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TREOSULFAN IN HSCT

Abstracts

HIGHLIGHTS
PRESENTED AT
ASH 2022
AND
TCT MEETINGS 2023

Dear Reader,

We are pleased to share with you some selected abstracts on the use of treosulfan-based conditioning treatment prior to stem cell transplantation in children and adults presented at the 64th Annual Meeting of the American Society of Hematology 2022 and the 2023 Tandem Meetings (Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR).

Following the MDS subgroup analyses of medac's pivotal phase III trial with treosulfan (NCT00822393) presented at the 2022 TCT-Meeting, this year's conferences included a presentation by Floeth et al. of real-world data, verifying the favourable outcome data in this patient population. Furthermore, several updates on the paediatric FORUM trial were presented. While the long-term evaluation by Locatelli et al. confirms that ALL patients older than 4 years benefit from conditioning based on TBI, the presentation by Peters et al. showed that treosulfan was significantly superior to busulfan in conditioning prior toHSCT in children younger than 4 years in terms of 3-year post relapse overall survival.

We hope you will enjoy reading this overview on recent results on treosulfan-based conditioning.
Best regards from Wedel,

Yours,
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Contents

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Treosulfan-Based Conditioning Prior to Allogeneic Hematopoietic Cell Transplantation (alloHCT) for Patients with Myelodysplastic Syndrome (MDS): Promising Survival Outcome Including Patients with High-Risk Disease

ASH 2022 #3377
Poster presentation
Tandem Meetings 2023 #137
Poster presentation

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Study design	Retrospective analysis	**Aim**	• Verification of MC-FludT.14/L study results in real-world setting • Evaluation of disease burden impact before haematopoietic stem cell transplantation (HSCT)
Parameters assessed	Relapse-free survival (RFS), overall survival (OS), cumulative incidence of relapse (CIR), non-relapse mortality (NRM), graft-versus-host disease (GvHD), donor chimerism (DCC)		
Patients	83	**Median age**	63 y (39 - 76)
Disease	Myelodysplastic syndrome (MDS)		
Conditioning regimen	Treosulfan 30 g/m² + Flu 150 mg/m² (FT10)		
Results*	• RFS 82% (1 y) 66% (2 y) • OS 86% (1 y) 72% (2 y)* • CIR 8% (1 y) 15% (2 y) • NRM 10% (1 y) 19% (2 y) * Significantly lower OS in VHR MDS pts after 2 years compared to HR or IR MDS (57% vs 81% vs 93%, $p < 0.05$) • Bone marrow blast count prior conditioning, age, donor type and HCT-CI had no impact on survival. • Cytogenetically defined HR and VHR mutations and presence of TP53 were associated with inferior survival outcomes. • aGvHD: n=13 (grade 2-4), n=5 (grade 3-4); cGvHD: n=9 (mild), n=10 (moderate), n=10 (severe). • Incomplete DCC was not associated with an increased risk of relapse.		
Conclusion	• Favorable outcome data for MDS patients treated with treosulfan-based conditioning prior to alloHSCT was verified. • Survival after alloHSCT seemed to depend on disease biology, rather than disease burden. • Future strategies should focus on timely alloHSCT, when indicated, postHSCT maintenance and not on preHSCT treatment intensification.		

*data according to talk presented during conference

Abstract

Introduction
AlloHCT plays an important role in the treatment of MDS and represents the only curative treatment option so far. Conditioning therapy with fludarabine/treosulfan for elderly (≥ 50 years) and/or comorbid (HCT-CI >2) patients with AML or MDS undergoing alloHCT showed improved outcomes compared to fludarabine/busulfan conditioning in randomized phase III study (NCT00822393). In this retrospective study, we analyzed MDS patients treated with a fludarabine/treosulfan conditioning aiming to verify the study results in a real-world setting.

Patients and Methods
Between August 2017 and July 2022, 83 elderly and / or comorbid patients (pts) with MDS underwent alloHCT at our center receiving conditioning treatment with 30 mg/m² BSA intravenous fludarabine (day -6 to d-2) and 10g/m² treosulfan (day -4 to d-2). Graft versus-host disease (GvHD) prophylaxis consisted of cyclosporin and methotrexate. Additionally, patients transplanted from an unrelated donor received anti-thymocyte globulin (3 x 10 mg/kg ATG/Neovii). Evaluation of remission and transplant function after transplant was scheduled 2, 3-4 months and later every 3 months including bone marrow evaluation with FACS-sorted lineage-specific donor chimerism (DCC). Incomplete DCC was defined as <95%, measured by VNTR-PCR and was an indication for preemptive immune intervention (rapid tapering of immunosuppressive medication and/or donor lymphocyte infusion).

Results
Median age of the patients was 63 years (range 39-76 years; 2 patients were <50 years of age), median HCT-CI was 2 (range 0-7) and median follow-up of surviving patients was 745 days (range 98-1692). According to the IPSS-R classification 42 pts (51%) had a very high risk (VHR), 22 pts (27%) a high risk (HR), 16 pts (19%) an intermediate risk (IR) and 3 pts (4%) a low risk (LR) disease. Prior start of conditioning 41 pts (49%) had bone marrow blast counts of 10-19%, 18 pts (22%) 5-9% and 24 pts (29%) <5%. As expected, disease biology defined by cyto- and molecular genetic changes varied, with cytogenetically defined high-risk mutations found in 42 patients. Most frequent molecular genetic mutations were detected in ASXL1 (27 pts) and TP53 (17 pts) genes. All patients received G-CSF mobilized stem cell graft from either HLA-identical sibling donors (19%), 10/10 HLA matched unrelated (63%) or 9/10 HLA matched unrelated donors (18%).

