapse rate was similar, thus resulting in a significant better OS for the FluTreo group (p=0.004). When regimens were compared according to their TCI scores (low vs intermediate) irrespective of chemotherapy agent included, OS differed significantly (p=0.02).

Table 1. Demographic characteristics of the patients

Patient Characteristics	FluMel	FluTreo	P value (univariate analysis)
Number of patients	36	23	N/A
Median Age (range)	47 (20-72)	52 (18-72)	0.58
Sex – M/F	22 / 14	17/6	0.27
Disease			
AML	22	16	0.35
MDS	8	5	
NHL	4	0	
B-ALL	1	0	
Other diseases	1	1	
Disease Stage before allo-HCT			
Refractory Disease	3	3	0.49
Partial Response	3	0	
Complete Response	26	18	
Untreated	4	1	
Donor			
Sibling	9	4	0.35
WMUD	15	14	
MMUD	10	5	
Haplo	2	0	
TCI score			
Low	17 (47%)	9 (39.1%)	0.61
Intermediate	19 (53%)	14 (60.7%)	
HCT-CI median (range)	1 (0-6)	0.5 (1-6)	ns
Engraftment			
WBC≥1000/mmc, day (range)	+15 (10-24)	+14 (10-23)	0.86
PLT≥ 20.000/mmc, day (range)	+16 (7-57)	+16.5 (8-29)	0.44
PLT≥ 50.000/mmc, day (range)	+17 (11-127)	+16.5 (13-33)	0.49
Graft Failure	2	1	0.052
Transplant Related Mortality (TRM)			
Yes	11 (31.4%)	2 (8.7%)	**0.042**
No	26 (68.6%)	21 (91.3%)	
Relapse			
Yes	9 (25.7%)	4 (17.4%)	0.55
No	26 (74.3%)	19 (82.6%)	
Overall Survival			
Days (range)	292 (12-2054)	**154 (6-896)**	**0.004**
Alive/Deceased	15/20	**18/5**	

Conclusions

With the limitation of using FluTreo in more recent years, our single center analysis indicates a better toxicity profile of FluTreo vs FluMel without affecting relapse incidence. These data need prospective confirmation but are capable of establishing FluTreo in our strategy as the appropriate reduced toxicity regimen in frail pts.

Promising Outcomes in Haploidentical Transplantation Using Abatacept in Combination with Post Transplant Cyclophosphamide in Treosulfan Based Conditioning Regimen

B124
Poster presentation

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Study design	Single center retrospective study	**Aim**	Treo-based conditioning with Abatacept and PTCy as GvHD prophylaxis before haploHSCTs
Endpoints	Engraftment, survival, toxicities		
Patients	14	**Median age (range)**	44 y (17 – 65)
Disease	AML (n=6), ALL (n=3), CML (n=2), SAA (n=2), MDS (n=1)		
Conditioning regimen	Flu (150 mg/m^2), Treo (30 – 42 g/m^2), LD-TBI (2 Gy), PTCy (100 mg/kg), 3 doses Abatacept		
Results			
Engraftment	100%; median 19 d [14 – 29] / 32 d [16 – 138] (neutrophil / platelet)		
OS	83.3% @5 y (median follow-up 630 d, range 74 – 1728); 2 deaths (relapse, sepsis)		
RI	14.28%		
RFS	median not reached		
GFS / GRFS	median 372 d / median 210 d		
aGvHD	21.4% (grade II-IV)		
cGvHD	41.6% (of which 20% mild and 80% severe)		
Conclusion	• Abatacept in combination with PTCy in haploHSCT using Treo-based conditioning showed promising outcome and acceptable toxicity. • Looking at the severity of cGVHD, this strategy needs to be further evaluated.		

Abstract

Background

Number of stem cell transplantation carried out using haplo-identical donor (Hap-SCT) is increasing worldwide. A lack of suitable matched donor, lower cost, easy donor availability and acceptable GVHD control with post transplant cyclophosphamide (PTCy) are main factors driving increased use of haploidentical donors. In some reported studies, survival data in Hap-SCT is now matching outcomes from matched donors. Optimizing GVHD control, preventing infections and mitigating risk of graft rejection remain some of the challenges following Hap-SCT. Abatacept was recently approved as GVHD prophylaxis in combination with calcineurin inhibitor (CNI) and Methotrexate post stem cell transplantation. Abatacept is a CTLA4 analog which blocks co-stimulatory signal and prevent T cell activation. Treosulfan is emerging as an effective component of reduced toxicity regimen. To our knowledge, outcome data of this combination is not reported in adult hap-SCT.

Methods

We present our single center experience of using Treosulfan based conditioning with Abatacept and PTCy as GVHD prophylaxis in 14 patients who underwent hap-SCT (institutional approval number 2223-94). Conditioning consisted of Fludarabine, Treosulfan and Low dose TBI (2Gy) followed by post transplant cyclophosphamide. Fludarabine dose was 30 mg/m^2 given on days -6 to -2, Treosulfan dose was 10 or 14 gram/m^2 given on days -6 to -4. PTCy was given at a dose of 50 mg/kg/day on days +3 and +4. Tacrolimus and Mycophenolate Mofetil (MMF) were commenced on day+5. All patients received 3 doses of Abatacept on days +5,+14,+28.

Results

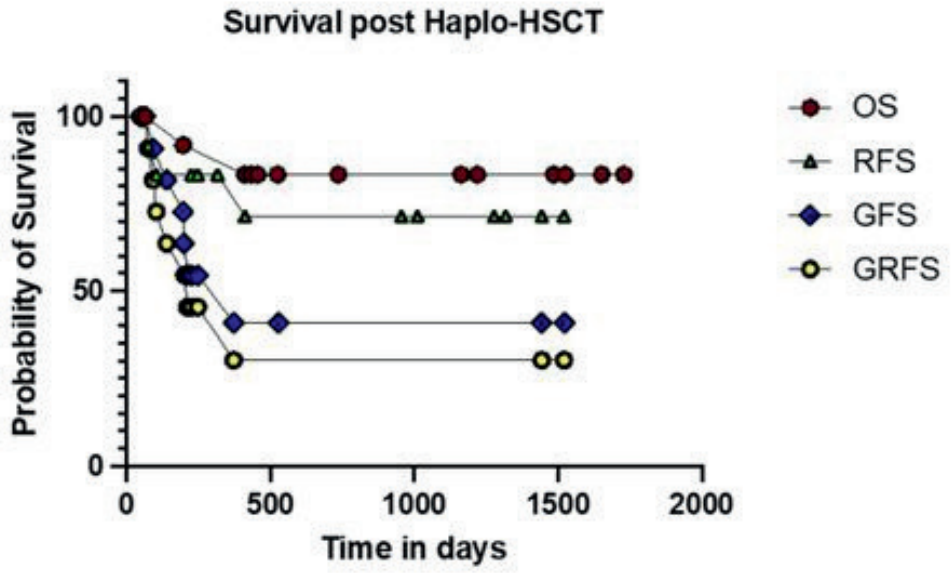
Gender	12 male/2 female
Performance score (Kernofsky)	80 (range 70-90)
Donor specific antibodies	0
Stem cell source	Peripheral blood stem cells in all patients
CD34 infused (Median)	5 x 106 /kg (range 3.25 – 6.11 x 106 /kg)
CMV match	6 matched/ 8 mismatched
Median age	44 years (range 17-65)
ABO match	5 (all minor ABO incompatibility), 9 ABO matched
HCT-CI (Median)	3
Indications for transplantation	3 ALL, 6 AML, 2 CML, 1 MDS and 2 SAA.

Our results show OS of 83.3% at 5 years with a median follow up of 630 days (range 47 – 1728 days). Out of 14 cases, 2 died at 7 and 14 months and 12 patients are alive. 1 patient died of AML relapse and the other died of sepsis. Relapse rate was 14.28%, 1 AML and 1 ALL. Incidence of acute GVHD (grade II-IV) was 21.4% and incidence of chronic GVHD was 41.6%. Within the chronic GVHD group, 20% had mild form while 80% had severe cGVHD as per NIH criteria. Median relapse free survival (RFS) was not reached in this cohort. Median GVHD free survival (GFS) was 372 days, and median of GVHD and relapse free survival (GRFS) was 210 days.

Median neutrophil engraftment was 19 days, range 14-29 days, while median platelet engraftment was 32 days, range 16-138 days. Post-transplant complications included CMV reactivation in 29%, urinary BK virus in 14%, neutropenic fever in 50%, pneumonia in 21% and CRS in 14%. Cumulative rate of other viral infections including EBV, Adenovirus, Herpes, respiratory viruses was 43% and Line infections were seen in 21%.

In addition, Haemophagocytic lymphohistiocytosis (HLH) occurred in 14%, 1 patient experienced transient ischemic attack (TIA), 2 developed diabetes and 1 developed adrenal insufficiency over course of follow up.

All patient engrafted and achieved 100% donor chimerism at 1 year (for both myeloid and CD3 chimerism).



Conclusions

Abatacept in combination with PTCy in hap-SCT using Treosulfan based conditioning appears to show promising outcome and acceptable toxicity. However, given the severity of chronic GVHD, larger prospective trials are required to evaluate this strategy.

