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Pharmacokinetics and Efficacy of Generic Melphalan Is Comparable to Innovator Formulation in Patients With Multiple Myeloma Undergoing Autologous Stem Cell Transplantation

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Abstract

Pharmacokinetics and therapeutic efficacy were investigated in patients with multiple myeloma receiving both generic and innovator melphalan (MEL) formulation for conditioning pre autologous stem cell transplantation. Both the MEL formulations were comparable in terms of pharmacokinetics and efficacy, suggesting generic MEL as a low-cost alternative to innovator MEL for autologous stem cell transplantation conditioning in multiple myeloma.

Background—High-dose melphalan (MEL) is the standard conditioning regimen used for autologous stem cell transplantation (ASCT) in patients with multiple myeloma (MM). Generic MEL is routinely used in various transplant centers across the world including ours due to its reduced cost and ease of availability. We compared the pharmacokinetics (PK) and the clinical efficacy of generic MEL with that of the innovator formulation in MM patients undergoing ASCT.

Patients and Methods—Sixty-three patients diagnosed with MM receiving high-dose MEL were included in this study. MEL levels in plasma were measured using a liquid chromatography tandem mass spectrometry (HPLC/MS-MS) protocol and non-linear mixed effects modeling was used to evaluate the PK of the data.

Results—The interindividual variability (IIV) in MEL area under the concentration versus time curve (AUC) and clearance (CL) were 4.39, 5.88-fold for generic, and 4.34, 6.85-fold for the innovator formulation, respectively. The median MEL AUC and CL were comparable between the 2 formulations. The population PK analysis showed age and creatinine CL as the only significant covariates explaining IIV in MEL AUC/CL. Analysis of MEL PK parameters with clinical outcome showed no significant differences in terms of onset and severity of mucositis, day to neutrophil and platelet engraftment, as well as response status on day 100 post ASCT between

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patients receiving generic or innovator formulations of MEL. In addition, neither MEL AUC nor CL was found to be associated with day +100 response.

Conclusion—Our study suggests that the PK and efficacy of the generic MEL is comparable to the innovator formulation.

Keywords

Autologous HSCT; Generic melphalan; Multiple myeloma; Population pharmacokinetics

Introduction

High-dose melphalan (MEL) is the most common conditioning regimen being used prior to autologous stem cell transplantation (ASCT) in patients with multiple myeloma (MM) since the 1980s.[1–6] Common toxicities after MEL administration include myelosuppression, nausea, vomiting, diarrhea, alopecia, and gastrointestinal mucositis. Oral and esophageal mucositis occurs frequently, affecting the nutritional status, hydration, and quality of life in patients during ASCT, thereby increasing the hospitalization duration and cost of care.[2] Several studies have evaluated pharmacokinetics (PK) of MEL and have related high MEL exposure with either increased toxicity,[7–11] improved therapeutic efficacy,[12,13] or no obvious perceptible effect.[14–16] However, PK-guided dosing for MEL is limited except for a few reported studies using the test dose PK approach.[17–22]

In many centers across the world, generic and innovator formulations of MEL are in clinical use. Generic MEL (Megval, Emcure Pharmaceuticals, Pune, India) costs less than 25% of innovator MEL (Alkeran, Aspen Pharmacare, New South Wales, Australia). In a country like India, majority of the patients pay from their own pocket for health care.[23] In this scenario, the availability of a low-cost generic formulation would enable the patient and the physician to maintain the cost of the transplantation within affordable limits. However, there is a paucity of data on the therapeutic equivalence of many of the generic drugs. To this date, there have been no reports on the PK and efficacy of the generic MEL in patients with MM undergoing ASCT. In this study, we evaluated the PK and compared therapeutic efficacy of both formulations in terms of ASCT outcomes and PK.

Patients and Methods

Reagents and Chemicals

MEL (Cat no: 148-82-3), internal standard (IS) N-phenyldiethanolamine (NPEA; Cat no: P22400), mass spectrometry grade acetonitrile (Cat no: 900667), formic acid (Cat no: F0507), and methanol (Cat no: 900688) were purchased from Sigma Aldrich (St Louis, MO).

