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TREOSULFAN IN HSCT

Abstracts

EBMT
49th Annual Meeting
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Paris Hybrid

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 49th Annual Meeting of the EBMT.

This year's meeting was the first EBMT since the start of the COVID-19 pandemic offering the opportunity to once again meet in person, which was much appreciated by the multitude of attendees from all over the world. 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
ALL	Acute lymphoblastic leukemia
ALS	Adrenoleukodystrophy
allo	Allogeneic
AML	Acute myeloid leukemia
APDS	Activated PI3Kδ syndrome
ATG	Anti-thymocyte globulin
AUC	Area under the curve
auto	autologous
BM	Bone marrow
BMF	Bone marrow failure
BSA	Body surface area
Bu	Busulfan
CB	Cord Blood
CC	Complete chimerism
CGD	Chronic granulomatous disease
CI	Confidence interval
CID	Combined immunodeficiency
CIR	Cumulative incidence of relapse
CML	Chronic myelogenous leukemia
CMML	Chronic myelomonocytic leukemia
CMV	Cytomegalovirus
CRFS	Chronic GvHD- and relapse-free survival
d	Day(s)
DBA	Diamond Blackfan anemia
DFS	Disease-free survival
DIPSS	Dynamic international prognostic scoring system
EBV	Epstein-Barr virus
EFS	Event-free survival
ES	Ewing sarcoma
FDC	Full donor chimerism
Flu	Fludarabine
FSH	Follicle-stimulating hormone
FT	Flu/Treo
f-up	Follow-up
GOF	Gain-of-function
GRFS	GvHD- and relapse-free survival
haplo	Haploidentical
HLH	Hemophagocytic lymphohistiocytosis
HR	High risk
HSCT	Hematopoietic stem cell transplantation
IEI	Inborn errors of immunity
IEM	Inborn errors of metabolism
IPEX	Immune dysregulation, polyendocrinopathy, enteropathy, X-linked
JIA	Juvenile idiopathic arthritis
JMML	Juvenile myelomonocytic leukemia
LAD	Leukocyte adhesion deficiency
LFS	Leukemia-free survival
LH	Luteinizing hormone
MC	Mixed chimerism
MDS (-EB)	Myelodysplastic syndrome (with excess blasts)
med.	Median
Mel	Melphalan
MF	Myelofibrosis
MHC	Major histocompatibility complex
(M)MUD	(Mis)matched unrelated donor
mo	Month(s)
MPS	Mucopolysaccharidosis
MRD	Matched related donor
MSD	Matched sibling donor
MTSS	Myelofibrosis transplant scoring system
OP	Osteopetrosis
OR	Odds ratio
OS	Overall survival
PB	Peripheral blood
PID	Primary immunodeficiencies
PIDD	Primary immunodeficiency disorders
PIRD	Primary immune regulatory disorders
PK	Pharmacokinetics
PTCy	Post-transplantation Cyclophosphamide
pts	Patients
RFS	Relapse-free survival
SC	Stem cells
SCD	Sickle-cell disease
SCID	Severe combined immunodeficiency
SOS	Sinusoidal obstruction syndrome
STAT3	Signal transducer and activator of transcription 3
TBF	Flu/Bu/TT
TBI	Total body irradiation
TCD	T-cell depletion
TDM	Therapeutic drug monitoring
TDT	Transfusion dependent thalassemia
TFS	Thalassemia -free survival
TM	Thalassemia major
TMA	Thrombotic Microangiopathy
Treo	Treosulfan
TRM	Transplant-related mortality
TT	Thiotepa
TTF	Flu/Treo/TT
VOD	Veno-occlusive disease
WAS	Wiskott–Aldrich syndrome
y	Year(s)

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Adult Patients

Previous Busulfan Is Not A Contraindication For Second Allograft With Reduced Intensity Treosulfan-Based Conditioning Regimen Followed By Allogeneic Haematopoietic Stem-Cell Transplant From Unrelated Donors

P559
Poster presentation

A. Maraj[1], D. Avenoso[1], M. Kenyon[1], P. Krishnamurthy[1], V. Mehra[1], A. Kulasekararaj[1], S. Gandhi[1], F. Dazzi[1], Y.T. Leung[1], S. Anteh[1], M. Cuadrado[1], M. Naresh Shah[1], H. Ullah[1], S. Bouziana[1], C. Bourlon[1], O.D. Dragoi[1], A. Pagliuca[1], V. Potter[1]

Affiliation: [1]King's College Hospital NHS Foundation Trust, London, United Kingdom

Study design	Single center study	**Aim**	Safety and efficacy of second HSCT using Treo-based conditioning
Endpoints	OS, TRM, CIR, GvHD		
Patients	10	**Median age (range)**	55 y (33 – 71 y)
Disease	AML (n=6), MDS-EB (n=4)		
Conditioning regimen	FT: Treo 30 g/m2, Flu 150 mg/m2		
Results			
OS	100% (d+100 and d+365), median not reached		
TRM	None (d+365)		
LFS	80% (12 mo), 70% (18 mo), median 566 d		
CIR	30%, median time to relapse 165 d		
aGvHD	60% (all grades), 10% (grade III-IV)		
cGvHD	10%		
VOD	None		
Conclusion	• Outcomes for this high-risk population are favorable with no deaths recorded from TRM, infection or graft failure. • OS is encouraging and the LFS and incidence of aGvHD are comparable to recorded rates in the literature. • Previous conditioning with Bu does not preclude the efficacy of Treo-based conditioning in second HSCT as it seems to offer an excellent anti-leukemia effect without life threatening toxicities.		

Abstract

Background

Despite the improvement in the treatment of relapsed myelodysplastic syndromes with excess of blasts(MDS-EB) and acute myeloid leukaemia(AML), second hematopoietic stem cell transplant(HSCT) is still associated with increased transplant related mortality(TRM) and relapse rate if compared to first transplants. Therefore, actions are needed to improve the safety and efficacy of second HSCT.Within the alkyl sulfonates used in conditioning, Treosulfan has better marrow penetration than Busulfan and also an high activity on both myeloid progenitors and blasts; also, its hydrophilic properties are associated with less tissue damage and therefore with decreased incidence of graft-versus-host disease (GVHD)and veno-occlusive disease(VOD) of the liver.

Based on these encouraging promises, between December 2020 to May 2022, 10 consecutive second HSCT conditioned with fludarabine and treosulfan(FluTreo) were performed at King's College Hospital, London, with the aim to offer a less toxic second transplant. All the patients were firstly transplanted with busulfan based regimens and had a complete remission(CR) period more than 12 months after first HSCT.

Methods

Second HSCT was performed using GCSF mobilized peripheral blood stem cells as consolidative strategy following re-induction therapy. Conditioning protocol was with Fludarabine 30mg/m^2 on days-6,-5,-4,-3,-2 and Treosulfan 10g/m^2 on days-4,-3,-2;GVHD prophylaxis consisted of ATG 2.5mg/kg on days-2,-1,Ciclosporin 1.5mg/kg BD from day-1and post-HSCT Methotrexate 10mg/m^2 on days+1,+3,+6. Donors were 6matched unrelated donors and 4mismatched unrelated donors. Probabilities of overall survival(OS) was calculated using the Kaplan-Meier method. Relapse incidence(RI) and transplant related mortality(TRM)rates were estimated using cumulative incidence(CI) functions and considered as competing risks. For GvHD, death and relapse were considered competing events.Statistical analyses were performed with GraphPad Prism Version 9.4.1.

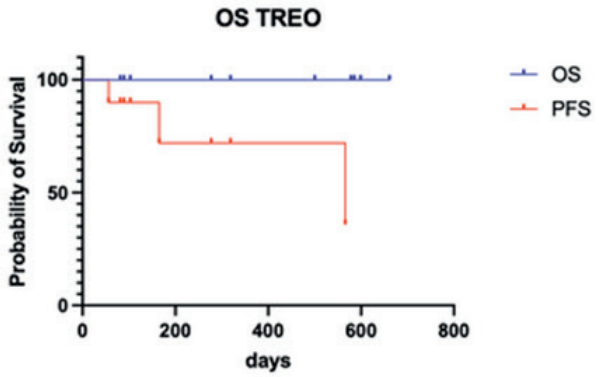
Results

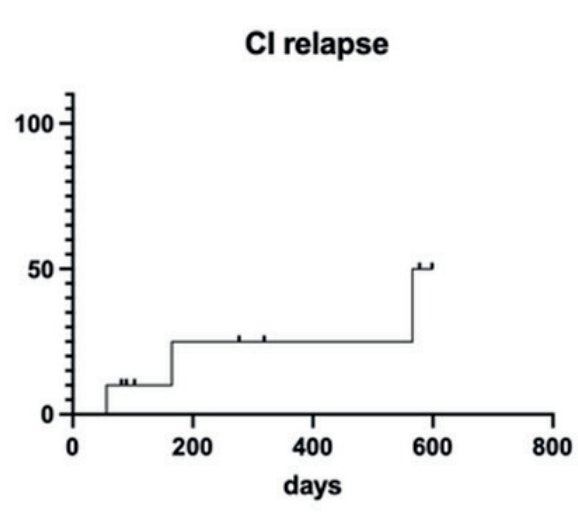
Table 1 summarizes the demographic of the population. Median follow up was 344 day(range 100 – 661).

The 100 and 365 days OS were 100%, with median OS not reached(figure 1) and with absent TRM. No septic death before engraftment or primary graft failure were noted.

The 12 months and 18months leukemia-free survival(LFS) were 80%and70% respectively(figure 1), median LFS was 566 days. Median time to neutrophils>1000/mL was 13 days(12-16), and 16 days(13-35) to platelets > 20.000/m. Median CD3 and CD15 chimerism at day 365 were 98%and 100%.Incidence of acute GVHD was 60% (grade III-IV 10%); 90% of observed acute GVHD was skin grade I-II.Overall chronic GVHD rate was 10% (n=1) and there were no moderate to severe cases. no VOD cases were recorded.Cumulative incidence of relapse was 30% with a relapse rate at 1 year of 20%. The median time to relapse was 165days(56-566) (figure 2).EBV reactivation rate was 90% (n=9)and 56% of these patients (n=5)required treatment with Rituximab, with 44% (n=4) having biopsy proven post-transplant lymphoproliferative disorder(PTLD).

Characteristic	Number of patients n=10
Age at HSCT in years, median (IQR)	55 (33-71)
Male Female	5 (50%) 5 (50%)
Diagnosis AML MDS-EB	 6 (60%) 4 (40%)
Adverse cytogenetic risk (ELN) Favourable/Intermediate Adverse	 4 (40%) 6 (60%)
Disease status at second HSCT CR 1/2 (MRD negative) CR 1/2 (MRD positive)	 5 (50%) 5 (50%)
HCT-CI 0-2 3+	 7 (70%) 3 (30%)
Follow up in days, median (IQR)	409 (100-661)





Conclusions

Outcomes for this high-risk population are favorable with no deaths recorded from TRM, infection or graft failure.While follow-up has been limited, the OS is encouraging and the LFS and incidence of acute GVHD are comparable to recorded rates in the literature. Previous conditioning with Busulfan does not preclude the efficacy of Treosulfan-based conditioning in second HSCT as it seems to offer an excellent anti-leukaemia effect without life threatening toxicities.

Treosulfan, Thiotepa And Fludarabine Conditioning Regimen Prior To Allogeneic Stem Cell Transplantation In Acute Myeloid Leukemia And High-Risk Myelodysplastic Syndromes: A Single Center Experience

P563
Poster presentation

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Study design	Single center analysis	**Aim**	TTF in myeloid malignancies
Parameters assessed	TRM, RFS, GRFS, OS		
Patients	37	**Median age (range)**	59 y (24 – 74 y)
Disease	AML (n=32), MDS (n=5)		
Graft-source	MSD, MUD, MMUD, Haplo-identical		
Conditioning regimen	TTF: Treo 10, 12 or 14 g/m2, Flu 150 mg/m2 (+ TT 5 mg/kg/d in n=18)		
Results TRM 2 y RFS 2 y GRFS 2 y OS	 11% (n=4) 59% 49% 67%		
Conclusion	• TTF conditioning resulted in low TRM rate. • Relapse was the main cause of death, a higher Treo dosing and/or a faster immunosuppression tapering might be considered given the low GvHD incidence. • High rate of GRFS with this transplant platform.		

Abstract

Background

Treosulfan-based conditioning prior to allogeneic transplantation has been shown to have myeloablative, immunosuppressive and antineoplastic effects associated with reduced transplant-related mortality (TRM) in adults. Emerging data are available for its use in myeloid malignancies.

Methods

We included patients diagnosed with acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) who underwent first allogeneic hematopoietic stem cell transplantation (HSCT) at a single hematologic center from 2016 to 2022.

All patients received treosulfan-thiotepa-fludarabine (TTF) conditioning regimen, followed by allogeneic peripheral blood stem cell (PBSC) infusion. Treosulfan at 10, 12 or 14 g/m^2/day per 3 days and thiotepa 5 mg/Kg/day per one or two days were administered based on patient age and fitness. Fludarabine was administered at 30 mg/m^2/day for 5 days in all patients.

For non-haploidentical donors, graft versus host disease (GvHD) prophylaxis consisted of cyclosporine (CsA) and short-course methotrexate; anti-thymocyte globulin (ATG) was administered in matched sibling donor (MSD), matched unrelated donor (MUD) 10/10 and MUD 9/10 at 2.5, 5 and 7.5 mg/Kg, respectively.

Haploidentical patients received ATG 2.5 mg/Kg, post-transplant cyclophosphamide (PTCy) 50 mg/Kg on days 3 and 4, CsA and mycophenolate mofetil from day 5.

GvHD was graded according to MAGIC and NIH criteria for acute and chronic forms, respectively.

Results

We included 37 consecutive patients, mainly affected by AML (86%), with a median age of 59 years (24-74) (table 1).

Treosulfan at 14, 12 and 10 g/m^2/day was administered to 13 (35%), 13 (35%) and 11 (30%)

patients respectively, while dose reduced thiotepa at 5 mg/Kg/day was administered in 18 patients (48%), most frequently combined with treosulfan 10 g/m^2/day.

Haploidentical donors were selected for 15 patients (40%), which mirrors the widespread use and favourable results reported with PTCy in recent years. 29 patients (78%) underwent HSCT in hematologic complete remission, the remaining were in partial remission (11%) or non-response (11%). Nearly half of patients were considered at high risk for TRM, as reflected by a comorbidity index (HCT-CI) ≥3 in 17 patients (46%) and an EBMT score ≥4 in 18 (49%).

Grade 2-4 acute GVHD was observed in 6 patients (16%), with only one experiencing an overall grade 3. A concomitant sinusoidal obstruction syndrome was observed in two patients (5%), consistent with the endothelial origin of both complications. 5 patients (14%) developed chronic GvHD, none of them of severe overall grade.

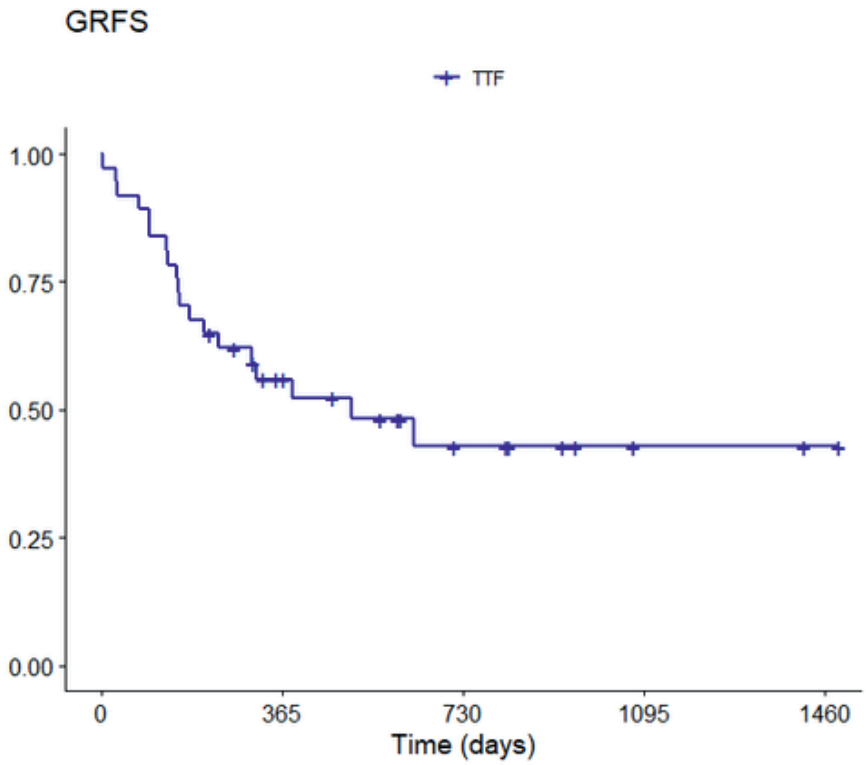
The only TRM cause was infection, occurring in 4 patients (11%). After a median follow up of 507 days (5-2469), 18 patients (49%) remained relapse- and GvHD-free (GRFS). The estimated 2-year relapse free survival (RFS) and overall survival (OS) were 59% and 67%, respectively.

Conclusions

In conclusion, despite an elevated HCT-CI and EBMT score in half of patients, TTF conditioning resulted in low TRM rate. Relapse was the main cause of death, hence a higher treosulfan dosing and/or a faster immunosuppression tapering might be considered given the low GVHD incidence. Finally, we observed a high rate of GRFS with this transplant platform, which may deserve further study if confirmed on large cohorts.

Table 1. Baseline features and outcome after TTF conditioning

TTF conditioned patients (N=37)	
Median age, years (range)	59 (24-74)
AML, N (%) / MDS, N (%)	32 (86%) / 5 (14%)
Graft source	
Matched sibling donor (MSD), N (%)	7 (19%)
MUD 10/10, N (%) / MMUD 9/10, N (%)	10 (27%) / 5 (14%)
Haploidentical donor, N (%)	15 (40%)
Pre-transplant risk assessment	
HCT-CI >2, N (%)	17 (46%)
EBMT >3, N (%)	18 (49%)
DRI intermediate, N (%) / High or Very high, N (%)	26 (70%) / 11 (30%)
Post-transplant complications	
Acute GvHD (grade 2-4), N (%) / (grade 3-4), N (%)	6 (16%) / 1 (3%)
Chronic GvHD, N (%)	5 (14%)
Sinusoidal obstruction syndrome (SOS), N (%)	2 (5%)
Transplant outcome	
Transplant related mortality (TRM) incidence, N(%)	4 (11%)
2-year relapse free survival (RFS), %	59%
2-year graft-relapse free survival (GRFS), %	49%
2-year overall survival (OS), %	67%



Clinical Trial Registry: not applicable

Previous Busulfan Exposure Is Not A Contraindication For Second Allograft With Reduced Intensity Treosulfan Based Conditioning Followed By In-Vivo T-Cell Depleted Unrelated Donor Haematopoietic Transplant

P568
Poster presentation

A. Maraj[1], D. Avenoso[1], M. Kenyon[1], P. Krishnamurthy[1], V. Mehra[1], A. Kulasekararaj[1], S. Gandhi[1], F. Dazzi[1], Y.T. Leung[1], S. Anteh[1], M. Cuadrado[1], M. Naresh Shah[1], H. Ullah[1], S. Bouziana[1], C. Bourlon[1], O.D. Dragoi[1], A. Pagliuca[1], V. Potter[1]

Affiliation: [1]King's College Hospital NHS Foundation Trust, London, United Kingdom

Study design	Single center study	**Aim**	Safety and efficacy of second HSCT
Endpoint	OS, TRM, CIR, GvHD		
Patients	10	**Median age (range)**	55 y (33 – 71 y)
Disease	AML (n=6), MDS-EB (n=4)		
Conditioning regimen	FT: Treo 30 g/m^2, Flu 150 mg/m^2		
Results			
OS	100% (d+100 and d+365), median not reached		
TRM	None (d+365)		
LFS	80% (12 mo), 70% (18 mo), median 566 d		
CIR	30%, median time to relapse 165 d		
aGvHD	60% (all grades), 10% (grade III-IV)		
cGvHD	10%		
VOD	None		
Conclusion	• Outcomes for this high-risk population are favorable with no deaths recorded from TRM, infection or graft failure. • OS is encouraging and the LFS and incidence of acute GvHD are comparable to recorded rates in the literature. • Previous conditioning with Bu does not preclude the efficacy of Treo-based conditioning in second HSCT as it seems to offer an excellent anti-leukemia effect without life threatening toxicities.		