Kaplan-Meier estimates for relapse-free survival (RFS) at 1 and 2 years were 82% (95% CI 73-90%) and 66% (95% CI 55-78%), for overall survival (OS) 86% (95% CI 78-94%) and 72% (95% CI 61-83%), respectively. Cumulative incidences of relapse at 1 and 2 years were 8% (95% CI 4-17%) and 15% (95% CI 8-27%), for non-relapse mortality (NRM) 10% (95% CI 5-20%) and 19% (95% CI 11-30%), respectively. Patients with VHR MDS showed a significant lower OS after 2 years compared to HR or IR MDS (57% vs 81% vs 93%, p < .05). Interestingly, bone marrow blast count prior conditioning, age, donor type and HCT-CI had no impact on survival. Cytogenetically defined high and very high-risk mutations as well as presence of TP53 were associated with inferior survival outcomes. Acute GvHD grade 2-4 occurred in 13 pts (grade 3 and 4 in 5 pts.). Mild chronic GvHD was diagnosed in 9 pts, moderate in 10 pts and severe in 10 pts.

2 months after transplantation 11 pts had an incomplete CD3 DCC and 15 pts an incomplete CD34 DCC. At 3-4 months incomplete CD3 DCC could be detected in 6 pts and for CD34 in 10 pts. Incomplete DCC was not associated with an increased risk of relapse, most likely due to early preemptive immune interventions.

Conclusion
Our data verify the favorable outcome data for MDS patients treated with treosulfan-based conditioning prior to alloHCT. Moreover, survival after alloHCT seemed to depend on disease biology, defined by cytogenetic and molecular changes, rather than on disease burden defined by bone marrow blast count. In context with recent published study data, future treatment strategies should focus on timely realization of alloHCT, when indicated, post-transplant maintenance and not on pre-transplant treatment intensification.

Relapse Is the Most Common Treatment Failure Post HSCT in Children with ALL below 4 Years of Age Given a Chemo-Based Conditioning Regimen. Results from the Prospective Multinational FORUM-Trial

ASH 2022
#370
Oral presentation

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Study design	Subgroup analysis of prospective randomised multinational trial	**Aim**	Comparison of fludarabine/treosulfan/thiotepa (FTT) and fludarabine/busulfan/thiotepa (FBT) within FORUM trial in children <4 y
Parameters assessed	OS, event-free survival (EFS), transplant-related mortality (TRM), CIR, acute/chronic GvHD (a/cGvHD), cGvHD- and relapse-free survival (CRFS)		
Patients	194	**Median age**	2.2 y (6 mo – 4 y)
Disease	High risk acute lymphoblastic leukaemia		

Conditioning regimen	FTT* (n=93)	FBT* (n=101)	p
Results*			
3 y OS	0.76 ± 0.05	0.63 ± 0.05	0.075
3 y OS if SCT in CR1	0.80 ± 0.06	0.68 ± 0.06	0.085
3 y OS if SCT in CR>1	0.61 ± 0.12	0.54 ± 0.09	0.724
3 y OS if relapse postSCT	0.38 ± 0.11	0.16 ± 0.07	0.012
3 y EFS	0.51 ± 0.06	0.52 ± 0.05	0.794
1 y CIR	0.38 ± 0.05	0.37 ± 0.05	0.931
1 y TRM	0.03 ± 0.02	0.06 ± 0.02	0.405
aGvHD/cGvHD	Comparable between treatment groups		0.849
3 y CRFS	0.41 ± 0.06	0.44 ± 0.05	0.943

Conclusion
• OS, EFS, CIR, NRM comparable between busulfan and treosulfan. • OS after relapse postSCT was better if conditioning was treosulfan-based. • Because of decreased NRM, results represent an improvement compared to previously reported series. • Further pre- and post-transplant immunotherapeutic strategies warranted to decrease relapse incidence.

*Treosulfan dose 42 g/m²; Busulfan was dosed once, twice, or four times a day according to local guidelines, age, and body weight, commonly with therapeutic drug monitoring and pharmacokinetic dose adjustment (Peters et al. J Clin Oncol. 2021;39(4):295-307)

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. Conditioning regimens for this high-risk population usually omit total body irradiation (TBI) to avoid acute and long-term side effects that are more pronounced in this age group. The optimal chemotherapeutic approach aiming improved event-free survival (EFS) and low NRM is not yet defined

Methods

The prospective FORUM trial used two myeloablative chemo-conditioning regimens for children <4 years (yrs) of age: fludarabine (FLU), thiotepa (THIO) and either intravenous busulfan (BU) or treosulfan (TREO) as described previously (Peters et al., JCO 2021). This report includes 194/202 patients (pts) (107 male, 87 female) from 26 countries enrolled in FORUM who received HSCT (5 pts received TBI-based conditioning and 3 pts with unknown conditioning were excluded). Median age at HSCT was 2.2 yrs (6 months – 4 yrs; 38 pts 0-1yrs (20%), 53 pts 1-2yrs (27%), 53 pts 2-3yrs (27%), 50 pts 3-4yrs (26%)). Stem cell source was bone marrow in 132 (68%) pts, peripheral blood stem cells in 37 (19%), and cord blood in 24 (13%). Donors were HLA-matched siblings (MSD) in 39 (20%) pts and 9 or 10/10 HLA allele-matched unrelated donors (MUD) in 155 (80%) pts.Clonal genetic abnormalities reported at diagnosis 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. Graft-versus-host-disease (GvHD)-prophylaxis was Cyclosporin-A-based in 90%; recipients of MUD-grafts also received ATG and 3 doses of methotrexate. At data cut-off, median follow-up (FU) was 3 yrs (range, 3 months – 7.2 yrs).

