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Is Less "Sufficient" and "Safe" in the MRD Era - Outcomes of Autologous Stem-Cell Transplant as per Melphalan Dose in Patients with Multiple Myeloma

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INTRODUCTION

Multiple Myeloma (MM), with an incidence of 1 per 100,000, accounts for 1.2% of all cancers in India [1]. Bortezomib-Lenalidomide-Dexamethasone (VRd) with or without Daratumumab, followed by autologous stem-cell transplant (ASCT) and lenalidomide maintenance is the standard-of-care (SOC) treatment for newly diagnosed transplant-eligible MM [2]. While melphalan 200 mg/m^2 is the standard conditioning, a lower dose of 140 mg/m^2 is used in patients perceived to be at risk of excess toxicity. The only randomized trial which compared Melphalan 200 mg/m^2 versus 140 mg/m^2 used an additional 8 gray total-body-irradiation in the Melphalan 140 mg/m^2 arm. It showed that the median survival was higher, with lesser toxicities in Melphalan 200 mg/m^2 arm, consequent to which it became the SOC [3]. Over last two decades, Melphalan 200 mg/m^2 has been compared with other intensive chemotherapy or radiation-based conditioning regimens. All of these showed lesser toxicity with equivalent survival for Melphalan 200 mg/m2. Hence, it still remains the undisputed standard after nearly 25 years [4]. Previous retrospective analyses of Melphalan 200 mg/m^2 versus 140 mg/m^2, including studies from EBMT [5], MDACC [6] and India [7], have shown similar survival for lower-dose of melphalan, especially in patients with ≥VGPR pre-ASCT. Additionally, while transplant-related mortality (TRM) remains <1% in west [5, 6], it varies between 2–7% for low-middle-income-countries (LMICs) like India [8]. This highlights the need for safer and less toxic conditioning in MM. Hence, with effective therapies and availability of MRD for response assessment, it is important to revisit the standard melphalan dose in today's era.

MATERIALS AND METHODS

This was a retrospective single-centre study from India, which included MM patients who underwent ASCT over the last 15 years. Our primary objective was to compare median PFS and OS in patients who received Melphalan 200 mg/m^2 (Mel-200) versus those who received ≤140 mg/m^2 (Mel-140). Our secondary objectives were to compare median PFS in Mel-200 vs Mel-140 for following subgroups: ≥VGPR pre-ASCT, those who underwent ASCT in first-remission, baseline cytogenetics (standard and high-risk), pre-ASCT bone-marrow (BM) flow-cytometry MRD status (Negative and positive), and 18-FDG-PET-CT status prior to ASCT (Negative and positive).

Between 1st March 2007–31st December, 2022, 178 patients underwent 192 ASCTs. Amongst these 178 patients, two patients with tandem transplants and patients who underwent second transplant at relapse were excluded (due to higher cumulative melphalan dose). Thus, we analysed 176 ASCTs in 176 patients (Supplementary Fig. 1). All methods were performed in accordance with the relevant guidelines and regulations. This study was approved by our Institutional Ethics Committee (IEC-III) [Project number 901182 approved on 09 August 2025]. Informed consent was obtained from all participants.

Pre-ASCT work-up included – Hemogram, renal and liver function tests, nutritional status (ferritin, B12, folate levels, transferrin saturation), virology (HIV, HBsAg, anti-HCV, Anti-HBc IgM and IgG, Anti-HBs), DTPA-GFR, MUGA scan for cardiac ejection fraction (EF) and pulmonary function tests (PFT) with diffusion capacity for carbon monoxide (DLCo). In view of literature of higher TRM (6%) in patients with renal impairment [9] and IMWG consensus guidelines for renal impairment [10], we used a GFR cut-off of 60 ml/minute for Melphalan dose-reduction to 140 mg/m^2. Apart from GFR, patients with borderline organ functions: EF 40–50%, and/or impaired PFTs (FEV1 or FEV1/FVC ratio <70% or corrected DLCo<65%) received Melphalan doses ≤140 mg/m^2, as per discretion of transplant physician.

