BLOOD RESEARCH
VOLUME 48 · NUMBER 3
September 2013
ORIGINAL ARTICLE

The impact of novel therapeutic agents before and after frontline autologous stem cell transplantation in patients with multiple myeloma

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p-ISSN 2287-979X / e-ISSN 2288-0011
http://dx.doi.org/10.5045/br.2013.48.3.198
Blood Res 2013;48:198-205.

Received on February 20, 2013
Revised on April 1, 2013
Accepted on July 12, 2013

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Background
Novel agents (NAs) such as thalidomide and bortezomib have been administered in combination with autologous stem-cell transplantation (ASCT) to effectively treat multiple myeloma (MM). However, whether NAs perform better as induction treatments prior to transplantation, or as post-transplant maintenance therapies remains unclear.

Methods
We retrospectively analyzed 106 consecutive patients with MM who underwent ASCT within 1 year of diagnosis as first-line therapy.

Results
Eighty-seven (82.1%) patients received NAs before ASCT, whereas 68 (64.2%) received NAs after ASCT. NAs were administered to each patient as follows: before ASCT alone (N=29, 27.4%), after ASCT alone (N=10, 9.4%) or both before and after ASCT (N=58, 54.7%). High-quality rates before and after ASCT were significantly higher for patients who received NAs as induction treatment compared to those who did not receive pre-transplant NAs. At a median follow-up of 37.9 months, the 3-year progression-free survival (PFS) and overall survival (OS) rates were 42.8% and 70.2%, respectively. The PFS and OS were significantly higher in patients with NAs as post-transplant maintenance treatment (P=0.03 and P=0.04, respectively), but not in those with NAs as pre-transplant induction treatment. The PFS of patients with NAs before and after ASCT was higher than that of the patients with NAs as induction therapy alone (P=0.05). Age, serum β2-microglobulin level, complete response after ASCT, and NA use post-ASCT independently predicted survival outcomes.

Conclusion
These findings suggest that integration of NAs post-ASCT could benefit patients with MM undergoing ASCT. Induction therapy using NAs also improves high-quality response rates before and after ASCT.

Key Words Multiple myeloma, Novel agents, Autologous stem cell transplantation, Induction and maintenance treatment

INTRODUCTION

High-dose chemotherapy and autologous stem cell transplantation (ASCT) have been an integral part of the initial treatment plan for younger patients with multiple myeloma (MM). More recently, highly efficacious agents, such as the immunomodulatory derivatives (IMiDs) thalidomide and lenalidomide, and the proteasome inhibitor bortezomib, have been developed and initially used in relapsed and refractory patients [1, 2].

Considerable efforts have been made towards improving the results of ASCT in MM through the incorporation of novel agents (NAs) into the transplantation sequence [3].

Many studies have integrated these novel therapeutic agents earlier in the disease course, and in conjunction with ASCT, evaluated their use in the following settings: pre-transplantation induction therapy, during the high-dose therapy itself, and as post-transplantation measures such as maintenance or consolidation therapy. However, it is not clear whether NAs perform better when administered prior to transplantation as induction treatment or as post-transplant maintenance therapy. The purpose of this study was to determine whether the treatments with NAs perform best when administered before or after the transplantation procedure in patients with MM.

MATERIALS AND METHODS

Patients

Between January 1, 2005 and December 31, 2010, we retrospectively analyzed 106 patients with newly diagnosed MM who received ASCT at our institution within 1 year of the initial diagnosis. We used a cutoff of December 2010 to allow for an adequate long-term follow-up period, given the potentially slow rate of disease progression. Patients who received tandem transplants or died from transplant-related mortalities within 100 days post-ASCT were excluded from the analysis. Only first transplantations, as part of frontline therapy, were included in the study. Approval by the Institutional Review Board was obtained in accordance with national regulations and the Declaration of Helsinki.

