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*Original Article*

# Reduced intensity melphalan conditioning for autologous hematopoietic stem cell transplantation in multiple myeloma-a single center experience

Juan Feng, Hong-Tao Gu, Mi-Mi Shu, Lan Yang, Rong Liang, Bao-Xia Dong, Qing-Xian Bai, Tao Zhang, Na Zhang, Li-Jie Yang, Li Xu, Hong-Juan Dong, Xin Lei, Hua-Feng Zhu, Xie-Qun Chen, Guang-Xun Gao

*Department of Hematology, People's Liberation Army Center of Hematologic Disorders, Xijing Hospital, Fourth Military Medical University, Xi'an, Shaanxi, China*

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**Abstract:** Although high dose melphalan (200 mg/m$^2$, MEL200) is widely used as a conditioning regimen for autologous stem cell transplantation (ASCT) in multiple myeloma (MM) patients, other optimal strategies are explored. To evaluate the effect of reduced intensity melphalan conditioning in MM patients undergoing single ASCT and explore prognostic factors after ASCT, we retrospectively analyzed records of 52 Chinese patients who received melphalan at a median dose of about 140 mg/m$^2$ (MEL140) conditioning in our center during 2008-2017. The depth of disease response was improved after ASCT in 26.9% patients. At a median follow-up of 30 months, estimated median overall survival (OS) and progression free survival (PFS) was 84±22.42 and 24±5.81 months, respectively, five-year OS was 52.5±8.9% and five-year PFS was 22.4±7%. The rate of severe oral mucositis, diarrhea and nausea/vomiting is lower than that of MEL200 reported. In multivariate cox proportional hazards model, the status of at least very good partial response (VGPR) after ASCT significantly improved PFS (*P*=.002), and OS (*P*=.004). In conclusion, reduced high dose of melphalan leads to excellent long-term outcomes and it is feasible for ASCT conditioning in MM patients. Outcome of MM patients is better for those who achieve at least VGPR after transplant.

**Keywords:** Multiple myeloma, autologous stem cell transplantation, melphalan, outcome

## Introduction

Multiple myeloma (MM) is a clonal hematologic malignancy characterized by infiltration of abnormal plasma cells within the bone marrow, as well as at extramedullary sites, mostly with monoclonal immunoglobulin secretion. MM remains an incurable disease. Conventional chemotherapy produced response rates (RR) of 50-60%, median remission duration and overall survival (OS) of 18 and 30-36 months, but complete response (CR) rate of less than 5% and ten-year survival rate of 2.2% [1]. Because of the unsatisfactory effect of conventional therapy, many new options have been explored. High-dose chemotherapy combined with autologous stem cell transplantation (ASCT) could improve RR, event free survival (EFS), and OS in patients with myeloma, so it has become the standard treatment for those transplantation-eligible patients [2, 3]. The use of novel drugs such as proteasome inhibitors and immunomodulatory agents has played promising roles in the treatment of MM during the last decades [4, 5]. However, ASCT is the standard of care in first line therapy for transplant eligible patients in the era of novel drugs. At the relapse setting it also has a place, mainly in patients who had prolonged remission after first ASCT, but the data is less strong, with only few prospective trials [6, 7]. The most frequent conditioning regimen before ASCT is high dose melphalan. Most centers use melphalan of 200 mg/m$^2$ (MEL200) as the "standard conditioning dosing" for ASCT in MM patients. Some reports have tried to compare other conditioning regimens with MEL200, but without distinct superiority over MEL200 observed [8-10]. Several studies reported no survival difference among older MM patients in comparison to younger patients who received high dose melphalan and ASCT but increased toxicities. Therefore, melphalan at a dose of 140 mg/m$^2$ (MEL140) is often used for older patients and also for

patients with risk factors. A retrospective study found MEL140 could achieve similar therapeutic effects to MEL200 [11]. Whether reduced intensity of melphalan condtioning is feasible in Chinese younger population, to answer this question, we conducted the retrospective analysis. Here, we evaluated the effect of reduced dosage of melphalan conditioning on toxicities and outcomes of MM patients undergoing single ASCT in our institution and documented the prognostic factors of survival.