Treosulfan-Based Conditioning and Sirolimus-PTCy GvHD Prophylaxis in Allogeneic Stem Cell Transplantation for Aggressive B-Cell NHL

B268
Poster presentation

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Affiliations: [1]IRCCS San Raffaele Scientific Institute, Milan, Italy, [2]Vita-Salute San Raffaele University, Milan, Italy

Study design	Retrospective analysis	**Aim**	Comparison of Sir-PTCy with MTX-based GvHD prophylaxis in B-NHL pts receiving Treo-based conditioning
Primary objectives	OS in Sir-PTCy group		
Patients	40	**Median age (range)**	55 y (29 - 69) Sir-PTCy 51 y (30 - 65) MTX-based
Disease	B-NHL (DLBCL, PMBCL, MCL)		
Conditioning regimen	FT14: Treo 42 g/m^2, Flu 150 mg/m^2 (in n=12 intensified with 140 mg/m^2 Mel)		
GvHD-prophylaxis	**Sir PTCy (n=26)**	**MTX-based (n=14)**	P
Results			
3 y OS	78.6%	35.7%	<0.01
3 y EFS	66.9%	28.6%	<0.01
RI (1 / 3 y)	3.8% / 17.7%		
TRM (d100 / 1 y)	7.7% / 15.4%		
aGvHD (grade ≥2 / ≥3)	15.4% / 7.7%		
3 y cGvHD (moderate / severe)	41.8% / 4.6%		
Conclusion	• AlloHSCT using Treo-based conditioning combined with Sir-PTCy GvHD prophylaxis is safe and effective in the treatment of advanced B-cell NHL. • cGvHD was not negligible but treateable in almost all cases. • Selected pts with B-NHL may benefit from alloSCT treatment.		

Abstract

Background

Since the advent of novel therapies, such as CAR-T cells, allogeneic stem cell transplantation (alloSCT) is progressively less considered as a therapeutic option in patients (pts) with aggressive relapsed/refractory B-cell NHL due to excessive morbidity and mortality associated with the procedure. Recently, improvements in conditioning regimens led to a reduction in TRM, while PTCy has been widely and successfully used across different alloSCT settings.

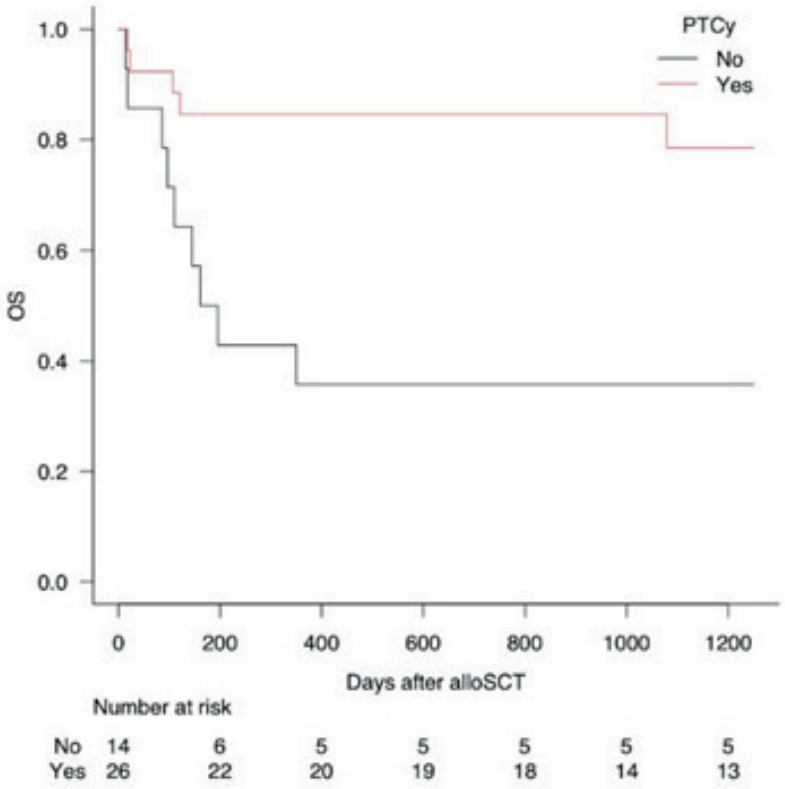
Methods

Between June 2005 and December 2022, 40 heavily pretreated adult pts affected by B-cell NHL, namely DLBCL, PMBCL, and MCL, underwent first alloSCT at our Center using a treosulfan-based conditioning. Of these, 26 pts received sirolimus and PTCy (Sir-PTCy)-based GvHD prophylaxis and were considered for the primary analysis. Conditioning regimen consisted of treosulfan (TD 42 g/m^2) and fludarabine (TD 150 mg/m^2) in 14 pts (transplant conditioning intensity [TCI] intermediate); intensification with melphalan (TD 140 mg/m^2) was applied on the remaining twelve (TCI high). We considered as a control group the 14 pts who mainly received standard MTX-based GvHD prophylaxis, with addition of ATG in 11 cases. Primary endpoint of the study was OS in the Sir-PTCy group.

Results

Pts and transplant characteristics are displayed in Table 1. Three pts received MRD, 14 MUD (with 2 MMUD), and 9 a MMRD unmanipulated peripheral blood stem cell alloSCT. At transplant, 17 pts were in CR, 6 were in PR, and 2 had PD. Two pts (1 PMCBL, 1 MCL) received a previous CAR-T cell therapy. Median follow-up was 41 months (range, 7-113). Median time to neutrophil and platelet engraftment was 19 (range, 12-42) and 22 days (range, 10-55), respectively; no graft failure was observed. OS and DFS at 3 years were 78.6% and 66.9%, respectively. One and 3-year relapse incidence was 3.8% and 17.7%, respectively. TRM was 7.7% at 100 days, 15.4% at 1 year and for the entire follow-up; overall, 4 pts died due to infections (1 CMV pneumonia, 1 COVID-19, and 2 bacteremia) and one from disease relapse. The 100-day cumulative incidence (CI) of acute GvHD grade≥2 and grade≥3 was 15.4% and 7.7%, respectively; 3-year CI of moderate and severe chronic GvHD was 41.8% and 4.6%, respectively. Undergoing alloSCT in CR projected better 3-year outcomes in terms of OS (94.1% vs 50%, p=0.01), DFS (72.8% vs 55.6%, p=0.09), and TRM (5.9% vs 33.3%, p=0.06). No statistical differences were found when pts were stratified according to disease subtype, donor type, HCT-CI, and intensity of conditioning. Seventeen pts are alive and disease-free at last follow-up, with only one pts on ongoing immunosuppression for GvHD. Compared to our control group, pts receiving Sir-PTCy displayed a significantly better OS (78.6% vs 35.7%, p<0.01; Figure 1) and DFS (66.9% vs 28.6%, p<0.01) at 3 years.

	Sir-PTCy group (N=26)	MTX-based group (N=14)	P
Age at diagnosis, median year (range)	53 (28-65)	49 (28-63)	0.2
Age at alloSCT, median year (range)	55 (29-69)	51 (30-65)	0.3
Female sex, number (%)	7 (27%)	8 (57%)	0.08
Previous lines of therapy, median (range)	3 (2-4)	3 (2-4)	0.9
Previous autoSCT, number (%)	20 (77%)	13 (93%)	0.07
Disease subtype, number (%)			0.03
DLBCL	8 (30%)	10 (71%)	
PMBCL	4 (15%)	-	
MCL	14 (54%)	4 (29%)	
Disease status at alloSCT, number (%)			0.3
CR	17 (65%)	6 (43%)	
PR	6 (23%)	4 (29%)	
SD	-	2 (14%)	
PD	3 (12%)	2 (14%)	
HCT-CI score, median (range)	2 (0-5)	2 (0-4)*	0.3
Time diagnosis to alloSCT, median months (range)	76 (25-416)	56 (21-222)	0.3
Donor type, number (%)			0.3
MRD	3 (12%)	3 (21%)	
MUD	12 (46%)	6 (43%)	
MMUD	2 (8%)	2 (14%)	
MMRD	9 (34%)	3 (21%)	
Intensity of conditioning, number (%)			0.08
TCI intermediate	14 (54%)	12 (86%)	
TCI high	12 (46%)	2 (14%)	
GvHD prophylaxis, number (%)			<0.001
PTCy+Sirolimus	3 (11%)	-	
PTCy+Sirolimus+MMF	21 (81%)	-	
PTCy+Sirolimus+MMF+ATG	2 (8%)	-	
MTX+CSA	-	3 (21%)	
MTX+CSA+ATG	-	7 (50%)	
MTX+Sirolimus+ATG	-	4 (29%)	
Infused CD34+/Kg x106, median (range)	5,82 (2,98-7,08)	7,5 (5,27-12,24)	0.001
Infused CD3+/Kg x108, median (range)	1,98 (0,72-3,65)	3,1 (1,31-6,89)	0.01
* 6 missing	26 (74.3%)		



Conclusions

AlloSCT using a treosulfan-based conditioning combined with Sir-PTCy GvHD prophylaxis is safe and effective in the treatment of advanced B-cell NHL. Chronic GvHD was not negligible but treatable in almost all cases. Selected pts with DLBCL, PMBCL, and MCL may still benefit from the inclusion of alloSCT in their treatment algorithm.

Real-World, Single-Centre Outcome Data of Allogeneic Hematopoietic Stem Cell Transplantation Utilising Treosulfan-Based Conditioning Regimens

P186
Poster presentation

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Study design	Single center Retrospective analysis	**Aim**	Real-world outcomes of alloHSCT comparing FT- conditioning regimens with different GvHD prophylaxis
Primary outcome	OS	**Secondory outcomes**	Engraftment, CIR, CRFS, GRFS, GvHD, infections
Patients	95	**Median age (range)**	50 y (19 – 66) FTA 52.5 y (19 – 70) FTT
Disease*	ALL (n=16), AML (n=30), CLL (n=1), CML (n=8), CMML (n=2), HD (n=5), MDS (n=14), MDS/MPN (n=11), NHL (n=7), plasma cell (n=1)		

Conditioning regimen	**FTA** (n=29) Treo 30 - 42 g/m², Flu 150 mg/m², ATG 5 mg/kg	**FTT** (n=66) Treo 30 - 42 g/m², Flu 150 mg/m², TBI 2 Gy, PTCy 100 mg/kg	P
Results*			
2 y pOS	67.7%	73.3%	0.17
CIR	13.79%	21.2%	0.57
Median engraftment neutrophiles	17.8 d	17.38 d	0.6178
Median engraftment platelets	19.5 d	28 d	0.0001
aGvHD (grade II-IV)	13.79%	5.71%	0.22
cGvHD (all grades)	24% (all mild)	20% (61.5% mild, 38.5% moderate-severe)	0.7
GRFS	similar in both groups	similar in both groups	0.55
Viral infections (until d100)	93.1%	57.14%	0.0014
Bacteremia (until d100)	48.28%	22.8%	0.03

Conclusion*

- Consistent with other studies, FT conditioning is an effective conditioning regimen with a manageable safety profile.
- ATG effectively mitigates severity of cGVHD relative to PTCy but increases incidence of infection. PTCy was associated with slower platelet engraftment in this cohort.
- GRFS is comparable between both groups, with a possible trend of less severe GvHD but more frequent relapses following FTT conditioning with PTCy.