We reported in ASH-2014 (Abstract#731) that pre-ASCT PET positivity predicted early relapse. Consequent to this, we mandated our institutional policy to do 18-FDG-PET-CT for all patients of MM pre-transplant. Results of pre-transplant PET-CT were considered as either negative or positive, as per IMWG 2016 criteria [11].

BM-MRD was evaluated using a highly-sensitive 13-colour flow-cytometry (sensitivity-0.0001% or 10^{-6}) method, as described before [12]. From 2016 onwards, all our patients underwent BM-MRD pre-transplant as part of institution policy. For analysis, BM-MRD at a threshold of <0.001% or <10^{-5} was considered negative, while ≥0.001% or 10^{-5} was defined as MRD positive.

Stem-cell mobilization, maintenance post-ASCT and response monitoring, were as described before [1, 13]. In absence of BM examination pre-ASCT, maximum response was graded as VGPR [11]. For analysis, patients with pre-induction serum creatinine >2 mg/dl were considered as those with baseline renal dysfunction (RD). For stratification as per cytogenetics [mSMART3.0], patients with any one of the following cytogenetics: t(4;14), t(14;16), t(14;20), chromosome-1 abnormalities (1q gain or amplification, 1p deletion) and deletion 17p were considered high-risk [2]. Rest was considered as standard-risk.

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Table 1. Baseline and peri-transplant characteristics of Mel-200 and Mel-140 cohorts.

	Group 1 – Mel-200	Group 2 – Mel-140	*P* value
Number of patients; n (%)	134 (76%) [$n = 132/134$ (99%) received Mel-200]	42 (24%) [$n = 34/42$ (81%) received Mel-140]	
Baseline characteristics			
Median age at ASCT, in years (Range)	49 (30–64)	52 (37–65)	0.028
> =60 years; *n* (%)	11 (8%)	4 (10%)	NS
Male gender; *n* (%)	97 (73%)	27 (65%)	NS
Baseline creatinine - available data (*n*)	128	39	0.045
Baseline creatinine >2 mg/dl; *n* (%)	26 (20%)	14 (36%)	
ISS stage; *n* (%)			
Available data (*n*)	127	40	
I	42 (33%)	11 (27.5%)	NS
II	37 (29%)	14 (35%)	
III	48 (38%)	15 (37.5%)	
Cytogenetics by FISH; *n* (%)			
Available data (*n*)	100	33	
Standard	67 (67%)	23 (70%)	NS
High	33 (33%)	10 (30%)	
Induction; *n* (%)			
Doublet	21 (17%)	5 (12%)	NS
Triplet	113 (83%)	37 (88%)	
PI + IMiD based induction; n (%)	42 (31%)	14 (33%)	NS
Radiotherapy at baseline; *n* (%)	49 (39%)	13 (31%)	NS
Peri-transplant characteristics			
Status at ASCT; *n* (%)			
< = PR	25 (20%)	9 (21%)	NS
> = VGPR	109 (80%)	33 (79%)	
Transplant in – remission; *n* (%)			
1st	96 (71%)	23 (55%)	NS
2nd	28 (21%)	13 (31%)	
> =3rd	10 (8%)	6 (14%)	
Pre transplant GFR (ml/min); Median	80	65	0.02
CD34 dose infused (million/kg)	3.9	4.02	NS
BM MRD prior to ASCT; *n* (%)			
Available data (*n*)	52	23	
Negative	32 (62%)	12 (52%)	NS
Positive	20 (38%)	11 (48%)	
Pre-transplant PET-CT; *n* (%)			
Available (*n*)	114	37	
Negative	74 (65%)	28 (76%)	NS
Positive	39 (34%)	8 (22%)	
Indeterminate	1 (1%)	1 (2%)	
Post ASCT maintenance; *n* (%)			
Yes	98 (73%)	31 (74%)	NS
Type of maintenance; *n* (%)			
- IMiD	70/98 (71%)	20/31 (65%)	NS
- PI	26/98 (27%)	9/31 (29%)	
- PI+IMiD	2/98 (2%)	2/31 (6%)	
Median duration of maintenance in months; range	20 (1–120)	21 (3–70)	NS
Post ASCT response; *n* (%)			
> = VGPR	116 (87%)	35 (83%)	NS
< =PR	14 (10%)	3 (7%)	
Not available	3 (3%)	4 (10%)	