## Materials and methods

### *Patients*

This study was approved by our institutional review board. We retrospectively analyzed clinical data of 52 patients who presented with symptomatic, measurable MM and most of whom received ASCT first line after induction therapy in our center between January 2008 and May 2017. The diagnosis was based on International Myeloma Working Group (IMWG) updated criteria [12], and clinical staging was based on the Durie and Salmon (DS) staging system and the International Staging System (ISS) [13, 14]. All transplantations were performed after informed consent.

### *Induction chemotherapy*

The main induction therapy regimens were bortezomib-based, such as bortezomib plus epirubicin plus dexamethasone (PAD). Other uncommon regimens included thalidomide plus epirubicin plus dexamethasone (TAD) and vincristine plus epirubicin plus dexamethasone (VAD). Second line chemotherapy such as dexamethasone plus thalidomide plus cisplatin plus epirubicin plus cyclophosphamide plus etoposide (DTPACE) or dexamethasone plus etoposide plus cyclophosphamide plus cisplatin (DECP) were initiated in those who hadn't achieved minimal response after first line therapy.

### *Peripheral progenitor cell mobilization*

All patients received peripheral blood stem cells (PBSC) mobilization, collection and cryopreservation. The main mobilization option was cyclophosphamide (CY, 1-2 g/m$^2$/d×2 d iv), and other rare regimens included DTPACE and PAD. G-CSF (5 ug/kg/day) was subcutaneously administered from about day 5-7 after mobilization chemotherapy until the completion of leukapheresis. PBSCs were collected with the Spectra Optia cell separator (Caridian BCT, USA), started when the peripheral white blood cells (WBC) had reached 5-10×10$^9$/L, taking into account of the percents of lymphocyte and monocyte as well. PBSCs were mobilized by G-CSF alone (5 ug/kg/d) for 4 d before PBSCs collection in one patient. A graft containing at least 4×10$^8$/kg mononuclear cells or 2×10$^6$/kg CD34+ cells were considered sufficient for ASCT engraftment. Patients who mobilized less mononuclear cells required re-mobilization. The frozen products were stored at -80°C in an electric freezer.

### *Transplantation*

The melphalan at a median dose of 140 mg/m$^2$ (range: 120-160 mg/m$^2$) was administered as a conditioning regimen according to patient tolerance. Stem cells were infused 48 h after final melphalan use. G-CSF 5 ug/kg/d was started from day + 2 until neutrophils achieved at least 1×10$^9$/L. If neutropenic fever occurred, broad-spectrum antibiotics were administered at once after cultures of blood and/or specimens of suspicious foci of infection. Red blood cell concentrates were given to keep the hemoglobin level >70 g/L and platelet concentrates were given to keep the platelet count >20×10$^9$/L. Hematologic and non-hematologic toxicities were graded according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE). We initiated mainly thalidomide (50-200 mg/day) as a maintenance therapy after HDM/ASCT in most patients provided that stable engraftment had occurred. A few patients received 2-3 cycles of bortezomib-based consolidation therapy after HDM/ASCT.

### *Hematopoietic engraftment*

Neutrophil and platelet engraftment were defined as the first of 3 consecutive days with a neutrophil count >0.5×10$^9$/L and a platelet count >20×10$^9$/L without transfusion supplement.

### *Response criteria*

All responses were evaluated according to the IMWG uniform criteria [15]. The quality of response was available prior to stem cell mobilization, at ASCT and post-transplant follow up.

**Table 1.** Patient characteristics

| Characteristics | Number of patients (%) |
|---|---|
| Median age, years (range) | 49 (23-66) |
| Male/female number | 35/17 |
| Myeloma subtype | |
| IgG kappa | 15 (28.8) |
| IgG lambda | 15 (28.8) |
| IgA kappa | 8 (15.4) |
| IgA lambda | 3 (5.78) |
| Kappa light chain | 1 (1.9) |
| Lambda light chain | 10 (19.2) |
| Durie-Salmon stage at diagnosis | |
| Stage IA | 3 (5.8) |
| Stage IIA | 6 (11.5) |
| Stage IIB | 1 (1.9) |
| Stage IIIA | 31 (59.6) |
| Stage IIIB | 11 (21.2) |
| ISS stage at diagnosis | |
| Stage I | 11 (21.2) |
| Stage II | 15 (28.8) |
| Stage III | 26 (50) |
| β2-Microglobulin at diagnosis, median mg/dl (range) | 5.345 (1.96-60.8) |
| Percentage of plasma cells in bone marrow (%) | 34 (3-88) |
| Cytogenetic Risk (n, %) | |
| Low | 11 (21.2) |
| Intermediate | 11 (21.2) |
| High | 0 (0) |
| Not known | 30 (57.7) |
| Transplant after | |
| One induction regimen | 38 (73.1) |
| More than one induction regimen | 14 (26.9) |
| Time from diagnosis to transplant, months (range) | 9 (3-96) |
| Karnofsky Performance Score at ASCT, Median (range) | 100 (80-100) |
| Maintenance after ASCT (n, %) | |
| Thalidomide/Lenalidomide | 41 (78.8) |
| Bortezomib based + thalidomide | 5 (9.6) |
| Other | 1 (1.9) |
| None | 5 (9.6) |
| Median follow-up, months (range) | 30 (2-92) |

