Novel agent induction therapy alone or followed by autologous stem cell transplantation in younger patients with multiple myeloma: A single-center retrospective study of 114 cases

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Abstract. To define the role of autologous stem cell transplantation (ASCT) in newly diagnosed multiple myeloma (MM) in the era of novel agents, we analyzed follow-up data of patients treated by these agents alone or followed by ASCT. From January, 2008 to December, 2012, 136 patients with *de novo* MM, aged <65 years, completed bortezomib- or thalidomide-based induction therapy and 114 patients achieved at least a partial response (PR). A total of 42 patients underwent ASCT. After a median follow-up of 39 months (range, 5-74 months), the median progression-free survival (PFS) was 23 months in the non-ASCT group vs. 42 months in the ASCT group (P=0.001), and the 5-year overall survival (OS) rate was 58.9 vs. 81.2%, respectively (P=0.03). The multivariate analysis revealed that complete response (CR) and maintenance therapy (MT) were independent factors of improved OS in both groups. Moreover, a subgroup analysis was performed according to the response status to evaluate the role of ASCT and MT. In the CR subgroup, neither ASCT nor MT exerted a significant effect on PFS or OS. In the very good PR subgroup, ASCT after MT (ASCT/MT) significantly improved PFS, but not OS. In patients exhibiting PR, ASCT/MT significantly prolonged PFS and OS. Therefore, ASCT in the era of novel agents maintains an important role in younger MM patients, particularly those achieving a PR after induction therapy. Furthermore, MT is a key factor associated with long-term survival in all MM patients.

Introduction

Multiple myeloma (MM) is the main type of hematological malignancy originating from plasma cells. MM is currently an incurable disease. With conventional chemotherapeutic regimens, such as melphalan and prednisone (MP), vincristine plus adriamycin and dexamethasone (VAD) and high-dose dexamethasone, the overall response rate (RR) of MM patients is 60%, with only <5% achieving a complete response (CR). The median survival is 2-3 years (1). High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) may achieve a higher RR and longer progression-free survival (PFS) and overall survival (OS) (2-4). Over the last decade, the introduction of the proteasome inhibitor bortezomib and the immunomodulatory agents thalidomide and lenalidomide, has revolutionised MM treatment (5,6). The high RR and CR rate achieved by these novel agents have also raised the question whether ASCT should still be considered as first-line therapy in MM. Several phase 3 trials comparing chemotherapy with first-line ASCT have reported an improved PFS, but no difference in OS (7,8), while others support ASCT as part of the treatment strategy (9,10). It is clear that ASCT enhances the response, even after the most active first-line regimens, including bortezomib plus thalidomide and dexamethasone (VTD) and lenalidomide plus bortezomib, pegylated liposomal doxorubicin and dexametasone (RVDD) (11,12). ASCT is currently considered the standard of care in younger MM patients according to the current National Comprehensive Cancer Network guidelines (13).

However, in China, the majority of the patients may be less likely to undergo transplantation due to multiple reasons, and data on which group of patients may benefit more from ASCT are currently limited. In this study, we performed a retrospective analysis of 114 MM patients, aged <65 years, who were treated with or without ASCT following novel agent-containing induction therapy in our hospital.

Patients and methods

Patients. From January, 2008 to December, 2012, 136 patients with *de novo* MM, aged <65 years, received bortezomib- or thalidomide-containing induction therapy at the Department of Hematology of Ruijin Hospital (Shanghai, China). Following induction therapy, 114 patients who achieved at least a PR and had no severe comorbidities, were eligible for ASCT. Among these, 42 patients received ASCT within 1 year of diagnosis

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Key words: multiple myeloma, autologous hematopoietic stem cell transplantation, maintenance treatment, progression-free survival, overall survival

Table I. Baseline characteristics of the 114 multiple myeloma patients.