Results

3-yrs OS was 0.69±0.04, 3-yrs EFS was 0.52±0.04; 3-yrs Cumulative incidence of relapse (CIR) was 0.44+0.04, and 3-yrs NRM was 0.05 ± 0.02. OS and EFS did not differ between pts < 2 and 2-4 yrs of age at HSCT (Table 1). Pts transplanted in CR 1 had significantly better EFS (0.58±0.04) as compared to >CR1pts (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 < 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). OS/EFS were not significantly different when donor type, stem cell source, and immunophenotype were compared (Table 1). At 3-yrs, OS was 0.63±0.05 and 0.76±0.05 and 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) with no significant difference in CIR and TRM. 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. Most relapses occurred prior to 1 yr after HSCT. Acute GVHD occurred in 32 pts (20 pts experienced grade III/IV) with no significant difference between the two conditioning regimen). The 3-yr incidence of chronic GVHD (cGVHD) was comparable between the BU- and -TREO-group (p = 0.943). cGVHD/relapse-free survival at 3 yrs 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 the presence of 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 (n.s.).

Conclusion

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. Pre- and post-transplant immunotherapeutic strategies aimed at reducing relapse-incidence without increasing chemotherapy-associated complications are needed.

Figure 1: 3-yrs OS according to Conditioning
Flu: fludarabine, Thio: thiotepa, Treo: treosulfan, Bu: busulfan

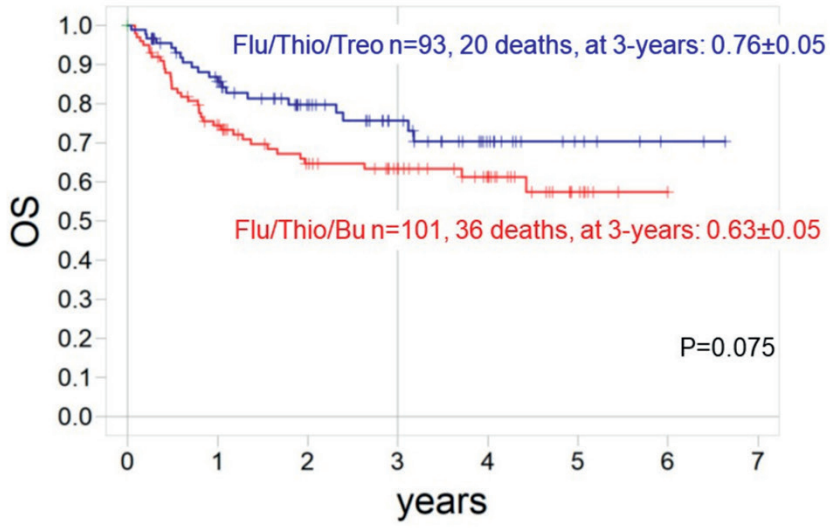

Table1: Uni- and multi-variable analysis of OS end EFS

				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

TCRαβ+/CD19+-Depletion in Hematopoietic Stem Cells Transplantation from Matched Unrelated and Haploidentical Donors in Pediatric Acute Lymphoblastic Leukemia Patients in Complete Remission

ASH 2022
#872
Oral presentation

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Study design	Retrospective analysis	**Aim**	TCRαβ+/CD19+ depleted graft to prevent GvHD, improve immune reconstitution, maintain leukemia control
Patients	236	**Median age**	8.7 y (0.5 - 20)
Disease / Donor	Acute lymphoblastic leukaemia (ALL) / 202 haplo, 34 MUD		
Intervention	• Conditioning: treosulfan-based (n=93, 42 g/m^2), 12 Gy total body irradiation (TBI; n=143) • TCR αβ and CD19-depleted graft		
Results	• Engraftment 98% (n=227) • 4 y TRM 9% (n=22) 7% (-ATG) vs 15% (+ATG), p=0.049 • 9% (haplo) vs 12% (MUD), p=0.64 • 4 y CIR 31% (n=72) 26% (TBI) vs 40% (treosulfan), p=0.06 • 4 y Survival OS 67%, GRFS 55% • 4 y EFS 57% 64% (TBI) vs 46% (treosulfan), p=0.019 • aGvHD grade 2-4 15% • cGvHD 11% (-ATG) vs 24% (+ATG), p=0.01 • 15% (haplo) vs 18% (MUD), p=0.78		
Conclusion	• TCRαβ+/CD19+ depletion from graft ensures high engraftment rate and acceptable TRM in paediatric ALL patients. • TBI and MRD negative status before HSCT had a significant correlation with good outcome (EFS and CIR).		

Abstract

Introduction

Relapse, graft-versus-host disease (GvHD) and GvHD-associated mortality are major obstacles to success of transplantation from unrelated and haploidentical donors in children with acute lymphoblastic leukemia (ALL). Depletion of α/β (+) T cells and CD19+ B lymphocytes is used to prevent GvHD, improve immune reconstitution and maintain the control of leukemia.