The patients were required to have symptomatic MM (Durie-Salmon stage II or III) diagnosed using standard criteria and with measurable disease parameters. All patients had a measurable level of monoclonal (M) protein, as determined by electrophoresis and immunofixation for serum and urinary M protein. ASCT patients were first evaluated to determine disease status before transplantation, including measurements of the M protein in serum or urine. We recorded the pre-transplant induction regimen, the conditioning regimen, and the post-transplant maintenance treatment used for all patients. The response criteria were defined by the International Myeloma Working Group uniform response criteria for MM [4]. A partial response (PR) was defined as a 50% reduction in serum M protein, along with a 90% reduction in urine M protein levels or achieving a level of $<$200 mg/24 hours. Complete response (CR) requires the disappearance of M protein as measured by serum and urine immunofixation along with bone marrow showing $<$5% plasma cells. Very good partial response (VGPR) was defined as serum and urine M protein detectable by immunofixation but not on electrophoresis, or a $\geq$90% reduction in serum M protein and achieving a urine M protein level of $<$100 mg/24 hours [5].

Treatment regimens

Induction therapy was administered for 3–4 months prior to transplantation in an attempt to reduce tumor cell burden. After induction therapy, treatment consisted of blood progenitor cell mobilization with cyclophosphamide and granulocyte colony-stimulating factor, and high-dose infusional chemotherapy with stem cell support with or without maintenance therapy. All patients underwent melphalan (140–200 mg/m^2) conditioning, which was generally given on day -2 and day -1 of transplantation, with half the melphalan dose administered on each day. Treatment regimen details have been previously published [6, 7].

The integration of NAs into the transplantation sequences includes their administration before and after the transplantation procedure. NAs were administered to each patient as follows: before ASCT alone (N=29, 27.5%), after ASCT alone (N=10, 9.4%), and both before and after the transplantation procedure (N=58, 54.7%). Nine (8.5%) patients did not receive any NAs before or after ASCT. Overall, 87 patients (82.1%) were treated with NAs prior to ASCT. The types of induction therapies were determined by protocols at our institution, as well as decisions made by the referring physicians regarding induction therapy selection. Patients were typically induced with vincristine, doxorubicin, and dexamethasone (VAD) or dexamethasone alone given in a pulsed-dose fashion at 40 mg/day on days 1–4, 9–12, and 17–20 of a 28-day treatment cycle according to their coverage by the National Health Insurance Corporation [8]. Patients who failed to achieve partial response or unacceptable toxicity to high-dose dexamethasone or VAD and who were also treated with bortezomib-containing regimens were included in the study. Some patients received NAs with bortezomib- or thalidomide-containing regimens as first-line induction therapy. Meanwhile, patients who received more than one treatment regimen owing to a lack of response to initial therapy with NAs were not administered additional NAs. Further, patients were treated with bortezomib alone (1.3 mg/m^2 intravenously twice weekly for 2 weeks in a 21-day cycle) or bortezomib in combination with dexamethasone 20 mg on the same day and day after bortezomib administration for all cycles (21-day cycle). Thalidomide was administered at varying doses of 100–200 mg/day with dexamethasone as tolerated.

Sixty-eight patients (64.2%) who did not develop peripheral neuropathy or resistance to previous thalidomide treatment received maintenance therapy using a thalidomide-based regimen (50–200 mg/day) with or without steroid starting between 2 and 3 months after ASCT without venous thrombus embolism prophylaxis until the patient experienced unacceptable toxicity or disease progression [9].

Statistical analysis

The association between the categorical variables was assessed using either χ^2 or Fisher's exact tests. The Mann-Whitney *U*-test was used to determine associations between continuous variables and categories, and Spearman correlation coefficients were used to evaluate associations of continuous variables. The prognostic outcomes were determined using regression techniques to analyze the univariate and multivariate influences of additional presenting and transplant covariates. Kaplan-Meier analysis was used to analyze

the progression-free survival (PFS) and overall survival (OS) data, and differences between survival curves were tested for statistical significance using the 2-tailed log-rank test [10]. Multivariate analysis was performed using the Cox's proportional hazards model [11].