Abstract

Background

Despite the improvement in the treatment of relapsed myelodysplastic syndromes and acute myeloid leukaemia, second hematopoietic stem cell transplant (HSCT) remains associated with increased transplant related mortality (TRM) and relapse rate compared to first transplants. Therefore, actions are needed to improve the safety and efficacy of second transplants. Within the alkyl sulfonates used in conditioning, Treosulfan has better marrow penetration than Busulfan and high activity on both myeloid progenitors and blasts; also, its hydrophilic properties are associated with less tissue damage and therefore decreased incidence of graft-versus-host disease (GVHD) and veno-occlusive disease (VOD) of the liver.

Based on these encouraging promises, between December 2020 to May 2022, 10 consecutive second HSCT conditioned with fludarabine and treosulfan (FluTreo) were performed at King's College Hospital, London with the aim to offer a less toxic second transplant. All the patients were firstly transplanted with busulfan based regimens.

Methods

Second HSCT was performed using GCSF mobilized peripheral blood stem cells. Conditioning protocol was with Fludarabine 30mg/m^2 on days-6,-5,-4,-3,-2 and Treosulfan 10g/m^2 on days-4,-3,-2; GVHD prophylaxis consisted of ATG 2.5mg/kg on days-2,-1, Ciclosporin 1.5mg/kg BD from day -1 and post-HSCT Methotrexate 10mg/m^2 on days+1,+3,+6. Donors were 6 matched unrelated donors and 4 mismatched unrelated donors. Probabilities of overall survival (OS) were calculated using the Kaplan-Meier method. Relapse incidence (RI) and transplant related mortality (TRM) rates were estimated using cumulative incidence (CI) functions and considered as competing risks. For GvHD, death and relapse were considered competing events. Statistical analyses were performed with GraphPad Prism Version 9.4.1.

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Table 1

Characteristic	Number of patients n=10
Age at HSCT in years, median (IQR)	55 (33-71)
Male Female	5 (50%) 5 (50%)
Diagnosis AML MDS-EB	 6 (60%) 4 (40%)
Adverse cytogenetic risk (ELN) Favourable/Intermediate Adverse	 4 (40%) 6 (60%)
Disease status at HSCT CR 1/2 (MRD negative) CR 1/2 (MRD positive) Primary induction failure Relapsed disease	 3 (30%) 5 (50%) 2 (20%) 0
HCT-CI 0-2 3+	 7 (70%) 3 (30%)
Follow up in days, median (IQR)	409 (100-661)

Figure 1

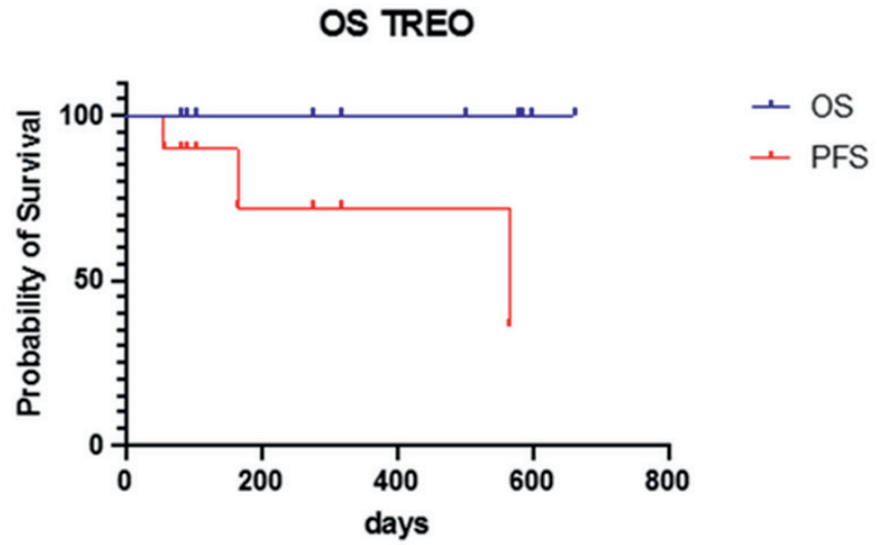
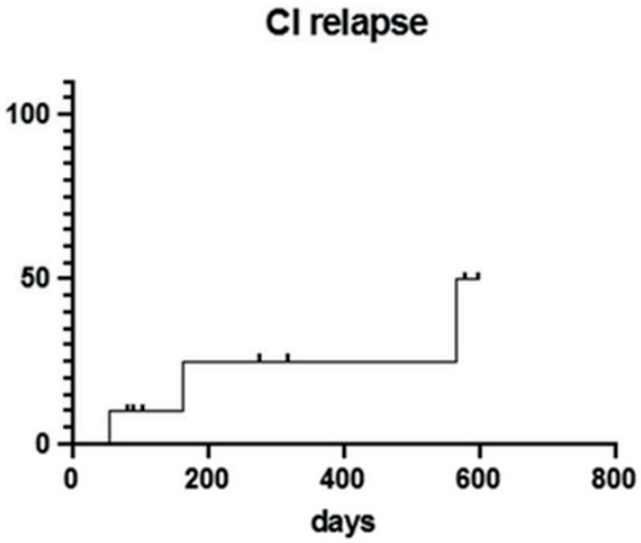


Figure 2



Conclusions

Outcomes for this high-risk population are favorable with no deaths recorded from TRM, infection or graft failure. While follow-up has been limited, the OS is encouraging and the LFS and incidence of acute GVHD are comparable to recorded rates in the literature.

Previous conditioning with Busulfan does not preclude the efficacy of Treosulfan-based conditioning in second HSCT as it seems to offer an excellent anti-leukaemia effect without life threatening toxicities.

Experience With Fludrabine/Treosulfan/Antithymocyteglobulin (Flu/Treo/ATG) Conditioning For Matched Donor Transplant In Myeloid Malignancies

P578
Poster presentation

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Study design	Retrospective analysis	**Aim**	Outcomes of Flu/Treo/ATG-based MRD or MUD alloHSCT
Parameters assessed	TRM, EFS, OS		
Patients	35	**Median age (range)**	40 y (17 – 68 y)
Population	AML, MDS, CMML, CML- Myeloid blast crisis		
Conditioning regimen	Flu/Treo/ATG		
Results			
Neutrophil engraftment	14 d (range 9 – 16 d)		
aGvHD	31.4%		
cGvHD	5.7%		
TRM	11.4% (n=4)		
Relapse	17.1% (n=6)		
EFS	12.7 mo (range 4 - 34 mo)		
OS	12.7 mo (range 4 - 37.5 mo)		
Conclusion	• AlloHSCT with Flu/Treo/ATG conditioning is feasible with acceptable TRM. • Longer follow-up is required to determine its aptness for deep-rooted control of the underlying disease.		

Abstract

Background
Flu/Treo represents a safe and effective reduced toxicity conditioning regimen. Recently, many studies have pointed towards favourable aspects of Treosulfan in terms of survival compared to conventional busulfan-based regimens, particularly in elderly patients.

Methods
We retrospectively analyzed the outcomes of 35 consecutive Flu/Treo/ATG-based matched related or unrelated stem cell transplants (allo-SCT) performed at our centre between November 2019 and August 2022.

Results
Median age was 40(17-68) years and females were 19(54.2%). Indications included myeloid malignancies {AML=23(65.7%), MDS transformed to AML=3(8.5%), MDS=4(11.4%), CMML=2(5.7%), CML- Myeloid blast crisis (8.5%)}. In all cases of MDS and AML, pre-transplant remission status was CR1(54.2%), CR2(8.5%), >CR2(5.7%) and refractory disease (5.7%). Eight (42%) patients were MRD-positive in a group of CR1 patients. Nineteen (82.6%) patients had high risk, 2(8.6%) patients had intermediate-risk whereas 2(8.6%) patients had standard risk AML at diagnosis. Twenty-four (68%) were matched related and 11(31.4%) were matched unrelated donor transplants. GVHD prophylaxis was calcineurin inhibitor and methotrexate in all cases. Peripheral blood stem cell was the predominant graft source. The majority had CMV reactive donor and recipient combination. Median cell dose (CD34) was 6(3.5-8.5) x106/kg. Median engraftment for neutrophils was 14(9-16) days. One (2.8%) patient had primary graft rejection. The cumulative incidence of acute and chronic GVHD was 31.4% and 5.7%. A common site of acute GVHD was GIT whereas chronic GVHD was commonly observed in oral mucosa and eyes. Treatment-related mortality (TRM) within 100 days was observed in 4(11.4%) patients and the cause of death in all these patients was septicemia. Six (17.1%) patients had relapses. At the last follow-up, 22(62.8%) patients were alive. Other than TRM, causes of death were relapse(n=6,46.1%), GVHD(n=2,15.3%), refractory disease(n=1,7.6%). The Median event-free survival (EFS) of the entire cohort was 12.7(4-34 months) and the median overall survival (OS) of the entire cohort was 12.7(4-37.5) months.

Conclusions
This single-center analysis demonstrates that allo-SCT with Flu/Treo/ATG conditioning is feasible with acceptable TRM. However, a longer follow-up inspection is required to determine its aptness for deep-rooted control of the underlying disease.

Thiotepa-Treosulfan-Fludarabine (TTF) As Conditioning Regimen In Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation (AlloHSCT) For Myelofibrosis

P738
Poster presentation

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Study design	Multicenter prospective observational study	**Aim**	Evaluate TTF in HR MF patients
Patients	9	**Median age (range)**	57 y (44 – 69 y)
Disease	MF		
Conditioning regimen	TTF: Treo 30 g/m^2, Flu 150 mg/m^2, TT 5 mg/kg		
Results	• DIPSS-plus: „intermediate-2“ 55%, „high“ 33.3%; MTSS: “very-high” 44.4% • Full donor early engraftment achieved in all cases except one • Median time to neutrophil recovery 17 d (range 15 – 21 d) • Median time to platelet engraftment >20 G/L 21 d (range 14 – 31 d) • Toxicities: mucositis grade 4 (n=1), transient mild hyperbilirubinemia (n=2), grade 3 systolic disfunction (n=1), neutropenic fever with 2 BSI, grade 3 myalgia (n=2), grade II aGvHD (n=1), cGvHD (n=2) • Three patients died; death and presence of MTSS „very-high“ were associated (p=0.048).		
Conclusion	• Data suggest feasibility for TTF in MF patients with manageable transplant-related toxicity.		

Abstract

Background
AlloHSCT remains the only potentially curative option for patients affected by myelofibrosis (MF) but there is no consensus on the best conditioning regimen. The use of treosulfan as alkylating agent in a RIC regimen demonstrated low toxic profile; on the other hand, the combination of two alkylating agents with the addiction of thiotepa seems to increase the chance of achieving engraftment with full donor chimerism in MF patients. Therefore a treosulfan-based dual alkylator regimen with thiotepa and fludarabine (TTF) could be a promising toxicity-reduced but myeloablative conditioning regimen for a kind of patients characterized by an advanced median age and usually with high comorbidity index (HCTI), at high risk of relapse and transplant-related mortality. No data are reported about the use TTF in alloHSCT for myelofibrosis: here we show the initial findings of our multi-centric prospective observational study regarding TTF in this setting.

Methods
A total of 9 patients (median age: 57, range 44-69, 55% male) affected by MF underwent alloHSCT with TTF conditioning (treosulfan 30 g/m^2, fludarabine 150 mg/m^2, thiotepa 5mg/kg) between January 2021 and November 2022. Six patients had primary disease, 1 patient had MF secondary to PV and 2 patients had a MF associated to LMC and MDS, respectively. DIPSS-plus was „intermediate-2“ in 55% and „high“ in 33,3% of cases respectively, while 44,4% of patients were at „very-high“ risk according to myelofibrosis transplant scoring system (MTSS). The median time from diagnosis to alloHSCT was 13 months (range, 4-158). Graft source was PBSC in all patients. Donor types were HLA-matched related (n=2), haploidentical (n=1) matched unrelated (n=2) and mismatched unrelated (n=4). GVHD-prophylaxis consisted of a calcineurin inhibitor plus methotrexate and ATG for 5 patients, while combination of cyclosporine with micophenolate and PTCy was used in 4 patients who underwent HSCT from mMUD or haploidentical donor.

Results
Full donor early engraftment was achieved in all cases except one. The median time to neutrophil recovery was 17 days (range, 15-21). The median time to achieve platelet engraftment >20 G/L was 21 (range, 14-31) days. Median follow-up was 7.2 (range, 0.5-22.8) months. Complications after HSCT included mucositis grade 4 in one patient, 2 cases of transient mild hyperbilirubinemia, one grade 3 systolic disfunction, neutropenic fever with 2 BSI, 2 cases of grade 3 myalgia. Two patients died early during aplasia: 1 for cerebral hemorrhage (at day 12) and 1 due to acute kidney disease and subsequent multi-organ failure (at day 32). One patient experienced grade II acute GVHD at day 35 which evolved in overlap chronic GVHD with atypical involvement of central nervous system and subsequently he died at day 342. Mild chronic GVHD occurred in another patient. No relapse was seen. There was an association between death and presence of MTSS „very-high“ (p=0.048).

Conclusions
These data suggest feasibility of TTF myeloablative regimen for alloHSCT in myelofibrosis, with manageable transplant-related toxicity. We will further evaluate TTF conditioning expanding patients cohort and with a longer follow-up, which are prerequisites mandatory for efficacy evaluation and for GRFS analysis.

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Pediatric and Adolescent Patients with Malignant Diseases

Low Toxicity With Myeloablative Chemo-Based Conditioning For Children With ALL Below 4 Years Of Age. Results From The Prospective Multinational Forum-Trial

Paed3-01
Oral presentation

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Study design	Prospective trial	**Aim**	Comparison of Treo-based vs. Bu-based conditioning in children < 4 y with ALL	
Primary objectives	OS, EFS			
Patients treated	194/202	**Median age (range)**	2.2 y	
Disease	ALL			
Conditioning regimen	**Treo-based (n=93)** TTF		**Bu-based (n=101)** TBF	p
Results				
3 y OS	0.76 ± 0.05		0.63 ± 0.05	0.075
3 y EFS	0.51 ± 0.06		0.52 ± 0.05	0.794
3 y GRFS	0.41 ± 0.06		0.44 ± 0.05	0.943
Conclusion	• Infants and young children receiving HSCT after conditioning with either Bu- or Treo-containing regimens have a lower OS and EFS as compared to children above the age of 4 y due to a higher CIR. • No significant difference in OS, EFS, CIR and NRM was found between Treo- and Bu-based regimens, however patients who relapsed post HSCT had a better 3 y post-relapse OS after TTF. *			

*Conclusion presented in oral presentation

Abstract

Background
Relapse and non-relapse mortality (NRM) are the major causes of treatment failure in infants and young children with high-risk ALL undergoing HSCT. The optimal chemotherapeutic approach aiming improved EFS and low NRM is not yet defined.

Methods
The prospective FORUM trial used two myeloablative chemo-conditioning regimens for children below 4 years of age: fludarabine (FLU), thiotepa (THIO) and either intravenous busulfan (BU) or treosulfan (TREO) (Peters et al., JCO 2021). This report includes 194/202 from 26 countries enrolled in FORUM. Median age at HSCT was 2.2 yrs.Stem cell source was BM in 132 (68%) pts, PBSC in 37 (19%), and UMCB in 24 (13%). Donors were HLA-matched siblings (MSD) in 39 (20%) pts and 9 or 10/10 HLA allele-matched UD in 155 (80%) pts. Clonal genetic abnormalities included 9 pts with BCR-ABL, 13 pts with TEL-AML, and 53 pts with KMT2A r-rearrangements; all pts underwent HSCT in complete morphological remission (CR) (142 pts CR1; 50 pts CR2, 2 pts CR3). FLU/THIO/BU and FLU/THIO/TREO were used in 101, and 93 HSCTs, respectively. GvHD-prophylaxis was Cyclosporin-A-based in 90%; recipients of MUD-grafts also received ATG (Grafalon or ATG Thymo, respectively) and methotrexate.

Results
At data cut-off, median follow-up was 3 yrs (range, 3 months – 7.2 yrs).3-yrs OS was 0.69±0.04, 3-yrs EFS was 0.52±0.04; 3-yrs CIR was 0.44+0.04, and 3-yrs NRM was 0.05 ± 0.02. OS and EFS did not differ between pts below 2 and 2-4 yrs of age at HSCT. Pts transplanted in CR 1 had significantly better EFS (0.58±0.04) as compared to >CR-pts (0.36±0.07, p=0.01); due to a higher CIR. OS was worse for the 53 pts with KMT2A-rearrangements (3-yrs OS 0.56±0.08 vs. 0.73±0.04, p=0.040). EFS for pts below 1 yr of age at diagnosis was significantly inferior as compared to older pts (3-yrs EFS 0.40±0.05 vs. 0.63±0.05, p=0.002). At 3-yrs, OS was 0.63±0.05 and 0.76±0.05; EFS was 0.52±0.05 and 0.51±0.06 (p=0.794) for the FLU/THIO/BU and FLU/THIO/TREO-group, respectively (p=0.075). However, pts who relapsed post-HSCT had a better 3-yr post-relapse OS after FLU/THIO/TREO compared to FLU/THIO/BU (0.38±0.11; 0.16±0.07. p = 0.012) respectively. 3-yrs cGVHD/relapse-free survival for FLU/THIO/BU was 0.44±0.05 and for FLU/THIO/TREO 0.41±0.06 (p=0.943). In multivariate analysis, remission > CR1 and KMT2A, negatively influence OS while EFS was worse for patients who underwent HSCT > CR1 or had ALL-diagnosis below 1 yr of age. Donor type, stem cell source, age between 1 and 4 yrs at HSCT, conditioning regimen, and PCR-MRD positivity pre-HSCT did not significantly influence outcome. 1-yr TRM was low for both conditioning regimens (0.06±0.02 for FLU/THIO/BU and 0.03±0.02 after FLU/THIO/TREO.