*Post-transplant follow-up*

The response of ASCT was evaluated 1-3 months after ASCT. The patient was visited once a month for one year, then once every 3 months subsequently, while adjusted according to disease condition. If the relapse or progression was confirmed, patients received the further salvage therapy.

*Statistical analysis*

Continuous variables were analyzed by the median and range, and categorical variables were summarized by counts and percentages. The first endpoints of this study were to report the overall response and CR/non-CR (nCR) rate after ASCT. Secondary endpoints were safety, progression free survival (PFS) and OS after ASCT. The duration of PFS was calculated from the day of stem cell infusion to progression, relapse, or reference date. OS was estimated from the day of stem cell infusion to the date of death or the last visit. All patients were followed up until death or reference date (August 28, 2017). Therapy-related mortality (TRM) included any deaths within 60 days of transplantation. To assess the effect of the preparative regimen and other clinical and biochemical factors on PFS and OS, univariate and multivariate predictive models were performed using Cox Regression. Survival curves were plotted according to Kaplan-Meier's method. SPSS system, version 17.0 was used for the whole data analyses.

## Results

*Patient characteristics*

Baseline patient characteristics and laboratory parameters are showed in **Table 1**. The median age was 49 years. IgG isotype was predominant. About 80% of the patients were diagnosed with Durie-Salmon stage III. Low and intermediate risk cytogenetic abnormalities accounted for 50% in the 22 patients with cytogenetic examination, respectively. Five patients received 2-3 cycles of bortezomib based consolidation therapy combined with thalidomide main-

**Table 2.** Engraftment and regimen-related toxicities

| Characteristic | Value |
|---|---|
| Engraftment, Days | |
| Neutrophil engraftment | 13 (9-23) |
| Platelet engraftment | 15.5 (11-120) |
| Febrile neutropenia | 39 (75%) |
| Fever of unknown origin | 21 (40.4%) |
| Microbiologically documented infection | 7 (13.5%) |
| Clinically documented infection | 11 (21.1%) |
| Antibiotic Days | 8 (0-30) |
| Antibiotic Number[a] | 1 (0-7) |
| Mucositis | |
| Any grades | 20 (38.5%) |
| Grade 3/4 | 8 (15.4%) |
| Diarrhea | |
| Any grades | 23 (44.2%) |
| Grade 3/4 | 3 (5.8%) |
| Nausea/vomiting | |
| Any grades | 18 (34.6%) |
| Grades 3/4 | 1 (1.9%) |
| Hepatic | |
| Transaminase increase | 8 (15.4%) |
| Others | |
| Arrhythmia | 2 (3.8%) |
| Transplant-related mortality | 0 |
| Length of Hospital Stay, Days | 23 (14-45) |

a. A mean number of antibiotics used per patient if a given antibiotic was used intravenously for more than 48 hours.

tenance after ASCT. Forty-one (78.8%) patients conducted thalidomide or lenalidomide maintenance within 3 months after ASCT. Median duration of follow-up for surviving patients was 30 months (range, 2-92 months, estimated from the day of stem cell infusion to the date of death or the last visit).

*Progenitor cell mobilization and collection*

43 (82.7%) patients gained sufficient stem cells during the first mobilization to proceed to ASCT. Nine (17.3%) patients were remobilized and the minimum collection target was reached in all of them. Median mononuclear cells collected were $5.98\times10^8$ cells/kg. Median CD34+ cells were $5.5\times10^6$ cells/kg.