RESULTS

The study population consisted of 106 patients, 56 (52.8%) of whom were male, and the median population age was 54 years (range, 34–65). The median time between diagnosis and ASCT was 5 months (range, 3–12). Fig. 1 shows details of incorporation of NAs in the ASCT procedure. As an induction treatment, bortezomib was administered for a median of 3 (2–4) cycles and thalidomide for 4 (3–5) months. The baseline characteristics of each treatment group are given in Table 1. There were no significant differences in the demographic characteristics according to the administration of NAs during induction or maintenance treatment, respectively, in terms of disease markers or presence of myeloma bone disease at diagnosis.

Sixty-one patients who experienced disease progression after ASCT underwent salvage therapy: bortezomib-based (22 patients), thalidomide-based (23 patients), lenalidomide (11 patients), or chemotherapy without NAs (5 patients).

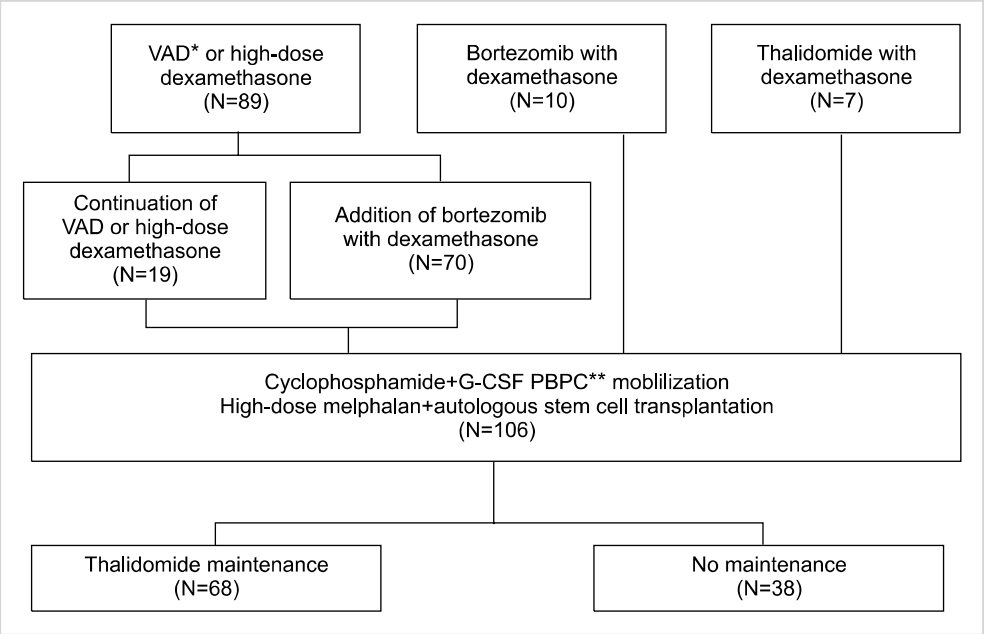

Fig. 1. Patient disposition. Abbreviations: G-CSF, granulocyte colony-stimulating factor; PBPC, peripheral blood progenitor cell; VAD, vincristine, doxorubicin, and dexamethasone.

Table 1. Patient characteristics according to treatment type.

Characteristics variables	Pre-ASCT treatment			Post-ASCT treatment		
	Use of NAs (N=87)	No Use of NAs (N=19)	*P*	Use of NAs (N=68)	No Use of NAs (N=38)	*P*
Median age, year, median (range)	54 (34–65)	56 (34–65)	NS	52 (34–63)	56 (38–65)	NS
Gender, M/F	47/40	9/10	NS	39/29	17/21	NS
Hemoglobin, g/dL, median (range)	9.9 (5.9–17.2)	10.1 (8.0–15.4)	NS	10.3 (6.3–17.2)	9.1 (5.9–12.6)	NS
Bone marrow plasma cells, %, median (range)	35.0 (0–99.0)	36.1 (2.0–99.0)	NS	30.0 (0–99.0)	44.0 (3.4–99.0)	NS
Serum creatinine, mg/dL, median (range)	1.06 (0.39–9.35)	0.98 (0.65–3.76)	NS	0.98 (0.39–5.49)	1.2 (0.63–9.35)	NS
Serum calcium, mg/dL, median (range)	9.1 (6.9–15.7)	8.7 (6.9–10.8)	NS	8.8 (7.6–10.8)	8.7 (6.9–16.0)	NS
Serum albumin, g/dL, median (range)	3.4 (2.2–4.3)	3.5 (2.2–4.7)	NS	3.6 (2.3–4.9)	3.5 (2.2–5.7)	NS
β2 microglobulin, mg/L, median (range)	4.0 (1.2–36.0)	3.5 (1.6–20.3)	NS	3.5 (1.2–36.0)	5.1 (1.7–28.8)	NS
Serum lactic dehydrogenase IU/L median (range)	362 (126–1,029)	455(114–1,072)	NS	3,572 (114–951)	405 (144–1,072)	NS
Bone lesions, Presence/absence	72/15	15/4	NS	57/11	30/8	NS
International staging system, 1/2/3/NA	18/37/29/3	6/6/7/0	NS	17/31/18/2	7/12/18/1	NS
Durie salmon stage II/IIIA/IIIB	12/58/17	2/13/4	NS	8/49/11	6/22/10	NS