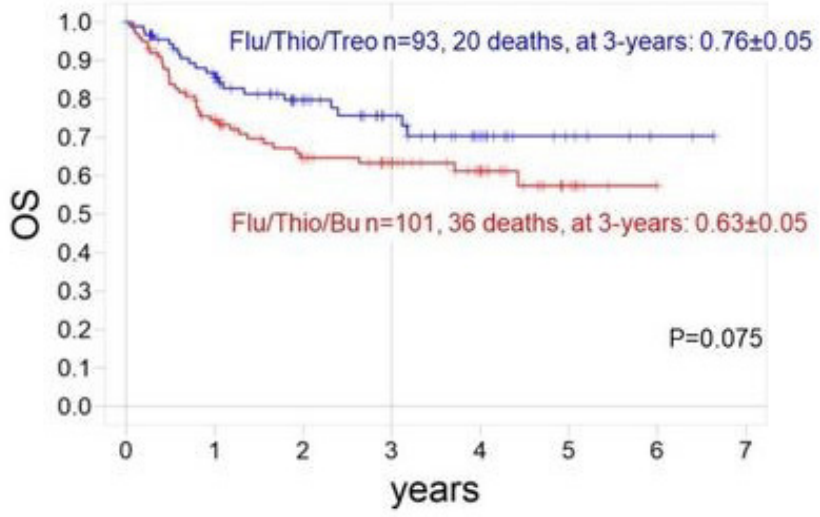

Table1: Uni- and multi-variable analysis of OS end EFS

				Univariate analyrsis		Multivariate analyrsis (Cox)	
Overall survival		**Patients**	**Deaths**	**3-year OS**	**p-value**	**HR [95% CI]**	**p-value**
Conditioning	Flu/Thio/Bu	101	36	0.63±0.05		1	
	Flu/Thio/Treo	93	20	0.76±0.05	0.075	0.62 [0.35- 1.09]	0.099
Donor	MSD	39	10	0.73±0.08		1	
	MD	155	46	0.68±0.04	0.883	1.08 [0.53- 2.23]	0.831
Remission status	CR1	142	34	0.74±0.04		1	
	> CR1	52	22	0.57±0.07	0.029	1.41 [0.74- 2.70]	0.297
Immunphenotype	BCP	155	48	0.67±0.04		1	
	T-ALL	27	5	0.81±0.08		0.80 [0.30- 2.18]	0.665
	other	11	3	0.67±0.16	0.295	0.71 [0.21- 2.43]	0.590
Age at SCT	<2 years	91	26	0.71±0.05		1	
	2-<4 years	103	30	0.68±0.05	0.793	1.56 [0.69- 3.52]	0.282
KMT2A	neg	129	33	0.73±0.04		1	
	pos	53	21	0.56±0.08	0.040	1.90 [1.01- 3.56]	0.046
Age at diagnosis	<1 year	92	30	0.64±0.06		1	
	>= 1 year	102	26	0.73±0.05	0.220	0.66 [0.30- 1.48]	0.316

Event Free Survival		**Total**	**Events**	**3-year EFS**	**p-value**	**HR [95% CI]**	**p-value**
Conditioning	Flu/Thio/Bu	101	47	0.52±0.05			
	Flu/Thio/Treo	93	40	0.51±0.06	0.794	0.90[0.57- 1.40]	0.638
Donor	MSD	39	14	0.58±0.09			
	MD	155	73	0.50±0.04	0.382	1.28[0.69- 2.35]	0.431
Remission status	CR1	142	55	0.58±0.04			
	> CR1	52	32	0.36±0.07	0.011	1.48[0.88- 2.49]	0.143
Immunphenotype	BCP	155	76	0.46±0.04			
	T-ALL	27	8	0.70±0.09		0.71[0.31- 1.63]	0.419
	other	11	3	0.71±0.14	0.083	0.42[0.13- 1.37]	0.150
Age at SCT	<2 years	91	44	0.48±0.06			
	2-<4 years	103	43	0.55±0.05	0.328	1.30[0.67- 2.52]	0.433
KMT2A	neg	129	53	0.56±0.05	0.075		
	pos	53	29	0.40±0.07	0.075	1.28[0.77- 2.13]	0.338
Age at diagnosis	<1 year	92	52	0.40±0.05			
	>= 1 year	102	35	0.63±0.05	0.002	0.48[0.25- 0.95]	0.034

Conclusions

Within the FORUM-trial, infants and young children receiving HSCT after conditioning with either BU- or TREO containing regimens have a lower OS and EFS as compared to children above the age of 4 yrs due to a higher CIR. Because of decreased NRM, these results represent an improvement as compared to previously reported series; however, KMT2A-rearrangement continues to be an obstacle to successful HSCT.

Clinical Trial Registry: EudraCT No. 2012-003032-22
ClinicalTrials.gov ID: NCT01949129

Treosulfan Based Conditioning For Haematopoietic Stem Cell Transplantation (HSCT) In Paediatric Malignant Disorders: On Behalf Of The UK Paediatric BMT Group

P022
Poster presentation

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Study design	Retrospective multicenter study	**Aim**	Transplant outcomes in children with malignant disorders after Treo-based conditioning
Primary endpoints	OS, EFS, TRM	**Secondary endpoints**	a/cGvHD, VOD
Patients	144	**Median age (range)**	6.7 y (0.4 - 19 y)
Disease	ALL (n=42), AML (n=45), biphenotypic leukemia (n=2), MDS (n=35), JMML (n=12), Lymphoma (n=8)		
Conditioning regimen	TTF (n=123), FT (n=9), other Treo-conditioning (n=12)		
Results*			
3 y OS	72% (indication: ALL 62%, AML 67%, MDS 91%, JMML 85%, lymphoma 88%)		
3 y EFS	58% (indication: ALL 45%, AML 50%, MDS 81%, JMML 54%, lymphoma 75%)		
1 y TRM	9%		
aGvHD d+90	26% (grade II), 14% (grade III-IV)		
cGvHD	7%		
VOD	5%		
Conclusion	• Treo-based conditioning is safe in pediatric malignant disorders with low TRM and early toxicities including VOD and TMA.		

*Based on poster at conference.

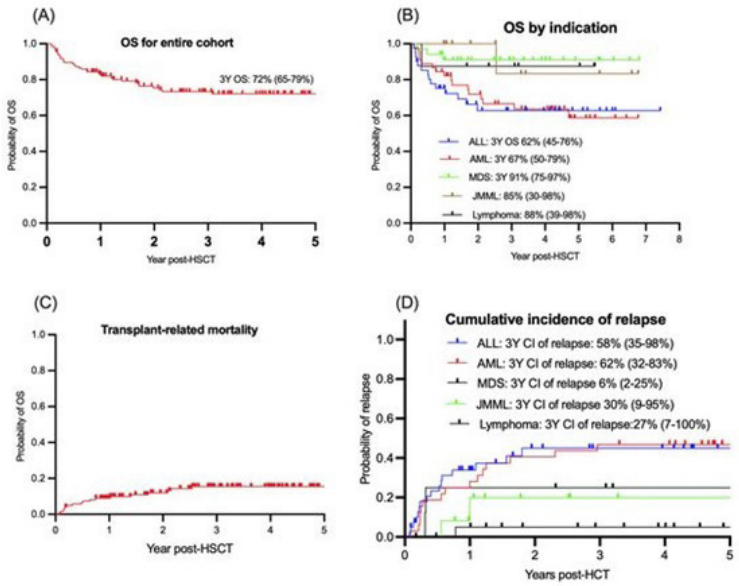
Abstract

Background
Treosulfan based conditioning in haematopoietic stem cell transplantation (HSCT) for malignant disorders is an option when myeloablative conditioning is unsuitable due to age or co-morbidities. This retrospective multicentre study reports transplant outcomes in 144 paediatric patients after treosulfan based conditioning for first HSCT in malignant disorders between 2015 and 2021 at 9 UK transplant centres.

Methods
The primary endpoints were overall survival (OS) and transplant-related mortality (TRM). Secondary endpoints were grade II-IV aGvHD, cGvHD and toxicities. Subgroup differences in OS was evaluated by log-rank test. Competing risks methods were used for the cumulative incidence of aGvHD, cGvHD and toxicities, with death as the competing event, subgroup differences were evaluated by Gray's test.

Results
144 patients (median age of 6.7 years; range= 0.4 to 19 years) were included in the study with a median follow up of 3.4 years (range= 0.2 to 7.4 years). Indications for transplant were ALL (n=42, 39%), AML (n=45, 31%), biphenotypic leukaemia (n=2, 1%), MDS (n=35, 24%) , JMML (n=12, 8%), Lymphoma (n=8, 7%). Donors were MFD (n=35, 24%), MUD (n=92, 64%), MMFD/MMUD (n=15, 10%) and haploidentical donor (n=2, 1%). Stem cell source was bone marrow (n=87, 60%), PBSC (n=25, 17%) , Cord Blood (n=30, 21%) and TCR ab/CD19 depleted PBSC (n=2, 1%). The most common conditioning regimen was Fludarabine-treosulfan-thiotepa in 123 (85%) patients. The remaining 21 patients (15%) received other treosulfan conditioning (2 Treo alone; 9 Flu-Treo; 3 Treo-Thioetapa; 3 Treo-Cy; 6 Treo-Cy) . Treosulfan dose was 42g/m^2 in 104 (74%) and 30-36gram/m^2 in 38 (26%). Serotherapy was ATG (n=45, 31%), Alemtuzumab (n=50, 35%) and none (n=49, 34%).

Median days to neutrophil and platelet recovery was 18 (range of 10-41) and 22 days (range of 9-81) respectively. 3 year cumulative incidence (CI) of relapse was 41%. CI of Grade II-IV GVHD was 43% and of Grade III-IV acute GVHD was 13%. CI of chronic GVHD was 7%. CI of VOD and TMA was 4% (2-9%) and 4.2% (2-10%) respectively. 3 year OS was 72% for the entire cohort (fig-a) By indication, OS was 62% in ALL, 67% in AML, 91% in MDS, 85% in JMML and 88% in lymphoma (p=0.03) (fig-b). TRM at 1 year post HSCT was 9% (figure c). CI of relapse was 58% in ALL, 62% in AML, 6% in MDS, 30% in JMML and 27% in lymphoma (figure d). Out of 25 deaths, 19 were due to relapse and 6 due to TRM.



Conclusions
Treosulfan based conditioning is safe in paediatric malignant disorders with low TRM and VOD rates.

Long-Term Complications In Children Undergoing Allogeneic HSCT For Malignancies With A Treosulfan Or A Busulfan Based Conditioning: Results Of An AIEOP Retrospective Study

P612
Poster presentation

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Study design	Retrospective multicenter analysis	**Aim**	Impact of Treo- or Bu-use on the occurrence of late effects
Parameters assessed	Occurrence of impairment of growth, gonadal, thyroid, and pulmonary function, cataract, and secondary malignancies		
Patients	693	**Median age (range)**	8 y (0 – 23 y)
Disease	ALL, AML or MDS		
Conditioning regimen	Treo or Bu		

Results	Treosulfan	Busulfan	p
n	109	584	
Gonadal toxicity (only pts >10 y, n=270)	12%	41%	0.002
Growth impairment (only pts <10 y, n=423)	2%	10%	0.1

- No statistically significant difference in terms of alteration of thyroid function, cataract, occurrence of secondary malignancies and alteration of pulmonary function.
- In multivariable analysis pts in the Treo group showed a reduced risk of developing gonadal toxicity (p=.0011), especially as male pts (p< 0.001) and younger children (> 5 y p<0.001; > 10 y p< 0.001; > 15 y p< 0.001).

Conclusion

- Treo is associated with a reduced risk of developing gonadal toxicity.
- No statistically significant association between growth impairment, alteration of thyroid function, cataract, occurrence of secondary malignancies and alteration of pulmonary function and the exposure of one of these two drugs.

Abstract

Background
Children undergoing hematopoietic stem cell transplantation (HSCT) and becoming long-term survivors have an increased risk of developing long-term toxicities, in part attributable to the conditioning regimen. In this retrospective multicenter study, we evaluated the impact of the use of either Treosulfan or Busulfan on the occurrence of late effects.

Methods
The study included all patients undergoing HSCT between 2006 and 2017 in AIEOP (Associazione Italiana Ematologia Oncologia Pediatrica) Centers for acute lymphoblastic leukemia (ALL), acute myelogenous leukemia or myelodysplastic syndrome (AML/MDS) after a conditioning regimen including either Treosulfan (Treo) or Busulfan (Bu). As long-term side effects, the occurrence of impairment of growth, gonadal, thyroid and pulmonary function, cataract, secondary malignancies were investigated. The occurrence of each late effect was calculated as cumulative incidence (CI) to adjust the analysis for competing risks (i.e., leukemia relapse and death). The differences in terms of CI were compared using Gray's test. Multivariable analysis was performed using logistic regression. All statistical analyses were performed using NCSS software (Hintze, 2001; NCSS PASS, Number Crunched Statistical System, Kaysville, UT, USA).

Results
The study included 693 patients (315 females and 378 males) with a median age of 8 y (range 0-23) at the time of HSCT: 584 received a Bu-based and 109 a Treo-based conditioning regimen. At baseline, patients in the Bu group were younger (p< 0.001), mostly affected by AML/MDS (p< 0.001) and in first complete remission (p< 0.001). The Treo group received an HSCT from a partially matched unrelated donor (MMUD) in a larger proportion of the cases (p= 0.04) and cord blood as stem source in fewer cases (p=0.02). The median follow-up was of 4.5 years. For gonadal toxicity we considered only patients older than 10 years (n= 270) and in univariable analysis Bu was correlated with a statistically significant increased risk of developing gonadal toxicity compared to Treo: 41% (95%CI 34-49) versus 12% (95%CI 5-25) (p= 0.002). For growth impairment we considered only patients younger than 10 years (n= 423): Bu was correlated with an increased risk of developing growth impairment compared to Treo: 10% (95%CI 7-15) versus 2% (95%CI 0-16) but this difference was not statistically significant (p= 0,1). The two groups didn't show any statistically significant difference in terms alteration of thyroid function, cataract, occurrence of secondary malignancies and alteration of pulmonary function. In multivariable analysis patients in the Treo group showed a reduced risk of developing gonadal toxicity (RR 0,27 95%CI 0,12-0,59 p=.0011), especially as male patients (RR 0,15 95%CI 0,09-0,23 p< 0.001) and younger children (> 5 years RR 3,66 95%CI 2-6,6 p<0.001; > 10 years RR 5,895%CI 3.3-10 p< 0.001; > 15 years RR 10.9 95%CI 6-19.7 p< 0.001).

Conclusions
This study shows that the use of Treosulfan in the conditioning regimen is associated with a reduced risk of developing gonadal toxicity, while in our study we did not observe a statistically significant association between growth impairment, alteration of thyroid function, cataract, occurrence of secondary malignancies and alteration of pulmonary function and the exposure of one of these two drugs.

Outcomes Of Busulfan Versus Treosulfan Based Regimens Followed By Autologous Stem Cell Transplant In Children With High Risk Ewing Sarcoma

P834
Poster presentation

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Study design	Retrospective single center analysis	**Aim**	Compare efficacy and toxicity of Treo-based and Bu-based in HR ES followed by autoHSCT	
Patients/Transplants	n=26	**Average age**	14.4 y (3.5 - 23.7 y)	
Disease	ES			
Conditioning regimen	Treo/Mel (n=8)		Bu/Mel (n=18)	p
Results				
OS	87.5% (7/8)		66.7% (12/18)	0.26
RFS	62.5% (5/8)		50% (9/18)	0.55
Bacteremia	0% (0/8)		22.2% (4/18)	0.27
Mucositis	62.5% (5/8)		100% (18/18)	0.02
Conclusion	• No statistically significant difference in OS and RFS mostly due to small cohort size. • Both regimens were relatively safe as shown by low incidence of major complications. • Lower incidence of mucositis in Treo/Mel group.			

Abstract

Background
The role of consolidation high-dose chemotherapy in high risk Ewing sarcoma (ES) is still controversial. The high dose regimens used consist of either busulfan and melphalan or treosulfan and melphalan followed by autologous stem cell rescue (ASCR). The goal of our study was to compare the efficacy and toxicity of both regimens.

Methods
We conducted a retrospective analysis of all the children who received high dose chemotherapy followed by ASCR for high risk ES in Tel Aviv Sourasky medical center, Israel. High risk ES was defined as: relapsed ES, ES with lung metastasis or localized high risk ES (tumor volume at diagnosis ≥ 200 ml or poor histologic response defined as viable cels ≥ 10%).

Treosulfan-based regimen (TBR) was given to patients with abdominal, pelvic or spinal masses with planned radiation therapy to the area. The rest of the patients received Busulfan-based regimen (BBR).

Overall survival (OS), relapse free survival (RFS), and the incidence of complications (Bacteremia, Fungal infections, VOD and mucositis) were compared between the two groups

Results
Between November 2010 and December 2021 26 children received high dose chemotherapy followed by ASCR for high risk ES. 18 were treated with BBR (10 with lung metastasis, 5 with relapsed disease and 3 with localized high risk disease) and 8 were treated with TBR (6 with lung metastasis and 2 with localized high risk disease).

The average age for the entire cohort was 14.4 years (range 3.5-23.7 years).

The median follow up time for the entire cohort was 3.6 years (range 0.9-11.6 years), 3 years (range 0.2-11.1 years) for the BBR group and 1.6 years (range 0.6-4.3 years) for the TBR group.

At the time of data analysis the OS of the TBR group was superior to the BBR group, 87.5% (7/8) versus 66.7% (12/18), but that was not statistically significant (p-0.26). The RFS was also superior in the TBR group (62.5%,5/8) compared to the BBR group (50%, 9/18) again without statistical significance (p-0.55).

There was increased incidence of bacteremia events in the BBR group (4/18, 22.2%) compared to the TBR group (0/8, 0%) that was not statistically significant (p value – 0.27).

There was statistically significant (p value – 0.02) increased incidence of mucositis in the BBR group (18/18, 100%) compared to the TBR group (5/8, 62.5%).

There were no events of veno-occlusive disease (VOD) nor fungal infections in both groups.

Conclusions
Our single center cohort showed no statistically significant differences in OS and RFS between the BBR group and the TBR group, mostly due to small cohort size.

Both regimens were relatively safe as shown by low incidence of major complications (i.e. no events of VOD) with statistically significant lower incidence of mucositis in the TBR group.

A larger cohort, using larger, multicenter database is required to better explore the difference in outcomes and toxicity between BBR and TBR.

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Pediatric and Adolescent Patients with Haemoglobinopathies

Haploidentical αβ T Cell Depleted HSCT Represents A Curative Alternative To MSD In Patients With Transfusion Dependent Thalassemia

OS03-07
Oral presentation

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Study design	Retrospective analysis	**Aim**	Explore haplo-identical transplant in patients with TDT
Patients/Transplants	n=18	**Median age**	11 y (2 – 23 y) (TCD-haplo) 10 y (4 – 11 y) (MSD)
Disease	TDT		
Donor	TCD-haplo (n=11), MSD (n=7)		
Conditioning regimen	TTF: Treo 42 g/m^2, Flu 160 mg/m^2, TT 10 mg/kg		
Results*	MSD		T-Haplo
2 y OS	7/7 (100%)		11/11 (100%)
DFS	7/7 (100%)		10/11 (91%)
TRM	0/7 (0%)		0/11 (0%)
VOD	0		1
Conclusion	• Excellent outcome rates with 100% OS. • No TRM, very low morbidity, no rejections. • T-Haplo HSCT is a safe alternative for TDT patients with no MSD available. • Only one case of VOD in this high-risk patient population. • The earlier any HSCT is applied the better.		

*Presented during oral presentation

Abstract

Background
Hematopoietic stem cell transplantation (HSCT) is currently the established curative therapeutic option for Transfusion Dependent Thalassemia (TDT), as quality of life remains severely compromised despite optimal supportive care. With a limited availability of matched donors (MSD and MUD), haploidentical donor HSCT is increasingly explored.

Methods
11 TDT-patients received either a CD3+/CD19+ (n=3; all class II/III) or aß/CD19+ (n=8; 6 class II/III) T-haplo-HSCT (median age: 11 years; range: 2-23) and were compared with 7 TDT-patients (5 class II/III) receiving a bone marrow (BM) graft from a MSD (median age: 10 years; range: 4-11). Indication for HSCT was standard of care for patients with MSD, and transfusion-associated complications in T-haplo HSCT patients. All patients received an identical conditioning regimen consisting of treosulfan, thiotepa, fludarabine (FTT) and ATG-Grafalon, with the only difference in the timing of ATG (upfront in T-haplo-HSCT, prior to d0 in MSD-HSCT). Immunosuppression (IST) consisted of a combination of calcineurin inhibitors (mainly tacrolimus, and in two cases cyclosporine A) and mycophenolate mofetil.