Patients

All patients diagnosed with MM and undergoing ASCT using a high-dose MEL conditioning regimen between March 2016 and August 2018 in the Department of Hematology, Christian Medical College, Vellore, India, were included in this study. Written

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informed consent was obtained from the patients. This study was approved by the institutional review board.

Stem Cell Mobilization and Collection

Stem cell mobilization was done with granulocyte-colony stimulating factor (G-CSF) given for 4 consecutive days at 10 μg/kg in 2 divided doses followed by stem cell harvest using a COBE Spectra apheresis system on day 5. A stem cell dose of 4×10^6 $CD34^+$ cells was targeted for ASCT. In case the stem cell dose was inadequate after the first day collection, patients were taken up for a second stem cell collection on the next day after administering G-CSF alone or G-CSF with plerixafor (0.24 mg/kg). Stem cells after collection were stored at 4°C in the blood bank refrigerator before infusion and were infused without cryopreservation.

Conditioning Regimen

MEL was administered on day −1 as a single dose of 200 mg/m^2. The dose was reduced to 140 mg/m^2 in cases for which the creatinine clearance (CL) was <60 mL/min or if the age was more than 65 years. MEL was administered as an intravenous bolus injection through a central venous catheter over 30 minutes. Cryotherapy with ice chips was initiated along with MEL to reduce the severity of mucositis. The choice of the MEL used (innovator vs. generic) was non-randomized and was purely on the basis of the discretion of the treating physician/resources of the patient. The generic MEL used was Megval (Emcure Pharmaceuticals, Pune, India).

Sample Collection for PK Analysis

Peripheral blood (5 mL) was collected in sodium heparin tubes before the start (0 hours), end of infusion, and 1, 2, 3, 6, and 24 hours after the end of MEL infusion. Plasma was separated immediately and stored at −80° C until further analysis.

Measurement of Plasma MEL in High Performance Liquid Chromatography-Tandem Mass Spectrometry (HPLC/MS-MS)

Measurement of plasma MEL levels was carried out as per the method reported previously with some modifications.[24] Briefly, MEL levels in plasma samples were measured using a validated LC/MS-MS using a Shimadzu-Nexera X2 ultra HPLC consisting of binary gradient pumps (LC-30AD), auto sampler (SIL-30AC), mobile phase degasser (DGU20ASR), and a column oven (CTO-20AC) coupled with an LCMS-8050 triple quadrupole mass spectrometer (Shimadzu, Kyoto, Japan). The data were analyzed using LC Solutions software (Shimadzu, Kyoto, Japan). The parameters were adjusted to yield maximum multiple reaction monitoring signals. The Q1/Q3 for MEL was set at 304.80 > 288.10 m/z and 182.70 > 119.80 m/z for IS NPEA in the positive electrospray ionization mode, respectively. Chromatographic separation of the analytes was done using Luna C_{18} (4.6 × 150 mm, 5 μm, Phenomenex, USA) protected with a C_{18} guard column from the same source. The liquid chromatography conditions were as follows: solvent A: water containing 0.1% formic acid and solvent B: 0.1%; formic acid in acetonitrile was used as mobile phase with gradient elution of solvent B at 20% (0-4.0 minutes); 80% (4.0-6.0 minutes); 20%

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(7.0-10.0 minutes) at a flow rate of 0.8 mL/min. The total run time was 10 minutes. Retention time for MEL was 2.2 minutes and the IS was 2.7 minutes. The concentration of MEL was expressed as ng/mL.

Population Pharmacokinetics (PopPK) Modeling

Non-linear mixed effects modeling analysis was performed with Monolix (version 5.0.1; Lixoft, France) using the stochastic approximation expectation-maximization (SAEM) method. A 2-compartment PK model was used to describe the data. The PK parameters estimated included CL (in L/h/m^2) and volume (V; in L/m^2) along with the intercompartmental CL and peripheral compartment (Q (L/h/m^2) and V_2 in L/m^2). In addition, the individual post hoc parameter values were used to estimate the area under the concentration versus time curve (AUC). The interindividual variability of the parameters was assumed to be log-normally distributed. A proportional residual error model was used with assumed normal distribution of the residuals.