Characteristics	Non-ASCT (n=72)	ASCT (n=42)
Age, years		
Median (range)	57 (29-65)	53 (41-65)
Gender, male/female	43/29	30/12
M component, n (%)		
IgG	41 (57.0)	25 (59.5)
IgA	19 (26.4)	6 (14.3)
IgD	2 (2.7)	5 (11.9)
Light chain	10 (13.9)	6 (14.3)
DS stage, n (%)		
I	0	0
II	15 (20.8)	14 (33.3)
III	57 (79.2)	28 (66.7)
ISS stage, n (%)		
I	1 (1.4)	1 (2.4)
II	61 (84.7)	32 (76.2)
III	10 (13.9)	9 (21.4)
Number of induction cycles, median (range)	5 (2-10)	4 (3-8)
Best response after induction therapy, n (%)		
CR	19 (26.4)	13 (31.0)
VGPR	22 (30.6)	14 (33.3)
PR	31 (43.0)	15 (35.7)
Induction regimen, n (%)		
Bortezomib	55 (76.4)	25 (59.5)
Thalidomide	17 (23.6)	17 (40.5)
Maintenance therapy, n (%)		
Yes	40 (55.6)	25 (59.5)
No	32 (44.4)	17 (40.5)

ASCT, autologous hematopoietic stem cell transplantation; DS, Durie-Salmon staging system; ISS, International Staging System; CR, complete response; PR, partial response; VGPR, very good PR.

(ASCT group). The remaining 72 patients declined ASCT for personal reasons (non-ASCT group). This study was approved by the Ethics Committee of Ruijin Hospital and conformed to the principles of the Declaration of Helsinki. Written informed consent was obtained from all the patients.

Evaluation. MM was diagnosed according to the uniform response criteria of the International Myeloma Working Group (IMWG) (14). All 114 patients had symptomatic MM, with measurable disease. Non-secretory MM cases were excluded. The response was classified as complete response (CR), very good partial response (VGPR), partial response (PR) and progressive disease (PD), according to the IMWG criteria.

Treatment regimens. All the patients were induced with chemotherapeutic regimens, including bortezomib plus adriamycin and dexamethasone (PAD), or bortezomib plus cyclophosphamide and dexamethasone (PCD), or VAD and thalidomide (VADT). Bortezomib was administered at a dose of 1.3 mg/m^2 i.v. twice/week for 2 weeks in a 21- or 28-day cycle. Thalidomide was administered at a dose of 100 mg daily. In the ASCT group, all the patients received peripheral blood progenitor cell mobilization with cyclophosphamide (4 g/m^2) and conditioning therapy with high-dose melphalan (100-200 mg/m^2). The main maintenance therapy (MT) regimen was thalidomide (50-150 mg/day), which, if tolerated, continued until disease progression.

Statistical analysis. PFS was calculated from the date of the initiation of induction therapy to the date of disease progression, relapse, or death. OS was measured from the date of diagnosis to the date of death; data on survivors were censored at the last follow-up. All analyses were performed with SPSS 19.0 statistical software (IBM SPSS, Armonk, NY, USA). Survival outcomes were analyzed with the Kaplan-Meier method and compared with the log-rank test. The Cox proportional hazards model was used for multivariate analysis, and all the variables achieving P<0.25 in the univariate ananlysis were considered.

Results

Patient characteristics. The study population comprised 114 patients, of whom 73 (64%) were male. The median age

Table II. Univariate analysis of the prognostic factors for survival in the non-ASCT group.

Factors	n	PFS (months)	P-value	OS (months)	P-value
DS stage			0.600		0.357
II	15	24±3.618		NR	
III	57	23±2.589		65±15.156	
ISS stage			0.004		0.171
I+II	62	26±2.828		65±8.145	
III	10	15±2.324		42±19.322	
Best response after induction therapy			0.010		0.007
CR	19	38±9.413		NR	
VGPR	22	23±4.462		65±4.605	
PR	31	18±2.226		42±10.882	
Induction regimen			0.982		0.765
Bortezomib	54	23±2.902		NR	
Thalidomide	18	25±3.135		55±9.832	
Maintenance therapy			0.015		0.004
Yes	40	27±2.726		NR	
No	32	17±2.62		36±6.924	

The values are presented as mean ± standard deviation. ASCT, autologous hematopoietic stem cell transplantation; DS, Durie-Salmon staging system; ISS, International Staging System; CR, complete response; PR, partial response; VGPR, very good PR; PFS, progression-free survival; OS, overall survival; NR, not reached.