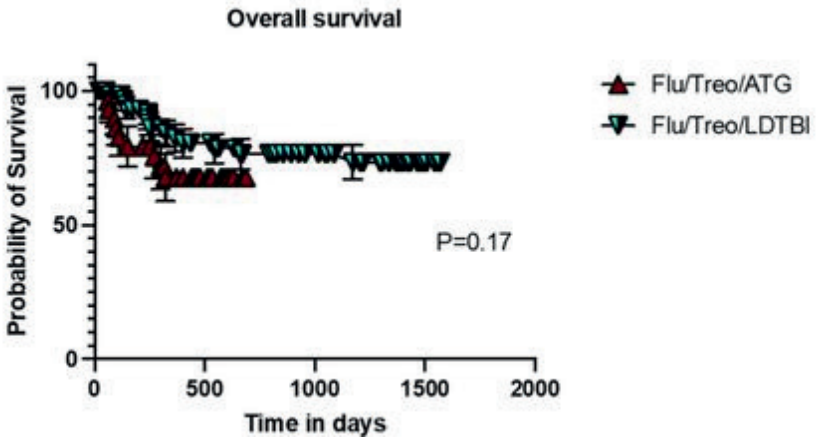
*Additional info and info different from abstract based on poster at conference

Abstract

Background
Combining fludarabine with treosulfan (FT) has emerged as an effective conditioning strategy for reduced-intensity (RIC) and reduced-toxicity myeloablative (RTC) allogeneic hematopoietic stem cell transplantation (allo-SCT). In this retrospective study, we present real-world outcomes of allo-SCT comparing two different FT-based conditioning regimens utilizing different GVHD prophylaxis.

Methods
We conducted a retrospective analysis of patients undergoing allo-SCT with FT-based conditioning at our center from 2019 to 2023. Cohort included 95 patients, 29 received Fludarabine, Treosulfan and ATG (FTA) while 66 received Fludarabine, Treosulfan, Low dose TBI with post transplant cyclophosphamide (FTT). Fludarabine dose was 30 mg/m^2 given at days -6 to -2, Treosulfan dose was 10 or 14 gram/m^2 (decided on basis of HCT CI and age) given on days -6 to -4.

ATG dose of 2.5 mg/kg/day was given on days -3 and -2 (total 5 mg/kg) and LDTBI dose was 2 Gy. Post Transplant Cyclophosphamide (PTCy) was given at a dose of 50 mg/kg/day on days +3 and +4. The primary outcome was overall survival (OS), with secondary outcomes including relapse-free survival (RFS), graft-versus-host disease (GvHD)-free survival (GFS), relapse, GvHD and cumulative incidence of infection within the first 100 days post-transplant.



Results
Median OS was not reached in both groups at the time of analysis. FTA group had shorter median follow up of 442 days (range 60 – 687 days) whilst FTT group had a median follow up of 840 days (range 21 – 1569 days). Two year probability of survival was 67.7% in FTA group compared to 73.3% for FTT (p= 0.17). GRFS was also similar HR 1.11, 95% CI (0.49 – 2.48), P=0.78. There was no difference in relapse incidence between two groups with a relapse rate of 13.79% in FTA and 21.2% in FTT (P=0.57). Whilst median time to neutrophil engraftment was also similar in both groups (FTA 17.8 days, FTT 17.38 days, P=0.61), platelet engraftment was significantly delayed in the FTT cohort (28 days) compared to FTA group (19.5 days, p=0.000). FTA had acute GVHD (grade II-IV) incidence of 13.79%, while the FTT group had aGVHD (II-IV) incidence of 5.71%, P=0.22.

In FTA group, chronic GVHD (all severities) incidence was 24%. In FTT group this incidence was 20% (p=0.7). However, all chronic GVHD cases in FTA cohort were mild while in FTT 61.5% had mild and 38.46% had moderate to severe chronic GVHD as per NIH criteria.

There was a higher incidence of infections in the FTA regimen in the first 100 days post-transplant. Within evaluable cases, rate of viral infections in FTA was 93.1% and 57.14% in FTT, P=0.0014. EBV was the most common viral infection in the FTA (68.9%). Also, incidence of bacteremia in FTA group was 48.28% whilst that in FTT was 22.8% (p=0.039).

Conclusions
Our findings are consistent with reported results from other retrospective and prospective studies, underscoring safety and efficacy of FT-based conditioning regimens. ATG effectively mitigates severity of chronic GVHD relative to PTCy but increases incidence of infection. PTCy was associated with slower platelet engraftment in this cohort.

High Graft Failure With Fludarabine, Treosulphan Conditioning Regimen In Myeloid Malignancies

P199
Poster presentation

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Study design	Retrospective single center study	**Aim**	Outcome of alloHSCT using Treo-based conditioning in pts with myeloid malignancies
Endpoints	Engraftment, aGvHD		
Patients	28	**Median age (range)**	62 y (48 – 70) MF pts 52 y (26 – 71) Remaining pts
Disease	AML (n=16), MF (n=7), HR-MDS (n=4), CMML-2 (n=1)		
Conditioning regimen	Fludarabine, Treosulfan		
Results Engraftment 2 y OS Progression during f-up aGvHD	 MF pts: median 16.5 d [14 – 28] / 28 d [21 – 113] (neutrophil / platelet) Remaining pts: median 12 d [10 – 14] / 17 d [10 – 40] (neutrophil / platelet) 20% 23% 33%		
Conclusion	• Engraftment was as a major issue with Treo-based regimens in myeloid malignancies. • In the myelofibrosis group most of the patients had massive splenomegaly and in the acute leukemia group the majority of the patients had advanced disease which can explain the high engraftment failure rates. • Progress and GvHD was not different with Bu- based regimens which have been used in previous studies.		

Abstract

Background
Fludarabine, busulphan has been widely used as conditioning regimen in allogeneic stem cell transplantation(alloHSCT) of myeloid malignancies. Recently, combination of fludarabine with treosulphan has been introduced as less toxic but regimens with similar efficacy especially in elderly patients.In our study, we aimed to analyze the outcome of treosulphan in myeloid malignancies who had alloHSCT.

Methods
We had retrospectively included twenty eight myeloid malignancy patients; who had alloHSCT with fludarabine, treosulphan conditioning regimen in Koç University School of Medicine BMT Unit. GVHD prophylaxis has been performed with cyclosporine and mycophenolate mofetil. Posttransplant cyclophoshamide has been used in all unrelated stem cell transplantations except 2 and in all haploidentical stem cell transplantations.

Results
We have included 16 AML, 7 Myelofibrosis, 4 High risk MDS and 1 CMML-2 patient. Seven intermediate 2 or high risk myelofibrosis patients had reduced intensity fludarabine treosulphan conditioning regimen. Stem cell source was peripheral blood in all patients and donors were unrelated in 5 out of 7 patients. Five patients had massive splenomegaly although ruxolitinib or radiotherapy has been used to reduce spleen size before transplantation. Median follow up of the patients were 7 months. Median day of neutrophile and platelet engrafmentwas 16,5(14-28) and 28(21-113), respectively. Neutrophile engraftment could not be observed in 1 patient and platelet engraftment could not be observed in 2 patients. One patient had a second alloHSCT as a consequence of graft failure and had no response. 3 out of 7 patients died during the follow up 2 in posttransplant 100 days. Acute GVHD has been observed only in 1 patient.

Median age of the patients excluding myelofibrosis 52(26-71),median follow up was 6.9 (0.4-52) months. Two years overall survival was observed in 20% of the patients and 23% of the patients progresed in the follow up. Neutrophile engraftment was observed in 12 (10-14) days.Neutrophile engraftment could not be observed in 3 patients. Platelet engraftment was observed in 17 (10-40) days and could not be observed in 6 patients. Acute GVHD has been observed 33 % of the patients.

Conclusions
Engraftment has been observed as a major issue with treosulphan based regimens in myeloid malignancies. In myelofibrosis group most of the patients had massive splenomegaly and in acute leukemia group majority of the patients had advanced disease which can explain the high engraftment failure rates. Progress and GVHD was not different with busulphan based regimens which have been used in previous studies.

Pretreatment With Rituximab is Suspected to Increase Risk for Occurrence of Veno-Occlusive Disease in Patients With Aggressive Lymphoma After Allogeneic Transplant

P297
Poster presentation

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Study design	Retrospective single center study	**Aim**	Evaluation if Rituximab pretreatment is a potential risk factor for VOD/SOS in pts transplanted for aggressive NHL
Outcome parameters	VOD/SOS, OS, RI, TRM		
Patients	83	**Medaian age (range)**	55 y (19 – 74)
Disease	DLBCL (n=60), T-NHL (n=23)		
Conditioning regimen	**Treo/Flu** (n=11)		**Bu/Cy/Flu** (n=80)
Results VOD/SOS 4 y OS Relapse/Progression 4 y TRM	 9.7% 57% 55% 17.5%		 15.4% 41% 39% 33.3%
	• n=11 of 60 pts with DLBCL who received pre-treatment with rituximab developed VOD/SOS within 21 d after HSCT, no VOD/SOS detected in the 23 patients with T-NHL (p=0.03). • n=10 of 11 pts with VOD/SOS had very severe grading acc. to EBMT scale and died, one patient with severe VOD/SOS survived.		
Conclusion	• Patients with DLBCL who received CHOP pre-treatment with rituximab had a highly increased risk for VOD/SOS compared to patients with T-NHL treated with CHOP/CHOEP without rituximab. • Rituximab is a risk factor for the induction of VOD/SOS in patients after HSCT.		