Results
The overall survival and disease-free survival for MSD and T-haplo-HSCT was 100%/100% and 100%/92%, respectively (Table 1). The median follow-up was 21 months for MSD (range 8-50) and 28 months for T-haplo-HSCT (range 7-74). Neutrophil engraftment was achieved after a median of 31 days for MSD patients and 18 days for T-haplo-HSCT (median of 5.3 x108 TNC/kg (range: 3.28–7.88) and 18x106 CD3+/CD19+ or ab/CD19+depleted CD34+ cells/kg (range: 9.2–24.2)). One patient received two T-haplo transplantations, due to primary graft failure in case of a major AB0 incompatibility. Another patient is currently transfusion-dependent with a chimerism of 45.3%. Mixed chimerism was observed in 3/7 MSD-HSCT (median 92.2%; range 24.2–100%). In T-haplo-HSCT mixed chimerism was seen in 4/11 patients (median 100%; range: 45.3 -100%). Transfusion independence was achieved in all MSD patients, and in all but one T-haplo (graft failure). In MSD and in T-haplo-HSCT, IST was terminated after a median of 173 days and 226 days (range: 112-347), respectively. The incidence of transplant-related morbidity was low: no case of acute or chronic graft-versus-host-disease (a/cGvHD) was observed in the MSD population. In T-haplo-HSCT, 3 patients experienced a grade I aGvHD (skin) which resolved with prednisolone and in 2 cases with additional extracorporeal photopheresis. Only the oldest patient experienced a grade I chronic skin cGvHD, resolved by day +580. No severe infectious complications occurred, with a chimerism-triggered withdrawal of IST (approximately at 6 months post-HSCT). As expected, all MSD patients reached CD4 counts >50/µl on day +53 (median; range: 25-125), whereas T-haplo-HSCT patients reached CD4 counts >50/µl on day +110 (median; range: 33-168). The conditioning regimen was well tolerated with no high-grade transplant related toxicity.

Results	MSD	T-haplo SCT
Follow-up (months) Median (range)	21 (8 - 50)	28 (7 - 74)
Engraftment (day) Median (range)	31 (20-45)	18 (12-58)
Chimerism Median (range)	92.2% (24.2% - 100%)	100% (45.3% - 100%)
Transfusion independency Median (range); days	100 % 34 (9-469)	91% 85 (6-298)
Withdrawal IST (day) Median (day)	173 (107-227)	226 (112-347; 2 pts still under IST)
Immunreconstitution >50 CD4+/µl (day) Median (range)	53 (25-125)	110 (33-168)
Immunreconstitution >500 CD4+/µl (day) Median (range)	243 (180-363; with 2 pts not yet reached)	326 (210-589)
Immunreconstitution >100 CD19+/µl (day) Median (range)	62 (31-89)	47 (34-223)
Viral reactivation rates	100%	100%
Treatment/Outcome	• no antiviral treatment necessary (self-limiting transient reactivations) • 100% solved	• 33.3% antiviral drugs (foscarnet, (val-) ganciclovir, rituximab, cidofovir) • 8.3% virus-specific T-cells • 100% solved

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

Conclusions

These preliminary safety and efficacy data of T-haplo-HSCT are encouraging for a transplant indication without delay in TDT patients lacking a MD. Furthermore, treosulfan demonstrated to be an excellent alternative to busulfan, with no case of VOD/SOS in this high-risk patient population.

Hematopoietic Stem Cell Transplantation In Patients With Thalassemia Major: Retrospective Comparison Of Busulfan Treosulfan Conditioning Regimens

P055
Poster presentation

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Study design	Retrospective analysis	**Aim**	Safety, tolerability, and efficacy of a Treo-based regimen in young patients
Patients	107	**Median age at HSCT**	2067 d
Disease	TM		
Conditioning regimen	Bu/Cy/ATG-based (n=58 patients), TTF (n=49 patients)		
Results	• Neutrophils and platelets engrafted at a median of 16.42 ± 4.0 d (range 9 - 32 d) and 23.63 ± 7.40 d (range 12- 43 d), respectively. • VOD 41% vs. 6% • No statistically significant difference between the conditioning regimen groups in terms of thrombocyte engraftment time, GvHD, chimerism and overall survival rates (p>0.05). • Thalassemia-free survival rates of the Bu regimen group were found to be higher than the Treo group (p=0.043; p<0.05).		
Conclusion	• The two myeloablative conditioning regimens are safe and efficacious for thalassemia patients. • Introduction of new prophylaxis strategies and application of highly stringent criteria for HLA typing for donor selection are fundamental for the safety of HSCT in thalassemia.		

Abstract

Background

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative treatment for patients with thalassemia major (TM). The most common used conditioning regimens incorporate busulfan (Bu), cyclophosphamide (Cy), and antithymocyte globulin (ATG). But the toxicity of this regimen is high especially for the children with TM who are called as class 3 in Pesaro risk classification. Treosulfan-based conditioning regimens are safe and effective especially in these group of patients.

Methods

We started to treat thalassemia major with a treosulfan/thiotepa/fludarabine (treo/thio/flu)-based conditioning regimen since April 2018 to minimize regimen-related toxicity. Here, the results of this new treatment were compared with Bu/Cy/ATG based regimen that was used before at our center to assess the safety, tolerability and efficacy of a treosulfan-based regimen in young patients with thalassemia. From October 2014 to December 2021, 107 patients with thalassemia major who underwent HLA-matched allogeneic HSCT were enrolled in the study at Altınbaş University MedicalPark Hospital Pediatric Bone Marrow Transplantation Unit in Turkey.

Results

Mean age of stem cell transplantation was 2688,26±1786,75 days, median age 2067days. Bu/Cy/ATG-based regimen was used in 58, Treo/thio/Flu based regimen was used in 49 patients. The study group included 55 (%51.4) females, 52 (%48.6) males. The median CD 34 stem cell dose was 6,07x106/kg. Neutrophils and platelets engrafted at a median of 16,42±4,0 days (range, 9-32 days) and 23,63±7,40 days (range, 12-43 days), respectively. The median duration of follow-up was 504,35±379,93 days (range 17-2030 days). In busulfan group (n=58), 24 patients had veno oclusive disease (VOD), 35 with CMV reactivation, 7 with BK virus reactivation, 4 with convulsion, 12 with Acute graft versus host disease (AGVHD), 4 deaths in the first 100 days. On the other hand, in treosulfan group (n= 49) patients had 3 VOD, 30 CMV reactivation, 10 BK reactivation, 2 with convulsion, 13 with AGVHD and 2 deaths in the first 100 days. No pulmonary and cardiac system toxicities were observed. Although defibrotide was only used in busulfan group (86.2%) for VOD prophylaxis, the VOD incidence rate was higher (41.4%) than treosulfan group (6.1%) (p:0.001; p<0.05).The neutrophil engraftment time was longer in treosulfan group (p:0.038; p<0.05). There was no statistically significant difference between the conditioning regimen groups in terms of thrombocyte engraftment time, GVHD, chimerism and overall survival rates (p>0.05). However, the thalassemia-free survival rates of the Busulfan regimen group were found to be higher than the Treosulfan group (p:0.043; p<0.05).

Table I: Characteristics of Patients Undergoing HSCT with Bu-Based and Treo -Based Conditioning Regimens

		Busulfan (n=58)	Treosulfan (n=49)	
		n (%)	n (%)	p
Gender	Female	35 (60,3)	20 (40,8)	[1]0,044*
	Male	23 (39,7)	29 (59,2)	
Donor type	Match Family	46 (79,3)	24 (49)	[2]0,002*
	Match Unrelated	12 (20,7)	25 (51)	
Defibrotide Prophylaxis	No	8 (13,8)	49 (100)	[2]0,001*
	Yes	50 (86,2)	0 (0)	
VOD	No	34 (58,6)	46 (93,9)	[2]0,001*
	Yes	24 (41,4)	3 (6,1)	
GVHD	No	45 (77,6)	35 (71,4)	[3]0,749
	Acute	12 (20,7)	13 (26,5)	
	Chronic	1 (1,7)	1 (2)	
CMV	No	23 (39,7)	19 (38,8)	[2]1,000
	Yes	35 (60,3)	30 (61,2)	
BKV	No	51 (87,9)	39 (79,6)	[2]0,363
	Yes	7 (12,1)	10 (20,4)	
Convulsion	No	54 (93,1)	47 (95,9)	[4]0,685
	Yes	4 (6,9)	2 (4,1)	

[1]Chi square test [2]Continuity (Yates) correction [3]Fisher Freeman Halton Exact Test [4]Fisher's Exact Test *p<0.05, VOD: veno occlusive disease, GVHD: graft versus host disease, CMV cytomegalovirus , BKV BK virus

Conclusions

These two myeloablative conditioning regimens are safe and efficacious for thalassemia patients. Additionally, the introduction of new prophylaxis strategies and application of highly stringent criteria for HLA typing for donor selection are fundamental for the safety of HSCT in thalassemia.

Ten-Year Follow Up Study Of Children With Thalassaemia Major Post Transplantation Using Treosulfan, Thiotepa, Fludarabine Based Conditioning Regimen And Its Impact On Growth And Puberty

P514
Poster presentation

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Study design	Retrospective analysis	**Aim**	Impact of Treo-based conditioning on growth and puberty
Patients	202	**Age at HSCT**	36% (n=73) <5 y 45% (n=90) 5 - 10 y 19% (n=39) >10 y
Disease	TM		
Conditioning regimen	TTF (+ATG for MUD), 2 Gy TBI + ATG for haploHSCT		
Results	• 59% were males, 41% females. • MFD: n=110 (54%); haploidentical: n=62 (31%); MUD: n=30 (15%) • No major reduction in growth potential; however, Children in class 1 thalassemia are able to catch up on their growth but the class 2 and 3 patients failed to catch up growth after HSCT (p=0.010). • 54.2% of female pts attained spontaneous menarche (mean age at HSCT 8 y, current mean age 14.8 y). • 6.9% require growth hormone.		
Conclusion	• Treo does not have a negative impact on growth and puberty in children with thalassemia major. • Only 6.9% children required growth hormone supplementation and there was no impact on puberty in both boys and girls. • Reduced late side effects and intact survival justifies the use of Treo-based conditioning in all children undergoing HSCT for thalassemia major.		

Abstract

Background
We present a uniform cohort of children with thalassaemia major who underwent treosulfan conditioning based HSCT and its impact on growth and puberty.

Methods
Our study is a retrospective analysis on children who underwent allogeneic HSCT for transfusion dependent thalassaemia major between 2010 to 2020 with a minimum follow up period of two years. All children were classified as per Lucarelli Class 1, 2 and 3 based on the iron overload status and received conditioning chemotherapy with treosulfan, thiotepa and fludarabine with ATG for MUD And ATG and 2 Gy total body radiotherapy for haploidentical HSCT. Data collection focussed on the presence of graft versus host disease both acute and chronic, and the need for steroid use for over 4 weeks. We documented the height and weight and Tanner stage if applicable at the time of HSCT and the current height, weight and Tanner stage and the need for growth hormone replacement. The study has been approved by our hospital Ethics Committee.

Results
Of 202 children in our study 59% were males and 41% females and 110/202 (54%) had a matched family donor (MFD), 62/202 (31%) haploidentical and 30/202 (15%) matched unrelated donor (MUD). 73 (36%) were in <5 years of age at HSCT, 90 (45%) between 5 to 10 years and 39 (19%) over 10 years of age. The mean height SDS at HSCT was -0.574 and at current assessment the mean height SDS was -0.669 (p=0.391). There was no major reduction in growth potential. 29 (14.4%) were short at the time of HSCT (height SDS <-2) and at current assessment only 6 (20.7%) were still short and 23 (79.3%) had catch up growth and moved to height SDS >=-2. The mean height SDS during HSCT in Class1 thalassemia was -0.216, -0.478 in Class 2 and -0.898 in Class 3 respectively (p=0.026). The current height SDS in these classes are -0.115, -0.710 and -0.929 respectively, confirming that children in Class 1 are able to catch up on their growth but the Class 2 and 3 patients failed to catch up growth after HSCT (p=0.010). In children with acute GVHD there was no difference in contrast to a statistically significant difference in mean current height SDS in chronic GVHD group (-0.468 against -0.920, p=0.020).

In the children currently above 10 years group, 17 (43.6%) were in Tanner stage 5 at HSCT and of the 83 female children, 45 (54.2%) attained spontaneous menarche. Their mean age during HSCT was 8 years and their current mean age is 14.8 years. 14 (6.9%) children are on growth hormone GH.

Conclusions
Our study clearly demonstrates that treosulfan does not have a negative impact on growth and puberty in children with thalassaemia major. Only 6.9 % children required growth hormone supplementation and there was no impact on puberty in both boys and girls with menarche at a median age of 14.8 years Despite the higher cost of treosulfan the reduced late side effects justifies its use in all children undergoing HSCT for thalassaemia major.

Thiotepa, Treosulfan And Fluadarabne (TTF) Versus Thiotepa, Busulfan And Fludarabine (TBF) Conditioning For Matched Related Donor Peripheral Blood Stem Cell Transplant For Thalassemia Major

P564
Poster presentation

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Study design	Retrospective analysis	**Aim**	Head-to-head comparison between TTF and TBF
Patients	20	**Median age**	5.7 y (TBF) 5.1 y (TTF)
Disease	TM		
Conditioning regimen	TTF: Treo 42 g/m^2, Flu 160 mg/m^2, TT 10 mg/kg vs TBF: Bu 12.8 mg/kg, Flu 160 mg/m^2, TT 10 mg/kg		
Results	• Mean neutrophil engraftment was significantly different between two groups which can be attributed to administration of Peg-GCSF to all TTF patients. • No statistically significant difference in platelet engraftment, acute or chronic GvHD, VOD, Transplant Associated TMA, mucositis, need for narcotic analgesics, diarrhea, central nervous system complications, pulmonary complications, poor graft function, sepsis, chimerism on last follow up, viral reactivation, duration of hospital stay and readmissions post discharge between TBF and TTF groups. • No primary graft failure in either group. • OS 100% for TTF (med. f-up 5 mo), 90% for TBF (med. f-up 41 mo).		
Conclusion	• Both TBF and TTF conditioning regimens are safe and effective for children with thalassemia major undergoing MRD PB HSCT.		

Abstract

Background

Traditionally used busulfan (BU) and cyclophosphamide (Cy) based conditioning for Haemopoietic Stem Cell Transplantation for Thalassemia Major is associated with higher veno-occlusive diseases (VOD) and mortality. Thus, recently Cy free reduced toxicity regimens – Thiotepa, Treosulfan, Fludarabine (TTF) and Thiotepa, Busulfan, Fludarabine (TBF) have been used. Here, we discuss the head-to-head comparison between TTF and TBF conditioning in children with thalassemia major who underwent matched related donor (MRD) Peripheral blood stem cell transplant (PBSCT).

Methods

Medical records of all children who underwent MRD PBSCT for Thalassemia Major from January 2018 to October 2022 were retrospectively analyzed. Patients received either TTF or TBF conditioning along with Anti-Thymocyte Globulin (ATG) after an informed written consent. Total doses were-Fludarabine-160mg/m^2, Thiotepa-10mg/kg and Rabbit ATG(Thymoglobulin)-4.5mg/kg. Dose of Busulfan was 3.2mg/kg/day for 4 days and Treosulfan-14g/m^2/day for 3 days. Graft vs. host disease (GVHD) prophylaxis was with cyclosporine and methotrexate (Day+1,3,6 and 11). From January 2022 all children received a single dose of Peg-GCSF on day+6. The two groups were analyzed for differences in various transplant related outcomes. Statistical analysis was conducted with IBM-SPSS version 21.0. $p < 0.05$ was taken to be significant.

Results

Our cohort comprised of 20 children, 10 in each group. Median age- 5.7 years (TBF) and 5.1 years (TTF). Male: Female was 1:1 in both groups. TBF group had 80%, 0% and 20% in Pesaro Class I, II and III respectively. TTF group had 80% class-I, 20% class-II and none class-III patients. Median pre-transplant ferritin was 1370 ng/ml (TBF) and 1520 ng/ml (TTF). Basic characteristics were similar in both groups without statistically significant differences. However, mean neutrophil engraftment was significantly different between two groups which can be attributed to administration of Peg-GCSF to all TTF patients. There was no statistically significant difference in platelet engraftment, acute or chronic GVHD, VOD, Transplant Associated Thrombotic Microangiopathy, mucositis, need for narcotic analgesics, diarrhea, central nervous system complications, pulmonary complications, poor graft function, sepsis, chimerism on last follow up, viral re-activation, duration of hospital stay and re-admissions post discharge between TBF and TTF groups (Table1). Only one patient (Class-III) died in TBF group with sepsis on day+140. None died in TTF. No primary graft failure in either group. Mixed chimerism at last follow up was seen in none and two patients (20%) in TBF and TTF respectively ($p=0.330$). Viral reactivation was seen in five patients in TBF and three patients in TTF ($p=0.646$). Overall survival (OS) was 90% for TBF group at a median follow up of 41 months. OS was 100% for TTF group at follow up of 5 months. The duration of follow up for TTF groups is short as it is recently adopted conditioning regimen in our unit.

Table1: Comparison of Transplant Related Outcomes between the 2 groups.

Parameters	TBF	TTF	P value
Neutrophil Engraftment (days)	14.80±3.05	11.70±0.95	0.007
Platelet Engraftment (days)	15.22±2.22	16.60±7.59	0.607
aGvHD	3(30%)	2(20%)	1.00
cGvHD	1(10%)	0(0%)	1.00
Veno-occlusive disease	3(30%)	0(0%)	0.211
HLH	2(20%)	0(0%)	0.474
Thrombotic micro-angiopathy	1(10%)	1(10%)	1.00
Mucositis	6(60%)	1(10%)	0.057
Need for narcotics for analgesia	5(50%)	1(10%)	0.141
Diarrhea	3(30%)	4(40%)	1.00
CNS Complication	1(10%)	1(10%)	1.00
Pulmonary Complication	1(10%)	0(0%)	1.00
Poor Graft Function	2(20%)	0(0%)	0.474
Sepsis	4(40%)	3(30%)	1.00
Mixed Chimerism at last follow-up	0(0%)	2(20%)	0.330
Viral Reactivation	5(50%)	3(30%)	0.646

Conclusions

Both TBF and TTF conditioning regimens are safe and effective for children with thalassemia major undergoing MRD PBSCT.

Would Monitorizing Treosulfan Levels In Patients Transplanted For Transfusion Dependent Thalassemia Be Beneficial In Terms Of Chimerizm? A Single Center Experience

P573
Poster presentation

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Study design	Retrospective single center analysis	**Aim**	Categorize Treo AUC values, effects of Treo-levels on HSCT *
Parameters assessed	Treo levels at 0, 1, 2, 4 hours on the first day of drug infusion		
Patients	30*	**Age**	4 y (12 mo - 16 y)*
Disease	TDT		
Conditioning regimen	TTF: Treo 36 g/m^2 (<1 y, 6.6%) or 42 g/m^2 (> 1 y, 93.4%), Flu 150 mg/m^2, TT 10 mg/kg		

Results	Low AUC level (<850 (mg*h/L))	medium AUC level (850 - 1100 (mg*h/L))	high AUC level (>1100(mg*h/L))
Percentage of patients	53.6%	21.4%	25.0%
Grade 3 - 4 mucositis	1	0	3
SOS	0	0	0

- TRM was 8.6% and no significant difference was detected between AUC groups.
- 15 patients for low AUC group, 6 patients for medium and 7 patients for high AUC levels were compared for the effect of Treo AUC levels on chimerism. There was no statistical difference between mixed chimerism and AUC levels ($p<0.357$).

Conclusion

- Although there are publications that state no correlation is needed for Treo, expanding patient group and repeating study for follow up in terms of posttransplant toxicity and long-term consequences will be beneficial.

*Based on poster at conference.

Abstract

Background
Allogeneic stem cell transplantation (SCT) is the only curative option for thalassemia major patients. Experience of allogeneic SCT in transfusion dependent thalassemia patients (TDT) using treosulfan based preparative regimen, a retrospective analysis of 23 patients' data, was presented in our study.

Methods
All TDT patients with HLA identical related (%52)/unrelated (%48) donor who underwent an allogeneic SCT at our center between September 2018- April 2022 were included. Conditioning regimen was treosulfan; 12 g/m^2/day under age 1 and 14 g/m^2/day above age 1, thiotepa 10 mg/kg/day, fludarabine 30 mg/m^2 /day -5 days (TreoFluT). Treosulfan levels measured for every patient at 0,1,2,4. hours of infusion and area under curve (AUC) was calculated in mg*h/L.