Patients and methods

A total of 236 children with ALL (T-ALL- 83, PB-ALL-153, 82 female, 154 male, median age 9,4 years) in CR underwent allo HSCT between May 2012 and March 2021. Two hundred and two patients received haplo graft, 34 – a graft from MUD. Disease status at transplant was a CR 1 in 81 pts, CR2 in 124 pts and CR≥2 in 31 pts. Transplantation in CR1 was performed according to risk stratification scheme in the current institutional ALL protocol. Flow cytometry-based MRD detection in bone marrow prior to HSCT was performed in 198 patients (84% of the total cohort). 143 patients were MRD-negative before HSCT, 55 were MRD-positive. 93 pts received treosulfan-based myeloablative preparative regimen, while TBI-based regimen was used in 143 pts.

Three regimens of GvHD prophylaxis were used: regimen 1 included horse ATG at 25 mg/kg/day and CsA+/-Mtx, regimen 2 (n=73): thymoglobulin 5mg/kg, rituximab 200 mg/m^2 on d-1 and bortezomib on day +2, +5 and regimen 2 (n=163): rituximab 200 mg/m^2 and tocilizumab at 8 mg/kg on day -1, abatacept at 10 mg/kg on day +2, +7, +14, +28 and post-transplant bortezomib on d+2, +5.

TCRαβ+/CD19+ depletion of HSCT with CliniMACS technology was implemented in all cases according to manufacturer's recommendations. The median dose of CD34+ cells in transplant was 10 x106/kg (range 3,9-18,8), TCRα/β - 19x103/kg (range 0,2-361).

Results

Four patients died before engraftment due to bacterial infection. Primary engraftment was achieved in 227 (98%) patients, surviving till day +30, with median time to engraftment of 13 days for neutrophils and 14 days for platelets. All evaluable patients achieved sustained complete donor chimerism by day +30. Five patients failed to engraft and required rescue with a second HSCT from the alternative donors.

Day +100 mortality was 2% (95%CI:1-5). The CI of TRM among all patients was 9% (95%CI:6-14), 9% (95%CI:6-14) for haplo and 12% (95%CI:5-29) for MUD, p = 0,64. The only factor, significantly associated with non-relapse mortality, was serotherapy, with TRM of 15% (95%CI: 9-26) among patients who received ATG versus 7% (95%CI: 2-13) in those without serotherapy, p = 0,05. The direct causes of non-relapse death included bacterial and viral infections.

CI of aGvHD grade II-IV was 15% (95% CI, 11 - 21), grade 3-4 was 6% (95% CI, 3 - 11). CI of cGvHD at 2 years was 15%(95%CI:11-21). The CI of cGVHD was 24% (95%CI:16-36) with serotherapy and 11% (95%CI: 7-17) without serotherapy, p = 0,01.

The CI of relapse at 4 years was 31% (95%CI:26-38) in the entire cohort. A pre-HSCT MRD level above 0.01% or unknown MRD status, non-TBI regimen, CR>1 were associated with increased risk for relapse in the univariable analysis (p = 0.000, p = 0.056 and p = 0.015 respectively).

EFS and OS at 4-years were 57% (95%:51-64) and 67% (95%:61-73), respectively. The 4-year GRFS in whole group was 55% (95%CI:49-62). Use of TBI regimen had a significant positive correlation with EFS outcomes: EFS for TBI 64% (95%CI:56-72) and for Treo 46%(95%CI:36-56), p=0,019, without effect on OS. In MRD (-) group EFS was 64% (95%CI: 56-72), as compared to 47%(95%CI:34-61) in the MRD (+) group, p=0,014 and OS was 75% (95%CI: 67-82), as compared to 58% (95%CI:45-71) respectively, p=0,007. In MVA in Haplo group number of CR (>1), MRD positive level pre HSCT reached statistical significance for OS (HR, 2.96 (1.42-6.17); P .004 and 1.94 (1.10-3.45); P .0023), for EFS (HR, 2.08 (1.17-3.69); P .012 and 1.91 (1.16-3.13); P .0011), and relapse rate (HR, 3.92 (1.93-7.94); P < .0001 and 3.80 (2.17-6.65); P <0.001). EFS was high (HR, 0.51 (0.30-0.89); P.017) and CIR was low (HR, 0.35 (0.20-0.62); P<0.001) for patients transplanted with TBI. Median time of follow-up for survivors was 4 years (range, 0,7 – 9,4).

Conclusion

We confirm that the depletion of TCR-alpha/beta and CD19 lymphocytes from the graft ensures high engraftment rate and acceptable transplant-related mortality in pediatric ALL patients. Use of TBI and MRD negative status before HSCT had a significant correlation with good outcome.

Long-Term Data Confirm the Superiority of Total Body Irradiation-Containing Conditioning Regimen in Comparison to a Chemotherapy-Based Preparation in Children with Acute Lymphoblastic Leukemia Above the Age of 4 Years Given an Unmanipulated Allograft. Results of the Forum Randomized Clinical Trial

ASH 2022
#2122
Poster presentation

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Study design	Long-term follow-up of prospective randomised multinational trial	**Aim**	Was benefit derived from use of TBI sustained over time?
Parameters assessed	OS, EFS, TRM, CIR, GvHD, GvHD- and relapse-free survival (GRFS), secondary malignancies		
Patients	413	**Age**	4 – 21 y
Disease	ALL		

Conditioning	TBI/VP16	FTT or FBT	p
Results			
n	212	201 (102 FBT, 99 FTT)	
3 y OS	0.90 ± 0.02	0.71 ± 0.03	<0.001
3 y EFS	0.81 ± 0.03	0.59 ± 0.04	<0.001
3 y CIR	0.12 ± 0.02	0.27 ± 0.03	<0.001
3 y TRM	0.02 ± 0.01	0.10 ± 0.02	0.007
3 y cGvHD	0.15 ± 0.03	0.12 ± 0.02	n.s.
3 y 2nd malignancies	0.01 ± 0.01	0.01 ± 0.01	n.s.
3 y GRFS	0.51 ± 0.05	0.62 ± 0.03	<0.001

Conclusion

- TBI conditioning is associated with better outcomes in children > 4 y and adolescents with ALL transplanted in CR, mainly due to a lower risk of leukaemia recurrence.
- Secondary malignancies, after TBI conditioning, deserves particular attention; continuous safety monitoring needed to evaluate the long-term sequels in this population.