Abstract

Background
Veno-occlusive disease, also known as sinusoidal obstruction syndrome (VOD/SOS), is a potentially life-threatening complication of allogeneic transplantation (SCT) most commonly associated with high-intensity conditioning regimens and chemotherapies. Recently, gemtuzumab ozogamicin and Inotuzumab ozogamicin have been identified as high risk factors for VOD/SOS. Here we aimed to evaluate in this retrospective, mono-center study, if a pretreatment with rituximab is a potential risk factor for the occurrence of VOD/SOS in pa-tients transplanted for aggressive lymphoma.

Methods
60 patients transplanted for DLBCL who were pretreated as first line therapy with RCHOP and received DHAP as salvage therapy were compared to 23 patients with T-NHL receiving CHOP/CHOEP pretreatment as first line therapy and DHAP as salvage therapy. Patients characteristic are given in table 1. VOD/SOS was diag-nosed only if the Baltimore criteria were fulfilled for adults with onset within the first 21 day after SCT, Bilirubin > 2mg/dL plus 2 or more of the following criteria: painful hepatomegaly, weigth gain > 5%, Ascites. All pa-tients with VOD had received a defribrotide therapy.

Results
11 of 60 patients with DLBCL who received a pretreatment with rituximab developed a VOD/SOS within 21 days after transplant while in none of the 23 patients with T-NHL a VOD/SOS was detected (p=0.03). Ten of 11 patients with VOD/SOS had a very severe grading according to the EBMT scale and died, while one patient with severe VOD/SOS survived. Multivariate analysis including LDH upper norm, gender, HLA-matched, high IPI >2, conditioning regimen with busulfan/cyclophosphamide/fludarabine (bu/cyc/flu), confirmed that rituximab was the only independent factor for the occurrence of VOD/SOS (ORR 34,7 (CI 95% 0,14 -867, p= 0,034). Conditioning with treosulfan/fludarabine (treo/flu) did not reduced the occurrence of VOD/SOS significantly compared to conditioning with bu/cyc/flu, (9,7% vs 15,4%, respectively). Estimates for OS was for treo/flu 57% for 4 years versus 41% for bu/cyc/flu. (n.s), while relapses/progress occurred in 55 % vs 39%, respec-tively (n.s.). TRM occurred after treo/flu conditioning in 17,5% vs 33,3% at 4 years (n.s.).

Conclusions
Here we report for the first time that patients with DLBCL who received CHOP-pretreatment with rituximab had a highly increased risk for VOD/SOS compared to patients with T-NHL treated with CHOP/CHOEP without rituximab. We suspect rituximab as a risk factor for the induction of VOD/SOS in patients after HSCT. More studies are required to confirm our findings.

medac

Pediatric Patients

Long-Term Results of Randomised Phase 2 Trial to Compare Treosulfan with Busulfan Based Conditioning in Children with Non-Malignant Diseases

Paed3-06
Oral presentation

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Study design	Prospective randomised phase 2 trial	**Aim**	Long-term efficacy results of prospective randomized trial comparing Treo- versus Bu-based conditioning in children with NMD
Exploratory analysis	Engraftment, safety, chimerism, GF, TRM, OS, EFS, a/cGvHD		
Patients	101	**Median age (range)***	4.0 y (0 - 17) Treo-based 5.0 y (0 - 17) Bu-based
Disease	IEM (n=7), PID (n=53 randomised), HBP (n=35 randomised), BMF (n=11)		

Conditioning regimen	**Treo-based (n=51)** Treosulfan (Σ 30 - 42 g/m²; BSA-adapted), Flu, TT (investigator's choice)	**Bu-based (n=50)** Bu (Σ 19.2 – 12.8 mg/kg, acc. to body weight), Flu, TT (investigator's choice)	P
Results*			
Freedom from TRM (d+100)	100.0%	90.0%	0.0528
36 mo TRM	3.9%	14.0%	0.1189
36 mo OS	94.1%	86.0%	0.2157
GF	22.0%	4.0%	0.0338
Chimerism ≥50%	52.3%	87.8%	0.3333
36 mo CRFS	84.5%	70.0%	0.0872
HSOS	2.0%	10.0%	0.1120
Infections	60.8%	70.0%	0.4044

Conclusion

- Children transplanted for non-malignant disorders with Treo-based conditioning had improved survival, including cGvHD-free survival.
- A higher risk of secondary graft failure when compared with busulfan-based conditioning was observed, nevertheless all but one subjects with graft failure after treosulfan were rescued and alive at last follow-up.
- This updated long-term evaluation confirms previously reported efficacy results analysed at 12 months.

*Additional info based on talk at conference

Abstract

Background

Different myeloablative conditioning regimens are recommended for allogeneic haematopoietic stem cell transplantation (alloHSCT) in children suffering from a variety of non-malignant diseases (NMD). We present updated long-term efficacy results of the recently published (Sykora et al., Bone Marrow Transplant, 2023) prospective, open label, randomised phase 2 trial comparing treosulfan versus busulfan based preparative regimens in children with inborn errors of metabolism (IEM), primary immunodeficiencies (PID), haemoglobinopathies HBP), or bone marrow failure syndromes (BMF).

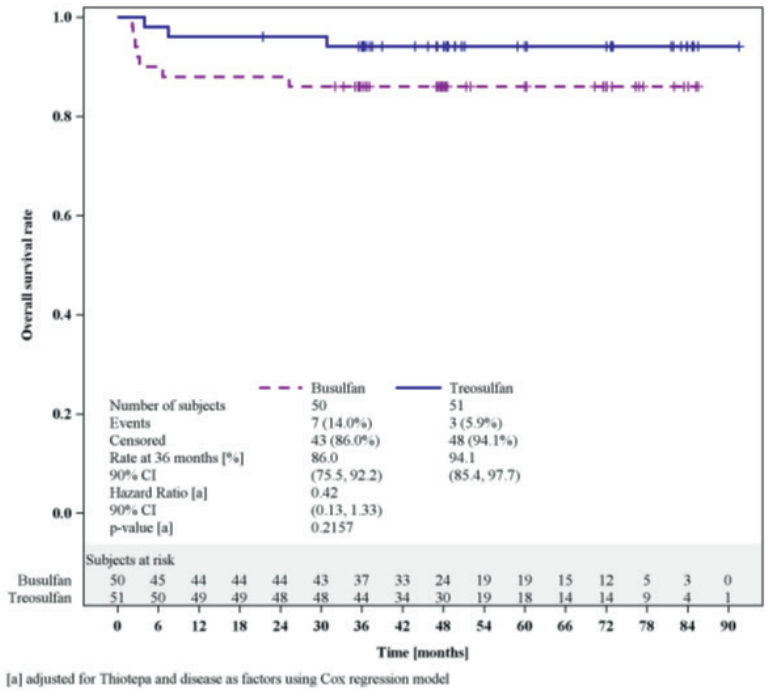
Methods

Children with NMD received treosulfan (10 [17.6%], 12 [62.7%], or 14 [19.6%] g/m²/day on Days 6, -5, -4, adapted to actual body surface area of ≤0.5, >0.5 to 1.0, or >1.0 m²) or busulfan (4.8 to 3.2 mg/kg/day on Days -7, 6, 5, 4, according to the actual body weight). Thiotepa (2 x 5 mg/kg on Day -2) was additionally administered in 84% of children. Matched sibling, family, unrelated or umbilical cord blood (MSD, MFD, MUD or UCB) donors were accepted for first alloHSCT. No formal confirmatory testing approach for efficacy was planned. This exploratory analysis is focused on engraftment, graft failures (GF), treatment-related mortality (TRM), overall survival (OS), acute and chronic Graft-versus-Host Disease (GvHD) at 3 years after alloHSCT.

Results

All of 101 treated patients (busulfan 50, treosulfan 51, median age: 5.5 years) with at least 36 (median 49) months follow-up are analysed. Randomization imbalances were seen for subjects with PID (busulfan 28, treosulfan 23) and HBP (busulfan 13, treosulfan 21). TRM at 36 months reached 14.0% (90% CI: 7.8, 24.5) after busulfan and remained at 3.9% (90% CI: 1.2, 12.0) after treosulfan (p=0.1189, HR of 0.28, 90% CI: 0.07, 1.07), confirming the previously reported trend towards less TRM after treosulfan. OS at 36 months was 86.0% (90% CI: 75.5, 92.2) after busulfan versus 94.1% (90% CI: 85.4, 97.7) after treosulfan (p=0.2157, HR of 0.42, 90% CI: 0.13, 1.33). Favourable cumulative incidence of primary and secondary graft failure for busulfan was confirmed: Busulfan 2 patients with IEM, 4.0% (90% CI: 0.0, 8.6) compared to finally 22.0% (90% CI: 12.3, 31.6) after treosulfan (p=0.0338, HR of 5.59, 90% CI: 1.47, 21.22). Most of the 11 GF after treosulfan were secondary (91%) and were reported in 4/23 PID, 4/21 HGP and 3/5 BMF patients. Chronic GvHD-free survival at 36 months was 70.0% (90% CI: 57.9, 79.2) for busulfan versus 84.5% (90% CI: 72.9, 91.4) for treosulfan (p=0.0872, HR of 0.45, 90% CI: 0.21, 0.97).