Abbreviations: ASCT, autologous stem-cell transplantation; NAs, novel agents.

Response rates

Table 2 shows the response rates for all groups before and after ASCT. Most patients responded to the induction treatment with NAs very well. CR+VGPR rates before ASCT were significantly higher for patients who received NAs as induction treatment compared to those who did not receive NAs as induction treatment (Table 2A, 49/87, 56.3% vs. 5/19, 26.4%, P=0.018); similarly, the post-ASCT CR rates were 68/87 (78.2%) and 8/19 (42.1%), respectively (Table 2B, P=0.002). These data indicate that induction treatment with NAs improved the rate and intensity of response before and after ASCT compared to conventional pre-transplantation treatments. Meanwhile, the corresponding CR+VGPR rates before ASCT and CR rates after ASCT according to administration of post-ASCT NAs were comparable (Table 2A, 38/68, 55.8% vs. 16/38, 42.1%, P=0.174; Table 2B, 51/68, 75.0% vs. 25/38, 65.8%, P=313, respectively).

Survival outcomes

At the time of our analysis, 60.4% patients exhibited disease progression and 30.2% of patients had died. The median estimated follow-up for the entire cohort from the time of diagnosis was 37.9 months (95% confidence interval [CI], 31.1–44.7 months). The 3-year PFS and OS rates were 42.8% and 70.2%, respectively. The median duration of PFS and OS was 32.7 months (95% CI, 28.0–37.5 months) and 66.8 months (95% CI, 50.8–82.8 days), respectively. Fig. 2 summarizes the PFS and OS according NA use. In order to analyze the improvement in treatment time, the association between survival outcomes and NA use according to either induction therapy regimen before ASCT or maintenance treatment after ASCT was evaluated. The PFS (Fig. 2A) and OS (Fig. 2B) were significantly higher in the patients with NAs as post-transplant maintenance treatment (P=0.03 and P=0.04, respectively), but not in those with NAs as pre-transplant induction treatment (P=0.51 and P=0.35, respectively). We next compared survival outcomes among the 3 groups that were divided by the time of administration of NAs: before and after the transplantation procedure, before ASCT alone, and after ASCT alone (Fig. 3). The patients who received NAs before and after ASCT showed higher PFS and OS compared to those who received NAs as induction therapy alone (P=0.05 and P=0.063, respectively). On the other hand, there was no difference in the survival outcomes of patients who received post-transplant maintenance treatment with the NAs without respect to their use as an induction treatment. Impact of quality of response pre-transplantation and post-transplantation on PFS and OS are shown in Fig. 4. PFS was associated with good response pre- and post-transplantation but OS was similar regardless of the responses.

The following factors were associated with a better PFS according to multivariate analysis: age <50 years (P=0.033), serum β2-microglobulin levels <5.5 ng/mL (P=0.042), and CR after ASCT (P=0.001). The only factor that remained significantly associated with a longer OS on multivariate models was the type of maintenance treatment (NA use, P=0.046).