The relationships between the PK parameters and covariates (age, sex, MEL dose, hemoglobin, albumin, and creatinine CL) were described using the following model: $\theta = \theta_{Base} \times \exp(\beta \times \text{covariate})$. A covariate was considered significant in the univariate analysis, if the addition of the covariate to the model reduced the objective function value at least 3.84 units ($P < .05$, on the basis of the χ^2 test for the difference in the −2 log likelihood between 2 hierarchical models that differ by 1 degree of freedom).

Stem Cell Transplantation and Post-Transplantation Care

The patients underwent ASCT as an in-patient either in HEPA filtered or non—HEPA filtered rooms. The collected stem cells were infused fresh without any modifications 12 hours after the MEL administration in patients with normal renal function. For patients with creatinine CL <60 mL/min, the stem cells were infused 24 hours after the administration of MEL. Post stem cell infusion, the patients were managed for the neutropenic period with antibiotics and blood products. Oral mucositis was graded as per the World Health Organization (WHO) grading system. During the period of mucositis, patients were supported with analgesics and total parenteral nutrition as and when required according to the severity reported by them. All patients were given G-CSF from day +7 post-transplant to enhance neutrophil engraftment.

ASCT Outcome

The influence of MEL PK parameters (CL or AUC) on the various outcome measures were analyzed. Patient demographic characteristics as well as clinical response such as duration to neutrophil and platelet engraftment, onset and grade of mucositis, duration of hospitalization, and response on day + 100 post ASCT were analyzed. Neutrophil engraftment was defined as the first day of a neutrophil count $>0.5 \times 10^9$/L or greater over 3 consecutive days. Platelet engraftment was defined as the first day of platelet count $>20 \times 10^9$/L or greater without needing transfusion support for at least 1 week in accordance with the Center for International Blood and Marrow Transplant Research (CIBMTR). Toxicity was graded as per National Cancer Institute Common Terminology Criteria for Adverse

Events (CTCAE) V.5.0. In our center, post-transplant minimal residual disease monitoring is not done.

Statistical Analysis

All statistical analysis was carried out using IBM SPSS statistics 21.0 (Armonk, NY) and GraphPad PRISM5 software (San Diego, CA). Relative risk of variables on ASCT outcome was performed using logistic regression.

Results

Patients

A total of 63 patients with MM underwent ASCT during the study period. Thirty-three received generic MEL, and 30 patients received innovator MEL. The 2 treatment groups were similar with respect to age, sex, pre-ASCT response, and creatinine CL. Baseline patient demographic characteristics are summarized in Table 1.

MEL Assay Validation

MEL assay was validated for its specificity, linearity, precision, accuracy, and recovery before it was used for measurement in patients' plasma. There was no peak detected in unspiked blank plasma at the retention times of MEL (2.2 minutes) and IS (2.7 minutes). The method was linear for a concentration range from 1 to 2000 ng/mL with mean R^2 = 0.99 ± 0.001. MEL was detected in most patient's plasma even at 7 hours after infusion but no traces of MEL were found after 24 hours. Linearity, accuracy, and interday precision are as shown in Supplemental Table 1 in the online version)

PopPK of MEL

The PopPK model parameters comprising body surface area normalized dose are shown in Table 2. The median MEL AUC and CL were comparable between the 2 formulations as well as with previous reports on MEL PK (Table 3). In a univariate analysis, age and creatinine CL were significant covariates explaining variability in MEL CL. Specifically, MEL CL decreased (P = .01) with increasing age and increased (P = .02) with increasing creatinine CL (Figure 1). Since age and creatinine CL are correlated (r = −0.48; P = .0002) the model including both covariates were not significantly different from either one alone.

Comparison of ASCT Outcomes Between 2 Formulations

There were no significant differences in terms of onset and severity of mucositis and duration of hospital stay between patients receiving generic or innovator formulations of MEL (Table 4). The time to platelet and neutrophil engraftment also were comparable between the 2 formulations. The post-transplant responses on day + 100 was also comparable in the 2 arms. There was no difference in the progression-free survival (74.3% ± 10.2% versus 82.6% ± 12.0%; P = .917) and overall survival (89.8% ± 5.6% vs. 82.6% ± 12.0%; P = .544) between the 2 groups of patients who received generic or innovator formulations of MEL (Figure 2). Also, there was no statistically significant difference in the status pre-transplant versus post-transplant between the generic and innovator MEL groups

(pretransplant to post-transplant status remained the same or improved: 30/33 in generic and 28/30 in innovator groups; 3/33 and 0/30 progressed; P = not significant).