Results
Treosulfan AUC levels (mg*h/L) was obtained for every patient and divided into three major groups as low (<850 (mg*h/L)), medium (850-1100(mg*h/L)), and high (>1100(mg*h/L)). Fifteen patients for low AUC group, 2 patients for medium and 6 patients for high AUC levels were compared for the effect of treosulfan AUC levels on transplant related toxicity as mucositis and sinusoidal obstruction syndrome (SOS) or transplant related mortality (TRM) along with mixed chimerism. Grade 3-4 mucositis was seen only one patient for low AUC group while 3(%50) patients had in high AUC group. None of the patients experienced SOS for each group. Transplant related mortality was %8.6 and no significant difference was detected between AUC groups. Mixed chimerism was detected for 7/23 patients (%30) and 6 patients (%25) belong to low AUC group although it has no difference statistically (p<0,357).

Conclusions
There are few studies which correlates treosulfan AUC level with posttransplant consequences in pediatric age group. Although there are publications state that no correlation is needed for treosulfan, expanding patient group and repeating study for follow up in terms of posttransplant toxicity and long term consequences will be beneficial.

Effect Of GvHD Prophylaxis And Serotherapy In 58 Pediatric Hemoglobinopathy Patients Conditioned With Treosulphan, Fludarabine And Thiotepa

P643
Poster presentation

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Study design	Retrospective single center analysis	**Aim**	Impact of evolving immunosuppressive strategies
Parameters assessed	OS, DFS, graft rejection, autologous regeneration, donor chimerism, aGvHD, cGvHD, engraftment of leucocytes and platelets		
Patients	58 (61 HSCTs)	**Median age (range)**	11.3 y (1.8 – 18.1 y)
Disease	Hemoglobinopathies: SCD (n=27) or TDT (n=31)		
Conditioning regimen	TTF		

Results*		**N**	**%**
OS		57	98.3
DFS		56	96.6
Graft rejection		1	1.64
Autologous regeneration		2	3.28
Donor chimerism	CC or ≥95%	47	77.05
	mixed chimerism	14	22.95
aGvHD	no / grade II-IV	53 / 8	86.89 / 13.11
cGvHD	no / grade II-IV	43 / 6	87.76 / 12.24
Last administration of immunosuppressive drug	no / grade II-IV	d+72 post HSCT	12 – 267 d
Leukocyte engraftment (>1000/µl)	no / grade II-IV	d+14 post HSCT	9 – 39 d
Platelet engraftment (>20,000 /µl)	no / grade II-IV	d+72 post HSCT	9 – 39 d

- Of all patients with donor chimerism below 90%, 9 were in the Thymoglobulin group and 4 were in the ATG-Grafalon® group (26.5 vs 14.8%).*
- EBV reactivation occurred more frequently in the thymoglobulin group as compared with the Grafalon® group (59% vs. 11%).

Conclusion

- Mixed donor chimerism was frequently observed in MSD transplants, whereas aGvHD (II-IV°) occurred more often in alternative donor transplants (MUD/MMUD).
- Severe steroid-refractory gut aGvHD was the dominating morbidity in this cohort. All but 1 surviving patient are GvHD-free today. Interestingly, ATG-Grafalon® + PTCy almost completely prevented severe aGvHD.
- Thymoglobulin-treated pts showed more mixed chimerism (<90%) and delayed immune reconstitution.
- ATG-Grafalon® in combination with short and low-dosed CsA/MMF has evolved as our favorite concept.

*Based on poster at conference.

Abstract

Background
Serotherapy and immunosuppression play an important role in allogeneic HSCT for hemoglobinopathies. We focused on a cohort with invariant conditioning as background to identify effects of evolving immunosuppressive strategies.

Methods
We collected data from 61 consecutive transplantations in 58 pediatric patients with hemoglobinopathies between 2011 and 2022 at our center.

Results
31 children had sickle cell disease and 27 β-thalassaemia major. All patients were uniformly conditioned with treosulphan, fludarabine and thiotepa (TFT). With a median follow-up of 3.5 years, overall survival was 98.3% and disease-fee survival 96.6%. Engraftment of leukocytes was reached at day 14.5 and of platelets on day 17 on average.

39 patients received a graft from an MSD, all of which survived and all but one are disease-free. While the incidence of GvHD was low in this cohort (no grade III-IV, 8 grade I-II), 7 patients had mixed donor chimerism below 80% and two of them had to undergo re-transplantation from the same sibling to achieve complete donor chimerism. 29 of 39 patients displayed incomplete donor chimerism at some point after 10 days of engraftment, but showed increasing donor chimerism after reduction or cessation of immunosuppression. Last administration of an immunosuppressive drug posttransplant was as early as day +72 (median; range 12 – 267 days posttransplant). In 10 patients donor chimerism was 90% or less. 9 of these 10 patients had received thymoglobulin, while CsA/MTX and CsA/MMF were equally distributed. Reactivation of CMV, HSV, HHV6 and BKV was equally distributed among the two serotherapy groups. However, EBV reactivation occurred more frequently in the thymoglobulin group as compared with the Grafalon® group (59% vs. 11%).

19 patients were transplanted from alternative donors, i. e. MUD (n=9), 9/10 MMUD (n=9) and 9/10 MMFD (n=1). One SCD patient transplanted from a 9/10 MMUD rejected, was re-transplanted T-cell depleted from a haploidentical parent, but died from viral infections. All surviving patients except for one achieved complete donor chimerism. However, 11 patients developed aGvHD, which progressed to severe gut GvHD in seven cases. At last follow-up, all of these patients are GvHD- and disease-free. Interestingly, only one of the seven patients who had received Grafalon® as serotherapy and ptCy encountered transient GvHD, whereas all but one patient with severe aGvHD had received CsA/MTX, CsA/MMF or CsA/MMF/MTX without ptCy. In the patient cohort with severe GvHD more patients had received thymoglobulin than Grafalon®.

Mixed donor chimerism was a frequent observation in MSD transplants, while aGvHD grade III-IV was prevalent in unrelated donor transplants. In MSD transplants with declining chimerism, thymoglobulin was applied as serotherapy more often than Grafalon®. Dominating morbidity was severe steroid-refractory aGvHD of the gut in 7/20 unrelated donor transplants. However, in MUD as well as in 9/10 MMUD, Grafalon® and ptCy almost completely eliminated the occurrence of severe aGvHD.

Conclusions
In TFT-conditioned MSD transplants for hemoglobinopathies, Grafalon® in combination with short and low-dosed CsA/MMF has evolved as our favourite concept. For UD transplants with TFT-conditioning, immune suppression with Grafalon® and ptCy/CsA achieved most promising outcome in our hands.

Haploidentical Related Donor Peripheral Blood Stem Cell Transplant For Thalassemia Major With Post Translant Cyclophosphamide And Thiotepa, Fluadarabne And Treosulfan Or Busulfan Conditioning

P749
Poster presentation

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Study design	Retrospective analysis	**Aim**	Outcome of haploidentical PB HSCT with PTCy in children with TM
Parameters assessed	Engraftment, chimerism, OS		
Patients	16	**Age**	2 y (1 - 14 y)
Population	Thalassemia Major		
Conditioning regimen	TTF: Treo 42 g/m^2, Flu 160 mg/m^2, TT 10 mg/kg (n=9) or TBF: Bu 12.8 mg/kg, Flu 160 mg/m^2, TT 10 mg/kg (n=7)		
Results	• Engraftment: Neutrophils median 12 d (range 11 – 20 d), platelets median 14 d (range 12 - 21). • GvHD: acute n=5 (grade III-IV: n= 2), chronic n=3 (extensive n=1). • Virus reactivation: CMV 50%, BK 25% • No VOD • n=12 full donor chimerism, n=1 stable mixed chimerism • OS 88% (med. f-up 180 d; 86% for TBF, 89% for TTF); TFS 81%. • OS for TBF regimen was 86% and for TTF was 89%.		
Conclusion	• Haploidentical related donor PBSCT with myeloablative conditioning (TBF or TTF) with PTCy for children with TM is highly effective and safe		

Abstract

Background
Reduced toxicity regimens – Thiotepa, Treosulfan, Fludarabine (TTF) and Thiotepa, Busulfan, Fludarabine (TBF) have been used for matched donor hematopoietic stem cell transplant (HSCT) for Thalassemia major. However, data regarding using these conditioning regimen in haploidentical related donor HSCT with post-transplant cyclophosphamide (PTCy) in thalassemia is lacking. Here, we report the outcomes of the same in children with thalassemia major.

Methods
Medical records of all children who underwent haploidentical related donor PBSCT with PTCy for Thalassemia Major from January 2017 to October 2022 were retrospectively analyzed. Patients received either TTF or TBF conditioning along with Anti-Thymocyte Globulin (ATG) after an informed written consent. Total doses were-Fludarabine-160mg/m^2, Thiotepa-10mg/kg and Rabbit ATG(Thymoglobulin)- 4.5mg/kg. Dose of Busulfan was 3.2mg/kg/day for 4 days and Treosulfan-14g/m^2/day for 3 days. Graft vs. host disease (GVHD) prophylaxis was with PTCy 50 mg/kg on day+3 &4 and Cyclosporine and mycophenolate mofetil. Children with donor specific antibody were desensitized as per John Hopkins protocol. Pre transplant immune suppression (PTIS) was given to all children with anti-HLA antibodies.

Results
Our cohort comprised of 16 children, 9 received TTF regimen and 7 received TBF regimen. Median age was 2 years (range 1-14 years). Male: Female was 2:1. Donors were parents in all cases (mother: father ratio was 1:1).PTIS was administered to 7 children (43%). Desensitization was done for 2 children with donor specific antibodies. All children received peripheral blood stem cell as graft with median CD34 cell dose of 8 million/kg (range 4-25 million/kg). One child died before engraftment on day+10 due to pulmonary hemorrhage. Another child had primary rejection followed by autologous recovery. Remaining 14 engrafted. Neutrophil engraftment was seen on median of 12 days (range 11-20) and platelet engraftment was seen on median 14 days (range-12-21). Acute GVHD was seen in 5 children (grade III-IV in 2) and chronic GVHD was seen in 3 children (extensive-1). CMV reactivation was seen in 50% children and BK virus reactivation was seen in 25% children. No child developed veno-occlusive disease. One child died on day+68 due to steroid refractory acute GVHD with massive gastrointestinal bleeding. Overall, 12 children are fully donor and one child has stable mixed chimerism. Overall, 14 children (88%) are alive at median follow up of 180 days. Thalassemia free survival of this cohort is 81%. Overall survival for TBF regimen was 86% and for TTF was 89%.

Conclusions
Haploidentical related donor PBSCT with myeloablative conditioning (TBF or TTF) with PTCy for children with Thalassemia major is highly effective and safe.

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Pediatric and Adolescent Patients with Various Non-Malignant Disorders

Outcome Of Fludarabine And Treosulfan Conditioning For Haematopoietic Stem Cell Transplantation In 415 Children With Non-SCID IEI: A Multicentre Retrospective Cohort Analysis

Paed4-04
Oral presentation

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Study design	Retrospective cohort analyses	**Aim**	Transplant outcomes in children with Non-SCID IEI receiving Flu and Treo
Primary endpoints	OS, EFS	**Secondary endpoints**	a/cGvHD. toxicities
Patients	415	**Median age (range)**	3.2 y (0.2 - 19.0 y)
Disease	IEI: CGD (n=62), HLH (n=51), WAS (n=36), MHC class II deficiency (n=33), CID (n=18), CD40L deficiency (n=17), autoimmune enteropathy (n=17), congenital neutropenia (n=13), DOCK8 deficiency (n=12), LAD (n=11), APDS (n=9), JIA (n=9), IPEX (n=9), STAT3 GOF (n=8), others (n=110)		
Conditioning regimen	FT (n=274), TTF (n=141); Treo dosage according to BSA		
Results*			
Graft failure	5% (of which 29% prim./sec. aplasia, 71% sec. autologous reconstitution)		
5 y OS	85%; additional TT and Treo dose not associated with OS		
5 y EFS	80%; PBSC and Treo 36 g/m² independently associated with improved EFS in pat <0.5 m² BSA		
5 y Alive-and-Engrafted	74%		
1 y TRM	7%		
aGvHD d+90	22% (grade II-IV), 5% (grade III-IV)		
1 y cGvHD	8%		
VOD	1.5%		
Conclusion	• Treo-based conditioning is associated with low TRM and VOD rates. •Optimal dosing needs further PK study in children with non-SCID IEI.		

*Numbers differing from abstract based on presentation at conference

Abstract

Background
Treosulfan has been increasingly used in children with inborn errors of immunity (IEI). This multicentre study compared transplant outcomes in 415 chilldren with non-SCID IEI who received fludarabine-treosulfan for first haematopoietic stem cell transplantation (HSCT) between 2006-2021 at 6 transplant centres in the UK.

Methods
Primary endpoints were overall survival (OS), event-free survival (EFS; survival without graft failure and second procedures). Secondary endpoints were grade II-IV aGvHD, cGvHD and toxicities. Subgroup differences in OS and EFS were evaluated by log-rank test. Competing risks methods were used for the cumulative incidence of aGvHD, cGvHD and VOD with death as the competing event, subgroup differences were evaluated by Gray's test.

Results
Median age at transplant was 3.2 years (range 0.2-19.0 years). Diagnoses were CGD (n=62), HLH (n=51), WAS (n=36), MHC class II deficiency (n=33), CID (n=18), CD40L deficiency (n=17), autoimmune enteropathy (n=17), congenital neutropenia (n=13), DOCK8 deficiency (n=12), LAD (n=11), APDS (n=9), JIA (n=9), IPEX (n=9), STAT3 GOF (n=8) and others (n=110). Donors were MFD (n=73, 18%), MUD (n=211, 37%), MMFD/MMUD (n=62, 15%) and haploidentical donor (HID, n=69, 17%). Stem cell sources were marrow (n=96, 23%), unmanipulated PBSC (n=220, 20%), T cell depleted PBSC (n=72, 17%; 64 TCRab/CD19 depletion; 2 CD3/CD19 depletion; 6 CD34 selection) and cord blood (CB) (n=27, 32%). 273 (66%) received treosulfan–fludarabine and 141 (34%) received fludarabine-treosulfan-thiotepa. Treosulfan dose was 30g/m^2 in 27 (7%), 36g/m^2 in 99 (24%) and 42g/m^2 in 289 (n=70%). Alemtuzumab was used in 302 (73%), ATG in 74 (18%) and 39 (9%) received no serotherapy. GvHD prophylaxis were CSA+MMF (n=323, 76%), CSA (n=53, 13%), none (n=32, 7%) and others (n=6, 1.3%).

Median duration of follow-up was 3.6 years (range, 0.09 to 13.2 years). 3-year OS and EFS for the entire cohort was 86% (95% CI, 82-89%) and 82% (77-85%) respectively (Fig-a). OS was inferior in cord blood recipients 70% (48-83%) compared to marrow (89%, 78-93%), PBSC (90%, 84-93%) and TCD PBSC (79%, 48-83%) (p=0.03). Age at transplant (p=0.89), donor (p=0.11), add-on thiotepa (p=0.31), Treosulfan dose (p=0.14) and serotherapy (p=0.09) were not associated with OS. TRM at 1 year was 7% (5-10%). EFS was significantly lower after Treo 30g/m^2 (63%, 40-79%) compared to Treo 36g/m^2 (83%, 72-89%) and Treo 42g/m^2 (82%, 78-87%) in the entire cohort (p=0.03, fig b), similar observation was seen in patients aged >1 years of age (p<0.001).

Day-90 cumulative incidence (CI) of grade II-IV and grade III-IV aGvHD was 22% (18-27%) and 5% (3-8%) respectively (fig-c). CI of cGvHD at 1 year was 8% (5-12%). CI of VOD was 1.5% (1-3%) for entire cohort.

Table 1: Treosulfan dose according to age and BSA

Treosulfan dose	Age < 1 (n=81)	Age >1	Age >1	Age >1
	BSA <0.5 (n=81)	BSA <0.5 (n=58)	BSA >0.5 to <1.0	BSA >1.0 (n=97)
30g/m^2	20	7	0	0
36g/m^2	46	10	43	0
42g/m^2	15	41	136	97

Conclusions
Treosulfan-based conditioning is associated with low TRM and VOD rates, but optimal dosing needs further PK study in children with non-SCID IEI.

Effect Of Busulfan And Treosulfan On Gonadal Function After Allogeneic Stem Cell Transplantation In Children And Adolescents With Nonmalignant Diseases Is Not Exposure-Dependent

P518
Poster presentation

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Study design	Retrospective single-center cohort study	**Aim**	Evaluate influence of Bu- and Treo- exposure on gonadal function
Patients	88	**Age**	Children ≤18 y
Parameters assessed	FSH, LH, testosterone, estradiol		
Disease	Nonmalignant diseases		
Conditioning regimen	Treo- (n=32) or Bu-based (n=56)		
Reference range gonadotropins	Gonadal dysfunction was defined as above reference range FSH ≥ 21.5 U/L and/or LH ≥ 60 U/L for females and FSH ≥ 12.5 U/L and/or LH ≥ 9.0 U/L for men.		
Results*	• Gonadal dysfunction: 63% (n=35) in the Bu-cohort and 28% (n=9) in the Treo cohort. • Lower Bu exposure (<70 mg*h/L) was not associated with a reduced risk of gonadal dysfunction (OR 0.92, 95% CI 0.25 - 3.49, p=0.90). • Lower Treo exposure (AUC <1750 mg*h/L) was not associated with a reduced risk of gonadal dysfunction (OR 1.6, 95%CI 0.16 - 16.36, p=0.71).		
Conclusion	• Gonadal dysfunction occurred at a much lower frequency in the Treo group. • No correlation was found between Treo exposure and gonadal dysfunction, but numbers in the study were limited. • Data does not support the premise that reduced intensity Bu-based conditioning lowers the risk for gonadal toxicity. • It is unlikely that TDM-based reduced Treo exposure will further reduce the risk for gonadal dysfunction.		

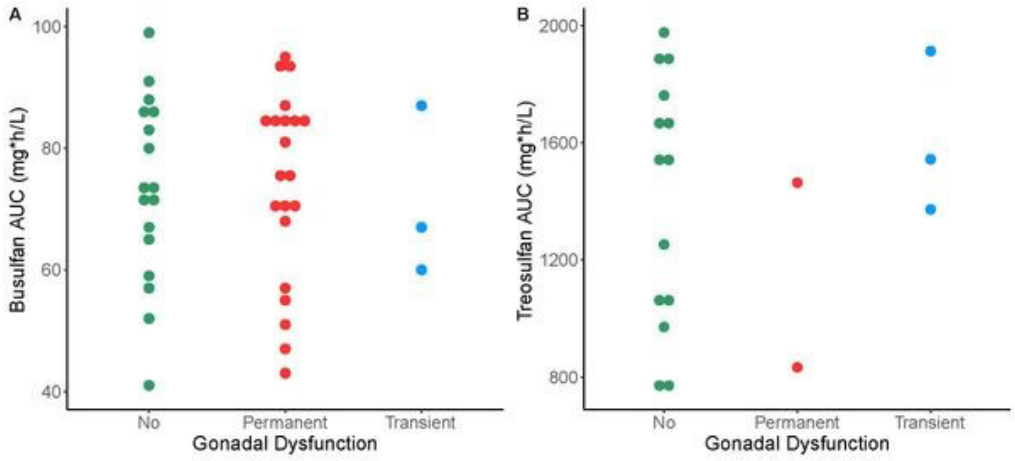
*Based on poster at conference.

Abstract

Background
With an increasing number of young patients surviving into adulthood after hematopoietic stem cell transplantation (HSCT), gonadal dysfunction becomes an important late effect with significant impact on quality of life. To date, it is unknown if drug exposure is of influence on the prevalence of endocrine complications.