Abstract

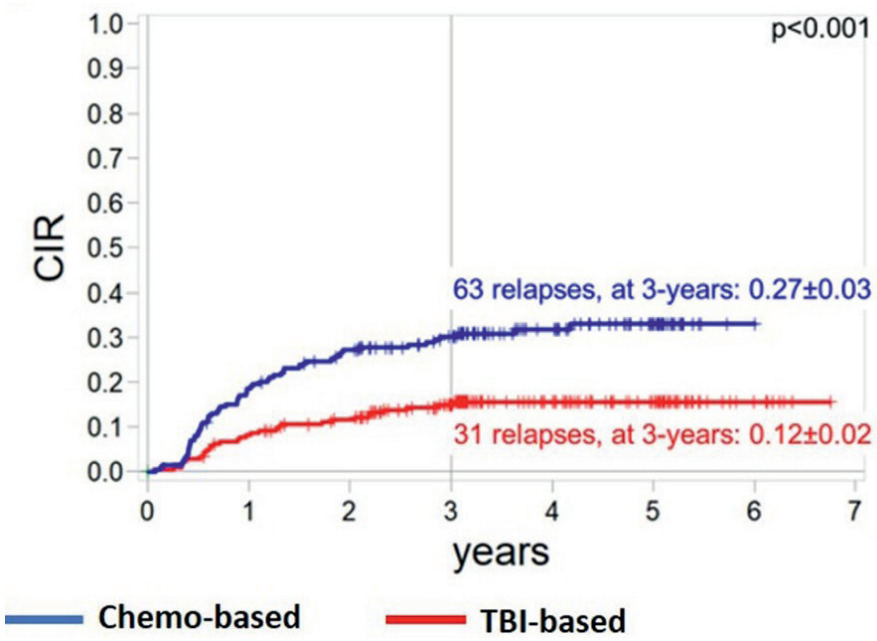
Background
Conditioning regimen plays a crucial role in determining the outcomes of patients with hematological malignancy treated with allogeneic hematopoietic stem cell transplantation (HSCT). In a multicenter, international, randomized, phase 3 clinical Trial (FORUM study), we documented (Peters C, et al. J Clin Oncol 2021) that children with acute lymphoblastic leukemia (ALL) given total body irradiation (TBI) in combination with etoposide had a superior probability of 2-year overall (OS) and event-free survival (EFS) in comparison to patients given either one of two myeloablative chemo-conditioning regimens. In this report, we assessed whether the benefit deriving from the use of TBI was sustained over time.

Patients and methods
Patients <18 years at diagnosis, 4-21 years at HSCT, in complete morphological remission (CR) pre-HSCT, and with an HLA-compatible related or unrelated donor (UD) were randomly assigned 1:1 to a myeloablative conditioning regimen with fractionated TBI and etoposide or fludarabine, thiotepa, and either busulfan (BU) or treosulfan (TREO). Children transplanted from a matched sibling donor (MSD) received cyclosporine A only as graft-versus-host disease (GvHD) prophylaxis, whereas recipients of UD HSCT also received short-term methotrexate and anti-thymocyte globulin (ATG). Further details on transplant procedure have been described elsewhere (Peters C, et al. J Clin Oncol 2021).