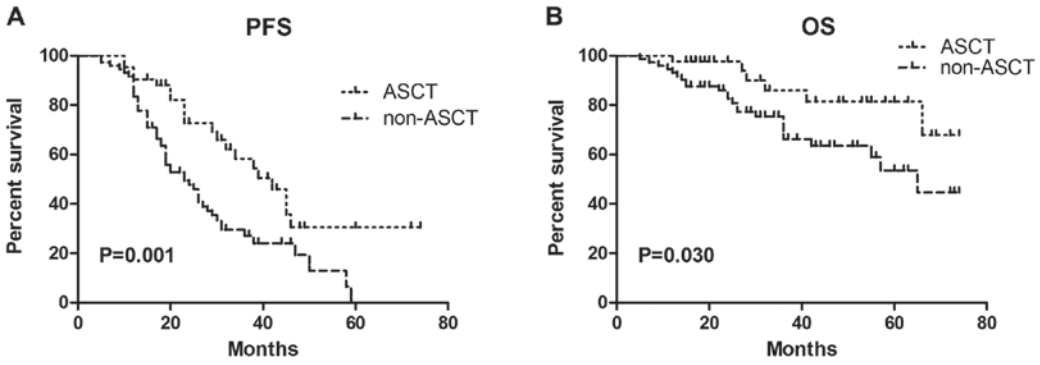

Figure 1. (A) PFS and (B) overall OS were superior in the ASCT group compared with those in the non-ASCT group. PFS, progression-free survival; OS, overall survival; ASCT, autologous hematopoietic stem cell transplantation.

of the patients was 56 years (range, 26-64 years) and 85 (75%) patients had Durie-Salmon stage III disease at diagnosis. A total of 80 patients received bortezomib-containing induction therapy, whereas the remaining patients received thalidomide-containing therapy. Following induction therapy, all the patients underwent response evaluation: A total of 32 patients had achieved CR, 36 patients had VGPR and 46 patients had PR. Of the 114 patients, 42 received high-dose chemotherapy followed by ASCT (ASCT group), whereas the remaining 72 patients did not receive ASCT (non-ASCT group). The baseline characteristics of the ASCT and non-ASCT groups are listed in Table I. No significant difference in clinical characteristics was observed between the two groups.

Disease outcome. The median follow-up time of the 114 patients was 39 months (range, 5-74 months). At the time of the last follow-up (March 31st, 2014), 52 of the 72 (72.2%) patients in the non-ASCT group had progressed or relapsed, whereas 24 patients (33.3%) had succumbed to the disease. In the ASCT group, 20 of the 42 (47.6%) patients had progressed or relapsed and 6 patients (14.3%) had succumbed to the disease. The median PFS in the non-ASCT and ASCT groups was 23 and 42 months, respectively (P=0.001, Fig. 1A). The median OS was not reached in neither of the groups. The 5-year OS rate was 58.9 and 81.2% in the non-ASCT and ASCT groups, respectively (P=0.03, Fig. 1B).

Prognostic indicators. The univariate analysis in the non-ASCT group (Table II) revealed that the prognostic factors associated with prolonged PFS and OS included CR (P=0.01 and 0.007, respectively) and MT (P=0.015 and 0.004, respectively). Lower International Staging System (ISS) stage

Table III. Univariate analysis of the prognostic factors for survival in the ASCT group.

Factors	n	PFS (months)[a]	P-value	3-year OS (%)	P-value
DS stage			0.903		0.407
II	14	42±7.574		81.3	
III	28	39±7.907		88.5	
ISS stage			0.781		0.625
I+II	33	42±6.674		86.7	
III	9	38±10.474		83.3	
Response after ASCT			0.020		0.067
CR	29	45±2.553		94.7	
VGPR	10	30±4.714		62.5	
PR	3	17±5.715		66.7	
Maintenance therapy			0.408		0.038
Yes	25	42±4.812		92.9	
No	17	34±5.837		77.0	

[a]Presented as mean ± standard deviation. ASCT, autologous hematopoietic stem cell transplantation; DS, Durie-Salmon staging system; ISS, international staging system; CR, complete response; PR, partial response; VGPR, very good PR; PFS, progression-free survival; OS, overall survival.

