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Reduced Toxicity Conditioning with Treosulfan Compared to Myeloablative Regimens in Elderly Patients with AML and MDS - Results of an EBMT Retrospective Matched Pair Analysis

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COMPARISON OF A NEW REDUCED TOXICITY MYELOABLATIVE TREOSULFAN AND FLUDARABINE PREPARATIVE REGIMEN WITH MYELOABLATIVE BUSULFAN OR MELPHALAN IN OLDER PATIENTS WITH ACUTE MYELOID LEUKEMIA OR MYELODYSPLASTIC SYNDROMES: A RETROSPECTIVE MATCHED PAIR ANALYSIS OF PATIENTS FROM A PROSPECTIVE RANDOMIZED TRIAL AND PATIENTS FROM THE EUROPEAN BLOOD AND MARROW TRANSPLANTATION SOCIETY REGISTRY

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Background

The best preparative regimen for the growing number of older AML or MDS patients undergoing allogeneic HCT from matched related (MRD) or unrelated donors (MUD) remains undefined. A large randomized phase III trial (MC-FludT.14/L study: ClinicalTrials.gov Identifier: NCT00822393) recently demonstrated that myeloablative intravenous (IV) treosulfan (10 g/m^2 IV on days -4 to -2) in combination with fludarabine (TreoFlu) improves outcome in older and/or comorbid patients with AML or MDS compared with reduced intensity busulfan and fludarabine regimen (RIC-BuFlu). The beneficial effect of the TreoFlu regimen resulted from a significantly reduced non-relapse mortality (NRM) and translated to improved event-free survival (EFS) and overall survival (OS) (Beelen DW et al. The Lancet Haematology, 2019). These results raised the question, how this new regimen compares to broadly applied myeloablative regimens, namely busulfan (0.8 mg/kg IV in 6-hour intervals over 4 days) plus cyclophosphamide (BuCy) or melphalan plus fludarabine (MelFlu) in older AML and MDS patients. To address this question, we performed a comparative analysis of MC-FludT.14/L study patients treated with the TreoFlu regimen and matched patients of the European Blood and Marrow Transplantation Society (EBMT) registry.

Patients / Treatment

Table 1: Conditioning regimens and overall patient numbers of EBMT Control Cohort and Treosulfan Treatment Cohort

	Control Cohort (AML and MDS) (N = 968)		Treatment Cohort (AML and MDS) (N = 252)
	MelFlu (EBMT)	BuCy (EBMT)	TreoFlu (CT)
Treatment	Melphalan	**Busulfan** 3.2 mg/kg IV over 4 days	**Treosulfan** 10 g/m^2 IV days -4 to -2
	Fludarabine	Cyclophosphamide	**Fludarabine** 30 mg/m^2 days -6 to -2
Total No. of patients	338	630	252

Patient Selection

Inclusion criteria were essentially the same as for the MC-FludT.14/L study (patient age 50 to 70 years [yrs], primary or secondary AML in CR or MDS, Karnofsky-index ≥ 60%, MRD or MUD, 1st HCT). The study objectives were to compare OS, relapse incidence (RI), and NRM at 2 yrs after HCT between the TreoFlu regimen and EBMT registry patients who underwent HCT from MRD or MUD after the BuCy or MelFlu regimen between 2010 and 2016. A total of 968 EMBT registry patients (AML: n=759 [78%], MDS: n=209 [22%]) with a median age of 58 yrs were identified for the comparison with the 252 MC-FludT.14/L patients (median age 61 yrs, AML: n=174 [69%], MDS: n=78 [31%]). A 1:1 matching method based on propensity scores (PS) with 14 patient-, donor-, and disease-characteristics was used to reduce confounding due to differences between regimens and was performed separately for AML and MDS patients. With the exception of comparison between the TreoFlu and BuCy regimen in AML patients, a significantly higher proportion of patients in the TreoFlu regimen subsets had a HCT-comorbidity index > 2 compared to patient subsets treated with the BuCy or MelFlu regimen.