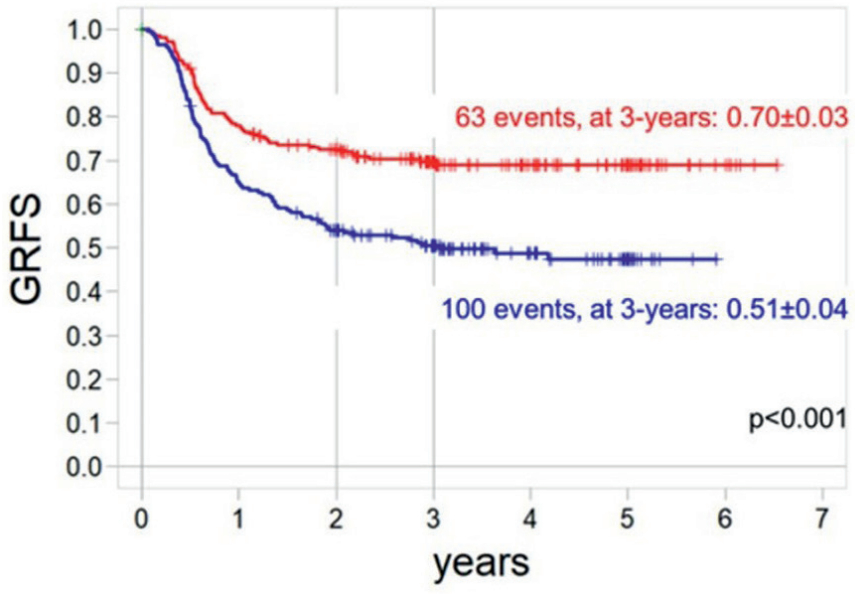
Results
Between 04/2013 and 12/2018, 413 patients were randomly assigned to receive either TBI (212) or a chemotherapy-based conditioning (201). Compliance with random assignment was 92%. Sixty-five percent of patients were male, 72% had B-cell precursor ALL, 73% were transplanted from a UD, and in 82% of patients bone marrow was the stem cell source employed. Fifty-four percent of patients were in CR1 at time of allograft, while 40% and 4% were transplanted in CR2 and CR3, respectively. Patient's outcomes were updated on February 1st, 2022. With a median follow-up of 3.7 years (range, 0.3-7.9), the 3-year probability of OS of patients allocated to TBI/etoposide or to the chemotherapy-based conditioning regimens was 90±2% and 71±3% ($p<0.001$), respectively, while that of 3-year EFS was 81±3% and 59±4% ($p<0.001$). OS and EFS remain comparable in patients receiving BU or TREO in combination with fludarabine and thiotepa. In detail, OS and EFS of the 102 patients given BU, fludarabine and thiotepa were 73±5% and 69±5% respectively, while those of the 99 patients treated with TREO, fludarabine and thiotepa were 62±5% and 61±5%. Multivariate analysis confirmed that the use of chemotherapy-based regimens correlated with worse OS [Hazard Ratio, HR, 2.63, 95% confidence interval, CI, (1.61- 4.31), $p<0.001$] and EFS [HR 2.30, 95%CI (1.58- 3.35) $p<0.001$]. Transplantation in >CR1 predicted a worse EFS in multivariate analysis, as well [HR 1.67, 95% CI (1.14- 2.45) $p=0.009$]. Patients given TBI benefited from a lower cumulative incidence of relapse (Figure 1A), as well as from a lower 3-year cumulative incidence of non-relapse mortality (2+1% vs. 10+2% in the chemo arm, $p=0.007$). The 3-year cumulative incidence of chronic GvHD was comparable between the 2 arms (15+3% vs. 12+2% in the TBI and chemo arm, respectively, p=n.s.). We also analyzed the probability of GvHD/relapse-free survival (GRFS) considering both relapse and chronic GvHD as events; children prepared with TBI had a better 3-year GRFS probability (Figure 1B) as compared to chemo-prepared patients. Five patients (all transplanted from an UD) developed secondary malignancies: 4 of them had received TBI.

Conclusion
With a significantly longer follow-up, we confirm that the use of TBI during the conditioning regimen is associated with better outcomes in children and adolescents with ALL above the age of 4 years transplanted in CR, mainly due to a lower risk of leukemia recurrence. The number of cases of secondary malignancies, particularly in patients offered radiotherapy, deserves particular attention and underlines the importance of continuous safety monitoring over time to comprehensively evaluate the long-term sequels observed in this population.

A


p<0.001
CIR
63 relapses, at 3-years: 0.27±0.03
31 relapses, at 3-years: 0.12±0.02
years
Chemo-based
TBI-based

B


GRFS
63 events, at 3-years: 0.70±0.03
100 events, at 3-years: 0.51±0.04
p<0.001
years

Glutathione S-Transferase Gene Promoter Polymorphism (GSTA1*B) Influences Haematopoietic Cell Transplantation (HCT) Outcome in Patients with β-Thalassemia Receiving Treosulfan/Fludarabine/Thiotepa Regimen

Tandem Meetings 2023
#207
Poster presentation

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Study design	Retrospective analysis	**Aim**	Impact of *NQO1* and *GST* polymorphisms on early clinical outcomes after SCT
Parameters assessed	*NQO1* and *GST* polymorphism, TRM at d+100, thalassaemia-free survival (TFS)		
Patients	314	**Median age**	8 y (range 1 - 25)
Disease	High-risk thalassaemia major		
F	Fludarabine/treosulfan/thiotepa		
Results Variant genotypes HSCT outcome	• 57.4% (n=180) *GSTA1*B* polymorphism • 26.8% (n=84) *NQO1* polymorphism • *GSTA1*B* variant: significantly higher TRM d+100 (p=0.01) and inferior 1-year TFS (p=0.01); in multivariate analysis trend for higher TRM and lower TFS. • *NQO1:* no association between polymorphism and HSCT outcome.		
Conclusion	• *GSTA1*B* polymorphism might affect treosulfan metabolism, increasing S, S-EBDM exposure causing early toxicities, GvHD, resulting in high TRM and inferior TFS.		

Abstract

Introduction and Aim

A toxicity-reduced Treosulfan (Treo) based conditioning regimen has significantly improved HCT outcomes in patients with high-risk thalassemia major (TM). However, complications related to regimen-related toxicities, mixed chimerism, and graft rejection limit its success. We previously explored pharmacokinetics (PK) and pharmacogenetics (PGx) of Treo and its active metabolite-S, S EBDM, where we observed that NAD(P)H Quinone Dehydrogenase-1 (NQO1) and Glutathione S-transferase (GST) polymorphisms contributed significant variability in Treo/S, S-EBDM PK that influenced regimen-related toxicities post HCT (Pai et al., Blood, 2019). We also recently proposed a therapeutic cut-off for Treo exposure for better HCT outcomes (Pai et al., TCT, 2022). In the present study, we assessed the impact of these genetic polymorphisms on early clinical outcomes, including Transplant related mortality (TRM+100) and 1-year Thalassemia-free survival (TFS).