Methods
In this retrospective single-center study, we evaluated the exposure of busulfan (BU) and treosulfan (TREO) in relation to gonadal function in pediatric patients transplanted for a nonmalignant disease between 1997 and 2018. All patients underwent a clinical and laboratory endocrine evaluation prior to HSCT. At annual follow-up visits after HSCT, pubertal stage was evaluated and laboratory investigations including FSH, LH, testosterone and estradiol, were performed. Gonadal dysfunction was defined as gonadotropins above the reference range, i.e. FSH ≥ 21.5 U/L and/or LH ≥ 60 U/L for females and FSH ≥ 12.5 U/L and/or LH ≥ 9.0 U/L for men. If elevated gonadotropins had normalized at subsequent visits gonadal dysfunction was classified as transient; if they remained elevated at last visit it was classified as permanent. BU and TREO exposure was divided in 2 exposure groups; low (< 70 mg*h/L for BU and < 1750 mg*h/L for TREO) and high (≥ 70 mg*h/L for BU and ≥ 1750 mg*h/L for TREO).

Results
A total of 157 patients were included, 90 were conditioned with BU and 67 with TREO. Of the 90 patients in the BU cohort, 56 patients were eligible for analysis; 27 patients were still prepubertal and data of 7 patients were incomplete or were excluded from the analysis because of gonadal dysfunction prior to HSCT. Of the 67 patients in the TREO cohort, 32 patients were eligible for analysis; 34 patients were still prepubertal and data of 1 patient was incomplete. In the BU cohort gonadal dysfunction occurred in 35 (63%) patients. Lower BU exposure (<70 mg*h/L) was not associated with a reduced risk of gonadal dysfunction (OR 0.92 95% CI 0.25-3.49, p=0.90). In the TREO cohort gonadal insufficiency occurred in 9 patients (28%). Lower TREO exposure (AUC <1750 mg*h/L on day 1) was not associated with a reduced risk of gonadal dysfunction (OR 1.6 95%CI 0.16-36.6, p=0.71) (Figure 1).



Conclusions
Our data do not support the premise that reduced intensity BU-based conditioning lowers the risk for gonadal toxicity and it is unlikely that TDM-based reduced treosulfan exposure will further reduce the risk for gonadal dysfunction.

Chimerism Analysis Post-HSCT With A Treosulfan-Based Conditioning Regimen For Pediatric Nonmalignant Diseases

P543
Poster presentation

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Study design	Retrospective single-center analysis	**Aim**	Impact of mixed chimerism post-HSCT
Patients/Transplants	92	**Mean age**	4.14 y (pts with FDC) 1.41 y (pts with MC)
Disease	Non-malignant diseases		
Conditioning regimen	Treo-based		
Results*			
FDC	70.7% (n=65)		
MC	29.3% (n=27, of which 3 with ensuing graft failure)		
OS	88.9% (MC)	90.8% (FDC)	p=0.882
aGvHD	14.8% (MC)	41.3% (FDC)	p=0.016
cGvHD	4.2% (MC)	15.6% (FDC)	
Conclusion	• Stable MC is a common condition in post-HSCT pediatric patients with non-malignant diseases treated with Treo-based conditioning. • aGvHD rate was significantly lower in the MC group. • Younger age was associated with developing MC.		

*Based on poster at conference

Abstract

Background

Allogeneic Hematopoietic stem cell transplantation (HSCT) offers cures for a wide variety of pediatric nonmalignant diseases by providing healthy stem cells, which may produce the missing enzymes or replace malfunctioning cells. Unlike HSCT for malignant diseases, in transplants for nonmalignant diseases, full-donor chimerism (FD) is not necessarily required and a state of stable mixed donor-recipient chimerism (MC) may suffice for a cure. The clinical significance of MC and the factors affecting the evolvement of this condition are poorly understood. In recent years, the use of treosulfan-based conditioning regimens for HSCT in nonmalignant diseases became popular due to the myeloablative quality and low toxicity profile of these regimens. Rates of MC with treosulfan-based regiments are relatively high. In this study, we aimed to shed light on the phenomenon of MC by analyzing clinical data and post-HSCT chimerism results of pediatric patients who received a treosulfan-based conditioning regimen in our center.

Methods

In this retrospective study, we collected and analyzed clinical and transplant data from medical charts of pediatric patients who underwent HSCT for nonmalignant diseases with a treosulfan-based conditioning regimen at Hadassah Medical Center. The collected clinical data included patient demographics, primary disease, post-HSCT clinical course, and outcomes. Transplant data included donor and graft parameters, time to engraftment, and chimerism at several time points post-HSCT.

Results

Out of the 92 patients who were included in the study, 27 (29.3%) developed MC, and 65 (70.7%) achieved full-donor chimerism. Survival rates were similar between the two groups (88.9% vs 90.8% overall survival in the MC and FD groups respectively, p=0.882). Acute GvHD rate was significantly lower in the MC group (14.8% vs 41.3% GvHD rate in the MC and FD groups respectively, p=0.016). Graft cellularity in the MC group was higher than in the FD group (mean TNC 5.3x108 vs 4.1x108 in the MC and FD groups respectively, p=0.047). No correlation was found between engraftment time and the development of mixed chimerism. Patient age at transplant was significantly lower in the MC group (mean age 1.41 years vs 4.14 years in the MC and FD groups respectively, p<0.001). Looking at primary disease, patients with SCID developed significantly more MC (9 out of 18 SCID patients, 50%) than patients with other diseases (p=0.033). Other factors associated with donor match such as family vs unrelated donors, degree of HLA match, blood type, donor and recipient pre-HSCT CMV status, were not found to be correlated to the development of MC in our cohort.

Conclusions

Stable MC is a common condition in post-HSCT pediatric nonmalignant patients treated with a treosulfan-based conditioning regimen. In our cohort, acute GvHD rate was significantly lower in the MC group, suggesting that a state of MC may pose as an advantage in nonmalignant diseases where FD chimerism is not mandatory. Younger age was associated with developing MC, possibly due to differences in chemotherapy bioavailability and metabolism in younger patients. Larger studies are required to better understand the factors associated with the development of MC and its possible advantages.

Treosulfan Based Conditioning In Pediatric Patients With Non-Malignant Haematological Indications For Transplant Is Associated With Very Low Treatment Related Mortality And High Overall Survival

P548
Poster presentation

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Study design	Retrospective multicenter analysis	**Aim**	Transplant outcomes in children with non-malignant disorders after Treo-based conditioning
Primary endpoints*	OS, EFS	**Secondary endpoints***	a/cGvHD, toxicities
Patients	96	**Median age (range)***	6.0 y (0.14 – 18.7 y)
Disease*	Thalassemia major (n=32), SCD (n=22), BMF (n=32), OP (n=5), others (n=5)		
Conditioning regimen*	TTF (n=86), other Treo-based (n=10)		
Results 4 y OS 4 y EFS deaths aGvHD d+90 cGvHD VOD	 95% 87% n=5 1% (grade II-IV) 6% 2%		
Conclusion	• Encouraging results with high OS and very low TRM and low graft failure. • This real-world data suggests a superiority over historical Bu conditioned cohorts. • With later follow-up, understanding of late effects, including on fertility and development will be improved.		

*Based on poster at conference

Abstract

Background

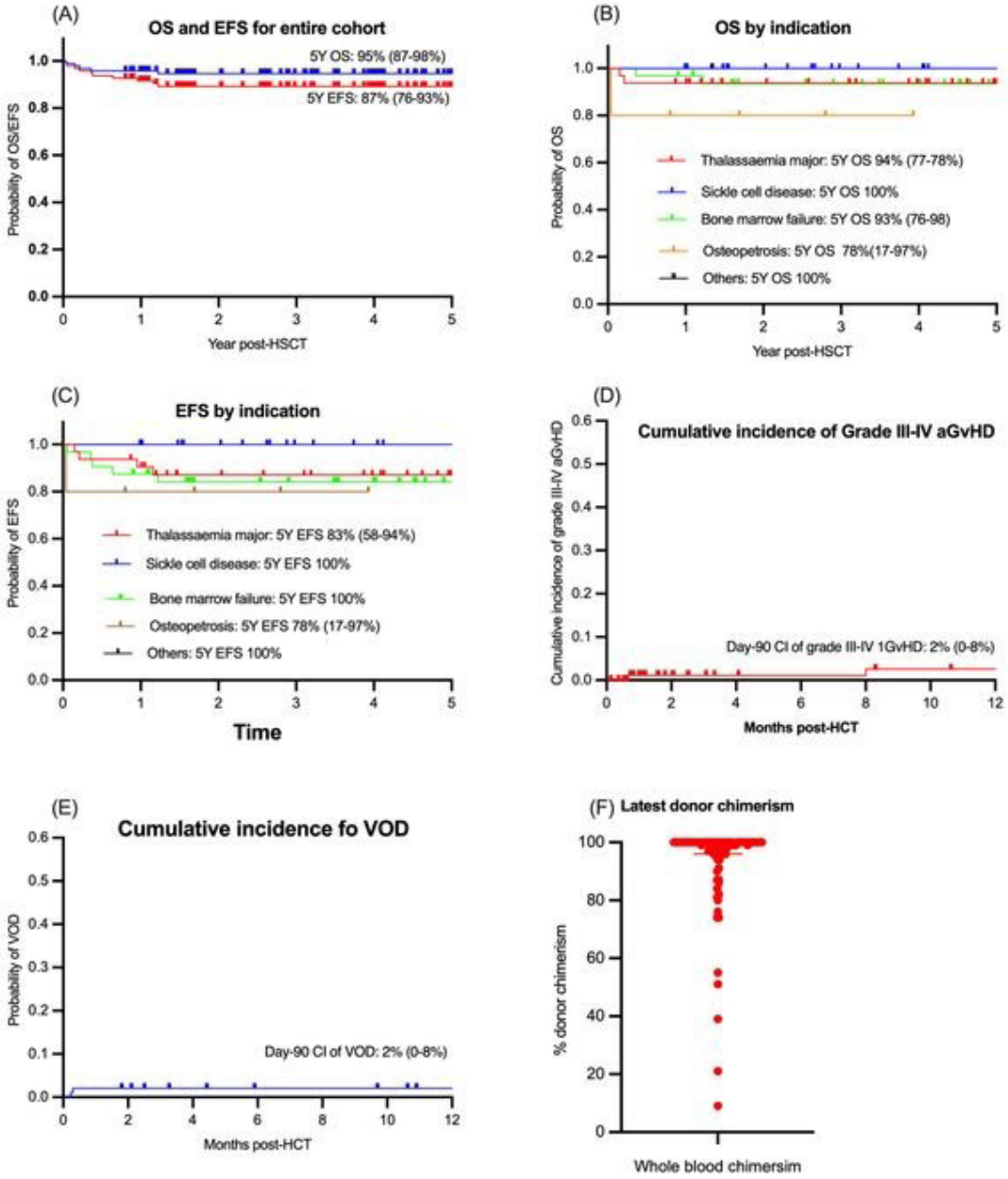
Treosulfan (L-treitol-1,4-bis-methanesulfonate) is a myeloablative alkylating agent with a comparatively favorable toxicity profile and more predictable pharmacokinetics than busulfan, which historically formed the backbone of many conditioning regimens. It is increasingly used in pediatric haematopoietic stem cell transplantation (HSCT) although there remains a paucity of data regarding toxicity and outcomes according to disease-specific pediatric cohorts.

Methods

A retrospective multi-center analysis was performed for consecutive pediatric patients who underwent a treosulfan conditioned HSCT in 9 BSBMTCT centers in the UK (Bristol; Glasgow; Great Ormond Street; Leeds; Manchester; Newcastle; Sheffield; Royal Marsden Hospital and University College, London) for non-malignant haematological indications between 2015 and 2021 inclusive, to determine the incidence of key treatment related toxicities, as well as treatment related mortality (TRM) and overall survival (OS).

Results

96 patients met the criteria, with haemoglobinopathy being the most common indication: 32 (33%) had thalassaemia major; 22 (30%) had sickle cell disease; followed by bone marrow failure in 32 (33%). The majority, 57 (60%), had a matched family donor, the source was bone marrow in 70 (93%) and the most common combination was fludarabine/ treosulfan/thiotepa in 87(90%). The OS was 95% with a median follow up of was 4 years, and EFS was similarly high at 87%. There were no significant predictors on univariate analysis. The 5 deaths were due to: respiratory failure (n=2); thrombotic microangiopathy with multi-organ failure (MOF; n=1); sepsis with MOF (n=1); and cerebral fungal infection associated with GVHD (n=1). Only 1% had Grade II-IV GVHD, and 6% chronic GVHD. VOD occurred in 2 (2%). Five patients (5%) had second procedures: 3 had an unconditioned stem cell boost; 1 had donor lymphocyte infusions and 1 patient with thalassaemia had a second transplant for primary aplasia. They are alive and well.



Conclusions

These results for treosulfan based conditioning are very encouraging, with high overall survival and very low treatment related mortality and low graft failure. The poorer outcomes in osteopetrosis are not dissimilar to other cohorts, reflecting the need for timely diagnosis and transplantation. A prospective randomized comparison with busulfan containing regimens is unlikely to happen, but this real world data suggests a superiority over historical busulfan conditioned cohorts. Further, as the data matures it will inform understanding of late effects, including on fertility and development.

Treosulfan-Based Conditioning For Allogeneic HSCT In Children: A Case Series Using PK Data And AUC Of Treosulfan In Single Center Experience - Adana, Turkey

P553
Poster presentation

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Study design	Retrospective single-center analysis	**Aim**	PK Analysis and AUC of Treo
Patients	63	**Average age**	4.9 y (0.2 – 17.0 y)
Disease	Malignant (n=2) and nonmalignant disorders: TM (n=35), SCD (n=12), severe immune deficiency (n=8), familial HLH (n=4); other (n=2)		
Conditioning regimen	Treo-based (age-guided, 10–14 g/m2)		
Results	• HSCT from unrelated donor n=24, haploHSCT n=1 • Treo was changed according to AUC in n=18 patients (increased n=8, decreased n=10) • No severe toxicities except mucositis (n=3); mild skin toxicity n=6, no VOD occurred. • Three patients died in the first 100 d due to severe GvHD and sepsis		
Conclusion	• Treo-based conditioning is a safe and effective treatment option in pediatric HSCT in different patient groups, even in those with high-risk clinical features pre-HSCT or those with no HLA-identical family donor.		

Abstract

Background

Treosulfan, a bifunctional alkylating agent with myeloablative and immunosuppressive effects, has been increasingly used as one of the main conditioning agents for hematopoetic stem cell transplantation (HSCT) for children with malignant and nonmalignant disorders. 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 treosulfan for allogeneic HSCT in children. We report our experiences with treosulfan-based conditioning regimen which is measured AUC levels in pediatric patients at our bone marrow transplantation center.

Methods

A total of 502 allogeneic hematopoetic cell transplantation were performed at Acıbadem Adana Hospital, Pediatric Bone Marrow Transplantation Unit in Turkey from 2013 to 2022. Sixty three cases of 502 patients were conditioned for allogeneic hematopoietic cell transplantation with a treosulfan. PK study was conducted using treosulfan concentration data (n = 63) collected from 63 children (median age 4.9, range 0.2–17.0 years) receiving three daily age-guided doses (10–14 g/m^2). We measured AUC level of treosulfan and were evaluated complications and treatment modalities from medical records retrospectively.

Results

In this study, 63 patients were conditioned with treosulfan, age ranging from 9 months to 17 years with a average of 4.9years. Thirty patients were males, 33 were female. There were 35 patients with thalassemia major, 12 patient with sickle cell anemia, 8 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, one patient with aplastic anemia. Twenty four patients had HSCT from an unrelated donor. One patient with Griscelli syndrome had haploidentical transplantation from mother. Patients received intravenous treosulfan doses of 10-14 g/m^2/day on days -6 to -4. Treosulfan concentration data were described using a one-compartment pharmacokinetics (PK) model with first-order elimination. The dose of treosulfan was changed according to AUC level in 18 patients. The dose of treosulfan was increased in eight of 18 patients, and the dose of treosulfan was reduced in ten of them. We did not see serious toxicity except severe mucositis. It was seen in three patients. Six patients had limited skin toxicity including pigment changes, and occasional peeling. Two patients showed skin erosions and exfoliation. Minimal liver toxicity occurred in two patients. No VOD occurred. Three patients died in the first 100 days due to severe GVHD and sepsis.

Conclusions

We show that using a treosulfan-based conditioning regimen is a safe treatment option in pediatric HSCT in different patients group, even in those with high-risk clinical features pre-HSCT or those with no HLA-identical family donor.

Treosulfan Versus Busulfan-Based Conditioning For Allogenic Hematopoietic Stem Cell Transplantation (HSCT) In Pediatric Patients With Primary Immunodeficiency (PID): A Single Center Report

P555
Poster presentation

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Study design	Retrospective study	**Aim**	Comparison of Treo- vs. Bu-based conditioning in patients with PID	
Patients	84 (93 HSCTs)	**Median age**	Children	
Parameters assessed	Toxicity, survival, immunological reconstitution, chimerism, GvHD			
Disease	PID			
Conditioning regimen	Treo-based (n=36)		Bu-based (n=57)	OR
Results				
Short-term tox				
VOD	1		1	0.63
Liver failure	1		0	
Cerebral toxcicity	1		2	1.27
TMA	2		3	0.94
Mucositis	5		13	1.83
Skin dyschromia	4		1	1.14
Infectious pneumonia	7		11	0.99
Sepsis	4		7	1.12
long-term tox				
Hematological toxicity	3/28		8/38	2.22
malignancy	0/28		1/38	
Hypothyroidism	3/28		9/38	1.43
Growth hormone deficiency	1/28		4/38	3.18
overall toxcicity	9/28		18/38	1.9
Conclusion	• Lower incidence of long-term side effects with superior overall survival was observed in patients who underwent conditioning with Treo. • In PID Treo appears to be an excellent alternative to Bu.			

Abstract

Background
Primary immunodeficiencies are an heterogeneous group of genetic diseases characterized by inefficient and dysregulated functioning of the immune system. In many of these patients HSCT is the gold standard therapy, the choice of conditioning regimen depends on patient and donor's characteristics. Busulfan is associated with high toxicity (especially veno-occlusive disease, VOD) and high peri-transplant mortality. Treosulfan has demonstrated a significant myeloablative potential with fewer toxic effects than Busulfan, and therefore represents a valid alternative in the conditioning of these patients.

Methods
The aim of this retrospective study is to compare Treosulfan (group A) and Busulfan (group B) in the conditioning of HSCT in patients with PID, in terms of toxicity, survival, immunological reconstitution, chimerism and incidence of GVHD (group A vs group B). Data were collected in the Bone Marrow Transplant Center in Brescia since 01/01/2010 to 12/31/2020.

Results
84 patients were included in the study, 9 of these underwent two transplants due to graft failure and therefore used both drugs. The total number of transplants performed was 93, 36 patients use Treosulfan, 57 patients use Busulfan. The short-term toxicity (within 1 month after HSCT) was: VOD 1/36 vs 1/57 (OR 0,63), liver failure 1/36 vs 0/57, cerebral toxicity 1/36 vs 2/57 (OR 1,27), TMA 2/36 vs 3/57 (OR 0,94), mucositis 5/36 vs 13/57 (OR 1,83), skin dyschromia 4/36 vs1 /57 (OR 1,14), infectious pneumonia 7/36 vs 11/57 (OR 0,99) and sepsis 4/36 vs 7/57 (OR 1,12). The long-term toxicity was: hematological toxicity 3/28 vs 8/38 (OR 2,22), malignancy 0/28 vs 1/38, hypothyroidism 3/28 vs 9/38 (OR 1,43), growth hormone deficiency 1/28 vs 4/38 (OR 3,18). The overall toxicity was 9/28 vs 18/38 (OR 1,9). The median day after HSCT with normal proliferative response to mitogens was 237 vs 309, suspension of immunoglobulin infusion was 231 vs 309, CD 4+ value > 200/mcL and > 500/mcL was 126 vs 224 and 237 vs 378.

Results on chimerism was at last evaluation: full donor chimerism 61% vs 62%, mixed donor chimerism 28% vs 25%, graft failure 11% vs 13%. The difference on engraftment in the two group is not statistically significant. Acute cutaneous GVHD has been found in 18/36 vs 25/56 (OR 0.80), hepatic GVHD in 6/36 vs 4/56 (OR 0.38), intestinal GVHD in 4/36 vs 8/56 (OR 1,33). Chronic cutaneous GVHD in 5/30 vs 5/44 (OR 0,64), hepatic GVHD in 1/30 vs 3/44 (OR 2,12), intestinal GVHD in 2/30 vs 6/44 (OR 2,21). We evaluate also overall survival in all transplants and in patients who received only one drug (Figure 1).

