Treosulfan conditioning for allogeneic transplantation in multiple myeloma - improved overall survival in first line haematopoietic stem cell transplantation - a large retrospective study by the Chronic Malignancies Working Party of the EBMT

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. All AEs, any grade, regardless of attribution to CA1P, by system organ class reported for All R/R AML and MDS patients treated with CA1P (OXi4503) as a single agent (N = 19).

Table SII. CA1P-related adverse events according to CTCAE severity grade in safety population (N = 19).

Data S1. Supplemental methods.

Data S2. Supplemental results.

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Allogeneic hematopoietic stem cell transplantation (allo-HSCT) for the treatment of multiple myeloma (MM) is controversial mainly due to the high non-relapse mortality (NRM) with myeloablative conditioning (MAC). Previous pilot studies of a number of patients have indicated that treosulfan-conditioning (Treo) in allo-HSCT for MM is feasible, and results in stable engraftment and low NRM.[1–5]

In this retrospective study, we compare outcomes of patients with MM undergoing first allo-HSCT after receiving Treo-based conditioning (n = 508) with those who received non-Treo reduced-intensity conditioning (RIC, n = 2830) and non-Treo MAC (n = 1177). Included patients were reported between 2008 and 2016 to the European Society for Blood and Marrow Transplantation. Out of the total of 4515 patients, 1098 (24·3%) were transplanted in first line, defined as first allo-HSCT, either as single allo-HSCT or in tandem as autologous (auto)-HSCT/allo-HSCT.

The primary endpoints were overall survival (OS) and relapse-free survival (RFS), and the secondary endpoints were relapse, NRM, and acute and chronic Graft-versus-Host-Disease (aGvHD and cGvHD). The starting point for the time-to-event analysis was the date of the first allogeneic transplantation, and patients who were alive without an event were censored at the last follow-up. For OS, the event was defined as death regardless of cause, while for RFS, the event was disease relapse or death, whichever happened first. Relapse and NRM were analysed as competing risks. We obtained cause-specific hazard ratios for Treo and RIC *versus* MAC-based conditioning for primary and secondary endpoints adjusted for age, Karnofsky score and remission status at transplantation, interval between diagnosis and transplantation, donor gender match and type of donor. Analyses were stratified by upfront single allogeneic and tandem autologous-allogeneic transplantation. The patient characteristics are summarised in Table I.

In the univariate analysis, the five-year overall survival (OS) in first line Treo was significantly superior, compared to the RIC and MAC patients, which was 62%, 57% and 47%, (log rank $P = 0{\cdot}04$, see Fig 1A and Table SI), respectively. A trend of lower NRM was observed with Treo (10%), in comparison to RIC (17%) and MAC (19%) (Gray's test $P = 0{\cdot}10$, Fig 1B), as was the tendency of higher relapse in Treo – 59%, 50% and 49% for Treo, RIC and MAC, respectively (Gray's test $P = 0{\cdot}08$, Fig 1C). RFS was not significantly different between the three groups in first line (logrank $P = 0{\cdot}70$, Fig 1D). In the multivariate analysis, both Treo and RIC gave a superior OS compared to MAC, HR 0·58 (95% CI: 0·39–0·88, $P = 0{\cdot}009$) and HR 0·66 (95% CI: 0·52–0·84, $P < 0{\cdot}001$) (Table SIII).

Information on the best post-transplantation response was available in 87% of patients. A complete response (CR), regardless of the line of treatment, was observed in 42% ($n = 192$) of Treo patients compared to 50% ($n = 1247$) for RIC and 57% ($n = 557$) for MAC ($P < 0{\cdot}001$). In the first line setting, CR was observed in 48% ($n = 61$), 59% ($n = 320$) and 64% ($n = 211$) for Treo, RIC and MAC ($P = 0{\cdot}008$), respectively.