Kaplan-Meier estimates of overall survival (Full Analysis Set; MC-FludT.16/NM)



[a] adjusted for Thiotepa and disease as factors using Cox regression model

Conclusions

This comparative, explorative analysis after at least three years of follow-up revealed that children transplanted for non-malignant disorders with treosulfan based conditioning had improved survival, including cGvHD-free survival. However, a higher risk of secondary graft failure when compared with busulfan-based conditioning was observed. Nevertheless, all but one of the 11 subjects with graft failure after treosulfan were successfully rescued and alive at last follow-up. This updated long-term evaluation confirms previously reported efficacy results analysed at 12 months after alloHSCT and contributes to reasonable clinical risk-benefit considerations on preparative treatment options for individual paediatric transplant candidates with non-malignant diseases.

Clinical Trial Registry: EudraCT number 2013-005508-33; Clinicaltrials.gov Identifier NCT02349906

Treosulfan Versus Busulfan-Based Conditioning Regimens for First Allogeneic Hematopoietic Cell Transplant in Children With Acute Myeloid Leukemia in Complete Remission: A Retrospective PDWP/EBMT Study

OS12-05
Oral presentation

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Study design	Retrospective EBMT study	**Aim**	Outcome of Treo-based vs. Bu-based conditioning in children with AML		
Primary outcome	LFS	**Secondary outcome**	OS, RI, NRM. GRFS, a/cGvHD		
Patients	988	**Median age (range)**	9.3 y (0.4 – 18)		
Disease	AML				
Conditioning regimen	Treo/Flu/TT (n=125), Bu/Cy (n=492), Bu/Cy/Mel (n=371)				
Results*	All	Tre/Flu/TT	Bu/Cy	Bu/Cy/Mel	
2 y LS	72.1%	70%	68%	77%	n.s.
2 y OS	79.3%	80%	76%	83%	n.s.
2 y GRFS	61.9%	62%	58%	66%	n.s.
2 y RI	21.8%	23%	27%	15%	Bu/Cy/Mel sign. better
2 y NRM	6.2%	7%	4%	8%	n.s.
aGvHD (grade II-IV)	26.4%	29%	24%	29%	n.s.
2 y cGvHD	15.1%	16%	17%	12%	n.s.
Conclusion	• RI was significantly lower following Bu/Cy/Mel-based conditioning, with other outcomes being not significantly different among the three groups. • Data collection on VOD post-HSCT is ongoing.				

*Additional info based on talk at conference

Abstract

Background

Treosulfan, with its favorable toxicity profile, is increasingly being considered for conditioning in pediatric patients with acute myeloid leukemia (AML) in need of an allogeneic hematopoietic cell transplantation (HCT). Published studies comparing outcomes following Treosulfan vs. Busulfan-based conditioning mainly include recipients of ≥ 2nd HCT. Therefore, we conducted a study comparing outcomes of pediatric AML patients undergoing first allogeneic HCT following either a Treosulfan or Busulfan-based conditioning.

Methods

This retrospective EBMT study included all children (< 18 years) with de novo AML in CR1 or CR2 who underwent first allogeneic HCT between 2014-2022 and received any of the following myeloablative regimens: Busulfan/Cyclophosphamide (BuCy), Busulfan/Cyclophosphamide/Melphalan (BuCyMel) and Treosulfan/Fludarabine/Thiotepa (TreoFluThio). We excluded recipients of cord blood, haploidentical and < 9/10 mismatched HCT due to low number of patients within at least one of the regimens of interest. We compared the following outcomes between the three groups: leukemia-free survival (LFS), overall survival (OS), non-relapse mortality (NRM), incidence of acute and chronic graft versus host disease (aGVHD, cGVHD), relapse incidence (RI), and GVHD relapse-free survival (GRFS).

Results

988 (575 males) patients with a median age of 9.3 years [IQR: 3.8-13.7] met the study inclusion criteria, of whom 492 received BuCy, 371 BuCyMel, and 125 TreoFluThio. Baseline characteristics of the three groups (BuCy vs. BuCyMel vs TreoFluThio) were comparable except that a significant proportion of BuCyMel recipients were younger [median age in years: 10.2 vs 7.8 vs 9.5; p < 0.001], received more often bone marrow graft (64.2% vs 74.7% vs 57.6%; p< 0.001), more TreoFluThio recipients had a performance score (PS) < 90 (10.2% vs. 15.1% vs. 28.8%; p < 0.001) and BuCy recipients less often received in-vivo T cell depletion (37.6% vs 66.7% vs 61.3%; p< 0.0001) and more often sibling donors (57.9% vs. 32.9% vs 33.6%; p < 0.001). At a median follow-up of 3.1 years, the 2-year LFS, OS, GRFS, RI, and NRM of the entire cohort were 72.1% (95% CI: 68.8-75), 79.3% (95% CI: 76.4-82), 61.9% (58.4-65.1%), 21.8% (95% CI: 19-24.7) and 6.2% (95% 4.7-7.9) respectively. The cumulative incidence of grade II-IV aGVHD by day+100 was 26.4% (95% CI: 23.6-29.2), and cGVHD at 2 years was 15.1% (95% CI: 12.7-17.6). In multivariable analysis, as shown in Table 1 below, TreoFluThio was not significantly different from BuCy or BuCyMel in terms of LFS, OS, NRM, and GRFS. The incidence of relapse was, however, greater following TreoFluThio compared to BuCyMel but not to BuCy. There were no differences in the incidence of aGVHD and cGVHD. Increasing age (5-year increments) was associated with higher NRM (HR 1.66; p < 0.001), cGVHD (HR 1.35; p =0.002), and PS of ≥ 90 with better LFS (HR: 0.66; p=0.03) and OS (HR:0.67; p=0.048).

Conclusions

In our study, RI was significantly lower following BuCyMel-based conditioning, with other outcomes being not significantly different among the three groups. Data collection on veno-occlusive disease post-HCT is ongoing. The prospective randomized trial comparing BuCyMel vs TreoFluThio in pediatric AML patients will provide more definitive answers on the differences in outcomes between these two regimens.

Table 1: Outcomes Mulitvariable Analysis

Variables	Modalities	LFS		OS		RI	
		HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Regimen	TreoFluThio	1		1		1	
	BuCy	0.92 (0.59-1.42)	0.69	1.01(0.63-1.63)	0.96	0.99 (0.59-1.66)	0.97
	BuCyMel	0.70 (0.44-1.10)		0.83 (0.51-1.37)	0.47	0.52 (0.30-0.90)	**0.02**
Donor type	MSD	1		1		1	
	Unrelated donor 10/10	0.77 (0.57-1.06)	0.12	0.80 (0.56-1.13)	0.2	0.66 (0.46-0.95)	**0.02**
	Unrelated donor 9/10	0.84 (0.55-1.27)	0.11	0.80 (0.50-1.29)	0.36	0.65 (0.39-1.08)	0.1
Cytogenetics (European LeukemiaNet)	Fav/Intermediate	1	0.4	1		1	
	Adverse	1.60 (1.18-2.18)	**0.003**	1.67 (1.18-2.37)	**0.004**	1.64 (1.15-2.35)	**0.006**
	Missing	1.44 (0.98-2.12)	0.06	1.48 (0.96-2.27)	0.07	1.46 (0.93-2.28)	0.1
Disease Status	CR1	1		1		1	
	CR2	1.37 (1.01-1.86)	**0.04**	1.38 (0.98-1.95)	0.06	1.52 (1.08-2.15)	0.**02**

Variables	Modalities	NRM		GRFS		aGVHD II-IV	
		HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Regimen	TreoFluThio	1		1		1	
	BuCy	0.63 (0.27-1.48)	0.29	0.99 (0.66-1.47)	0.94	0.79 (0.48-1.28)	0.34
	BuCyMel	1.33 (0.60-2.97)	0.48	0.85 (0.57-1.28)	0.45	1.06 (0.66-1.72)	0.8
Donor type	MSD	1		1		1	
	Unrelated donor 10/10	1.19 (0.63-2.27)	0.59	0.81 (0.61-1.06)	0.12	1.02 (0.73-1.41)	0.91
	Unrelated donor 9/10	1.46 (0.67-3.17)	0.34	0.94 (0.66-1.34)	0.75	1.37 (0.93-2.02)	0.11
Cytogenetics (European LeukemiaNet)	Fav/Intermediate	1	0.18	1		1	
	Adverse	1.53 (0.82-2.84)	0.13	1.17 (0.90-1.54)	0.24	0.95 (0.71-1.29)	0.75
	Missing	1.76 (0.85-3.66)		1.34 (0.96-1.87)	0.09	0.85 (0.56-1.28)	0.43
Disease Status	CR1	1		1		1	
	CR2	0.91 (0.46-1.81)	0.78	1.32 (1.02-1.72)	**0.04**	0.88 (0.64-1.21)	0.43

Variables	Modalities	cGVHD	
		HR (95% CI)	p value
Regimen	TreoFluThio	1	
	BuCy	1.41 (0.76-2.61)	0.27
	BuCyMel	0.98 (0.52-1.85)	0.95
Donor type	MSD	1	
	Unrelated donor 10/10	1.13 (0.73-1.75)	0.57
	Unrelated donor 9/10	1.32 (0.76-2.31)	0.33
Cytogenetics (European LeukemiaNet)	Fav/Intermediate	1	
	Adverse	0.77 (0.50-1.18)	0.23
	Missing	0.93 (0.54-1.60)	0.81
Disease Status	CR1	1	
	CR2	0.94 (0.61-1.47)	0.8

Outcomes Of Allogeneic Haematopoietic Stem Cell Transplantation In Children With Wiskott-Aldrich Syndrome

A012
Poster presentation

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Study design	Single center retrospective study		**Aim**	Impact of HSCT for the treatment of WAS	
Outcome parameters	OS, EFS, GvHD, long-term disease outcomes				
Patients	27		**Median age (range)**	3.5 y (0.4 – 14.9)	
Disease	WAS				
Conditioning regimen	Bu/Cy (n=11)	Flu/Treo (n=9)	Flu/Treo/TT (n=7)	Flu/Mel (n=1)	Bu/Flu/TT (n=1)
Results 5 y OS 5 y EFS	89% 76% Three patients developed post-transplant autoimmunity: 2 had immune thrombocytopenia (100% donor chimerism) which resolved with steroids and high dose immunoglobulin, and one patient (myeloid chimerism2%; 35% T-cell chimerism) developed hypothyroidism and IgA nephropathy requiring a renal transplant.				
Conclusion	• The cohort's survival was good with a low rate of mild GvHD. • Flu/Treo/TT has been adopted as the institutions' standard conditioning for WAS to achieve robust myeloid chimerism.				