DISCUSSION

Recently, highly efficacious NAs for patients with MM have been administered early in the disease course. NAs have mainly been incorporated in treatment regimens in conjunction with ASCT as pre-ASCT induction therapies or post-ASCT measures such as maintenance and consolidation therapies. Although NAs have shown efficacy in phase 2/3 trials when integrated before and after ASCT,

Table 2. Response rates during pre- **(A)** and post-transplantation **(B)**.

(A)

Types of treatment		Response before ASCT (%)			
		CR	VGPR	PR	SD or less
Pre-ASCT	NAs (N=87)	35 (40.2)	14 (16.1)	33 (37.9)	5 (5.7)
	No NAs (N=19)	3 (15.8)	2 (10.6)	6 (31.6)	8 (42.1)
Post-ASCT	NAs (N=68)	29 (42.6)	9 (13.2)	27 (39.7)	3 (4.4)
	No NAs (N=38)	9 (23.7)	7 (18.4)	12 (31.6)	10 (26.3)

(B)

Types of treatment		Response after ASCT (%)			
		CR	VGPR	PR	SD or less
Pre-ASCT	NAs (N=87)	68 (78.2)	12 (13.8)	6 (6.9)	1 (1.1)
	No NAs (N=19)	8 (42.1)	2 (10.5)	7 (36.9)	2 (10.5)
Post-ASCT	NAs (N=68)	51 (75.0)	8 (11.8)	7 (10.3)	2 (2.9)
	No NAs (N=38)	25 (65.8)	6 (15.8)	6 (15.8)	1 (2.6)

Abbreviations: ASCT, autologous stem-cell transplantation; CR, complete response; NAs, novel agents; PR, partial response; VGPR, very good partial response.