In patients transplanted either as a second- or third-line treatment or as later lines there was no significant difference

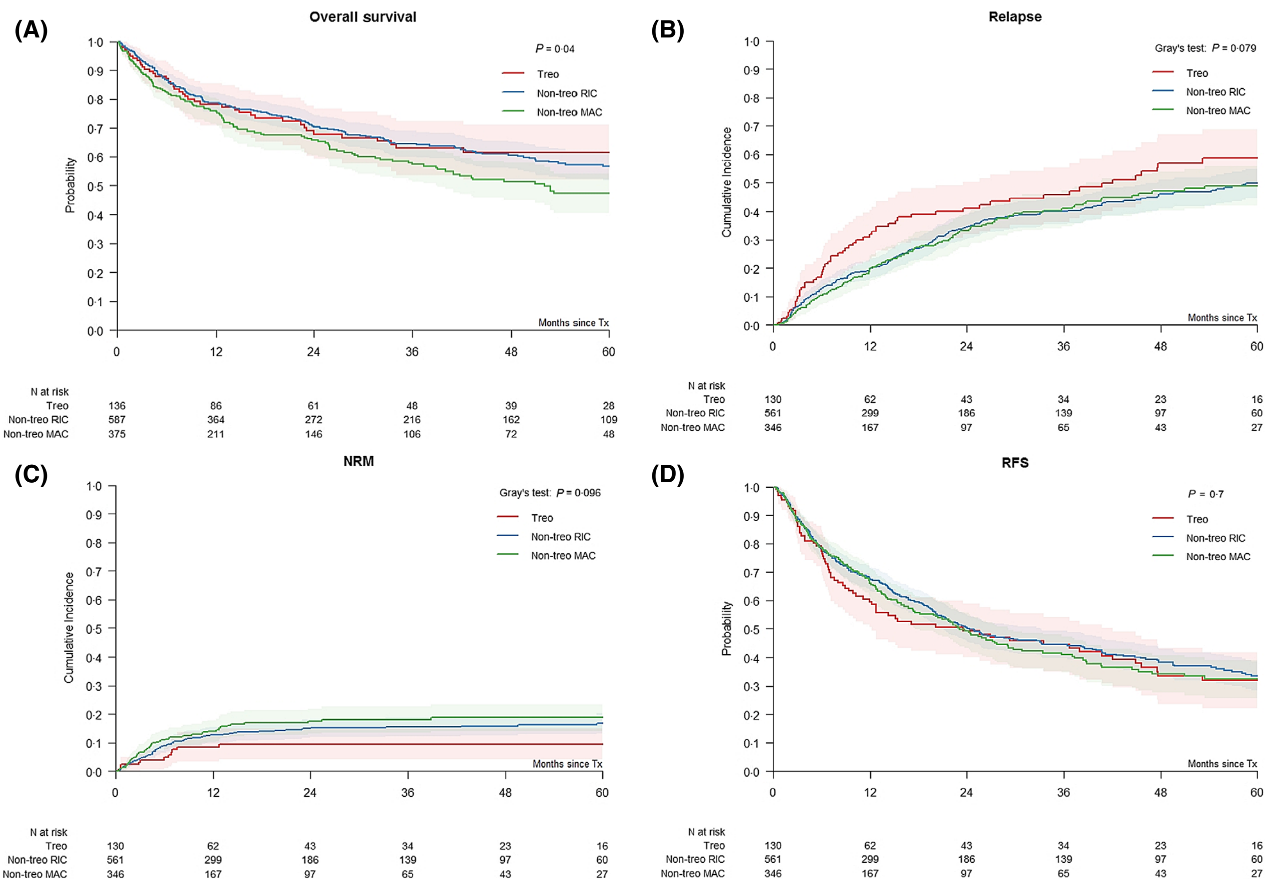

Fig 1. Outcomes in first line treatment. (A) Kaplan-Meier curve of overall survival (OS). (B) Cumulative incidence curve of non-relapse mortality (NRM). (C) Cumulative incidence curve of relapse. (D) Kaplan-Meier curve of progression-free survival (PFS).