Patients and Methods

All patients with TM undergoing HCT between January 2012 and June 2022 who received Fludarabine/Treo/Thiotepa-based conditioning regimen were included. NQO1 (rs10517) and GST (GSTA1*B) polymorphisms were screened in all patients. Any deaths occurring within the first 100-days post HCT were considered TRM+100. 1-year TFS was defined as survival without graft rejection within the first year post HCT. The influence of these genetic polymorphisms on TRM D+100 and 1-year TFS was estimated using cox regression analysis.

Results

A total of 314 patients were included, in which 180 (57.4%) and 84 (26.8%) patients carried variant genotypes for GSTA1*B & NQO1 polymorphisms, respectively. Patients with variant genotype for GSTA1*B polymorphism had a significantly higher TRM+100 (p=0.01) and inferior 1-year TFS (p=0.01). There was no association between NQO1 polymorphism and HCT outcome. Patients carrying variant genotype for GSTA1*B polymorphism had significantly higher TRM+100 (82.2% Vs 92.4%, p=0.01) and inferior TFS (73.5% Vs 86.4%, p=0.009) (Figure). Multivariate analysis adjusting for known clinical risk factors revealed only a trend towards higher TRM+100 (HR=1.95; 95% CI=0.92-4.13; p=0.07) and inferior TFS (HR=1.77; 95% CI=0.97-3.23; p=0.06) in patients with GSTA1*B variants.

Conclusion

The present study further strengthens our previous findings on Treo PK and PGx. It is possible that GSTA1*B polymorphism affects Treo metabolism, increasing S, S-EBDM exposure causing early toxicities, Graft versus Host disease (GvHD), resulting in high TRM and inferior TFS. We continue to explore the functional relevance of this variant in Treo metabolism.

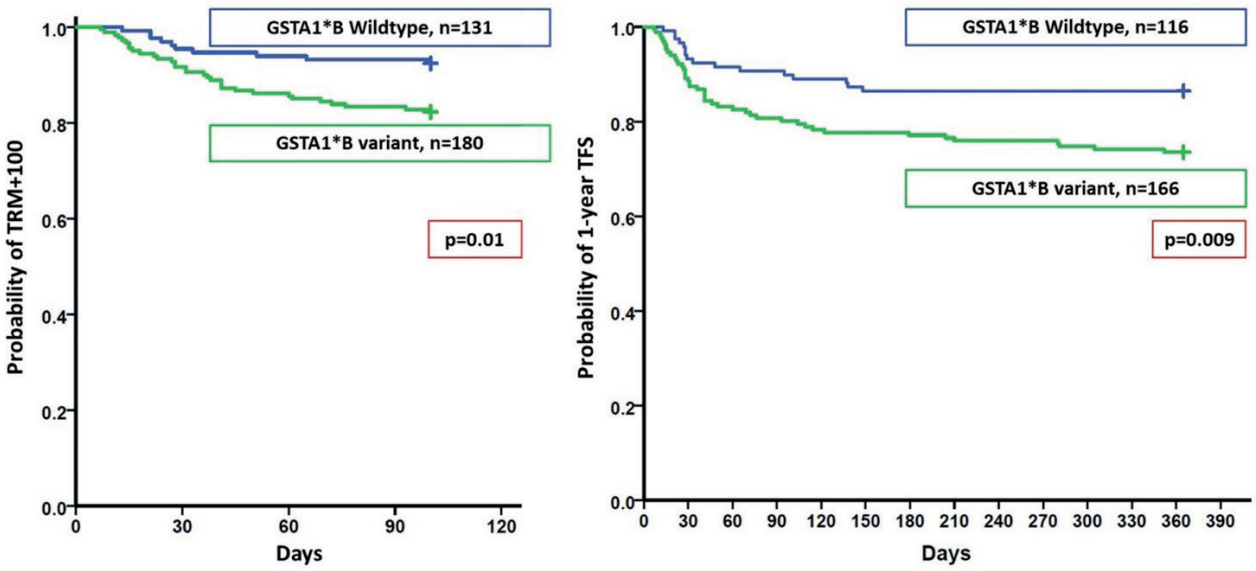

Figure: GSTA1*B variant genotype is significantly associated with increased TRM+100 and inferior 1-year TFS

Early Immune Reconstitution Following Treosulfan-Based Reduced Toxicity Conditioning in Patients Undergoing Allogeneic Transplantation

Tandem Meetings 2023
#420
Poster presentation

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Study design	Prospective study	**Aim**	Immune reconstitution kinetics in alloHSCT recipients receiving treosulfan-based conditioning
Parameters assessed	Engraftment, chimerism, rejection and acute aGvHD status		
Patients	32	**Median age**	7 y (range 1 - 52)
Disease	Thalassaemia (n=22), acute myeloid leukaemia/juvenile myelomonocytic leukaemia (n=4), primary immunodeficiencies (n=4), severe aplastic anaemia (n=1), pure red cell aplasia (n=1)		
Conditioning regimen	Treosulfan-based		
Results Immune reconstitution	• NK cells had a faster recovery by day+28 than other subsets. • T cells recovered by day+28 and gradually increased until day+90: - cytotoxic T cells recovered faster than helper T cells. - γδ T cells recovered faster than αβ T cells at day+28 and gradually increased until day+90. • B cells did not recover up to day+90 post HCT.		
aGvHD	• Patients who did not have aGvHD had faster recovery in NK cells and T-cells at day+28 (preliminary data). • Unique pattern of triggered Tc subsets in patients with aGvHD at d+90 compared to patients who did not have aGvHD.		
Conclusion	• The study provides insights into the early immune reconstitution pattern and could offer cues to the immunologic complications following treosulfan-based conditioning. Further analysis is ongoing.		