Influence of MEL PK on ASCT Outcome

None of the MEL PK parameters (AUC and CL) influenced ASCT outcomes such as mucositis onset and severity, platelet and neutrophil engraftment, and duration of hospitalization.

Discussion

Generic MEL is widely used across the world as conditioning regimen for patients with MM undergoing ASCT. Despite their wide clinical utility, to our knowledge there are no reports comparing PK and therapeutic efficacy of generic and innovator MEL. Previous studies have shown wide variability in MEL PK with higher MEL exposure associated with increased toxicity with improved or no significant effect on efficacy.[8–17] In the present study, we compared PK and therapeutic efficacy between generic and innovator MEL.

We developed a PopPK model of MEL in patients who received generic or innovator MEL. Age and creatinine CL were identified as the most significant covariates accounting for a large proportion of the interindividual variability in MEL CL. MEL elimination is primarily through renal excretion and hence creatinine CL is a well-known predictor of MEL CL. We also observed that MEL CL increases with increasing creatinine CL, which is consistent with previous findings.[7,11,25,26] In addition, our model showed MEL CL decreases with increasing age, probably because of the decreased renal function with age.[27] However, age was not a significant covariate in previous PopPK studies in MEL PK.[7,11,25,26]

Comparison of PK profiles of both generic and innovator formulations of MEL showed that the PK estimates (AUC and CL) were comparable to each other and previously reported studies on MEL PK.[7,11,25,28,29]

ASCT outcomes such as onset and severity of mucositis, day to neutrophil and platelet engraftment, duration of hospitalization between both formulations were also comparable. None of the MEL PK parameters (irrespective of formulation) showed any association with ASCT outcomes including overall survival, which was consistent with a previous study.[11] However, this observation was contrary to a previous finding, which showed that high MEL exposure improves overall survival.[13] One of the limitations of our study is its non-randomized nature. This study is also not powered to address the influence of MEL PK on ASCT outcomes/toxicity.

Conclusion

This study demonstrates that the therapeutic efficacy and PK of generic MEL is comparable to innovator MEL. Generic MEL is therefore a good alternative to its innovator formulation to cut the cost of transplantation in a country like ours.

Clinical Practice Points

- In many centers across the world, both generic and innovator formulations of high-dose MEL are in use as conditioning regimen in ASCT.
- Previous studies on MEL PK were demonstrated in innovator formulations, and to date, there are no reports on the PK and efficacy of the generic MEL in patients with MM undergoing ASCT.
- The present study evaluated the PK and compared the therapeutic efficacy of both formulations in terms of ASCT outcomes and PK, demonstrating that the therapeutic efficacy and PK of generic MEL is comparable to innovator MEL.
- Generic MEL is therefore a good alternative to its innovator formulation to cut the cost of transplantation, especially in developing countries.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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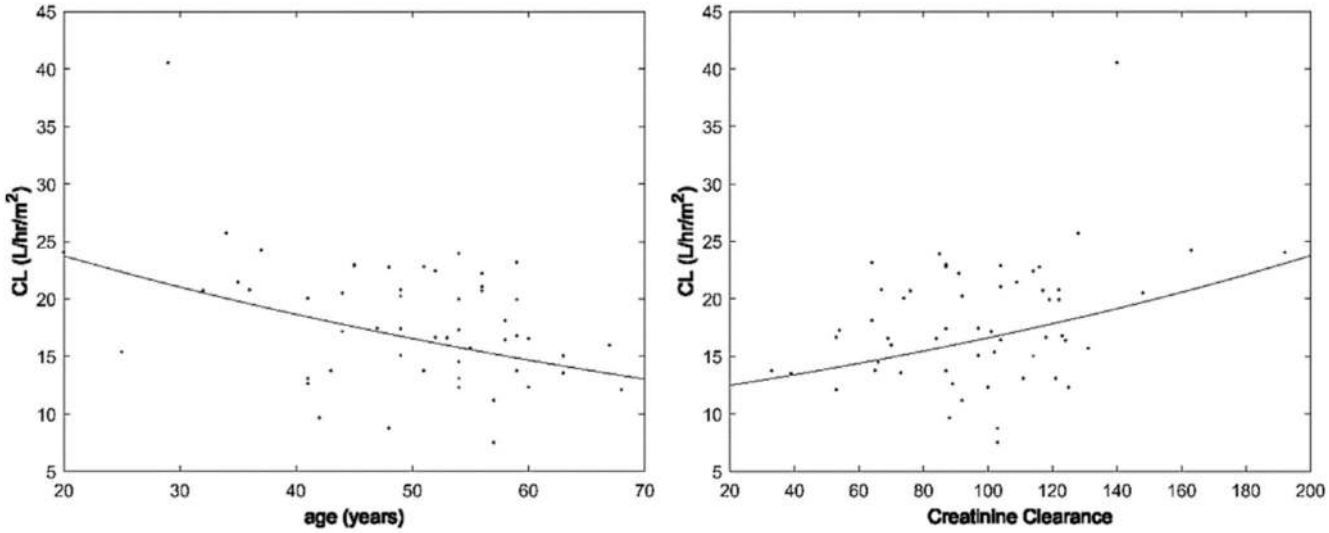