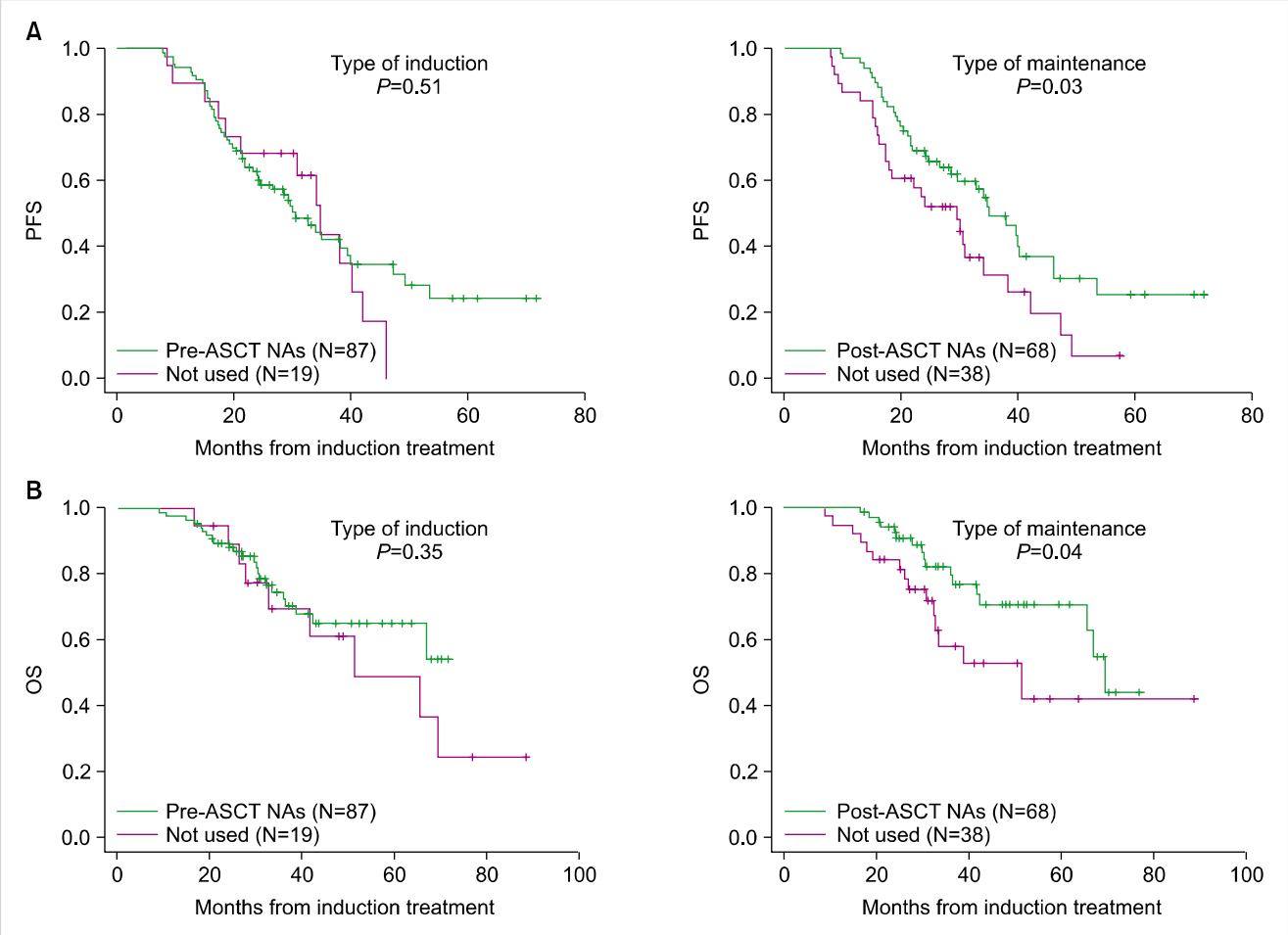

Fig. 2. **(A)** Progression-free survival according to novel agent use. **(B)** Overall survival according to novel agent use. Abbreviations: ASCT, autologous stem-cell transplantation; NAs, novel agents; PFS, progression-free survival; OS, overall survival.

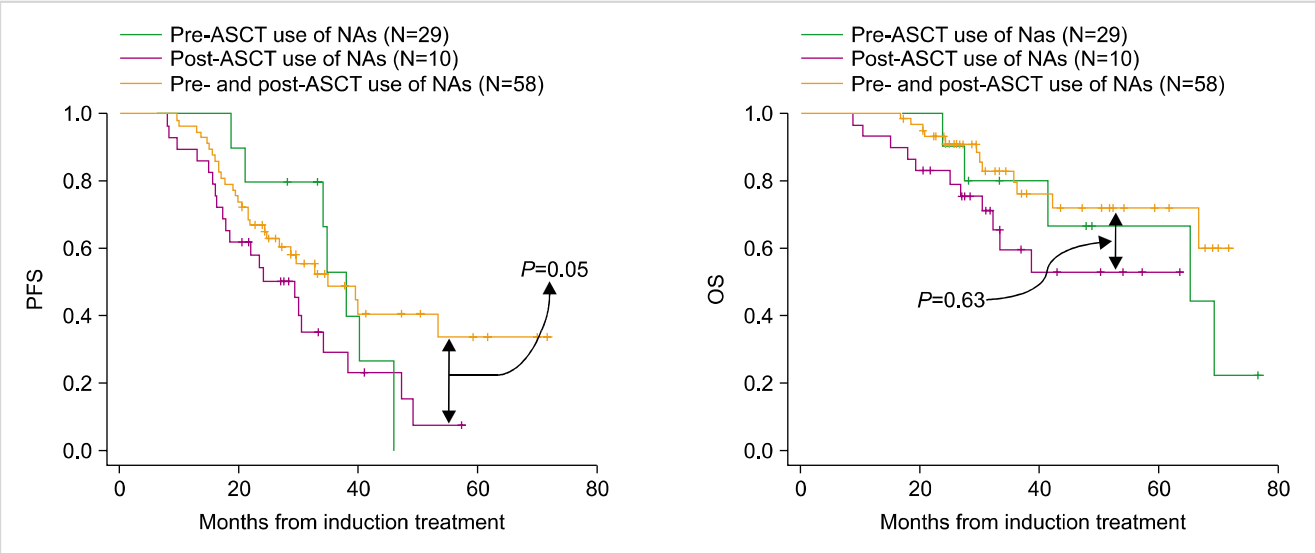

Fig. 3. Kaplan-Meier curves for progression-free survival and overall survival according to the treatment time of novel agents. Abbreviations: ASCT, autologous stem-cell transplantation; NAs, novel agents; OS, overall survival; PFS, progression-free survival.