ASCT Autologous stem-cell transplant, *BM MRD* Bone marrow – minimal residual disease, *IMiD* Immunomodulatory drug, *ISS* International staging system, *FISH* Fluorescence in-situ hybridisation, *NS* Not significant, *PI* Proteasome inhibitor, *PR* Partial response, *PET-CT* Positron Emission Tomography, computerised tomography, *VGPR* Very good partial response.

An additional matched-pair analysis was done (4:1 ratio for Mel200:Mel140 with a caliper-size of 0.2). This analysis was done using a propensity score from logistic regression with a probit-link function. The score was estimated by adjusting age, ISS-stage, type-of-induction, lines-of-treatment, disease status pre-ASCT and time from diagnosis-to-ASCT (in months). Data was updated till 30th November, 2024. Survival and follow-up were calculated from date of ASCT. Data was tabulated in a Microsoft excel-sheet and analysed using SPSSv23.0. For categorical variables and numerical data analysis, Chi-square test and Mann-Whitney test were used respectively. Survival was calculated using Kaplan–Meier method and compared using Log-rank test. Subgroup analysis was reported using Forest-Plot. Reported *p*-values were two-sided and $p < 0.05$ was considered statistically significant.

RESULTS

Amongst 176 patients, 134 (76%) received Mel-200 and 42 (24%) received Mel-140. In the Mel-200 group, 99% ($n = 132$) received Melphalan at 200 mg/m^2, while in Mel-140 group, 81% ($n = 34$) received Melphalan at 140 mg/m^2. Remaining two patients in Mel-200 group received Melphalan 180 mg/m2. Amongst remaining eight patients in Mel-140 group – five received Melphalan 120 mg/m^2, while three received Melphalan 100 mg/m^2. Median age of the whole cohort was 49 years (Range:30–65 years), with a male predominance (70%; $n = 124/176$). Twenty-three percent patients ($n = 40$) had baseline RD. Majority of patients in our cohort had baseline standard-risk cytogenetics (67%), were treated with triplet induction (85%), transplanted in first-remission (67%) and in ≥VGPR prior to ASCT (80%). Amongst 176 patients, 91 (51%) underwent BM examination prior to ASCT, of which 75 (43%) had BM-MRD evaluation. Amongst these 75 patients, 44 (59%) were BM-MRD negative at 10^{-5}. Similarly, amongst patients with pre-transplant PET-CT ($n = 151$), 67% ($n = 102$) patients were PET-CT MRD negative. Seventy-four percent of the whole cohort ($n = 129$) received maintenance post-ASCT. For baseline and peri-transplant characteristics, Mel-200 was comparable to Mel-140, except for age at transplant, baseline RD and pre-transplant GFR (Table 1). Supplementary Table 1 enlists the reasons for reducing Melphalan dose to ≤140 mg/m2.

At a median follow-up of 85.5 months post-ASCT, median PFS and OS of the whole cohort was 57 months, and NR, respectively. Importantly, there was no difference in median PFS (57 months vs