Abstract

Introduction and Aim

Allogeneic hematopoietic cell transplantation (alloHCT) is the only potentially curative modality for various hematologic diseases. Early Immune reconstitution (eIR) after alloHCT represents a crucial determinant of the therapeutic success of alloHCT since most transplant outcomes are associated with immune recovery, which is partly attributed to the conditioning regimen. Treosulfan (Treo) based conditioning is increasingly used as the preparative regimen for alloHCT owing to its reduced toxicity. However, there are no reports on the immune reconstitution pattern with this regimen. We evaluated the immune reconstitution kinetics in alloHCT recipients receiving Treo-based conditioning.

Patients and Methods

Thirty-two patients with various underlying diagnoses receiving Treo-based conditioning undergoing alloHCT between October 2021 and May 2022 were prospectively enrolled in the study. The patient demographics are listed in Table. Peripheral blood samples from the patients were collected before the start of conditioning, day of neutrophil engraftment (ANC), days +28, +60, and +90 post HCT. Lymphocyte subsets - T cells and subsets, Natural Killer (NK) cells, and B cells were enumerated using multicolor flow cytometry. Clinical outcomes such as engraftment, chimerism, rejection and acute Graft versus Host Disease status (aGvHD)were documented prospectively.

Results

Flow cytometry analysis revealed that NK cells had a faster recovery by day+28 compared to other lymphocyte subsets. Following NK cells, T cells recovered by day+28 and gradually increased until day+90 post alloHCT. Among the T cell subsets, cytotoxic T cells (Tc) recovered faster [Median: 366 (59-1199) cells/µL, Ref range: ≥200 cells/µL], while helper T cells (Th) did not recover [Median: 161 (9-267) cells/µL, Ref range: ≥200 cells/µL] until day+90. Among Tc subsets, there was an increase in central memory (CM), effector memory (EM) & terminally differentiated effector memory (TD) cells, and a reduction in naïve T cells at day+90 compared to pre-conditioning. The eIR pattern of NK cells and T cells- subsets are represented in the figure. Among T cells, γδ T cells recovered faster than αβ T cells at day+28 and gradually increased until day+90. B cells did not recover up to day+90 post HCT. Of the 32 patients, ten (36%) had aGvHD, and twenty-seven (84%) were alive at the last follow-up. Preliminary data suggests that patients who did not have GvHD had faster recovery in NK cells (Median: 295 Vs. 146 cells/µL, p=0.05) and T cells (Median: 658 Vs. 305 cells/µL, p=0.04) at day+28 post alloHCT.

Conclusion

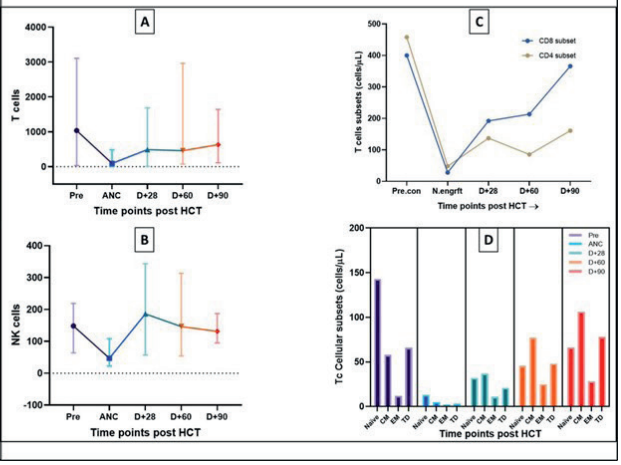
The present study provides insights into the eIR pattern and could offer cues to the immunologic complications following Treo-based conditioning. Further analysis is ongoing to delineate immune reconstitution signature in predicting immunologic complications such as GvHD post Treo-based conditioning.

Table: Baseline characteristics and early outcomes of patients enrolled in the prospective study (n=32)

Patient Characteristics (n=32)	Median (range)/ %
Age	7 (1-52)
Sex	
Male	18 (56)
Female	14 (46)
Diagnoses	
Thalassaemia	22 (69)
AML/JMML	04 (12.5)
PIDD	04 (12.5)
SAA	01 (3)
PRCA	01 (3)
Graft Source	
Peripheral Blood	30 (94)
Bone marrow	02 (6)
Neutrophil Engraftment	
Yes	31
Not evaluable	01
Chimerism status	
Day +28	CC-29, MC-1 and NE-2
Day +60	CC-25, MC-1, Rejection-1, NE-4 and 1 not applicable
Day +90	CC-24, MC-2, Rejection-1, NE-4 and 1 not applicable
Acute GvHD	
Yes	10 (36)
No	18 (64)
Not evaluable	04
Alive Status at LFU	
Alive	27 (84)
Dead	05 (16)

AML- Acute myeloid leukaemia, JMML- Juvenile myelomonocytic Leukemia, PIDD- Primary Immunodeficiency Disease, SAA- Severe Aplastic Anaemia, PRCA- Pure Red Cell Aplasia , CC- Complete chimerism, MC- Mixed chimerism, NE- Not evaluable

Figure: Post-transplant immune reconstitution measured by lymphocyte subset- (A) T-cell counts (/µL), (B) NK cell, counts (/µL), (C) T cell subsets- CD8+ and CD4+ T-cell counts (/µL), and (D) CD8+ T cell subsets (/µL).



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**: 11/2023 Trecondi has been authorised in all countries of the EU as well as in Belarus, Iceland, Kazakhstan, Norway, Liechtenstein, Russia, Switzerland (Ideogen AG), United Kingdom, Ukraine

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