Table I. Patient characteristics. Lines of treatment defined as first line for upfront allo-HSCT and first line auto/allo-HSCT, with an interval between transplants <6 months and no relapse. Second line for salvage allo-HSCT, and third line and later lines include patients with allo-HSCT in third and fourth line, interval between transplants 6–12 months with or without relapse.

	Treosulfan conditioning	Non-myeloablative conditioning	Myeloablative conditioning	*P*-value
Gender, no. (%)				
Male	307 (60%)	1763 (62%)	765 (65%)	0·14
Female	201 (40%)	1067 (38%)	412 (35%)	
Age, years median (range)	54·2 (31·4–77·6)	54·5 (19·2–73·8)	50·9 (18·5–72·7)	<0·0001
Type of myeloma, no. (%)				
IgG	208 (42%)	1366 (49%)	556 (49%)	<0·0001
IgA	78 (16%)	543 (20%)	197 (17%)	
Light chain	191 (39%)	761 (27%)	334 (29%)	
Other Ig	4 (1%)	42 (2%)	23 (2%)	
Non-secretory	9 (2%)	64 (2%)	37 (3%)	
Line of treatment, no. (%)				
Upfront	136 (27%)	587 (21%)	375 (32%)	<0·0001
Single allo (% of upfront)	38 (28%)	143 (24%)	227 (61%)	
Tandem auto/allo (% of upfront)	98 (72%)	444 (76%)	148 (39%)	
Second line	165 (33%)	1123 (40%)	394 (34%)	
Beyond second line	207 (41%)	1120 (40%)	408 (35%)	
CMV status, no. (%)				
Positive	319 (63%)	1752 (63%)	709 (63%)	0·99
Negative	186 (37%)	1019 (37%)	409 (37%)	
Cytogenetic risk, no. (%)				
High	21 (4%)	95 (3%)	47 (4%)	0·82
Standard	69 (14%)	396 (14%)	159 (14%)	
Unknown	418 (83%)	2339 (83%)	971 (83%)	
Stage ISS (or Durie & Salom) at diagnosis, no. (%)				
I	31 (6%)	183 (7%)	80 (7%)	0·77
II	32 (6%)	161 (6%)	65 (6%)	
III	20 (4%)	146 (5%)	49 (4%)	
Unknown	425 (84%)	2340 (83%)	983 (84%)	
Response status at conditioning, no. (%)				
<PR	101 (20%)	485 (18%)	248 (22%)	<0·0005
VGPR/PR	314 (63%)	1655 (60%)	680 (60%)	
CR	80 (16%)	623 (23%)	215 (19%)	
Donor, no. (%)				
Identical sibling	137 (27%)	1231 (44%)	478 (42%)	<0·0001
Other	367 (73%)	1575 (56%)	672 (58%)	
Karnofsky, no. (%)				
<90	92 (20%)	664 (26%)	302 (28%)	0·005
≥90	368 (80%)	1938 (74%)	781 (72%)	
Year of allogeneic transplantation, no. (%)				
2008	27 (5%)	309 (11%)	96 (8%)	<0·0001
2009	36 (7%)	315 (11%)	126 (11%)	
2010	69 (14%)	378 (13%)	121 (10%)	
2011	75 (15%)	348 (12%)	145 (12%)	
2012	77 (15%)	373 (13%)	167 (14%)	
2013	53 (10%)	348 (12%)	164 (14%)	
2014	67 (13%)	292 (10%)	132 (11%)	
2015	62 (12%)	263 (9%)	127 (11%)	
2016	42 (8%)	204 (7%)	99 (8%)	

PR, partial response; VGPR, very good partial response; CR, complete response; ISS, International Staging System.

observed in the OS for Treo compared to RIC and MAC in either the univariate or multivariate analysis, while the relapse incidence was significantly higher for Treo given as a second line.