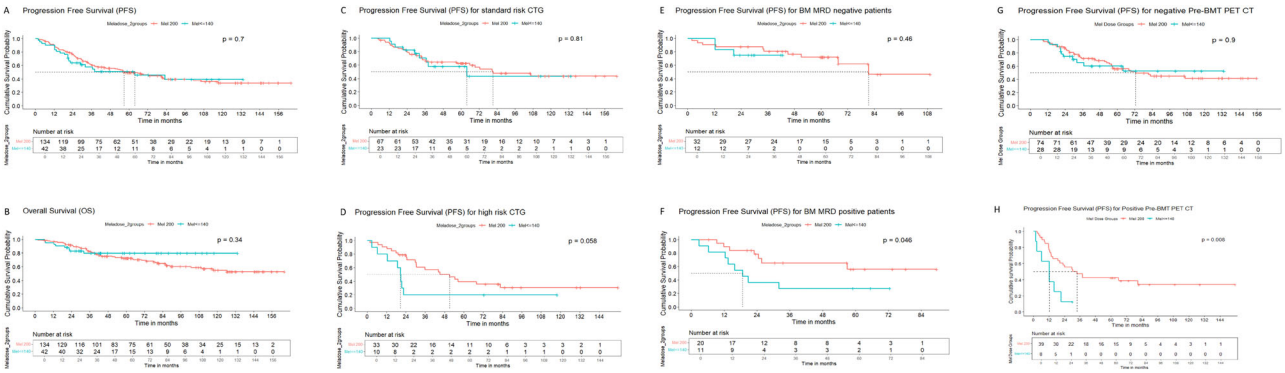

Fig. 1 Kaplan–Meier survival curves comparison of Melphalan 200 mg/m^2 (Mel-200) vs ≤140 mg/m^2 (Mel-140) groups. Survival curves for: Whole cohort - Median PFS (**A**) and OS (**B**); PFS as per cytogenetics [standard risk (**C**) and high risk (**D**)], PFS as per pre-transplant bone marrow MRD [negative (**E**) and positive (**F**)], and PFS as per pre-transplant PET-CT [negative (**G**) and positive (**H**)].

64 months; $p = 0.7$) and OS (NR vs NR; $p = 0.34$) between Mel-200 vs Mel-140 (Fig. 1). With respect to subgroups, there was no difference in median PFS between Mel-200 vs Mel-140 for patients with standard-risk cytogenetics ($p = 0.81$), negative BM-MRD ($p = 0.46$) and negative PET-CT ($p = 0.9$) before transplant (Fig. 1), transplant in first remission ($p = 0.76$), ≥VGPR pre-ASCT ($p = 0.94$), and receipt of maintenance post-ASCT ($p = 0.68$). However, PFS was significantly better with Mel-200 for high-risk cytogenetics ($p = 0.058$), positive BM-MRD ($p = 0.046$) and PET-CT ($p = 0.008$) (Fig. 1) before transplant. The same is reflected in the forest-plot for PFS, with the maximum benefit in terms of effect size in favour of Mel-200 for those who were PET-CT positive pre-transplant (Supplementary Fig. 2).

Additional matched-pair analysis ($n = 141$) revealed same results as in whole cohort. Median PFS was 56 months (95%C.I. 37.9–101), and median OS was NR (95%C.I. 110-NR). Median PFS was better with Mel-200 for high-risk cytogenetics ($p = 0.024$), BM-MRD positive ($p = 0.049$), positive PET-CT pre-ASCT ($p = 0.01$). In patients with positive PET-CT pre-ASCT, the median OS was better with Mel-200 ($p = 0.032$) (Supplementary Fig. 3).

With respect to toxicities, the incidence of grade 3–4 mucositis was significantly higher in Mel-200 cohort (50% vs 26%; $p = 0.006$). However, there was no difference between the two groups with respect to median duration of grade 3–4 mucositis, use of total parenteral nutrition (TPN), and median day of neutrophil or platelet engraftment. In our cohort, there was one TRM (<1%) and five patients (2.8%) developed second primary malignancy (SPM). (Supplementary Table. 2)