Abstract

Background
Haematopoietic stem cell transplantation (HSCT) is a curative treatment for Wiskott-Aldrich syndrome (WAS).

Methods
We examined the outcome of 27 children with WAS who received first HSCT at the Great North Children's Hospital between January 1994 and June 2023. One patient who was referred for second transplant was ex-cluded. Outcomes of interest were overall survival (OS) and event-free survival (EFS; event was defined as death, graft failure or second procedures), graft-versus-host disease (GvHD) and long-term disease out-comes. Busulfan-based conditioning was predominantly used before switching to treosulfan-based condi-tioning in 2007.

Results
Median age at diagnosis was 11.5 months (birth to 9.32 years) and median age at HSCT was 3.5 years (0.4-14.9). The interval between diagnosis and transplant was 9.6 months (2.4 months to 13.9 years). Conditioning was busulfan-cyclophosphamide (n=11), fludarabine-treosulfan (n=9), fludarabine-treosulfan-thiotepa (n=7), fludarabine-melphalan (n=1), and busulfan-fludarabine-thiotepa (n=1). Serotherapy was alemtuzumab (n=14), ATG (n=9) or none (n=4). GvHD prophylaxis was ciclosporin alone (n=4) or in combination with methotrexate (n=9) or MMF (n=13); none in three. Donors were matched related (MRD, n=6), matched unrelated (MUD, n=14), mismatched unrelated (MMUD, n =4) and mismatched related donor (MMRD, n=5). Stem cell source was bone marrow (BM, n=14), unmanipulated peripheral blood (PBSC, n=9), TCRab/CD19 depleted PBSC (n=4), CD34-selected marrow (n=1) and double cord (n=1). Median CD34+ cell dose was 7.1 x 106/kg (1- 50.9 x 106/kg). Median day to neutrophil and platelet engraftment was 16 days (10-41) and 18 days (9-51) respectively. Two developed veno-occlusive after receiving busulfan and none had transplant associated microangiopathy. Two patients developed grade 2 cutaneous GvHD, none had grade III-IV acute GvHD or chronic GvHD. Three (11%) developed CMV viraemia, 3 (11%) adenoviraemia, 3 (11%) EBV viraemia and 7 (26%) HHV6 viraemia.

Median duration of follow-up was 11 years (0.5-24). The 5-years OS and EFS was 89% (95%CI 69-96%) and 76% (55-89%) (Figure1). Details of 3 deceased patients were summarized in table 1. Three patients (Busulfan-Cyclophosphamide (2); Fludarabine-Treosulfan (1)) received second procedures: 1 CD34+ stem cell boost, 1 conditioned second transplant, 1 had CD34+ stem cell boost and then a conditioned second transplant.

Three patients developed post-transplant autoimmunity: 2 had immune thrombocytopenia (100% donor chimerism) which resolved with steroids and high dose immunoglobulin, and one patient (myeloid chimerism 2%; 35% T-cell chimerism) developed hypothyroidism and IgA nephropathy requiring a renal transplant. Median myeloid chimerism was 100% (2-100%) and median T cell chimerism was 100% (35-100%). All surviving patients with follow-up > 2 years are free from immunoglobulin replacement except one patient with myeloid chimerism of 2%. All had normal platelet counts except two patients with myeloid chimerism <= 5%.

Table 1: Details of deceased patients

Year	Age @ HSCT (year)	Pre-transplant issues	Transplant details	Cause of death
2000	7.4	CMV, EBV, Salmonella enteritis, recurrent pneumonia, vasculitis	Flu-Melphalan-ATG MUD, marrow	CMV pneumonitis and hepatitis
2006	1.1	HHV6, colitis	BuCy-Alemtuzumab MUD, marrow	Pulmonary hemorrhage and VOD
2017	12.7	CMV, EBV, Hepatitis B and C, colitis, osteomyelitis, hypothyroidism, AIHA	Fludarabine-Treosulfan-Thiotepa-ATG-Rituximab Haplo, TCRab/CD19-depleted PBSC	Encephalitis

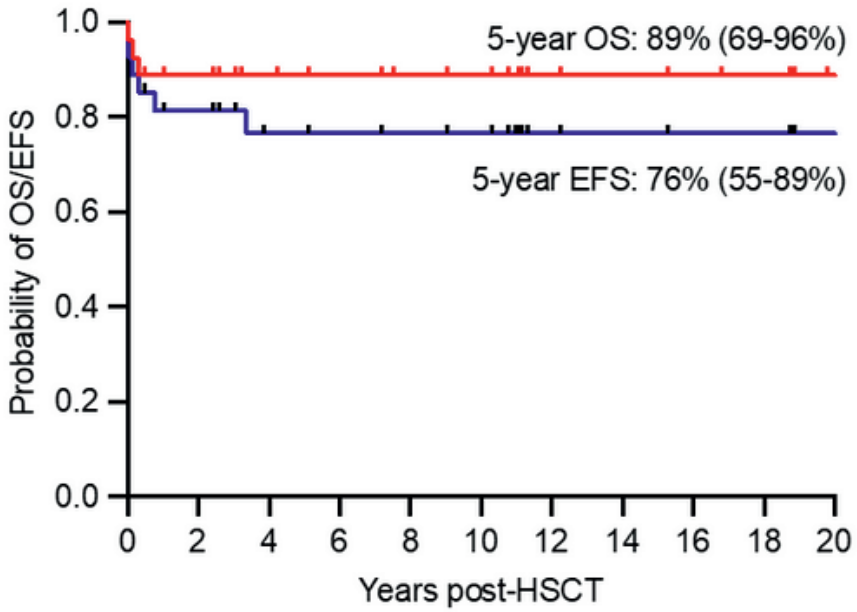

Figure 1: Overall and event free survival

Conclusions

Our Cohort's survival for WAS was good with a low rate of mild GvHD. Fludarabine-treosulfan-thiotepa has been adopted as our institutional standard conditioning for WAS to achieve robust myeloid chimerism.

Analysis of Safety of Treosulfan-Based Conditioning Regimen for Autologous Hematopoietic Stem Cell in 117 Children with Solid Tumors: Single Center Experience

A232
Poster presentation

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Study design	Retrospective single center study	**Aim**	AutoHSCT experience in children with solid tumors after Treo-based conditioning
Parameters assessed	Engraftment, TRM, toxicities		
Patients	117	**Median age (range)**	9.2 y (9 mo – 17.5 y)
Disease	NB (n=84), ES (n=32), pleuropulmonary blastoma (n=1)		
Conditioning regimen	Treo/Mel: Treo 36 – 42 g/m^2, Mel 140 mg/m^2		
Results Engraftment TRM Toxicities DFS	 100% None Mucositis/Enterocolitis (94% grade 1-2, 6% grade 3), skin (82% grade 1 - 2), hepatic (18.5% grade 1 -2), infectious episodes comparatively low Low compared to Bu/Mel and CEAM regimens		
Conclusion	• AutoHSCT with Treo-based conditioning for children with solid tumors was safe and effective both for NB and ES. • No TRM was seen in this study and all pts. engrafted.		

Abstract

Background
Autologous hematopoietic stem cell transplantation (aHSCT) improves treatment outcomes in patients with solid tumors. Myeloablative conditioning regimens are the “golden standards” for such aHSCT. Toxicity is the most challenging problem in myeloablative aHSCT. We aimed to present our experience of aHSCT with treosulfan-based conditioning regimen for children with solid tumors.

Methods
One hundred seventeen pts. with solid tumors received aHSCT in Lev Durnov Research Institute of Pediatric Oncology and Hematology of Nikolay Blokhin National Cancer Center during the period of January 2021 – October 2023. Pts. received treosulfan-based conditioning aHSCT: treosulfan (36-42 g/sq.m.), melphalan (140 mg/sq.m.). Most of the pts. (n=84) were with neuroblastoma (NB), 32 pts. were with Ewing‘s sarcoma (ES) and one pt. was with pleuropulmonary blastoma. Gender: M:F=68:49. Age median: 9.2 y.o. (9 m.o. - 17.5 y.o.). Source of cells – PBSC with the median of CD34-pos. cells 5.1x10 6 per kg (2.0 – 15.1).

Results
All pts. engrafted, no TRM were registered. Following toxic effects were found. All pts. suffered of mucositic and enterocolitis, but most of episodes were not severe, gr. 1-2 (94% of episodes), 6% - gr. 3. Mild skin toxicity of gr. 1-2 was found in 94 pts. (82%), no 3-4 gr. was found. Hepatotoxicity 1-2 gr. was found only in 24 pts. (18.5%), no 3-4 gr. was found. Infection episodes were comparable low. Toxic effects of pts. of the first year of life (n=8) were comparable low. Disease-free survival was comparable low in comparison with bu/mel and CEAM regimens.

Conclusions
aHSCT with treosulfan-based conditioning regimen for children with solid tumors showed safety and efficacy both for NB and ES. No TRM was registered in our study and all pts. engrafted. Our experience showed possibility of treo/mel regimen usage in routine pediatric practice in big transplant centers.