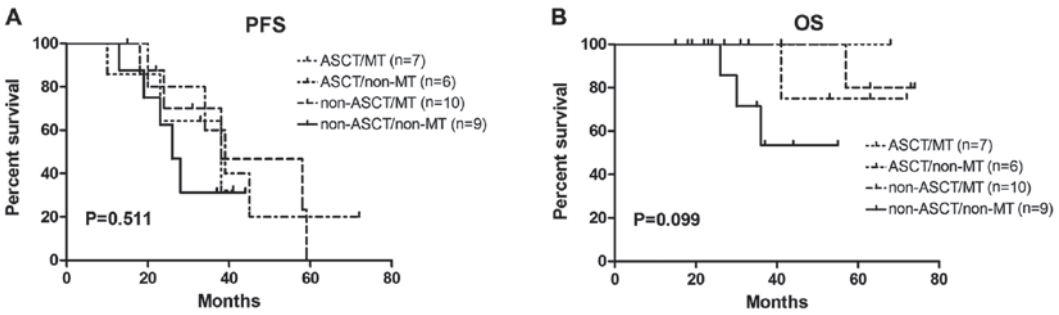

Figure 2. ASCT and MT did not significantly affect the outcome of the patients achieving a complete response prior to ASCT. (A) The median PFS ± standard deviation of the four arms (ASCT/MT, ASCT/non-MT, non-ASCT/MT, non-ASCT/non-MT) was 38±11.688, 39±6.736, 58±15.88 and 26±2.947, respectively. (B) The 3-year OS rate of the four arms (ASCT/MT, ASCT/non-MT, non-ASCT/MT, non-ASCT/non-MT) was 100, 80, 80 and 53.6%, respectively. PFS, progression-free survival; OS, overall survival; ASCT, autologous hematopoietic stem cell transplantation; MT, maintenance therapy.

(I+II) was associated with superior PFS (P=0.004), but not OS (P=0.171).

The univariate analysis in the ASCT group (Table III) revealed that the prognostic factors of a favorable outcome included CR post-ASCT, which prolonged PFS (P=0.02), but not OS (P=0.067). MT significantly prolonged OS (P=0.038).

The multivariate analysis revealed that, for all the patients, CR post-induction therapy, ASCT and MT were prognostic factors of improved PFS and OS, whereas ISS stage affected PFS, but not OS (Table IV).

Effect of ASCT and MT on subgroups. Furthermore, we performed a subgroup analysis base on the response evaluation. Following induction therapy, the patients were divided into three subgroups, namely the CR, VGPR and PR subgroups. For each subgroup, the effect of ASCT and MT on PFS and OS was analyzed. According to the two factors (ASCT and MT), four arms were formed as follows: ASCT/MT, ASCT/non-MT, non-ASCT/MT, and non-ASCT/non-MT. In the CR subgroup (Fig. 2), no significant differences in PFS and OS were observed

Table IV. Multivariate analysis of prognostic factors for survival in all multiple myeloma patients.

Variables	P-value	HR	95% CI
PFS			
ISS stage III vs. I-II	0.009	2.202	1.223-3.965
No CR vs. CR	0.004	2.284	1.301-4.011
No ASCT vs. ASCT	0.000	2.871	1.659-4.966
No MT vs. MT	0.002	2.170	1.336-3.525
OS			
ISS stage III vs. I-II	0.720	1.184	0.471-2.978
No CR vs. CR	0.041	2.743	1.040-7.233
No ASCT vs. ASCT	0.023	2.912	1.161-7.305
No MT vs. MT	0.001	3.917	1.795-8.549

PFS, progression-free survival; OS, overall survival; ISS, International Staging System; CR, complete response; ASCT, autologous hematopoietic stem cell transplantation; MT, maintenance therapy. HR, hazard ratio; CI, confidence interval.