Table 2: Number of patients by treatment group and disease indication. Control Cohort received MelFlu or BuCy with no additional treatments, while Treatment Cohort represents MC-FludT.14/L patients treated with TreoFlu (Beelen et al. Lancet Haematol, 2019)

		Control Cohort (N = 968)		Treatment Cohort (N = 252)
		MelFlu (EBMT)	BuCy (EBMT)	TreoFlu (CT)
Disease	MDS	82	127	78
	AML	256	503	174
Total		338	630	252

Patient Characteristics

Table 3: AML patient's characteristics and disease criteria that were considered as potential confounding factors for the matched pair comparisons and for the multivariable Cox analysis

		AML Conditioning Regimen				
		MelFlu %	p*	BuCy %	p*	TreoFlu %
Age	Median in years	60.9	0.782	54.4	<0.001	61.0
Time of diagnosis-transplant	Median in months	4.9	0.059	5.7	0.111	5.2
Sex	Male	48.8	0.078	52.9	0.295	57.5
	Female	51.2		47.1		42.5
HCT-CI class	≤ 2	80.0	<0.001	84.2	<0.001	45.4
	>2	20.0		15.8		54.6
Karnofsky status	60	0.0	<0.001	0.2	<0.001	3.7
	70	1.7		1.9		9.2
	80	15.5		13.8		30.7
	90	47.2		40.6		44.2
	100	35.6		43.5		12.3
Prognostic score	Favorable	12.9	0.325	19.0	0.003	7.5
	Intermediate	33.7		28.0		37.4
	Adverse	53.5		53.1		55.2
Donor type	MRD	34.0	0.020	52.7	<0.001	23.6
	MUD	66.0		47.3		76.4

Table 4: MDS patient's characteristics and disease criteria that were considered as potential confounding factors for the matched pair comparisons and for the multivariable Cox analysis

		MDS - Conditioning Regimen				
		MelFlu %	p*	BuCy %	p*	TreoFlu %
Age	Median in years	62.2	0.302	55.9	<0.001	61.0
Time of diagnosis-transplant	Median in months	8.3	0.130	8.4	0.063	6.4
Sex	Male	75.6	0.467	55.9	0.037	70.5
	Female	24.4		44.1		29.5
HCT-CI class	≤ 2	87.0	<0.001	85.5	<0.001	42.3
	>2	13.0		14.5		57.7
MDS subclassification WHO/FAB	Low/Int	51.3	0.014	36.3	0.538	32.1
	High	48.8		63.7		67.9
Karnofsky status	60	0.0	<0.001	0.8	<0.001	10.5
	70	7.0		1.6		13.2
	80	22.5		18.7		38.2
	90	32.4		43.9		27.6
	100	38.0		35.0		10.5
Prognostic score	Favorable	55.2	0.063	50.0	0.763	47.1
	Intermediate	17.2		29.5		26.5
	Adverse	27.6		20.5		26.5
Donor type	MRD	46.3	<0.001	48.0	<0.001	17.9
	MUD	53.7		52.0		82.1

*All p-values were calculated by Pearson' Chi Square test for the comparison of variables for MelFlu and BuCy with TreoFlu with the exception of age, donor age, and time of diagnosis-transplant where p-values were calculated by the Mann-Whitney test. [Data for donor age, secondary origin of disease, disease stage (untreated/treated), stem cell source, gender mismatch, CMV status are provided on request]

Results

Table 5: Summary of matched-pair and multivariable Cox regression analyses for AML patients

	AML Matched Pair Analysis					
	2-years OS % (95% CI)	P	RI % (95% CI)	P	NRM % (95% CI)	P
MelFlu	59 (48 - 69)	0.21	25 (16 - 34)	0.11	18 (10 - 26)	0.11
TreoFlu	72 (64 - 81)		31 (22 - 39)		6 (2 - 11)	
BuCy	49 (36 - 62)	<0.01	30 (18 - 42)	0.46	24 (13 - 34)	<0.01
TreoFlu	76 (66 - 85)		29 (19 - 39)		4 (0 - 8)	
	AML Multivariable Cox Analysis					
	HR for OS (95% CI)	P	HR for RI (95% CI)	P	HR for NRM (95% CI)	P
TreoFlu vs. MelFlu	0.34 (0.20 - 0.57)	<0.01	0.84 (0.45 - 1.57)	0.59	0.26 (0.12 - 0.56)	<0.01
TreoFlu vs. BuCy	0.48 (0.30 - 0.78)	<0.01	0.67 (0.40 - 1.12)	0.13	0.31 (0.15 - 0.66)	<0.01

Note: Each comparison in the matched pair analysis is accompanied by a paired p-value.