Conclusions
A lower incidence of long-term side effects with superior overall survival was observed in patients who underwent transplant conditioning using Treosulfan. In primary immunodeficiencies, Treosulfan appears to be an excellent alternative to Busulfan, presenting fewer long-term side effects with the same efficacy on chimerism. Further studies with a longer follow-up and with a more homogeneous group of patients (in terms of disease and year of transplantation) are needed to confirm these data.

The Impact Of Treosulfan -Based Conditioning For Primary Immune Deficiencies: Single Center Experience

P570
Poster presentation

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Study design	Retrospective single-center observational analysis	**Aim**	Early and long-term outcome in alloHSCT according to AUC
Patients/Transplants	58	**Age**	Children
Disease	PID		
Conditioning regimen	FT: Treo 36 g/m^2 (<1 y, n=28) or 42 g/m^2 (> 1 y, n=30), Flu 150 mg/m^2		
Results	• AUCs were calculated and divided into three based on tertiles; low: <625 m.h/L; medium:625 - 950 m.h/L and high: >950 m.h/L • Treatment-related toxicities and the presence of acute or chronic GvHD were similar for each dose and AUC group • Mixed chimerism rates were found to be higher in the group of FT14 • 2 y OS: 76%		
Conclusion	• Treo-based conditioning is effective and causes reduced toxicity for PIDs. • No significant change in toxicities or outcomes related to HSCT according to AUCs		

Please note: Data of poster presentation focused on n=73 patients with IEI. For consistency reasons we decided to summarize abstract information here.

Abstract

Background

The use of treosulfan-based conditioning for hematopoietic stem cell transplantation (HSCT) in pediatric practice is increasing because of its effective myeloablative and immunosuppressive properties while proposing less systemic toxicity. Reduced-toxicity conditioning is preferred in patients with primary immune deficiency (PID), many of whom enter HSCT with chronic infection and end-organ comorbidities. This study aims to explore the relationship between systemic treosulfan exposure and early and long-term clinical outcomes in patients undergoing allogeneic HSCT for PID.

Methods

This retrospective observational study is conducted in the Pediatric Stem Cell Transplantation Unit of Altinbas University Medical Park Bahcelievler Hospital. Our cohort comprised 58 PID patients who underwent HCST with treosulfan-based conditioning between April 2018 and April 2022. Collected data included age at the time of transplantation, sex, type of PID, transplantation type, donor relatedness, human leukocyte antigen (HLA) donor matching, stem cell source, treosulfan dose, and area under curve ratio (AUC) of treosulfan, the presence, and grade of treatment-related early toxicity (mucositis, hepatic, neurologic and skin toxicity); acute graft-versus-host disease (aGVHD), and chronic GVHD (cGVHD), chimerism status, event-free survival (EFS) and overall survival (OS). All patients received homogenous conditioning containing treosulfan (14 gr /m^2 for patients > one-year-old, 12 gr/m^2 for patients < one-year-old) for three days and fludarabine 30 mg/m^2 for five days. Serotherapy was done with anti-thymocyte globulin (ATG). GVHD prophylaxis consists of calcineurin inhibitors (cyclosporine for MSD and MUD; tacrolimus for MMD) and micofenolat mofetil (MMF) for MMD. Blood samples for treosulfan measure were collected at 0,1,2 and 4th hours of treosulfan exposure, and AUCs were calculated and divided into three based on tertiles; low: <625 m.h/L; medium:625-950 m.h/L and high: >950 m.h/L.

Results

Treosulfan dose groups (12 gr/m^2:27 patients-14 gr/m^2:30 patients) and AUCs are compared according to mucositis grade, early hepatic, neurologic, and skin toxicity; donor chimerism at 1st, 3rd, 6th months and last chimerism; the presence of acute or chronic GVHD and its grade; the presence of transplant-related mortality and overall survival. Treatment-related toxicities and the presence of acute or chronic GVHD were similar for each dose and AUC group. The 1st-month and last chimerism ratios were identical in all groups and >90% in 51 patients (89,6%). Mixed chimerism increased in the 14 gr/m^2 group (OR:5). 2 years of overall survival for PID patients who underwent treosulfan-based conditioning was 76%.

Conclusions

Treosulfan-based conditioning regimens are effective and cause reduced toxicity for PIDs. Like the previous literature, we did not find any significant change in toxicities or outcomes related to HSCT according to AUCs. Although the efficacy of 12gr/m^2 and 14 gr/m^2 doses is the same, mixed chimerism rates are higher in the 14 gr/m^2 group. This study raised whether the dose of treosulfan could be modified in the > one-year-old group who take the dose of 14 gr/m^2. However, this conclusion might have been affected by the retrospective structure of this study and should be supported with prospective trials.

Treosulfan Based Conditioning For Haematopoietic Stem Cell Transplantation (HSCT) In Children: On Behalf Of The UK Paediatric BMT Group

P606
Poster presentation

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Study design	Retrospective multicenter study	**Aim**	Transplant outcomes in children receiving Flu and Treo
Primary endpoints*	OS, TRM	**Secondary endpoints**	a/cGvHD, VOD, TMA
Patients/Transplants	537	**Median age (range)**	3.9 y (0.1 - 19 y)
Disease*	Malignant disorders (n=132): ALL (n=39), AML (n=71), JMML (n=7), lymphoma (n=8), acute biphenotypic leukemia (n=2); non-malignant disorders (n=405): non-SCID IEI (n=268), SCID (n=42), TM (n=32), SCD (n=21), DBA (n=11), BMF (n=6), OP (n=5), other (n=9)		
Conditioning regimen	FT (n=185), TTF (n=352)		
Results			
3 y OS	85% (malignant: 72%, non-malignant 89%); no difference between pts receiving Treo/Flu vs Treo/Flu/TT		
5 y EFS	Malignant 58%, non-malignant 83%; Treo/Flu 82%, Treo/Flu/TT 75%		
TRM	9%; no difference between pts receiving Treo/Flu vs Treo/Flu/TT and between malignant and non-malignant disorders.		
aGvHD d+90	Significantly more Grade II-IV and III-IV aGvHD in malignant pts.		
1 y cGvHD	6%		
VOD	2%; no difference acc. to indication or additional TT		
Conclusion	• Treo-based conditioning offers good OS and EFS in children that require HSCT for a variety of conditions. • The addition of TT does not affect OS or TRM.		

*Based on poster at conference

Abstract

Background

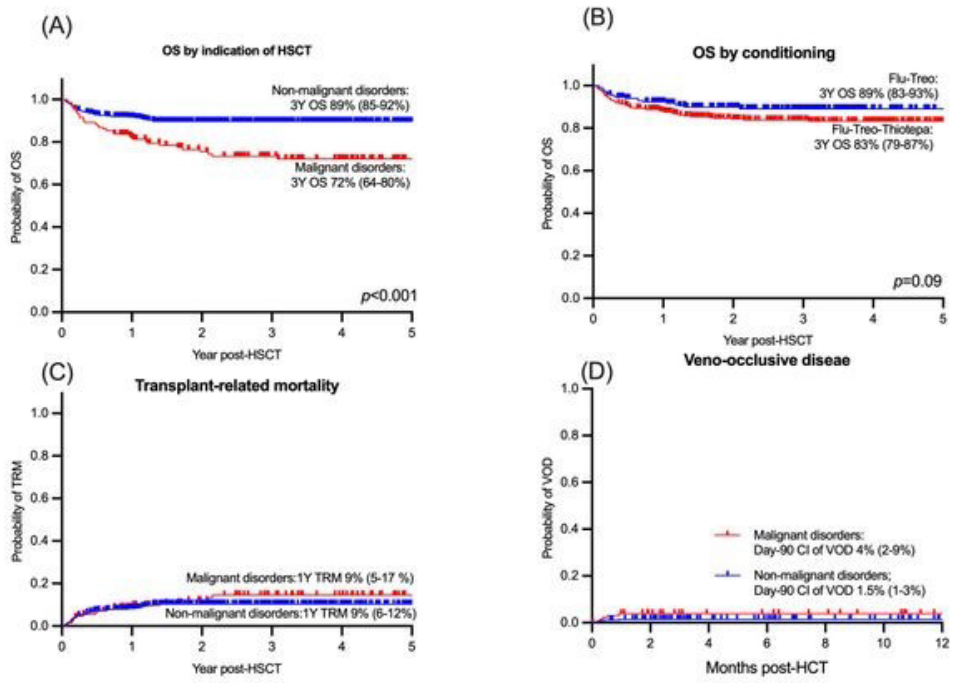
Treosulfan, in combination with fludarabine, is increasingly used as part of pre-HSCT conditioning for malignant and non-malignant disorders in children. This multicentre study compared transplant outcomes in 537 paediatric patients after treosulfan based conditioning for first haematopoietic stem cell transplantation (HSCT) between 2015 and 2021 at 9 transplant centres in the UK..

Methods

The primary endpoints were overall survival (OS), event-free survival (EFS; survival without graft failure, relapse/recurrence, and second procedures) and transplant-related mortality (TRM). Secondary endpoints were grade II-IV aGvHD, cGvHD, veno-occlusive disease (VOD) and thrombotic microangiopathy (TMA). Subgroup differences in OS, EFS were evaluated by log-rank test. Cox-regression model was used for multivariate analysis. Competing risks methods were used for the cumulative incidence of aGvHD, cGvHD, VOD and TMA, with death as the competing event, subgroup differences were evaluated by the Fine-and-Gray model.

Results

Figure 1: A. Probability of overall survival in non-malginant disorders compared to malignant disorders. B. Probability of overall survival between conditioning groups. C. Probability of transplant related mortality between malignant and non-malignant disorders. D. Probability of overall occurence of VOD in malignant and non-malignant disorders.



537 paediatric patients received fludarabine-treosulfan based conditioning. Median age at transplantation: 3.9 years (range: 0.1-19 years). 132 (25%) patients had malignant disorders and 405 (75%) had non-malignant disorders: 268 non-SCID inborn errors of immunity, 42 SCID, 79 non-malignant haematological disorders, 11 inborn errors of metabolism and 5 osteopetrosis. Donors were: 169 matched family, 269 matched unrelated, 29 mismatched family/unrelated and 70 haploidentical (>2 antigen mismatches). Stem cell source was: marrow 215, unmanipulated peripheral blood stem cell (PBSC) 205, T cell receptor

(TCR) ab/CD19 deleted PBSC 83, and cord blood 34. 352 (66%) patients received fludarabine, treosulfan and thiotepa, 185 (34%) receiving only fludarabine and treosulfan. 52 (10%) patients received no serotherapy. 42 (8%) received no post HSCT GvHD prophylaxis. Median duration of follow up was 3.1 years (range 0.2-7.8). 3-year overall survival (OS) was 85% for the whole cohort, 72% for malignant, and 89% for non-malignant disorders ($p<0.001$). There was no significant difference in OS between those who received fludarabine-treosulfan only compared to additional thiotepa. Event-free survival (EFS) was inferior in malignant (58%) compared to non-malignant disorders (83%, $p=0.001$). EFS was significantly better (82%) in patients receiving fludarabine-treosulfan compared to 75% with additional thiotepa ($p=0.03$). There was no difference in TRM (9%) between malignant and non-malignant groups and no difference between fludarabine-treosulfan (7%) and additional thiotepa (9%, $p=0.61$). Malignant patients had significantly more Grade II-IV and III-IV aGVHD. The incidence of chronic GVHD at 1 year for the whole cohort was low at 6%. The incidence of VOD was 2% and TMA 4% and no differences were found according to indication or additional thiotepa.

Conclusions

This large, multicentre, multi-disease cohort shows that treosulfan based conditioning offers good overall and event-free survival in children that require HSCT for a variety of conditions. The addition of thiotepa does not affect overall survival or TRM.

Hematopoetic Stem Cell Transplantation In Inborn Errors Of Metabolism - Polish Experience

P645
Poster presentation

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Study design	Retrospective analysis	**Aim**	Results of HSCT for IEM in Poland
Patients	66 (75 HSCTs)	**Median age (range)**	42 mo (1.5 mo – 12.8 y)
Disease	ALD (n=25), MPS type I (n=13), OP (n=11), MPS type II (n=7), other IEM (n=19)		
Conditioning regimen	Myeloablative Bu-based (n=34), reduced toxicity Treo-based (n=34), other (n=7)		
Results OS Death	80% (88% if HSCT after 2010 vs. 61% if HSCT between 2001 and 2010); Trend for better OS: standard IEM, Treo-based conditioning, BM as SC source n=14 (progression n=4; infection n=10)		
Conclusion	• In Poland fewer patients with IEM referred to HSCT compared to other European countries. • OS comparable to published data. • All surviving MPS patients do not require enzyme replacement therapy.		

Abstract

Background
According to EBMT survey data in 2019, 5% of allo-HSCT in children were performed due to inborn errors of metabolism (IEM). Our Polish data indicate that out of 2392 allo-HSCT performed in our country in all pediatric centers only 75 (3%) were done for IEM. We aimed to analyze retrospectively the results of all reported 75 HSCT in 66 children with IEM performed in years 2001-2022 in four Polish transplantation centers.

Methods
The indications for HSCT included: adrenoleukodystrophy (25 patients), mucopolysaccharidosis type I (13 patients), osteopetrosis (11 patients), mucopolysaccharidosis type II (7 patients) and other (not standard) IEM (19 patients). The median of recipient's age at the moment of HSCT was 42 months. The conditioning regimen was myeloablative (busulfan based) in half of the cases and the other half received treosulfan based reduced toxicity conditioning with few non-myeloablative regiments used for second transplant in 7 procedures. In 52 cases stem cells were collected from matched unrelated donor (MUD), in 12 cases from matched sibling donor (MSD) and 6 donors were mismatched. The most common stem cell source was peripheral blood (40 procedures). The median number of transfused CD34 cells was 6,8 x 106 per kilogram of patient's bodyweight.

Results
The median of post-transplant follow-up in our study was 3 years (6 months – 17 years) Overall survival of entire group was 0,8 and was significantly higher in patients transplanted after 2010 (n=42) as compared to children who had HSCT between 2001 and 2010 (0,88 vs 0,61 respectively, p=0,02). There was a trend towards better OS in patients: transplanted for standard indications as compared to not standard (0,83 vs 0,72); receiving treosulfan based regimen as compared to full busulfan based or non-myeloablative and for bone marrow as the stem cell source as compared to peripheral blood or cord blood - however these differences were not statistically significant. Fourteen children died: 4 pts (X-ALD) form progression of disease and 10 pts (2 osteopetrosis, 1 MPS type I, 2 MPS type II, 5 non-standard indications) from transplant related complications.

Conclusions
Fewer patients with IEM, especially with indication considered as standard of care, are referred to transplantation in Poland as compared to majority European countries. Overall survival is comparable to published data especially in recent 10 years. All survived MPS patients do not require enzyme replacement therapy.

Haploidentical Stem Cell Transplantation With Ex-Vivo T-Depletion In Primary Immunodeficiency And Immune Regulatory Syndromes: A Multicenter Experience

P756
Poster presentation

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Study design	Retrospective multicenter study	**Aim**	Outcome of PIDD/PIRD patients after TCD haploHSCT, comparison of different graft manipulation approaches
Variables for outcome	Diagnosis group, pre-HSCT status, conditioning regimen, graft manipulation approaches		
Patients	41 (48 HSCTs)	**Median age (range)**	2.5 y (0.1 – 21.6 y)
Disease	PIDD (n=32), PIRD (n=16)		
Conditioning regimen	Treo-based (n=20), Flu/Mel-based (n=14), Flu-based (n=5), Bu-based (n=4), no conditioning (n=5)		
Results			
Engraftment	92.5% neutrophils, 70.1% platelets (among 40 evaluable haploHSCTs)		
Graft rejection	22.9% (n=5 primary, n=6 secondary)		
3 y OS	74.5%; trend for higher survival: PIRD vs PIDD, Karnovsky/Lansky score >50, Treo-based conditioning, TCR-ab+/CD19+-depletion		
3 y CRFS	58.0%		
aGvHD	23.8% (grade I-II), 7.1% (grade III)		
cGvHD	15.4% (all), 7.7% (extensive)		
Conclusion	• Ex vivo TCD haploHSCT is feasible and effective in patients lacking a full matched donor. • Treo-based conditioning and TCR-αß+/CD19+-depletion seem to lead to best outcome. • Viral infection main issue after TCD haploHSCT, careful monitoring for and accessibility of pre-emptive treatment is needed.		

Abstract

Background

Allogeneic hematopoietic stem cell transplantation from haploidentical donor(haplo-HSCT) represents the alternative treatment for patients with Primary Immunodeficiency Disorders (PIDD) and Primary Immune Regulatory Disorders (PIRD) lacking a full-matched donor. In the last decade advanced T-depletion approaches have been introduced, but few data regarding outcomes of haplo-HSCT with graft manipulation are currently reported.

The aim of this multicentric retrospective study is to report the outcome of a large cohort of PIDD/PIRD patients who underwent T-depleted haplo-HSCT and to compare different graft manipulation approaches.

Methods

Haplo-HSCTs performed in patients with PID or PIRD in 3 pediatric centers (Genoa-Italy, Tuebingen-Germany, Lund-Sweden) were eligible. Clinical and biological information about the disease and details on transplant procedures and outcomes were collected retrospectively. Diagnosis group, pre-HSCT status, conditioning regimen (CR) and graft manipulation approaches have been considered as main variables for the outcome. A part of the patients' data included in this study was previously published in different contexts.

Results

Fourty-eight haplo-HSCTs performed in 41 patients were included in the study, 7 patients received 2 haplo-HSCTs. The median age at transplant was 2.5 years (0.1-21.6). Table 1 summarized the transplants features.