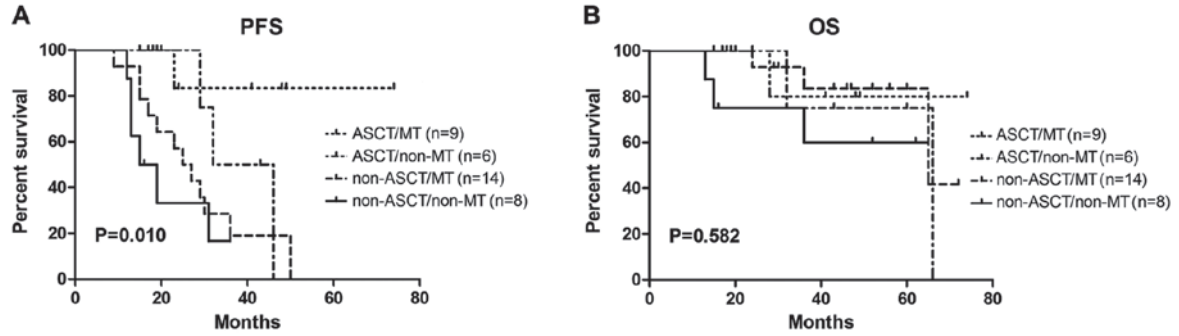

Figure 3. ASCT and MT affected PFS but not OS in the patients achieving a very good partial response prior to ASCT. (A) The median PFS ± standard deviation of the four arms (ASCT/MT, ASCT/non-MT, non-ASCT/MT, non-ASCT/non-MT) was NR (not reached), 32±5.667, 25±3.742, 15±3.637, respectively. (B) The 3-year OS rate of the four arms was 80, 75, 83 and 60%, respectively. PFS, progression-free survival; OS, overall survival; ASCT, autologous hematopoietic stem cell transplantation; MT, maintenance therapy.

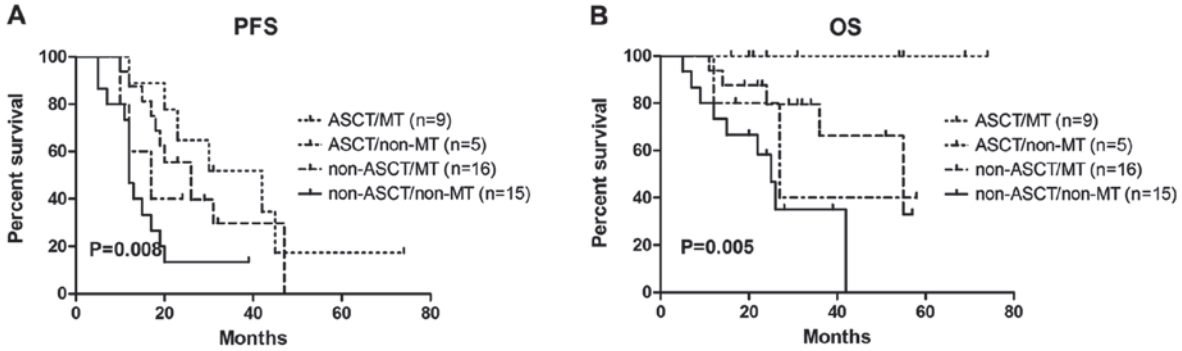

Figure 4. ASCT and MT affected both PFS and OS in the patients achieving a partial response prior to ASCT. (A) The median PFS ± standard deviation of the four arms (ASCT/MT, ASCT/non-MT, non-ASCT/MT, non-ASCT/non-MT) was 42±11.52, 17±5.477, 26±4.942 and 12±7.73, respectively. (B) The 3-year OS rate of the four arms (ASCT/MT, ASCT/non-MT, non-ASCT/MT, non-ASCT/non-MT) (ASCT/MT, ASCT/non-MT, non-ASCT/MT, non-ASCT/non-MT) was 100, 40, 66 and 35%, respectively. PFS, progression-free survival; OS, overall survival; ASCT, autologous hematopoietic stem cell transplantation; MT, maintenance therapy.

among the four arms (P=0.099 and P=0.511, respectively); patients without ASCT but with MT still reached the median PFS of 58±15.88 months, with a 3-year OS rate of 80%. In the VGPR subgroup (Fig. 3), PFS prolongation was achieved by the patients undergoing ASCT following MT (P=0.012), but there was no statistical difference in OS (P=0.582) among the four arms. In the PR subgroup (Fig. 4), the greatest benefit from ASCT and MT was observed. There were statistically significant differences in PFS (P=0.008) and OS (P=0.005) among the four arms.