DISCUSSION

In contrast to previous literature of Mel-140 vs Mel-200, our cohort was younger (consistent with prior reports of younger presentation in India [7, 8]), with higher proportion of ISS-III (40% {our-study} vs 14% [5]) and high-risk cytogenetics (35% {our-study} vs 8–14% [5,6]). Unlike prior studies, our VGPR or deeper responses (80% vs 45–50% [5,6]) and flow-MRD negative rates (58% vs 28% [14]) are higher. This could be because of a greater number of patients receiving triplet induction (85% vs 52–60% [5,6]) and PI +IMiD-based triplets (60% vs 40% [5]) in our study. Whether higher MRD negativity rates in our study is a reflection of prolonged induction prior to ASCT (Median induction cycles before transplant was 9 cycles) is not known. This is important from an LMIC perspective, wherein median time from diagnosis-to-transplant is usually 10 months [1, 7, 8]. Another important finding relevant to LMICs, is acute toxicities post-ASCT which contribute to morbidity. Our incidence of grade 3–4 mucositis of 50% with Mel-200 is significantly higher than in the west (<5%) [6]. Whether this is due different pharmacokinetics of melphalan in our patients or related to compromised oral/dental hygiene, remains to be studied.

Limitations of our study include – large study period (2007–2022; wherein treatment strategies evolved at our centre and globally), absence of daratumumab-based induction regimens, and lack of comparison as per recent IMS-IMWG risk stratification [15]. While we report that lower melphalan dose (vs Mel-200) is efficacious and safe, an ideal comparison would be to compare it with patients who were not transplanted, especially in MRD-negative cohort. A recent study showed equivalent efficacy, safety and MRD negativity post-ASCT with Mel-200 vs Mel-140. However, this study was only in older, frail patients, and MRD assessment was done post-ASCT [16]. In contrast, our study includes all patients, irrespective of age, and focuses on pre-transplant MRD, which in clinical practice can help modulate conditioning doses. To our knowledge, this is the first study comparing Mel-200 vs Mel-140 in the MRD era with a large sample size and median follow-up duration post-ASCT of more than 7 years. In today's era, wherein majority of patients achieve a deep response (≥VGPR pre-ASCT) with a triplet induction (even in LMICs) [17] followed by indefinite lenalidomide maintenance, the role of Mel-200 as the "standard" conditioning needs to be challenged. Whether there is a dose-dependent effect of Melphalan on mutations at relapse [18] and/or development of SPMs [13] needs to be studied.

To conclude, Mel-140 is comparable to Mel-200, except for high-risk cytogenetics, BM-MRD and PET positivity before ASCT. Prospective studies are needed to elucidate if MRD can help "individualise" melphalan dose for conditioning in the era of effective induction therapies, especially for those with standard-risk cytogenetics and negative MRD.