Our study shows that Treo-conditioning in upfront-treated patients is superior to other RIC- or MAC-conditioning regimens for reducing NRM without hampering long-term survival, despite a slightly increased relapse rate. This could not be documented in later lines of treatment, possibly due to a greater heterogeneity of the patients, late in the course of the disease.

Identifying conditioning regimens resulting in low NRM, without increasing relapse rate, and which translate into improved OS, is of importance for the future of allo-HSCT in MM. Our results show a five-year NRM of 17% with Treo, regardless of the treatment line, and a one-year NRM as low as 13% (results not shown), lower than previously shown by Schmidt-Hieber *et al.* (25·5% at one year)[3] and corroborates with the previous indicative studies shown in a few patients, by Nahi *et al.*[1]

The one-year cumulative incidence of NRM for upfront allo-HSCT was even lower for Treo, 9%, as compared to 13%, and 14% for RIC, and MAC, respectively. The RIC and MAC incidences are in line with previously published rates between 11–16%.[6–8] The cumulative incidence at five years for Treo was only modestly higher, 10% compared to 17% and 19% for RIC, and MAC, respectively, which indicates that complications after allo-HSCT with Treo occur early.

We adjusted for factors independently associated with OS and NRM, i.e. Karnofsky score and type of donor. In our study, patients conditioned with Treo received stem cells more often from an unrelated donor, as compared to RIC and MAC (73%, 56% and 58%, respectively), and still showed a significantly lower NRM. In contrast, the Karnofsky score was somewhat better in Treo compared to MAC and RIC, which could have favourably affected the higher OS in Treo. However, in multivariate analysis, Treo was still an independent prognostic factor, but due to the possibility of residual confounding, our results should be interpreted cautiously.

In the great majority of patients, Treo-conditioned allo-HSCT, as well as RIC, were performed as tandem auto/allo-HSCT. Overall, the five-year OS in these patients was 59%, as compared to 46% for allo-HSCT without prior auto-HSCT, and the NRM was low compared to allo-HSCT without prior auto-HSCT (Table SII), as previously published.[6,9,10,11] No significant differences could be observed for conditioning regimes in tandem auto/allo-HSCT ($P = 0{\cdot}4$), with a five-year OS at 65% for Treo, 59% for RIC and 53% for MAC.

In conclusion, these findings suggest that conditioning with Treo, especially early in the course of the disease, is of benefit in allo-HSCT.

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Supporting Information

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Table SI. Univariate analysis of the conditioning regimes for outcomes OS, RFS, relapse, NRM, aGvHD, and cGvHD. First line – conditioning received in first allo-HSCT. Treosulfan, treosulfan included in a conditioning regime; RIC, non-treosulfan-reduced intensity conditioning; MAC, non-treosulfan myeloablative conditioning.

Table SII. Univariate analysis, factors associated with OS, RFS, relapse, and NRM. Tandem auto/allo-HSCT = first line auto/allo-HSCT, where the interval between transplants is <6 months and with no relapse. Upfront allo-HSCT, upfront allo-HSCT without previous auto-HSCT.

Table SIII. Multivariate analysis, factors associated with OS, RFS, relapse, and NRM (restricted to patients in the first line). First line – conditioning received in first allo-HSCT. Treosulfan, treosulfan included in the conditioning regime; RIC, non-treosulfan-reduced intensity conditioning; MAC, non-treosulfan myeloablative conditioning; PR, partial response; VGPR, very good partial response; CR, complete response.