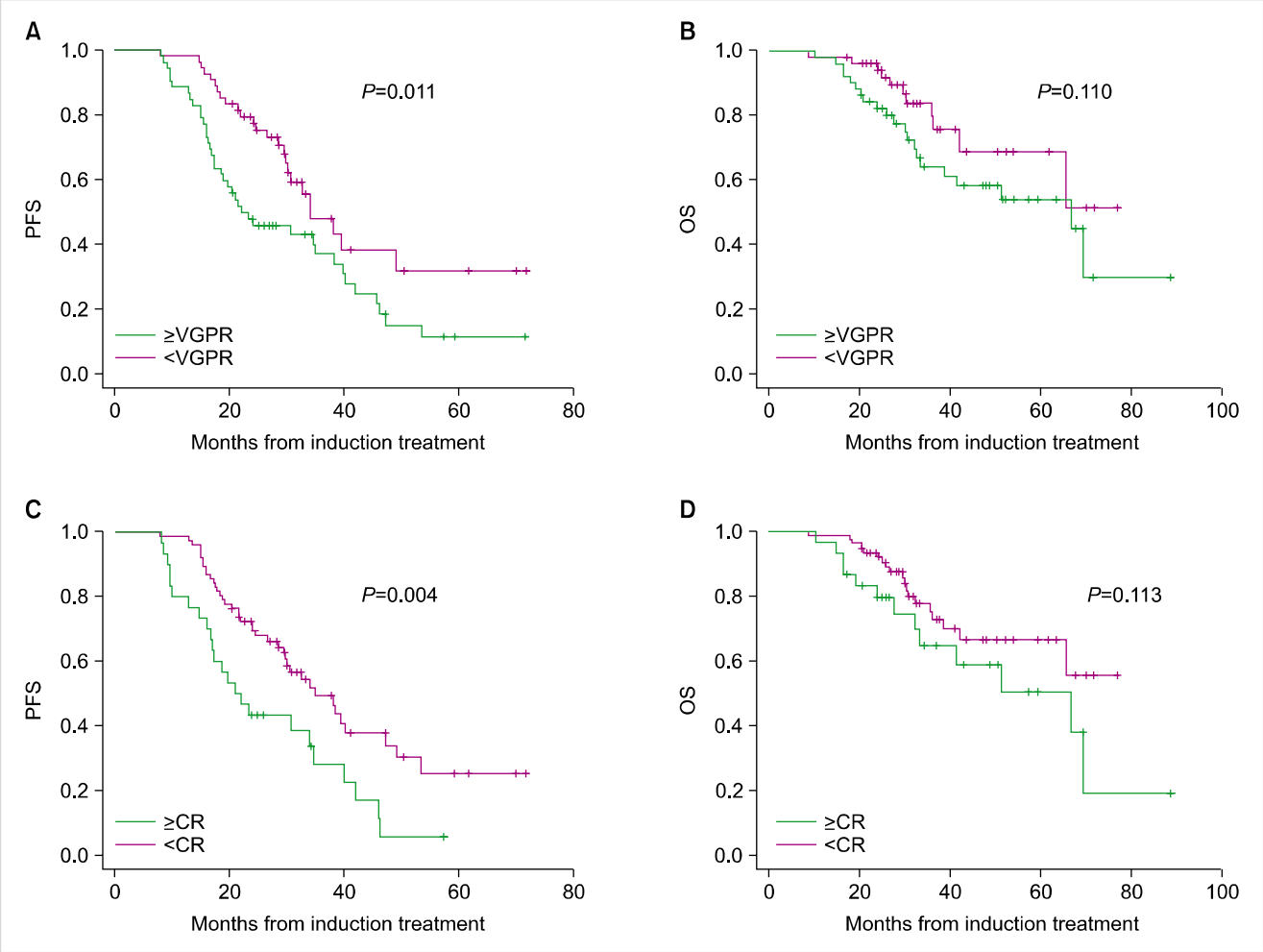

Fig. 4. Influence of response (≥VGPR vs. <VGPR) obtained after induction therapy on **(A)** progression-free survival (PFS) and **(B)** overall survival (OS); Influence of response (≥CR vs. <CR) obtained after transplantation on **(C)** PFS an **(D)** OS. Abbreviations: CR, complete response; VGPR, very good partial response.