Treosulfan-Based Haploidentical T Cell Depleted HSCT for Adolescents and Young Adults (AYA) with Advanced Stage Sickle Cell Disease and Thalassemia

A266
Poster presentation

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Study design	Retrospective analysis	**Aim**	Explore haploHSCT in patients with SCD or TDT
Patients*	n=28	**Median age (range)***	19 y (11 – 32)
Disease*	Advanced stage SCD / SCD-ß-Thal (n=21), TDT (n=7)		
Conditioning regimen	FTT: Treo 42 g/m^2, Flu 160 mg/m^2, TT 10 mg/kg, ATG		
Results			
Engraftment	Median 18 d [11 – 24] (neutrophil)		
OS	92.9%		
EFS	82.1%		
Chimerism, median (range)	98.8% (73.4 – 100%)		
a/cGvHD (≥grade III, extensive)	0		
Viral reactivation	64%		
Efficacy	100% Transfusion independence (TDT) and 100% cessation of SCD-related complications (SCD) in surviving patients		
Toxicities	n=2 moderate VOD/SOS, n=1 CNS infarction, n=1 PRES		
Fertility	n=1 successful pregancy		
Conclusion	• Safety and efficacy data of this HR AYA patient population with advanced stage HBPs reveal that outcome with a T-haplo-HSCT can even exceed that of a MSD-HSCT with regard to EFS. • Diligent infectious and viral monitoring with early interventions is mandatory in SCD pts.		

*Numbers differing from abstracts were based on final presentation at conference

Abstract

Background

Inherited hemoglobinopathies, such as sickle cell disease (SCD) and transfusion dependent thalassemia (TDT) are associated with considerable morbidity and mortality. Availability of a matched sibling donor (MSD) bone marrow transplant as standard of care curative treatment is limited. Therefore, we explored T cell depleted haploidentical stem cell transplantation (T-haplo-HSCT) as alternative treatment to further reduce the risk of acute and chronic graft-versus-host disease (GvHD) in SCD and TDT.

Methods

: 29 patients (pts) with advanced stage SCD, SCD-ß-Thal or TDT (median age: 18 years; range: 11-32) received a T-haplo-HSCT (CD3+/CD19+; n=16 or aß/CD19+ depleted; n=13) in Regensburg/Germany between July 2012 and July 2023. Indications for HSCT in SCD pts (n=22) included severe or moderate SCD complications such as recurrent pain crisis (>5/year), acute chest syndrome, neurological events, osteonecrosis, nephropathy, and transfusion-refractory allo-immunization; and in TDT severe transfusion-dependent iron overload with complications (n=7). In SCD only, conditioning was preceded by an exchange transfusion. SCD and TDT pts were conditioned with a regimen consisting of ATG-Grafalon (45mg/kg), treosulfan (42g/m^2), thiotepa (10mg/kg) and fludarabine (160mg/m^2). Immunosuppression (IST) with a calcineurin inhibitor (mainly tacrolimus; with target levels between 5ng/ml and 8ng/ml) and MMF, was maintained for a minimum of 180 days, based on chimerism and split-chimerism analyses.

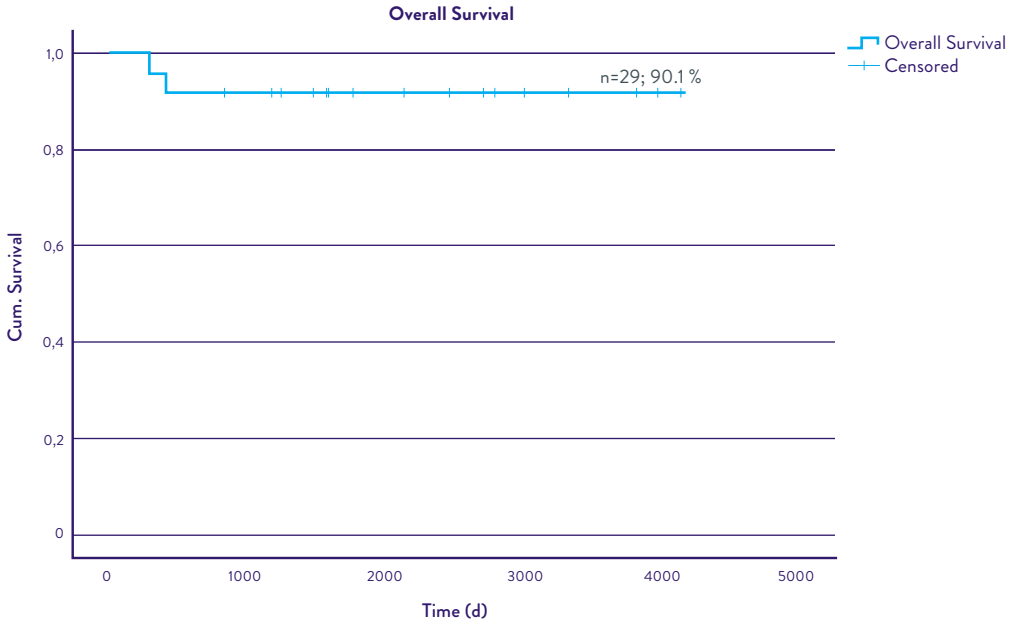
Results

Pts. received a median of 10.3 x 106 T cell depleted CD34+ cells/kg (range: 4.8–29). Neutrophil engraftment was achieved after a median of 18 days. With a median follow-up was 70 months (range 5-137 mo), the overall survival (OS) was 93% (Fig 1). Two pts (one SCD and one TDT) needed a second haplo-HSCT due to primary graft failure and achieved disease-free survival.

Median chimerism off-IST was 99% (range 73.4–100%). T cell recovery with T cell counts >200/µl was achieved in all but two pt at a median of 152 days (range 34-516 d), with one pt requiring regulatory T cell infusions and one developing fatal viral infection. No severe cases of ≥°III aGvHD or extended cGvHD were observed. Viral reactivation occurred in 63% of pts. Two SCD pts died of HHV6-associated complications accompanied by hyperinflammation, macrophage activation and acute respiratory distress despite antiviral and anti-inflammatory treatment. One pt developed kidney failure after prolonged BKV reactivation. All remaining patients achieved transfusion independence in TDT and cessation of SCD-related complications. Meanwhile, one female patient gave birth to a healthy child. Overall, the treosulfan-based conditioning regimen was well tolerated with two cases of moderate VOD/SOS and only one case of CNS infarction in a SCD pt being observed in this high-risk population. 1/19 pts developed PRES early after conditioning while on immunosuppression with CSA and MMF.

Results

	T-habplo HSCT
OS (%); EFS (%)	93; 86
Follow-up (months); median (range)	70 (25-137)
Neutrophil engraftment (days); median (range)	18 (11-41)
Chimerism (%); median (range)	99 (74.3-100)
Immune reconstitution >200/µl CD3+/µl (days); median (range)	152 (34-516)
Sepsis/ severe bacterial infection (outcome)	34% (resolved with antibiotic treatment)
Viral infections/reactivation (outcome)	62% viral reactivation; (1 kidney failure (BKV); 2 fatal HHV6-associated complications)



Conclusions

The safety and efficacy data of this high-risk AYA patient population with advanced stage hemoglobinopathies reveal that outcome with a T-haplo-HSCT can even exceed that of a MSD-HSCT with regard to a disease-free, GvHD free overall survival (EFS). However, diligent infectious and viral monitoring and early, effective treatment of viral reactivation, in particular HHV6 and CMV is mandatory in SCD pts.

The Results of Allogeneic HSCT After Treosulfan–Based Conditioning Regimen in Children With AML: Multicenter Retrospective Study of The Polish Pediatric Study Group for HSCT

B107
Poster presentation

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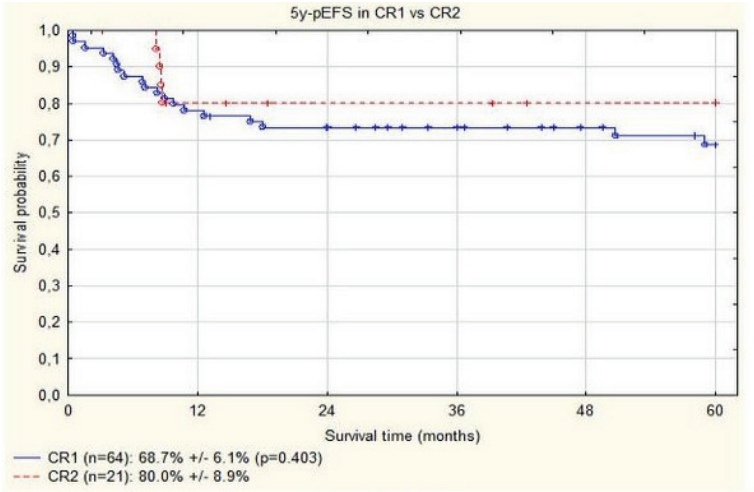
Study design	Retrospective analysis	**Aim**	Outcome of alloHSCT with Treo-based regimen in children with AML
Patients	85	**Median age (range)**	6.5 y (0.5 – 18.3)
Disease	AML		
Conditioning regimen	Treo-based in combination with cytostatics (mostly Flu, n=72 or Cy, n=11)		
Results	• High engraftment, complete donor chimerism 93.5% • Low early regimen-related toxicities, no VOD • NRM 5.9% • 5 y pOS 75.4%, no significant difference between HSCT in CR1 vs CR2 or MSD vs MUD • 5 y pEFS 71.3%, no significant difference between HSCT in CR1 vs CR2 or MSD vs MUD • CIR 23.8% • 5 y pRFS 76.9%, no significant difference between HSCT in CR1 vs CR or MSD vs MUD • aGvHD grade II-IV 31.8%, extensive cGvHD 8.2% • GRFS 64.7% at two years after HSCT		
Conclusion	• A Treo-based regimen seems to be safe and effective in pediatric AML patients and may be used as an alternative to busulfan-based protocols, especially in patients with pre-HSCT high risk factors of severe regimen-related toxicities		

Abstract

Background
Allogenic HSCT is indicated in high risk pediatric AML patients in first CR and in all patients with relapsed disease. However, so far there was no study concerning outcomes of allo-HSCT after treosulfan-based preparative regimen exclusively in children suffering from AML.