Fig S1. Kaplan-Meier curves of overall survival; (A) regardless of treatment line, (B) first line conditioning by upfront allo-HSCT and auto/allo-HSCT, (C) upfront allo-HSCT by conditioning regime, and (D) first line auto/allo-HSCT by conditioning regimen. Treo = treosulfan included in conditioning regime. Non-RIC = non-treosulfan-reduced intensity conditioning, and non-MAC = non-treosulfan myeloablative conditioning. In the univariate analysis at five years, regardless of the treatment line, there was a trend for a better OS with Treo, 41% compared to 39% and 37% (CI, 95% 36–46, 37–41, and 33–40, $P = 0{\cdot}05$) for RIC and MAC, respectively (Fig 1A). In the Treo dose, no difference was observed for the low dose (≤36 g/m^2) and high dose (>36 g/m^2) compared to RIC and MAC. The five-year OS in the first line setting using tandem auto/allo-HSCT was higher compared to allo-HSCT without prior auto-HSCT, 59% and 46% (CI, 95% 54–63 and 40–53, $P < 0{\cdot}001$). No significant difference was observed for the conditioning regimen for either the tandem auto/allo-HSCT or allo-HSCT without prior auto-HSCT (Fig 1B–D). In the multivariate analyses, both first line Treo retained a significant superiority when compared to MAC, (HR 0·63; CI 95% 0·42–0·96, $P = 0{\cdot}03$), while RIC exhibited a trend of improved OS (HR 0·77; CI 95% 0·59–1·00, $P = 0{\cdot}05$.

Fig S2. Cumulative incidence curve of non-relapse mortality, regardless of treatment line. Treo = treosulfan included in conditioning regime. Non-RIC = non-treosulfan-reduced intensity conditioning, and non-MAC = non-treosulfan myeloablative conditioning. In the univariate analysis, the five-year NRM, regardless of the treatment line, was 17% for Treo compared to 21% and 23% (CI, 95% 13–21, 19–23 and 21–26, $P = 0{\cdot}017$) for RIC and MAC, respectively (Fig 2A). No difference was observed for the Treo dose, ≤36 g/m^2 (19%; CI, 95% 11–28) and >36 g/m^2 (19%; CI, 95% 13–23). A tendency for a lower NRM with Treo (10%) was observed in comparison to RIC (17%) and MAC (19%) ($P = 0{\cdot}096$) in the first line setting (Table 2, Fig 2B). In the tandem auto/allo-HSCT, the NRM was 14% (CI, 95% 11–17) at five years, compared to 22% (CI, 95% 17–26) in allo-HSCT without prior auto-HSCT ($P = 0{\cdot}001$).

Fig S3. Cumulative incidence curve of relapse, regardless of treatment line. Treo = treosulfan included in the conditioning regime. Non-RIC = non-treosulfan-reduced intensity conditioning, and non-MAC = non-treosulfan myeloablative conditioning. In the univariate analysis, the overall five-year cumulative incidence of relapse was significantly higher for Treo, regardless of the treatment line, i.e., 64% compared to 60% in RIC and 55% in MAC (CI, 95% 58–69, 58–63, and 52–59, $P < 0{\cdot}001$), while in the first line setting, no significant difference was noted between Treo, RIC and MAC (Table 2, Fig 3A,B). A low Treo dose, ≤36 g/m^2, demonstrated a higher relapse rate, 66% (CI, 95% 57–77), compared to a higher dose (>36 g/m^2), RIC, and MAC, 60%, 60%, and 55% (CI, 95% 53–97, 58–63, 51–59 $P = 0{\cdot}002$), respectively.

Fig S4. Kaplan-Meier curve of the progression-free survival, regardless of treatment line. Treo = treosulfan included in conditioning regime. Non-RIC = non-treosulfan-reduced intensity conditioning, and non-MAC = non-treosulfan myeloablative conditioning. In the univariate analysis, there was no significant difference in the five-year cumulative incidence of RFS between the cohorts, regardless of the line of treatment or in the first line setting (Table 2, Fig 4A,B). No difference was observed for the dose of Treo compared to RIC and MAC (Table 2). No difference was observed for the tandem auto/allo-HSCT as compared to allo-HSCT without a prior auto-HSCT.

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