Discussion

Multiple myeloma is currently considered incurable. The aim of the treatment of this disease is to prolong PFS, and eventually OS. The majority of the available studies indicate that achievement of CR was associated with prolonged PFS and OS (6,15). With conventional chemotherapy, the CR rate is currently 5-8%. High-dose therapy followed by ASCT increases the response rate and improves response to treatment, achieving a CR rate of 22-44% (16,17). More recently, novel agent-containing induction therapy has achieved a high response rate and CR rate. In the phase 3 VISTA study of bortezomib plus MP (VMP) vs. MP alone, the CR rate was 28% in the VMP group (18). In other bortezomib-containing induction regimens, the CR rate reached 22-47%, with a 1-year PFS of 83-100% (5). The improved outcome of the novel agents may challenge the role of ASCT in the treatment of MM.

In this retrospective study, CR rate reached 28% (32/114) with the novel-agent induction therapy. Further benefits were obtained in the ASCT group, with the CR rate increasing from 31% (pre-ASCT) to 69% (post-ASCT). The survival analysis also revealed that PFS and OS were significantly prolonged in the ASCT group, supporting the beneficial role of ASCT in younger MM patients in the era of novel agents (19,20). However, different results were reported by other studies. Boccadoro *et al* (7) compared MP/lenalidomide (MPR) vs. ASCT plus lenalidomide maintenance or no maintenance and indicated that ASCT improved PFS, while the effect on OS was insignificant, suggesting that lenalidomide maintenance may balance the OS in the two groups. The improved OS in our study may be due to a higher number of cases achieving CR in the ASCT group (n=29 case, 69%).

Thalidomide, commonly used as MT and sequential therapy, was shown to improve PFS and OS (21,22). In our study, the multivariate analysis revealed that MT was an independent factor of improved PFS and OS in the non-ASCT as well as the ASCT group. However, a study conducted by Barlogie *et al* (23) reported a beneficial effect on PFS, but not OS and suggested that the similar OS between the two groups is partially due to the shorter survival following relapse in the thalidomide maintenance group. In addition, Attal *et al* (22,24)

reported an OS advantage from thalidomide maintenance with a follow-up of 39 months, while the OS advantage was lost when the follow-up was prolonged to 5.7 years. In our study, the median OS time has not yet been reached, and elucidating the survival advantages of MT requires a longer follow-up and further investigation.

CR achievement was another independent factor in our study, which was consistent with previous studies (4,6). Attaining a CR has been the major objective in the management of younger patients. However, the data on whether patients who achieved CR following induction therapy may further benefit from ASCT are currently limited. We performed a subgroup analysis according to the response status following induction therapy. Considering the important role of MT on survival, we analyzed ASCT as well as MT. Interestingly, in the subgroup of CR, with or without ASCT/MT, no statistically significant difference in PFS or OS was observed. It was previously demonstrated that stringent complete response (sCR) was an attainable goal following ASCT, which significantly improved survival outcome compared with conventional CR (25). As shown in our study, a better OS (5-year OS rate of 100%) may be achieved in the ASCT/MT arm, which may be due to more sCRs obtained, although the difference was not statistically significant. Our findings support the role of ASCT and MT in deepening the CR.

In the VGPR subgroup, ASCT and MT prolonged the PFS (P=0.010), but without an OS benefit (P=0.582). However, through constructing Kaplan-Meier curves, modest differences were observed among arms. Since the median OS time has not been reached, we hypothesized that different findings may emerged after long-term follow-up. In the PR subset, the patients undoubtedly benefited the most from ASCT and MT in terms of survival (P<0.01). The median PFS of the ASCT/MT arm was 42 months, with a 3-year OS rate of 100%, whereas in the non-ASCT/non-MT arm, the median PFS was only 12 months, with a 3-year OS rate of 35%. A poor PFS (17 months) and a 3-year OS rate of 40% was noted in the ASCT/no-MT arm. In this arm, the sample was too small (n=5) and 3 patients remained in PR following ASCT. Similar to other reports, any response less than VGPR following ASCT was always associated with a poor outcome (26,27).

In summary, novel-agent induction therapy resulted in a higher response rate and response quality. ASCT further increased the CR rate and improved PFS and OS, particularly in patients achieving a PR following induction therapy. In the patients who achieved CR following induction therapy, the role of ASCT requires further investigation. As an independent prognostic factor of better PFS and OS, MT has become an important part of the treatment strategy in MM.

Acknowledgements

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