*Engraftment and transplant-related complications*

These are listed in **Table 2**. All the patients developed neutropenia and platelet decrease of grade 4. Median platelet concentrates infused were 2.5 therapeutical doses (range 1-10). 12 patients received red blood cell concentrates transfusion (range 2-12 units).

Febrile neutropenia was the most frequent non-hematologic complication. The most common gastrointestinal toxicities were diarrhea, followed by mucositis and nausea/vomiting. Arrhythmia occurred in 2 patients and both were improved quickly after treatment. Hepatic transaminase increased in 8 patients, while all of them were increased less than 2-fold of upper limit. No renal injuries were found. There was no transplant-related mortality.

*Treatment outcomes*

The results are showed in **Table 3**. An improvement in response (CR + VGPR) was observed in 14 patients (26.9%), and maintenance of the previous disease status in 34 (65.4%). At a median follow-up of 30 months, the estimated median OS and PFS for the whole group were 84.00±22.42 (95% confidence interval [CI], 40.07-127.94) and 24±5.81 (95% CI, 12.61-35.40) months, respectively. Estimated 5-year OS was 52.5±8.9%, and the corresponding figure for PFS was 22.4±7%. Concerning the subgroup of patients who achieved at least VGPR after transplant, they had both a significantly longer PFS (median 33 vs. 8 months; P=0.000) and OS (median 84 vs. 18 months; P=0.009) than those who attained a lower degree of response (**Figure 1**).

*Prognostic analysis*

First, we performed a univariate analysis to identify the predictors related to PFS and OS using the Cox proportional hazards model. ISS stage I and II at diagnosis, status of at least VGPR at and after ASCT were significant for predicting OS. BM plasma cells <5% at ASCT, Status of at least VGPR at ASCT and after ASCT were significant for predicting PFS (**Table 4**). Multivariate analysis using Cox proportional hazards model showed ISS stage I and II at diagnosis and status of at least VGPR after ASCT to be independent prognostic variables associated with improved OS, while BM plasma cells <5% at ASCT and status of at least VGPR after ASCT were independent prognostic factors associated with improved PFS (**Table 5**).

**Table 3.** Pretransplant disease status versus posttransplant status

| Disease Status Before Transplant | Disease Status After Transplant | | | | | Total Pretransplant Status |
|---|---|---|---|---|---|---|
| | CR | VGPR | PR | SD | PD/Refractory | |
| CR | 9 | 1 | 0 | 0 | 0 | 10 (19.2%) |
| VGPR | 5 | 16 | 1 | 0 | 0 | 22 (42.3%) |
| PR | 2 | 5 | 8 | 0 | 2 | 17 (32.7%) |
| SD | 1 | 0 | 0 | 1 | 0 | 2 (3.8%) |
| PD/Refractory | 0 | 1 | 0 | 0 | 0 | 1 (1.9%) |
| Total Responses After Transplant | 17 (32.7%) | 23 (44.2%) | 9 (17.3%) | 1 (1.9%) | 2 (3.8%) | 52 (100%) |

Abbreviations: CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; PD: progressive disease.

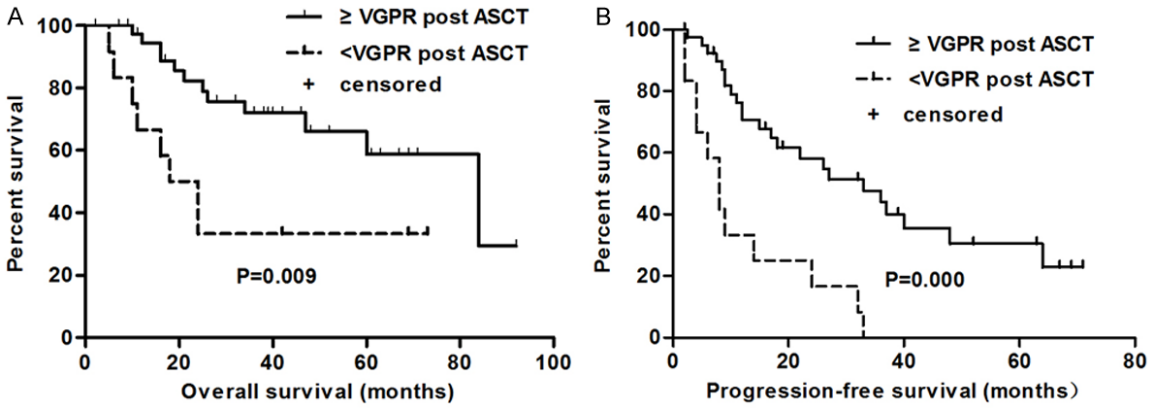


**Figure 1.** Kaplan-Meier curves for OS (A) and PFS (B) according to the degree of response after autologous transplantation (40 patients in at least VGPR vs. 12 patients in less than VGPR).