Table 1. Characteristics of the 48 haplo-HSCTs

Characteristics	n	%
Diagnosis		
• PIDD [#]	32	66.7
• PIRD [##]	16	33.3
Haploplatform		
• TCR ab+/CD19+ negative selection	34	70.8
• CD3+/CD19+ negative selection	13	27.1
• CD34+ positive selection	1	2.1
Karnofsky/Lansky at Haplo		
• <50	7	14.6
• > 60	41	85.4
Conditioning regimens		
• Flu-based*	19	39.6
• Bus-based	4	8.3
• Treo-based**	20	41.7
• No conditioning	5	10.4
Radiotherapy		
• Yes	8	16.7
• TLI / 4 Gy	6	
• TBI 4 Gy	2	
• No	40	83.3
Serotherapy		
• ATG[§]	31	64.6
• Early(before day -6)	6	
• Late(after day -6)	22	
• Not available	3	
• OKT3	8	16.6
• Alemtuzumab	3	6.3
• None	6	12.5

Rituximab		
• YES	28	58.3
• 375 mg/m2 D +1	9	
• 200 mg/m2 D -1	18	
• missing	1	
• NO	18	37.5
• missing	2	4.2
GvHD prophylaxis post-HSCT		
• No prophylaxis	31	64.6
• Prophylaxis	17	35.4
• MMF	12	
• CyA	2	
• FK506	1	
• PT-Cy	2	

[#] IL2-R, IFNG R2, MHCII, RFXANK, RAG-1, DCLRE1C (ARTEMIS), WAS, HAX-1, IL7RA (n 2), IL2RG (n 3), IL7RA, PNP, IL7RA, HAX-1, ADA, IFNGR1, WAS (n 2), ARPC1B (n 2), RAG1, TACI (n 2), RMRP

[##] LRBA (n 2), LYST, NSF2, CYBB, TACI+CASP10+CARD11, GATA2 (n 2), SAMD9L, CASP10 (n 2), MVK (n 3), CARD11, UNC13D

* Flu-Mel-TT N=13, Flu-Mel N=1, Fly-Cy N=1, Flu-TT N=1, Flu alone N=2, Flu-VP16 N=1

**Treosulfan (+Thiotepa, +Fludarabine); Treosulfan + ciclofosfamyde;Tresosulfan + Fludarabine

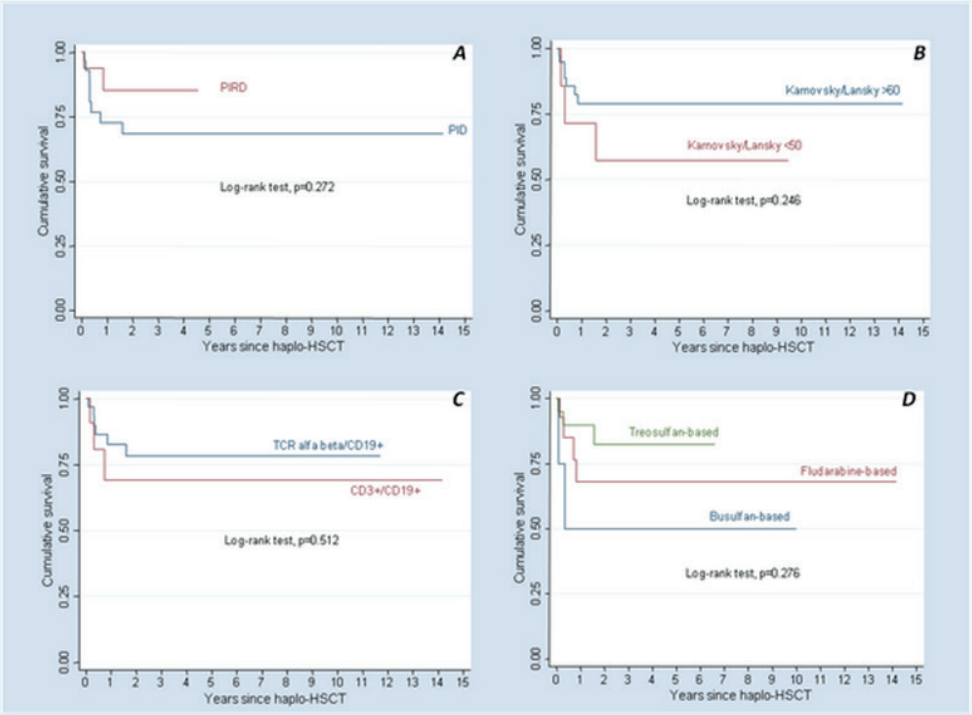
[§]ATG-Fresenius N=23, ATG Thymoglobuline N=5, ATG not specified N=4

TCR-ab+/CD19+-depletion was the graft manipulation approach in the most of haplo-HSCT(n=34, 70.8%), while CD3+/CD19+-depletion was performed in the remaining(n=13, 27.1%). In the majority of haplo-HSCTs, the CR was reduce-intensity fludarabine-based(n=19, 39.6%)or myeloablative treosulfan-based(n=20, 41.7%). Radiotherapy (TBI 200-400 cGy/TLI 400 cGy) was part of CR in 8 transplants (16.7%).

Among 40 haplo-HSCTs evaluable (83.3%), engraftment occurred in 37(92.5%) and 34 HSCTs(70.1%) for neutrophils and platelets, respectively, after a median of 13 days (9-27; 10-41) for both. Rejection have been diagnosed in 11(22.9%) haplo-HSCTs(5 primary, 6 secondary). Among the 42 evaluable HSCTs for acute GvHD, 13 (30.9%) were complicated by acute-GvHD [n=10 grade I-II (23.8%) and n=3 grade III (7.1%)]. Chronic GvHD occurred in 6/39(15.4%) HSCTs (extensive in 3, 7.7%).

At a median follow-up of 3.0 years (IQR 0.8-6.7) after haplo-HSCTs, 29 patients are alive, 2 lost and 10 dead, resulting in a 3-years-overall survival probability of 74.5% (CI 57.4-85.5) and 3-year-chronicGvHD/rejection-free survival of 58.0% (CI 40.7-71.9). Most causes of death were infections, with higher frequency of viral etiology. Higher cumulative survival was observed in patients with a diagnosis of PIRD respect to PIDD, with a Karnovsky/Lansky score >50 at the time of haplo-HSCT and when Treosulfan-based CR and TCR-ab+/CD19+-depletion were performed (Figure 1).

Figure 1. Cumulative survival by group of diagnosis *(A)*, by Karnovsky/Lansky score *(B)*, by depletion approach *(C)* and by conditioning regimens *(D)*



Conclusions

Ex vivo T-depleted haplo-HSCT is a feasible and effective alternative in patients lacking a full matched donor that allows to not delay the transplant in presence of a diagnosis of PIDD or PIRD. This is further supported by the negative effect on the outcome of the lower patient's Karnovsky/Lansky score before HSCT, which is more likely in PIDD/PIRDs patients who reach haplo-HSCT with delay. Moreover, Treosulfan-based CR and TCR-ab+/CD19+-depletion seem to lead to the best outcome confirming the importance of the evolution in graft selection methods. Viral infection remained the main issue after T-deplete haplo-HSCT, therefore careful monitoring for pre-emptive treatment is needed and the access to antiviral adoptive cell therapy should be available.

Infants

Outcome Of Treosulfan-Based Condition In 93 Infants With SCID – A Multicentre Retrospective Cohort Analysis

P624
Poster presentation

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Study design	Retrospective multicenter analysis	**Aim**	Transplant outcomes in infants with SCID receiving Flu and Treo
Primary endpoints	OS, EFS, TRM	**Secondary endpoints**	a/cGvHD, VOD
Patients	93	**Median age (range)**	6 mo (1.2 - 17 mo)
Disease	SCID		
Conditioning regimen	FT (n=90), TTF (n=3)		
Results 5 y OS 5 y EFS deaths aGvHD d+90 1 y cGvHD VOD	 86% (donor: 75% MFD, 79% MUD, 83% CB, 93% haplo) 82% •Donor, stem cell source and serotherapy had no impact of survival. n=15 (infections, pneumonitis, GvHD, TMA, leukemia, encephalopathy, unknown) 19% (grade II-IV), 5% (grade III-IV) 6% 1%		
Conclusion	• Treo-based conditioning is well tolerated in infants with SCID. • Very low risk of VOD. • Myeloid chimerism >10% was achieved in 95% of long-term survivors.		

*Based on poster at conference.

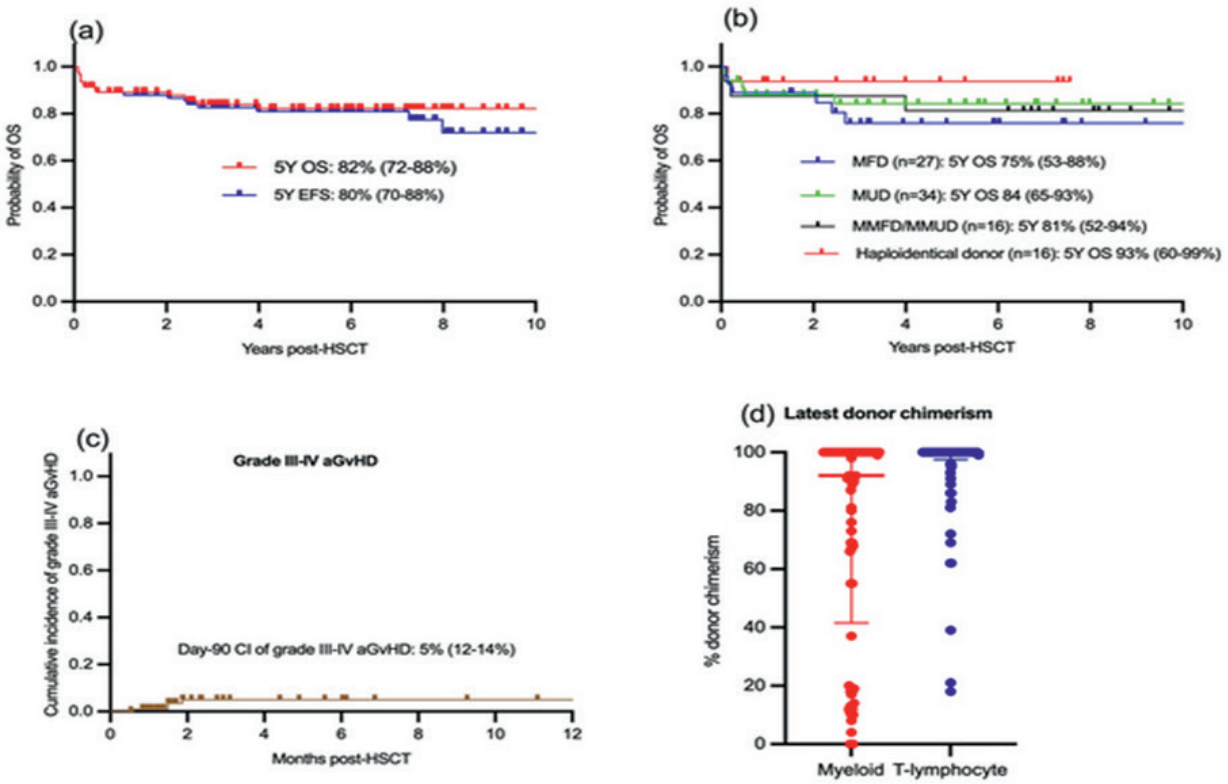
Abstract

Background
Conditioning is associated with long-term outcomes in infants with severe combined immunodeficiency (SCID). This multicentre study compared transplant outcomes in 93 infants with SCID who received fludarabine-treosulfan for first haematopoietic stem cell transplantation (HSCT) between 2006-2021 at two supraregional immunology transplant centres in the UK.

Methods
Primary endpoints were overall survival (OS), event-free survival (EFS; survival without graft failure and second procedures) and transplant-related mortality (TRM). Secondary endpoints were grade II-IV aGvHD, cGvHD and graft failure. Subgroup differences in OS and EFS were evaluated by log-rank test. Competing risks methods were used for the cumulative incidence of aGvHD, cGvHD, VOD with death as the competing event, subgroup differences were evaluated by Gray's test.

Results
Median age at transplant was 6 months (range 1.2-17 months). Donors were matched family donor (MFD, n=27, 29%), matched unrelated donor (MUD, n=34, 37%), mismatched unrelated donor (MMUD, n=16, 17%) and haploidentical donor (HID, n=16, 17%). Stem cell sources were marrow (n=28, 30%), unmanipulated peripheral blood stem cells (PBSC) (n=19, 20%), T cell depleted PBSC (n=16, 17%; 13 TCRab/CD19 depletion; 2 CD3/CD19 depletion; 1 CD34 selection) and cord blood (CB) (n=30, 32%). Ninety (97%) received treosulfan–fludarabine based conditioning and three (3%) received fludarabine-treosulfan-thiotepa based conditioning. Alemtuzumab was the most common serotherapy (n=59, 63%), then ATG (n=19, 20%) and 15 (16%) received no serotherapy. GvHD prophylaxis were CSA+MMF (n=71, 76%), CSA (n=11, 12%), CSA+MTX (n=1, 1%) and none (n=10, 11%).

Median time to neutrophil and platelet engraftment was 18 (range 9-73) and 19 (7-61) days respectively. The 5-year OS and EFS for the entire cohort was 82% (95% CI, 72-88) and 80% (95% CI, 70-88) respectively (Fig-a). Five year OS in MFD was 75% (95% CI, 53-88), MUD 84% (95% CI, 65-93%), MMFD/MMUD 81% (95% CI, 52-94), HID 93% (95% CI, 60-99) (p=0.66) (Fig-b). Cumulative incidence of VOD was 1.1% (0-8%). Cumulative incidence of grade II-IV aGvHD was 19% (11-32%) and grade III-IV aGvHD was 5% (2-13%) (fig c). 1-year cumulative incidence of chronic GvHD was 6% (2-13%). Median follow-up was 5.3 years (0.24-14.9). Donor (p=0.66), stem cell source (p=0.6) and serotherapy (p=0.34) had no impact of survival. 5 patients had second procedures: 2 second transplants (GvHD; poor T cell immune reconstitution), 1 CD34 stem cell boost and 2 donor lymphocyte infusion for poor immune reconstitution. The cause of death in 15 patients was: infection (n=6), pneumonitis (n=3), GvHD (n=2), TMA (n=1), leukaemia (n=1) encephalopathy (n=1), and unknown (n=1). In long-term survivors, median myeloid chimerism was 99.5% (range 0-100) and median T-lymphocyte chimerism was 100% (range 18-100%) (fig d). Long-term disease outcome and immune reconstitution are being evaluated.



Conclusions

Treosulfan-based conditioning is well tolerated in infants with SCID with very low risk of VOD.

Real-Time Treosulfan Pharmacokinetics For SCID Infants Identified By Newborn Screening

P651
Poster presentation

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Study design	Feasibility study	**Aim**	Feasibility of performing real-time Treo PK for SCID infants, necessity of daily dose adjustment.
Parameters assessed	Treo clearance and AUC		
Patients	5	**Age**	3 - 8 mo
Disease	SCID		
Conditioning regimen	FT or TTF (in 2 infants with RAG1 deficiency): Treo (3 doses, once daily, 10 – 12 g/m², subject to dose adjustment), 150 mg/m² Flu		

Results*	Infant A		Infant B		Infant C		Infant D		Infant E	
Conditioning regimen	Treo/Flu		Treo/Flu		Treo/Flu		Treo/Flu/Thio		Treo/Flu/Thio	
	Dose (g)	Cl (L/h)	Dose (g)	Cl (L/h)	Dose (g)	Cl (L/h)	Dose (g)	Cl (L/h)	Dose (g)	Cl (L/h)
Day 1	3.6	1.6	3.4	1.4	3.3	1.9	5.0	3.5	3.0	2.3
Day 2	2.6	1.8	2.2	1.3	3.3	1.7	5.0	3.9	3.0	2.1
Day 3	3.2	1.7	2.0	1.5	3.3	1.8	5.0	3.2	3.0	-**
Cumulative AUC (mg*h/L)	5.560		5.503		5.457		4.284		4.116	

Conclusion	• The current data shows significant intra-patient and inter-occasion variability in Treo PK that suggests PK monitoring may be needed to avoid high exposure, although optimization of a weight or BSA-based dose may be sufficient.

*Based on poster at conference.
** Day 3 PK was not performed due to complications with the central line.

Abstract

Background

The introduction of newborn screening (NBS) for identification of SCID in New South Wales, Australia, has allowed development of a platform for early HSCT based on treosulfan and fludarabine conditioning. A cumulative treosulfan exposure (AUC) of 4,800 (range 3,800 – 6,000) mg*h/L when combined with fludarabine has been proposed for this cohort, and we aimed to evaluate the feasibility of performing real-time treosulfan pharmacokinetics for SCID infants and determine the necessity of daily dose adjustment.

Methods

Five infants (ages 3 – 8 months) diagnosed with SCID by NBS underwent HSCT. Patients were conditioned with treosulfan (three doses once-daily, 10 – 12 g/m², subject to dose adjustment), fludarabine (cumulative 150 mg/m²), and either alemtuzumab (cumulative 0.3 – 1 mg/kg) or ATG (Grafalon) (cumulative 15 mg/kg) prior to HSCT. Two infants with RAG1 deficiency also received thiotepa conditioning. Seven blood samples were collected at timed intervals after infusion and measured on the same day using high performance liquid chromatography. Treosulfan clearance and AUC was evaluated using Kinetica v4 non-compartmental analysis software and reported to clinical staff prior to preparation of the next dose.

Results

Table 1 provides details on daily and cumulative treosulfan AUC for five SCID infants in addition to an extrapolated cumulative AUC from a BSA-guided dose.

Infant A was 87 days old at transplant and received 10 g/m² treosulfan, with no requirement for dose adjustment. Infant A is currently 10 months post-transplant and D+30 whole blood chimerism was 93%. Low T-cell chimerism at D+100 was observed due to EBV reactivation, but recovered after rituximab.

Infant B was 121 days old at transplant and received an initial dose of 12 g/m² treosulfan, with dose adjustments on days 2 and 3. A BSA-guided dose of 10 g/m² would not have required dose adjustment. Infant B is currently 6 months post-transplant. D+100 sorted chimerism was >83% for T, B, NK and granulocyte cell lines.

Infant C was 118 days old at transplant and received an initial dose of 12 g/m², with dose adjustments on days 2 and 3. A BSA-guided dose of 10 g/m² would achieve an extrapolated AUC >6,000 mg*h/L, requiring dose adjustment. Infant C is currently 6 months post-transplant with complete donor T-cell chimerism and low B and granulocyte chimerism.

Infant D was 94 days old at transplant and received 10 g/m² treosulfan, with no requirement for dose adjustment. Infant D is currently 2 months post-transplant, with no chimerism data currently available.

Infant E was 241 days old at transplant and received 12 g/m² treosulfan with no requirement for dose adjustment. A BSA-guided dose of 10 g/m²would have achieved an extrapolated AUC of <3,800 mg*h/L, requiring dose adjustment. Infant E is currently 1 month post-transplant, with no chimerism currently available.

Table 1	Infant A	Infant B	Infant C	Infant D	Infant E
Conditioning regimen	Treosulfan/fludarabine			Treosulfan/fludarabine/thiotepa	
Day 1 dose (g) [1]	3.0	3.6	3.4	3.3	5.0
Day 1 clearance (L/h)	2.3	1.6	1.4	1.9	3.5
Day 1 AUC (mg*h/L)	1,304	2,223	2,512	1,740	1,428
Day 2 dose (g)	3.0	2.6	2.2	3.3	5.0
Day 2 clearance (L/h)	2.1	1.8	1.3	1.7	3.9
Day 2 AUC (mg*h/L)	1,406	1,468	1,645	1,913	1,281
Day 3 dose (g)	3.0	3.2	2.0	3.3	5.0
Day 3 clearance (L/h)	2.1	1.7	1.5	1.8	3.2
Day 3 AUC (mg*h/L)	1,406	1,869	1,346	1,804	1,552
Cumulative AUC (mg*h/L)	4,116	5,560	5,503	5,457	4,284
Cumulative AUC without dose adjustment	4,116	6,368	7,310	5,457	4,284
Dose if BSA-guided dosing was used (g) [2]	3.0	3.0	2.8	3.3	2.9
Extrapolated cumulative AUC for BSA-guided dosing (mg*h/L) [3]	4,116	5,261	6,138	5,457	3,589

[1]Initial treosulfan dose was based on an age-guided criteria: for patients <3 months: 10 g/m^2;≥3 months and <12 months: 12 g/m^2
[2]BSA-guided dosing criteria: BSA <0.5 m^2: 10 g/m^2; ≥0.5 m^2 and <1.0 m^2: 12 g/m^2
[3]Extrapolated cumulative AUC was calculated by dividing the BSA-guided dose by the daily pharmacokinetic clearance and summing the values.

Conclusions

Treosulfan cumulative exposure was within the proposed therapeutic range for all infants, but dose adjustment was required in two cases. The current data shows significant intra-patient and inter-occasion variability in treosulfan pharmacokinetics that suggests pharmacokinetic monitoring may be needed to avoid high exposure, although optimisation of a weight or BSA-based dose may be sufficient.

Clinical Trial Registry: This study was registered with the Australian Clinical Trials Registry (registration number: ACTRN12615000038594)

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 noninfective cystitis, dysuria. *Reproductive system:* Scrotal erythema, penile pain. *General, administration site:* Very commonly asthenic conditions (fatigue, asthenia, lethargy), pyrexia. Commonly oedema, chills. Uncommonly non cardiac chest pain, pain, face oedema. *Investigations:* Very commonly blood bilirubin increased, ALT increased. Commonly AST increased, γGT increased, C-reactive protein increased, weight decreased, weight increased. Uncommonly blood alkaline phosphatase increased. Blood lactate dehydrogenase (LDH) increased. **Legal classification**: POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH Theaterstraße 6; 22880 Wedel, Germany. **Date of revision of text**: 03/2023

Trecondi has been authorised in all countries of the EU as well as in Iceland, Norway, Liechtenstein, Switzerland (OpoPharma AG) and United Kingdom

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