Table 6: Summary of matched-pair and multivariable Cox regression analyses for MDS patients

	MDS Matched Pair Analysis					
	2-years OS % (95% CI)	P	RI % (95% CI)	P	NRM % (95% CI)	P
MelFlu	56 (34 - 79)	0.62	24 (5 - 42)	0.74	12 (0 - 26)	0.71
TreoFlu	70 (54 - 86)		13 (1 - 26)		17 (3 - 30)	
BuCy	30 (6 - 55)	0.01	26 (2 - 50)	0.31	43 (17 - 69)	0.13
TreoFlu	72 (54 - 90)		4 (0 - 12)		24 (7 - 40)	
	MDS Multivariable Cox Analysis					
	HR for OS (95% CI)	P	HR for RI (95% CI)	P	HR for NRM (95% CI)	P
TreoFlu vs. MelFlu	NA*		NA*		NA*	
TreoFlu vs. BuCy	0.29 (0.14 - 0.60)	<0.01	NA*		0.46 (0.19 - 1.11)	0.08

Note: Each comparison in the matched pair analysis is accompanied by a paired p-value.
*) Due to low patient numbers adjusted HRs could not be calculated

Acknowledgements / References

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References:
EudraCT number: 2008-002356-18
ClinicalTrials.gov identifier: NCT00822393
Beelen DW et al.: The Lancet Haematology 2020, 7(1), e28-e39: https://doi.org/10.1016/S2352-3026(19)30157-7

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Results

Figure 1: Kaplan Meier curves for OS and cumulative incidence curves for NRM and RI based on matched pairs in AML patients. [FluMel and BuCy (control groups) versus TreoFlu (treatment group)]

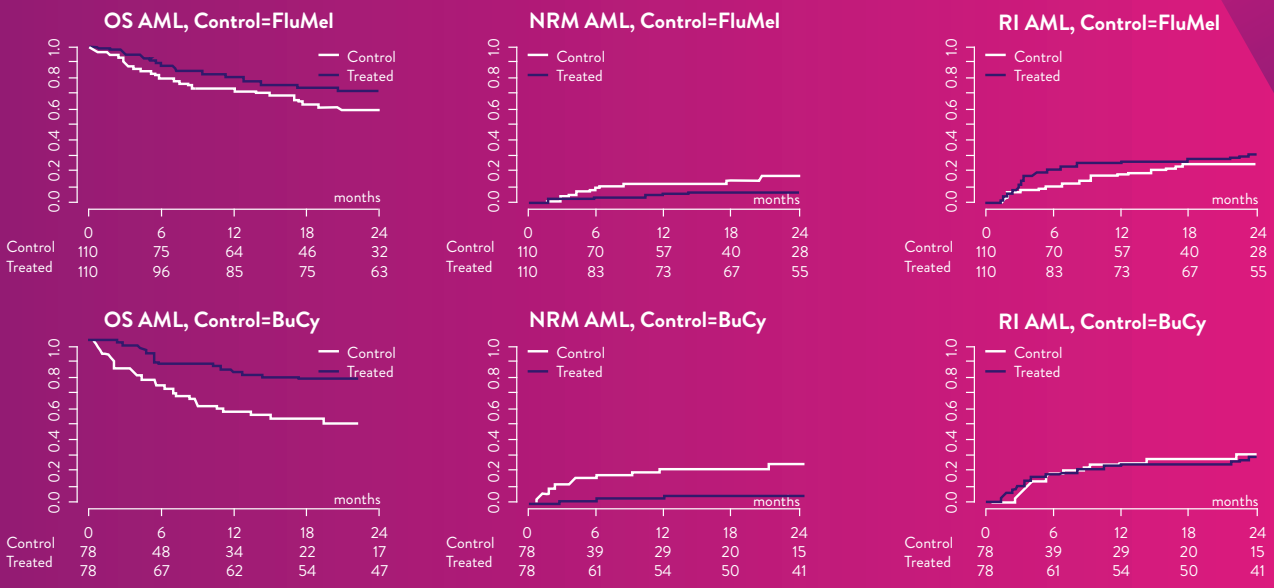
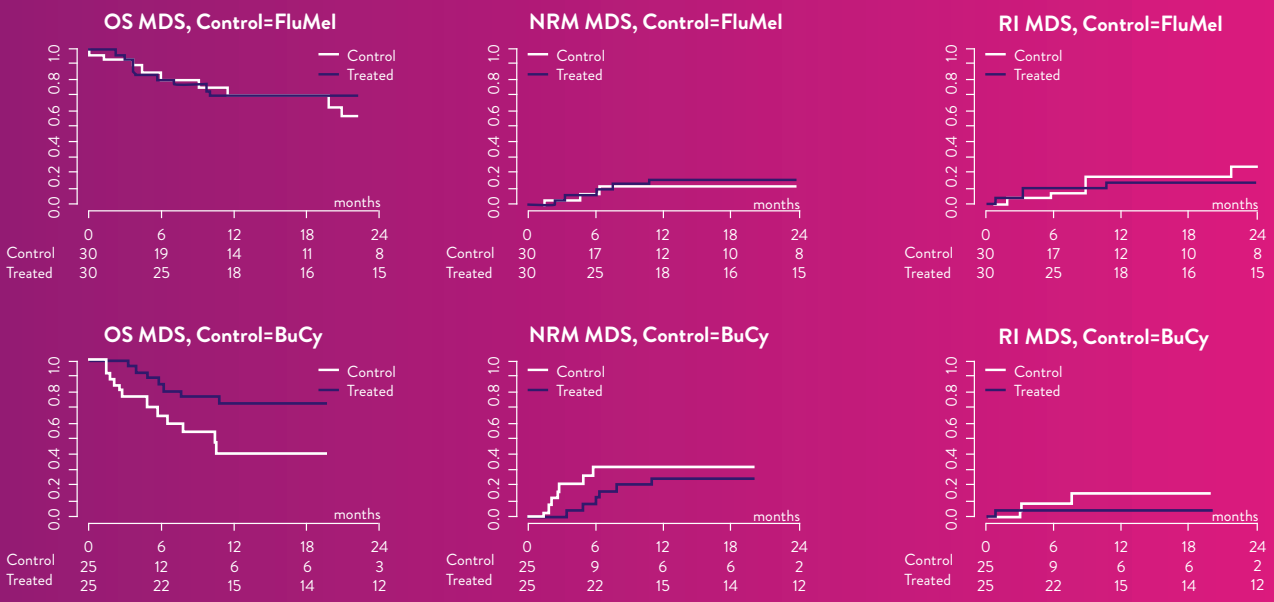