## Discussion

MEL200 is usually considered as a standard conditioning regimen for ASCT of MM patients. MEL140 is also acceptable [16]. In elder patients, the dose is always reduced to 140 mg/m$^2$ for safety. One study reported that there were no significant differences in treatment related mortality and morbidity, relapse free survival (RFS) and OS between the two groups of MEL200 and MEL140, although the number of elder patients in MEL140 group was more than MEL200 group [11]. In order to explore whether reduced high dosage of melphalan is applicable to the younger and healthier patients as well, we retrospectively analyzed the toxicities and outcomes of reduced high dose melphalan combined with ASCT in MM patients in our institution.

In this study, the response rate (at least PR) at ASCT was 94.2%, with a ≥VGPR response rate of 61.5%. The encouraging result of previous therapy should be due to the active use of novel agents. A ≥VGPR response rate of 76.9% including complete response rate of 32.7% was achieved after ASCT. The ≥VGPR response rate after ASCT is even higher than those reported in previous studies of ASCT with conditioning regimens including MEL200 or melphalan combined with other conventional agents and/or novel agents, with ≥VGPR response rate ranging from about 21% to 76%, while CR rate ranging from 8%-66.3% [1, 11, 17-27].

It has been reported median OS after ASCT using variable conditioning regimens in newly diagnosed patients is ranging from 31.2-141 months, PFS ranging from 18-121 months; In MEL200 conditioning ASCT, the figures are 57-141 months and 18-97 months [9, 11, 17, 22-25, 28-31] (**Table 6**). The OS and PFS in our patients are in accordance with the previous results.

Myelosupression of grade 4 occurred in all patients in our report. No engraftment failure happened. Median days to neutrophil and platelet engraftment were similar to that of MEL200 reported, about 11-14 days [11, 17, 22, 27]. Oral mucositis, diarrhea and nausea/vomiting are common high dose melphalan chemo-

**Table 4.** Overall and progression free survival: analysis of prognostic factors

| Factor | Patients, n | OS (months) | P | PFS (months) | P |
|---|---|---|---|---|---|
| Age | | | | | |
| <50 y vs. ≥50 y | 28 vs. 24 | 84 vs. 34 | 0.104 | 22 vs. 26 | 0.279 |
| Gender | | | | | |
| Male vs. female | 35 vs. 17 | 84 vs. 84 | 0.335 | 15 vs. 33 | 0.477 |
| Myeloma subtype | | | | | |
| IgG vs. IgA vs. LC | 30 vs. 11 vs. 11 | MNR vs. 60 vs. 25 | 0.103 | 33 vs. 22 vs. 15 | 0.172 |
| DS Stage at diagnosis | | | | | |
| I + II vs. III | 10 vs. 42 | MNR vs. 60 | 0.452 | 27 vs. 22 | 0.358 |
| ISS stage at diagnosis | | | | | |
| I + II vs. III | 26 vs. 26 | MNR vs. 34 | 0.028 | 27 vs. 17 | 0.174 |
| Haemoglobin at diagnosis | | | | | |
| <85 g/l vs. ≥85 g/l | 28 vs. 24 | 60 vs. 84 | 0.264 | 15 vs. 27 | 0.057 |
| Albumin at diagnosis | | | | | |
| <35 g/l vs. ≥35 g/l | 23 vs. 29 | 34 vs. 84 | 0.336 | 24 vs. 27 | 0.451 |
| BM plasma cells at diagnosis | | | | | |
| <40% vs. ≥40% | 32 vs. 20 | 84 vs. 60 | 0.423 | 18 vs. 24 | 0.665 |
| Prior therapy | | | | | |
| 1 vs. >1 regimen | 38 vs. 14 | 84 vs. 60 | 0.626 | 27 vs. 11 | 0.063 |
| Time from diagnosis to transplant | | | | | |
| <12 months vs. ≥12 months | 38 vs. 14 | 84 vs. 26 | 0.154 | 26 vs. 12 | 0.167 |
| Mononuclear cells infused | | | | | |
| $<5.98*10^8$/kg vs. $\geq 5.98*10^8$/kg | 26 vs. 26 | 60 vs. 84 | 0.99 | 26 vs. 22 | 0.665 |
| BM plasma cells at ASCT | | | | | |
| <5% vs. ≥5% | 43 vs. 9 | 84 vs. 60 | 0.277 | 32 vs. 8 | 0.002 |
| Status at ASCT | | | | | |
| ≥VGPR vs. <VGPR | 32 vs. 20 | MNR vs. 47 | 0.039 | 40 vs. 9 | 0.000 |
| Status after ASCT | | | | | |
| ≥VGPR vs. <VGPR | 40 vs. 12 | 84 vs. 18 | 0.009 | 33 vs. 8 | 0.000 |
| Dose of melphalan | | | | | |
| <140 mg/m$^2$ vs. ≥140 mg/m$^2$ | 34 vs. 18 | 60 vs. MNR | 0.078 | 15 vs. 33 | 0.129 |

