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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



IMPROVING PERSPECTIVES

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

Authors: Dietrich W. Beelen¹, Simona Iacobelli², Linda Koster³, Dirk-Jan Eikema³, Anja van Biezen³, Friedrich Stoelzel4, Fabio Ciceri⁵, Wolfgang Bethge⁰, Peter Dreger7, Eva-Maria Wagner8, Péter Reményi9, Matthias Stelljes¹º and Miroslaw Markiewicz¹¹

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/m² 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 (MeIFlu) 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

	Control Cohort ((N =	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 IV² days -4 to -2	
	Fludarabine	Cyclophosphamide	Fludarabine 30 mg/m² days -6 to -2	
Total No. of patients	338	630	252	

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

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 \geq 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 HCTcomorbidity 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

		AML Conditioning Regimen				
		MelFlu %	Р*	BuCy %	р*	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
C	Male	48.8	0.078	52.9	0.295	57.5
	Female	51.2		47.1		42.5
	≤2	80.0	<0.001	84.2	<0.001	45.4
	>2	20.0		15.8		54.6
	60	0.0	<0.001	0.2	<0.001	3.7
	70	1.7		1.9		9.2
Karnofsky status	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
Denestar	MRD	34.0	0.020	52.7	<0.001	23.6
Donor type	MUD	66.0		47.3		76.4

 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

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 %	Р*	BuCy %	Р*	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
S	Male	75.6	0.467	55.9	0.037	70.5
Sex	Female	24.4		44.1		29.5
	≤2	87.0	<0.001	85.5	<0.001	42.3
	>2	13.0		14.5		57.7
MDS subclassification	Low/Int	51.3	0.014	36.3	0.538	32.1
WHO/FAB	High	48.8		63.7		67.9
	60	0.0	<0.001	0.8	<0.001	10.5
	70	7.0		1.6		13.2
Karnofsky status	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

	AML Matched Pair Analysis					
	2-years OS % (95% CI)	Р	RI % (95% CI)	р	NRM % (95% CI)	Р
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)	Р	HR for RI (95% CI)	Р	HR for NRM (95% CI)	Р
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

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

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)	Р	RI % (95% CI)	Р	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)	Р	HR for RI (95% CI)	Р	HR for NRM (95% CI)	Р
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

Acknowledgements:

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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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¹ Department of Bone Marrow Transplantation, West German Cancer Center, University Hospital of Essen, University of Duisburg-Essen, Essen, Germany; ² Department of Biology, University Tor Vergata of Rome, Rome, Italy; ³ EBMT Data Office Leiden, Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, Netherlands; ⁴ Department of Internal Medicine 1, University Hospital Carl Gustav Carus Dresden, Technical University Dresden, Dresden, Germany; ⁵ Hematology and Bone Marrow Transplantation Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy; ⁶ Department of Hematology and Oncology, University Hospital Tuebingen, Tuebingen, Germany; ⁷ Department of Internal Medicine V, University of Heidelberg, Heidelberg, Germany; ⁸ 3rd Department of Medicine - Hematology, Internal Oncology & Pneumology, Johannes Gutenberg-University Medical Center, Mainz, Germany; ⁸ St. István and St. László Hospital of Budapest, Budapest, Hungary; ¹⁰ Department of Medicine, University of Rzeszow, Rzeszow, Poland

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.



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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