Methods
We performed a retrospective analysis of 85 pediatric patients with AML who underwent first allogenic HSCT following treosulfan between July 2000 and December 2022 in Polish pediatric transplant centers. The majority of patients were transplanted in CR1 (n=64; 75,2%) and had Lansky or Karnofsky score >80% (n=76; 89,4%) at HSCT. Most children were transplanted from unrelated donor (n=62; 72,9%) – in this group peripheral blood stem cells (PBSC) were the main stem cell source (n=47; 75,8%). Patients transplanted from matched sibling donor (n=23; 24,2%) mostly received stem cells from the bone marrow (BM) (n=17; 73,9%). In the conditioning regimen treosulfan was combined with different cytostatics, mostly fludarabine (n=72; 84,7%) and cyclophosphamide (n=11; 12,9%).

Results
Engraftment rate was high, the incidence of complete donor-type chimerism was 93,5%. Early regimen related toxicity was low and mainly affected oral cavity and gastrointestinal tract. No SOS/VOD was diagnosed. Non-relapse mortality (NRM) was low at 5,9% and occurred mainly in patients with pre-HSCT risk factors of NRM. Five-year probability of overall (5y-pOS) and event-free survival (5y-pEFS) was 75,4%±5% and 71,3%±5,1%, respectively. No statistically significant difference between 5y-pOS and 5y-pEFS was found in patients who were transplanted in CR1 and CR2 as well as those who received HSCT from MSD and MUD. The cumulative incidence of relapse was 23,8% (n=20). Five-year probability of relapse-free survival was 76,9%±4,7% and did not correlate with remission status (CR1 vs CR2) and type of donor. There was no significant difference in outcome after treosulfan-fludarabine-thiotepa regimen versus other treosulfan-based regimens. Acute graft versus host disease (GvHD) grade II-IV incidence was 31,8%. Extensive chronic GvHD was diagnosed in 8,2% of patients. One patient developed secondary malignancy.



Conclusions
Treosulfan-based regimen seems to be safe and effective in pediatric AML patients and may be used as an alternative to busulfan-based protocols, especially in patients with pre-HSCT high risk factors of severe regimen-related toxicities.

Treosulfan-Based Conditioning Regimen in Pediatric Allogeneic Hematopoietic Stem Cell Transplantation: A Case Series of Single Center Experience

P190
Poster presentation

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Affiliations: [1]Acibadem Adana Hospital, Adana, Turkey, [2]Cukurova University, Adana, Turkey

Study design	Retrospective single center analysis	**Aim**	Experiences with Treo-based conditioning in pediatric patients
Parameters assessed	Toxicities		
Patients	62	**Average age (range)**	8.8 y (9 mo – 17 y)
Disease	TM (n=31), SCD (n=11), SCID (n=13), FHLH (n=4), MDS (n=1), MLD (n=1), DBA (n=1)		
Conditioning regimen	Treo-based (Σ30 – 42 g/m^2)		
Results	• No serious toxicities occurred, n=3 severe mucositis, n=9 limited skin toxicities, n=3 skin erosions and exfoliation, n=2 minimal liver toxicity, n=1 VOD • N=4 deaths due to severe GvHD and sepsis		
Conclusion	• Treo-based conditioning is safe and effective in pediatric HSCT recipients, even in those with high-risk pre-HSCT clinical features or those with no MFD.		

Abstract

Background

Treosulfan is being increasingly used as part of conditioning regimens in pediatric allogeneic hematopoietic stem cell transplantation (HSCT) for both malignant and nonmalignant diseases. It has a low-toxicity profile, with the most commonly reported acute toxicities being skin, including nappy rash; diarrhea; mucositis; and hepatic toxicity; however, these are generally mild, and importantly, veno occlusive disease (VOD) is very rare. There are few reports using od treosulfan for allogeneic hematopoietic cell transplantation in children. We report our experiences with treosulfan based conditioning regimens in pediatric patients at our center.

Methods

A total of 545 allogeneic hematopoietic stem cell transplantations were performed at Acıbadem Adana Hospital Pediatric Bone Marrow Transplantation Unit in Turkey from 2013 to 2023. Sixty two patients out of 545 patients were conditioned for allogeneic hematopoietic cell transplantation with a treosulfan. Medical records and treatment modalities were evaluated retrospectively.

Results

In this study, 62 patients were conditioned with treosulfan, age ranging from 9 months to 17 years with an average of 8.8 years. Twenty nine patients were males, 33 were female. There were 31 patients with thalassemia major, 11 patient with sickle cell anemia, 13 patients with severe immune deficiency, 4 patients with familial hemophagocytic lymphohistiocytosis, one patient with myelodysplastic syndrome, one patient with metachromatic leukodystrophy, one patient with Diamond Blackfan anemia. Twenty six patients had HSCT from an unrelated donor. One patient with Griscelli syndrome had a haploidentical transplantation from mother. Patients received intravenous treosulfan doses of 10-14 g/m^2/day on days -6 to -4. The dose of treosulfan was changed according to blood level in 14 patients. The dose of treosulfan was increased in seven of 14 patients, and the dose of treosulfan was reduced in seven of them. There was no serious toxicity. Severe mucositis was seen in three patients. Nine patients had limited skin toxicity including pigment changes, and occasional peeling. Three patients showed skin erosions and exfoliation. Minimal liver toxicity occurred in two patients. VOD developed only in one patient with thalassemia majör class 3. Four patients died in the first 100 days due to severe GVHD and sepsis.

Conclusions

In this retrospective study, we show that treosulfan-based conditioning regimen is a safe and effective treatment option in pediatric HSCT recipients, even in those with high-risk pre-HSCT clinical features or those with no HLA-identical family donor.

Comparison of Busulfan-Based and Treosulfan-Based High-Dose Chemotherapy and Autologous Stem Cell Transplantation in High-Risk Neuroblastoma

P214
Poster presentation

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Study design	Retrospective single center study	**Aim**	Comparison of safety of Treo- vs. Bu-based conditioning in patients with HR NB receiving autoHSCT
Patients	32	**Median age (range)***	46.2 mo (15.4 – 491.4) Bu/Mel 41.2 mo (17.1 – 58.8) Treo/Mel
Parameters assessed	Survival, toxicities		
Disease	HR NB		
Conditioning regimen	Treo/Mel (n=12)		Bu/Mel (n=20)
Results*			
Median hospital stay (range)	23 d (21 – 26)		25 d (21 – 42)
Neutrophile engraftment (range)	10 d (9 – 11)		10 d (8 – 12)
Platelet engraftment (range)	20 d (14 – 24)		18.5 d (12 – 56)
Mucositis	75%		95%
Neutropenic fever	58%		55%
Pulmonary hypertension	0%		20%
Chronic kidney disease	0%		15%
Hepatic VOD	0%		10%
	• 5 y OS was 76.4% (all pts; OS for Bu/Mel pts was 69.2%) and 5 y EFS 57.0% (all pts)		
Conclusion	• Treo has similar therapeutic efficacy to Bu. • Treo may offer a better toxicity profile than Bu in the initial HD-CT/autoHSCT for HR NB, with fewer severe side effects observed.		

Abstract

Background

Although the combination of tandem high-dose chemotherapy and autologous stem cell transplantation (HDCT/ASCT) has improved survival outcomes in high-risk neuroblastoma patients, it has also presented notable toxicity challenges. The purpose of this study was to evaluate and compare the effectiveness and side effects of busulfan and treosulfan in high-dose chemotherapy used for HDCT/ASCT in patients with high-risk neuroblastoma.

Methods

A cohort of 32 patients diagnosed with high-risk neuroblastoma was identified at Asan Medical Center Children's Hospital between October 2013 and February 2022. The treatment protocol included 8 to 10 cycles of induction chemotherapy and tandem HDCT/ASCT combined with 131I-MIBG therapy. For the first round of HDCT/ASCT, 20 patients received a busulfan/melphalan regimen between 2014 and 2019, and 12 patients received a treosulfan/melphalan regimen between 2020 and the present. The second HDCT regimen consisted of thiotepa and cyclophosphamide.

Results

The 5-year overall survival (OS) and event-free survival (EFS) rates were 76.4% and 57.0%, respectively. In the initial high-dose chemotherapy and autologous stem cell transplantation (HDCT/ASCT) phase, patients in the busulfan group had a median hospital stay of 25 days (ranging from 21 to 42 days), compared to 23 days (ranging from 21 to 26 days) in the treosulfan group. Neutrophil engraftment occurred around day 10 in both groups, with a range of 8-12 days in the busulfan group and 9-11 days in the treosulfan group. Mucositis was a common side effect, affecting 19 out of 20 patients in the busulfan group and 9 out of 12 in the treosulfan group. Neutropenic fever was similarly prevalent, occurring in 55% of the busulfan group and 58% of the treosulfan group. Notably, pulmonary hypertension was reported in 4 patients (20%) receiving busulfan, but not in any patients receiving treosulfan. Additionally, chronic kidney disease developed in 3 busulfan patients (15%) and hepatic veno-occlusive disease in 2 (10%), whereas none of these complications were observed in the treosulfan group.

Conclusions

This preliminary study suggests that treosulfan may offer a better toxicity profile than busulfan in the initial HDCT/ASCT for high-risk neuroblastoma, with fewer severe side effects observed. However, due to the small patient cohort, further research is needed to confirm these findings and establish treosulfan‘s long-term safety and efficacy in this treatment context.

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. A*dults 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 non-infective 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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