Abbreviations: LC: light chain; MNR: median not reached.

**Table 5.** Multivariate analysis for progression free survival and overall survival

| Factor | HR | 95% CI | *P*-value |
|---|---|---|---|
| OS | | | |
| ISS stage at diagnosis | | | |
| I + II vs. III | 0.291 | 0.109-0.774 | 0.013 |
| Status after ASCT | | | |
| ≥VGPR vs. <VGPR | 0.252 | 0.099-0.642 | 0.004 |
| PFS | | | |
| BM plasma cells at ASCT | | | |
| <5% vs. ≥5% | 0.42 | 0.187-0.944 | 0.036 |
| Status after ASCT | | | |
| ≥VGPR vs. <VGPR | 0.295 | 0.137-0.635 | 0.002 |

Abbreviations: HR, hazard ratio; These results are from a Cox regression model selected by forward stepwise procedure.

therapy related gastrointestinal toxicities. Roussel reported the incidence rate of mucositis was 70%, with 47% of grade 3-4 [19]. Kumar found mucositis occurred in 99.5% patients, with 71.4% of grade 3-4; both nausea/vomiting and diarrhea developed in more than 97% patients [17]. Another study reported that the rate of mucositis, nausea/vomiting and diarrhea was 65%, 56% and 74%, respectively [11]. Some other studies found the rate of grade 3-4 gastrointestinal toxicities was about 20-40% [1, 8, 22]. It seems that the gastrointestinal toxicities especially severe toxicities (grade 3-4) in our result are less than MEL200 reported. The occurrence