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DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Mirgh S, Bagal B, Punatar S, Gokarn A, Jindal N, Chichra A, et al. Moving beyond G-CSF mobilization-learning from a 15-year experience of different stem cell mobilization regimens in multiple myeloma. Cancer Med. 2025;14:e71068.
2. Rajkumar SV. Multiple myeloma: 2022 update on diagnosis, risk stratification, and management. Am J Hematol. 2022;97:1086–107.
3. Moreau P, Facon T, Attal M, Hulin C, Michallet M, Maloisel F, et al. Comparison of 200 mg/m(2) melphalan and 8 Gy total body irradiation plus 140 mg/m(2) melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myélome 9502 randomized trial. Blood. 2002;99:731–5.
4. Ali MO, Al Hadidi S. High dose (conditioning) regimens used prior to autologous stem cell transplantation in multiple myeloma. Transplant Cell Ther. 2022;28:572–80.
5. Auner HW, Iacobelli S, Sbianchi G, Knol-Bout C, Blaise D, Russell NH, et al. Melphalan 140 mg/m^2 or 200 mg/m^2 for autologous transplantation in myeloma: results from the Collaboration to Collect Autologous Transplant Outcomes in Lymphoma and Myeloma (CALM) study. A report by the EBMT Chronic Malignancies Working Party. Haematologica. 2018;103:514–21.
6. Srour SA, Milton DR, Bashir Q, Nieto Y, Saini N, Daher M, et al. Melphalan dose intensity for autologous stem cell transplantation in multiple myeloma. Haematologica. 2021;106:3211–4.
7. Kumar L, Sahoo RK, Kumar S, Baa AK, Tansir G, Pathak N, et al. Autologous stem cell transplant for multiple myeloma: Impact of melphalan dose on the transplant outcome. Leuk Lymphoma. 2023;64:378–87.
8. Yanamandra U, Malhotra P. Stem cell transplantation in multiple myeloma: very much alive and kicking. Indian J Hematol Blood Transfus. 2019;35:205–7.
9. Badros A, Barlogie B, Siegel E, Roberts J, Langmaid C, Zangari M, et al. Results of autologous stem cell transplant in multiple myeloma patients with renal failure. Br J Haematol. 2001;114:822–9.
10. Dimopoulos MA, Terpos E, Chanan-Khan A, Leung N, Ludwig H, Jagannath S, et al. Renal impairment in patients with multiple myeloma: a consensus statement on behalf of the International Myeloma Working Group. J Clin Oncol. 2010;28:4976–84.
11. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. The Lancet Oncology. 2016;17:e328–46.
12. Tembhare PR, Sriram H, Khanka T, Gawai S, Bagal B, Ghogale SG, et al. Circulating tumor plasma cells and peripheral blood measurable residual disease assessment in multiple myeloma patients not planned for upfront transplant. Hemasphere. 2024;8:e63.
13. Mirgh S, Surendran A, Punatar S, Gokarn A, Jindal N, Chichra A, et al. Second primary malignancies post autologous stem-cell transplant in multiple myeloma from India – knowing the unknown. Indian J Hematol Blood Transfus. 2025. https://doi.org/10.1007/s12288-025-01984-2.
14. Paiva B, Puig N, Cedena MT, Rosiñol L, Cordón L, Vidriales MB. et al. Measurable residual disease by next-generation flow cytometry in multiple myeloma. J Clin Oncol. 2020;38:784–92.
15. Avet-Loiseau H, Davies FE, Samur MK, Corre J, D'Agostino M, Kaiser MF, et al. International Myeloma Society/International Myeloma Working Group consensus recommendations on the definition of high-risk multiple myeloma [published online ahead of print, 2025 June 9]. J Clin Oncol. https://doi.org/10.1200/JCO-24-01893.
16. Kort J, Naleid N, Oley F, Ignatz-Hoover J, Margevicius S, Fu P, et al. Melphalan 140 mg/m^2 is safe and effective for frail and older multiple myeloma patients with comparable rates of minimal residual disease negativity. Clin Lymphoma Myeloma Leuk. 2025;25:e443–51.e3.
17. Mirgh S, Kapoor J, Bhatia N, Singh R, Khushoo V, Garg A, et al. Is it necessary to achieve a very good partial response prior to transplant? Comparison of outcomes in pre-transplant partial response versus very good partial response or deeper. Indian J Hematol Blood Transfus. 2025. https://doi.org/10.1007/s12288-025-02140-6.
18. Samur MK, Roncador M, Aktas Samur A, Fulciniti M, Bazarbachi AH, Szalat R, et al. High-dose melphalan treatment significantly increases mutational burden at relapse in multiple myeloma. Blood. 2023;141:1724–36.

AUTHOR CONTRIBUTIONS

SM, and NK conceptualized the study; SM, CN, PM, KD, AK contributed to data entry; SM, SP, NJ, SK contributed to data analysis and validation; SM, SP, AG, NJ, AC, LN, GB, BB, NK were involved in clinical management of transplant patients; PT, NP, DR, GC, PG contributed to MRD analysis of patients, SM analysed the data and wrote the first draft of the manuscript; BB and NK contributed to data validation and supervision of the study; all authors contributed to editing and approval of the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All methods were performed in accordance with the relevant guidelines and regulations. This study was approved by our Institutional Ethics Committee (IEC-III) [Project number 901182 approved on 09 August 2025]. Informed consent was obtained from all participants. No identifiable human images have been used in this study.

ADDITIONAL INFORMATION

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