Figure 1.
Linear Dependency Between Melphalan (MEL) Clearance (CL) and Age (Left) and Between MEL CL and Creatinine CL (Right)

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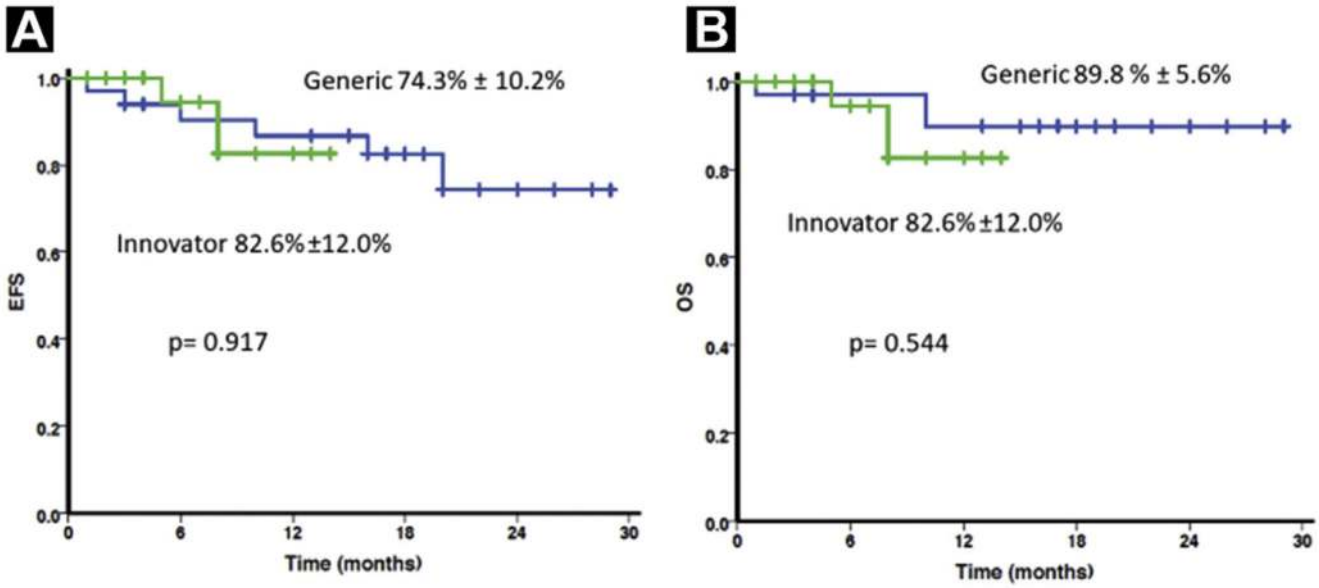

Figure 2.