Figure 2: Kaplan Meier curves for OS and cumulative incidence curves for NRM and RI based on matched pairs in MDS patients. [FluMel and BuCy (control groups) versus TreoFlu (treatment group)]



Conclusions

This comparative EBMT registry study applied two “state of the art” statistical methods (matched pairs using propensity score adjustment and multivariable Cox regression analysis).

Some differences were observed in the patient characteristics and disease variables within the entire control cohort selected from the EBMT-registry. However, these variables were included in the multivariable Cox regression model and therefore, any observed differences were considered in these additional analyses and treatment effects were appropriately adjusted for these variables. Therefore, these differences did not contribute to the overall observed treatment effects.

The two-year overall survival analysis consistently demonstrated clinically relevant improvement after TreoFlu (range 70% - 76%) compared with MelFlu (range: 56% - 59%) or BuCy (range 30% - 49%) in older AML and MDS patients.

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COMPARED TO THE REGIMENS CONSISTING OF BUSULFAN/ CYCLOPHOSPHAMIDE OR MELPHALAN/FLUDARABINE, THE TREOSULFAN-BASED REGIMENS RESULTED IN:

- Clinically relevant improvement in overall survival after 2 years in elderly patients with AML and MDS
- Significant reduction in Non-relapse Mortality in elderly AML patients