**Table 6.** Response and survival values after ASCT with different conditioning regimens in multiple myeloma

| Authors | Year | NO. of patients | Median age | Percent ISS stage III | Conditioning regimen | Median follow-up (months) | Response rate | CR rate after ASCT | OS from ASCT (months) | PFS from ASCT (months) | EFS from ASCT (months) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Bang et al [1] | 2003 | 80 | 53 | 85% | MEL200 | 30 | 94.9% | 60% | 60 | NA | 18 |
| Moreau et al [8] | 2002 | 282 | 61 vs. 60 | 75% vs. 79% | MEL200 vs. MEL140 + TBI | 20 | 94% vs. 89% | 35% vs. 29% | Not reached vs. 43 | NA | 20.5 vs. 21 |
| Ria et al [9] | 2004 | 30 | NA | NA | MEL200 vs. Bu + MEL100 | NA | NA | NA | 108 vs. 126 | 97 vs. 121 | NA |
| Katragadda et al [11] | 2016 | 129 | 71 vs. 61 | 67% vs. 68% | MEL140 vs. MEL200 | 74 | NA | NA | Not provided vs. 141 | 31.2 vs. 36.2 | NA |
| Kumar et al [17] | 2013 | 170 | 52 | 95.8% | MEL200 | 84 | 90.6% | 44.7% | 85 | NA | 41 |
| Palumbo et al [18] | 2010 | 298 | 58 vs. 57 | 68% vs. 67% | MEL200 vs. MEL100 | 44.6 | 78.5% vs. 71.8% | 14.8% vs. 8.1% | Not reached vs. 60 (from diagnosis) | 31.4 vs. 26.2 (from diagnosis) | NA |
| Jantunen et al [22] | 2006 | 101 | 57 (younger group) vs. 68 (elder group) | 52% vs. 50% | MEL200 | 21 vs. 32 | 74% vs. 94% | 44% vs. 36% | 66 vs. 57 | 21 vs. 23 | NA |
| Lahuerta et al [23] | 2010 | 767 | 56 vs. 58 | 20% vs. 18% | Bu + MEL140 vs. MEL200 | 72 vs. 47 | 90% vs. 92% | 38% vs. 36% | 79 vs. 71 | 41 vs. 31 | NA |
| Remenyi et al [24] | 2016 | 548 | 57 | 58.9% | MEL200, MEL140 (cases with creatinine clearance <50 mL/min) | NA | 95.3% | 54.6% | 97.6 | 28.2 | NA |
| Nadal et al [25] | 2004 | 59 | 54 | 47% | MEL200, MEL140 + TBI, busulfan-based | NA | NA | 37% | NA | 59.5 | 32.5 |
| Lee et al [26] | 2013 | 92 | 52 | 34.8% | MEL140-200 | 28 | 92.4% | 66.3% | Not reached | 25.5 | |
| Dunavin et al [32] | 2013 | 167 | 56.6 (early ASCT) vs. 55.3 (late ASCT) | 22% vs. 18% | MEL200 | 23.2 vs. 29 | 99% vs. 97% | 50% vs. 28% | Not reached vs. 57.3 | 28 vs. 18 | NA |
| Benson et al [29] | 2007 | 110 | 56.1 | 39% vs. 58% | BCV vs. MEL200 | 34 vs. 16 | 77% vs. 74% | 24% vs. 23% | 31.2 vs. Not reached | 26.7 vs. 25 | NA |
| Blanes et al [30] | 2012 | 153 | 61 | 22% vs. 20% | BU + MEL140 vs. MEL200 | 50 vs. 63 | 90% vs. 91% | 23.5% vs. 33% | 65.5 vs. 63 | 33 vs. 24 | NA |
| Cogle et al [31] | 2003 | 26 | 55 | 77% | BuCy + VP16 | 23 | 96% | 38% | 43 | NA | 24 |

rate of neutropenic fever is in line with the previous reports [11, 22]. Severe organ toxicities such as cardiac, hepatic and renal injuries were not found in our patients. So the non-hematologic toxicities of MEL140 are slight.

Referring to the effect of early versus late transplants, Remenyi et al found patients transplanted within 12 months from the start of their therapy had significantly better responses and post-ASCT PFS benefit than those having delayed ASCT, whether novel agents were used or not, but no significant prolonged overall survival [24]. Other reports showed that early transplants (≤12 months) could induce better response rate, OS and EFS in the pre-era of novel agents, but the effect was no longer present in the era of novel agents for induction therapy [17, 32]. In our study, no significant advantages of early transplant were observed in either OS or PFS, maybe attributed to the wide use of novel agents in induction chemotherapy.

Achievement of CR is an important event in myeloma and represents the major surrogate marker for long-term OS and EFS [17, 25]. Some researchers identified achievement of 'at least VGPR' as an important predictor of OS and PFS/EFS post-ASCT [24, 33]. In our study, status of at least VGPR post-transplant predicted longer OS and PFS. Additional predictors of extended OS and PFS were ISS stage and BM plasma cells <5% at ASCT, respectively, although we can't rule out maintainence therapy as a confounder. But in a word, lower tumor burden and favorable response to ASCT treatment predict good prognosis.

In conclusion, we found reduced intensity melphalan conditioning (MEL140) could lead to excellent survival effect, with less severe gastrointestinal toxicities. Response of at least VGPR post-transplant is a good predictor for both OS and PFS. Nevertheless, the study was a retrospective analysis with limited patients. Therefore, the results should be further investigated in larger prospective trials.

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## Disclosure of conflict of interest

None.

**Address correspondence to:** Guang-Xun Gao and Xie-Qun Chen, Department of Hematology, Xijing Hospital, Fourth Military Medical University, Xi'an 710032, Shaanxi, China. Tel: +86-2984775199; Fax: +86-2984775205; E-mail: gaoguangxun@fmmu.edu.cn (GXG); Tel: +86-2984771857; Fax: +86-2984775205; E-mail: xiequnchen@fmmu.edu.cn (XQC)

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