Kaplan—Meier Survival Curves Showing Influence of MEL Formulation on Overall Survival (OS) and Progression-Free Survival (EFS). No Significant Differences in EFS (A) and OS (B) Were Observed Between Generic (n = 33) and Innovator (n = 30) MEL Formulations

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Table 1

Patient Demographic Characteristics

Characteristic	Generic MEL	Innovator MEL	*P*
Patients, n	33	30	NS
Age, y	52 (26-63)	54 (20-68)	NS
Male:Female Sex	22:11 (2:1)	20:10 (2:1)	NS
Pretransplantation Response			NS
CR	19 (58%)	13 (43%)	
VGPR	10 (30%)	9 (30%)	
PR	4 (12%)	8 (27%)	
MEL Dose			NS
200 mg/m^2	33	22	
140 mg/m^2	-	8	
CD34, × 10^6/kg	5.39 (3.22-13.36)	5.2 (3.05-13.58)	NS

Data are presented as n (%) or median (range) except where otherwise noted. Abbreviations: CR = complete response; NS = not significant; PR = partial response; VGPR = very good partial response.

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Table 2
Population Pharmacokinetics of Melphalan

Parameter	Base	RSE, %	Age	RSE, %	*P*	Creatinine CL	RSE, %	*P*
CL, L/h/m^2	16.4	4.7	19.8	8.7		11.6	15.5	
β [a]			–0.012	38.9	0.010	0.0036	42.9	.020
V, L/m^2	14.5	6.5	14.4	7.3		14.6	6.5	
Q, L/h/m^2	4.8	23.3	5.2	25.9		4.8	29.1	
V_2, L/m^2	8.9	12.9	8.9	14.7		8.7	15.4	
σ Additive, mg/mL	0.0005	Fixed	0.0005	Fixed		0.0005	Fixed	
σ Prop, CV%	0.32	6.9	0.31	6.6		0.31	6.4	
—2 Log-Likelihood [b]	469.7		464.3		0.020		465.0	.030
IIV	**CV%**	**RSE, %**	**CV%**	**RSE, %**	*P*	**CV%**	**RSE, %**	*P*
CL	0.31	11.3	0.32	12.1		0.31	11.6	
V	0.32	16.9	0.37	15.6		0.34	15.7	
Q	0.85	21.8	0.97	22.0		0.93	27.4	
V_2	0.73	14.9	0.71	15.5		0.77	15.6	

Abbreviations: CL = clearance; CV% = coefficient of variation; IIV = interindividual variability; Q = intercompartmental clearance; RSE = relative standard error; V = volume of distribution into the central compartment; V_2 = volume of distribution into the peripheral compartment.

[a] Covariate model: θ × exp (β × covariate).

[b] *P* value represents the significance of the change in the —2 log likelihood (on the basis of the χ^2 test) relative to base model.

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Table 3
Comparison of MEL PK With Existing Literature

PK Parameter	Generic MEL (n = 32) [a]	Innovator MEL (n= 23) [a]		Cho et al[11] (n = 146)[b]	Nath et al[7] (n = 100)[b]
Age (Range), Years	52 (26-63)	54 (20-68)		59 (35-72)	57 (36-73)
Median AUC (Range), mg/h/L	10.7 (6.7-23.7)	MEL 140	MEL 200	14.4 (5.6-27.3)	12.8 (4.9-24.6)
		9.9 (8.3-11.1)	11.6 (5.6-22.4)		
Mean Clearance, L/h/m^2	27.12	27.07		29.0	27.8

Abbreviations:AUC = area under the curve; MEL = melphalan; PK = pharmacokinetics.

[a] Present study.

[b] Reported studies that evaluated innovator MEL.

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Table 4
Comparison of ASCT Outcomes in Patients Who Received Generic and Innovator MEL

ASCT Outcomes Days (Range)	Generic MEL (n = 33)	Innovator MEL (n = 30)	*P*
Day of Onset of Mucositis (Range)	3(1-7)	3(1-7)	NS
Mucositis Grade			NS
3	1	–	
2	18	16	
1	14	14	
Duration to Neutrophil Engraftment	12 (10-16)	12 (10-21)	NS
Duration to Platelet Engraftment	16 (13-33)	17 (14-33)	NS
Duration of Hospitalization	22 (17-55)	21 (15-42)	NS
Day 100 Post ASCT Response			NS
CR	20	16	
VGPR	9	4	
PR	1	4	
Others [a]	3	6	

Abbreviations: ASCT = autologous stem cell transplantation; CR = complete response; MEL = melphalan; NS = not significant; PR = partial response; VGPR = very good partial response.

[a]Others includes in generic MEL (1 expired, 1 progression, and 1 response not reached) and in innovator MEL (4, response not reached and 2, lost to follow-up).