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Qualitative and quantitative composition: One vial Trecondi 1 g (5 g) powder for solution for infusion contains 1 g (5 g) of treosulfan. When reconstituted, 1 mL of the solution for infusion contains 50 mg treosulfan. **Therapeutic indications:** Treosulfan in combination with fludarabine is indicated as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in adult patients and in paediatric patients older than one month with malignant and non-malignant diseases. **Posology and method of administration:** Administration should be supervised by a physician experienced in conditioning treatment followed by alloHSCT. *Adults with malignant disease:* Treosulfan is given in combination with fludarabine. Treosulfan 10 g/m² body surface area (BSA) per day as a two-hour intravenous infusion, given on three consecutive days (day -4, -3, -2) before stem cell infusion (day 0). The total treosulfan dose is 30 g/m²; Treosulfan should be administered before fludarabine. *Adults with non malignant disease:* Treosulfan is given in combination with fludarabine with or without thiotepa. Treosulfan 14 g/m² body surface area (BSA) per day as a two-hour intravenous infusion, given on three consecutive days (day -6, -5, -4) before stem cell infusion (day 0). The total treosulfan dose is 42 g/m²; Treosulfan should be administered before fludarabine. *Paediatric population:* Treosulfan is given in combination with fludarabine, with or without thiotepa. **Contraindications:** Hypersensitivity to the active substance; active non-controlled infectious disease; severe concomitant cardiac, lung, liver, and renal impairment; Fanconi anaemia and other DNA breakage repair disorders; pregnancy; administration of live vaccine. **Undesirable effects:** *Infections, infestations:* Very commonly infections (bacterial, viral, fungal). Commonly **s**epsis. Septic shock. *Neoplasms:* Treatment related second malignancy. *Blood, lymphatic system:* Very commonly myelosuppression, pancytopenia, febrile neutropenia. *Immune system:* Commonly hypersensitivity. *Metabolism and nutrition:* Commonly decreased appetite. Uncommonly glucose tolerance impaired including hyperglycaemia and hypoglycaemia. Acidosis, alkalosis, electrolyte imbalance, hypomagnesaemia. *Psychiatric:* Commonly insomnia. Uncommonly confusional state. *Nervous system:* Commonly headache, dizziness. Uncommonly intracranial haemorrhage, peripheral sensory neuropathy. Encephalopathy, intracranial haemorrhage, extrapyramidal disorder, syncope, paraesthesia, seizure. *Eye:* Dry eye, conjunctival haemorrhage. *Ear:* Uncommonly vertigo. *Cardiac:* Commonly cardiac arrhythmias (e.g. atrial fibrillation, sinus arrhythmia). Cardiac arrest, cardiac failure, myocardial infarction, pericardial effusion. *Vascular:* Commonly hypertension, hypotension, flushing. Uncommon haematoma. Embolism, capillary leak syndrome. *Respiratory, thoracic, mediastinal:* Commonly dyspnoea, epistaxis, oropharyngeal pain. Uncommonly pneumonitis, pleural effusion, pharyngeal or laryngeal inflammation, hiccups. Laryngeal pain, cough, dysphonia, hypoxia. *Gastrointestinal:* Very commonly stomatitis/mucositis, diarrhoea, nausea, vomiting, abdominal pain. Commonly oral pain, gastritis, dyspepsia, constipation, dysphagia, oesophageal or gastrointestinal pain, anal inflammation. Uncommonly mouth haemorrhage, abdominal distension, dry mouth. Gastric haemorrhage, neutropenic colitis, oesophagitis, proctitis, gingival pain. *Hepatobiliary:* Very commonly hepatotoxicity. Uncommonly veno-occlusive liver disease. Hepatomegaly. *Skin, subcutaneous tissue:* Very commonly pruritus, alopecia. Commonly (maculo-papular) rash, purpura, erythema, urticaria, palmar plantar erythrodysaesthesia syndrome, dermatitis exfoliative, pain of skin, skin hyperpigmentation. Uncommonly erythema multiforme, dermatitis acneiform, dry skin. Skin necrosis or ulcer, dermatitis, dermatitis bullous, dermatitis diaper. *Musculoskeletal and connective tissue:* Commonly pain in extremity, back pain, bone pain, arthralgia. Uncommonly myalgia. *Renal, urinary:* Commonly acute kidney injury, haematuria. Uncommonly urinary tract pain. Renal failure, haemorrhagic or noninfective cystitis, dysuria. *Reproductive system:* Scrotal erythema, penile pain. *General, administration site:* Very commonly asthenic conditions (fatigue, asthenia, lethargy), pyrexia. Commonly oedema, chills. Uncommonly non cardiac chest pain, pain, face oedema. *Investigations:* Very commonly blood bilirubin increased, ALT increased. Commonly AST increased, γGT increased, C-reactive protein increased, weight decreased, weight increased. Uncommonly blood alkaline phosphatase increased. Blood lactate dehydrogenase (LDH) increased. **Legal classification**: POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH Theaterstraße 6; 22880 Wedel, Germany. **Date of revision of text**: 01/2026
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