their use has produced uncertainty regarding the best treatment approach for transplant-eligible patients. In the absence of consistent and reproducible data regarding the survival benefits of a particular approach, the choice between induction and maintenance regimens is difficult [3]. To investigate the effect of NAs as part of frontline ASCT, we evaluated survival outcomes among patients who received NAs before and/or after ASCT. On the basis of these results, we suggest that integration of NAs after ASCT could be beneficial to patients with MM undergoing ASCT. Furthermore, induction therapy using NAs improved high-quality response rates before and after ASCT.

Complete pre-transplant response was predictive of higher survival rates compared to near-complete and partial responders in a previous study [12, 13]. In contrast, the higher response rates seen with the use of IMiDs as part of induction therapy before transplantation do not translate longer relapse-free survival among patients receiving upfront ASCT [14]. However, none of the patients in those studies received the new therapeutic agents after transplantation. The clinical relevance of these previous studies is limited because many patients receive various post-transplantation maintenance treatments as well as the induction therapies containing IMiDs with or without bortezomib in combination with steroids [15-17]. The use of post-transplantation therapy may complicate the interpretation of the role of induction treatments with NAs.

Our results show that a post-transplantation response classification, such as CR is a surrogate marker for PFS with significant benefit for patients achieving it after ASCT. Post-transplantation response was strongly influenced by post-induction response among patients receiving NAs. Among induction treatments, bortezomib-based induction is associated with improved disease control after transplantation and should be considered for the standard for care [18]. A majority of our patients received bortezomib-based induction before ASCT (Fig. 1). The patients who did not achieve ≥VGPR following induction therapy did not benefit from ASCT compared to those achieving ≥VGPR (Fig. 4). This is consistent with the observation that absence of a response to induction therapy with IMiDs predicts a poorer outcome after high-dose therapy [19]. NAs ad-

ministered before ASCT, however, did not improve PFS or OS, even though they increased CR rates post-transplantation. Several large phase 3 trials comparing novel combinations with older induction regimens followed by ASCT have now been reported [20, 21]. Further intensification of the induction regimen has been shown to improve response rates before ASCT and PFS, but the impact on OS has not been established. Moreover, a meta-analysis of randomized controlled trials regarding NA-based regimens as induction treatment prior to ASCT in newly diagnosed MM showed improved CR and PFS, but not OS [22]. Our data similarly indicate that higher CR+VGPR rates before ASCT following induction with NAs did not translate into survival benefit despite sustaining the depth of response after ASCT.

A myeloma consensus panel recently defined maintenance therapy as any treatment administered after the completion of induction therapy in patients whose disease is either responsive or nonprogressive at that time with the goal of prolonging survival [23]. Earlier ASCT studies used less potent agents, such as corticosteroids or interferon-α, with variable results and toxicity concerns. The availability of more effective novel agents, such as thalidomide, has generated a renewed interest in maintenance therapy, and several phase 3 trials have now been reported [21, 24, 25]. However, the long-term effects on survival have not been determined. It has been shown that post-transplant thalidomide therapy improved the quality of response and the response rate, but the beneficial effect of maintenance thalidomide on PFS and OS was mainly due to improved response in patients not already in CR and VGPR [24]. Moreover, thalidomide as part of induction therapy before and as maintenance therapy after ASCT led to improved PFS, but showed no improvement in OS owing to reduced survival from relapse [21, 26]. The results of our study are not consistent with those of previous studies with respect to PFS and OS, as thalidomide added during maintenance after ASCT resulted in a better OS independently. Moreover, our study supports the role of maintenance thalidomide in an improved OS regardless of the type of induction treatments. A meta-analysis suggests that thalidomide maintenance with corticosteroids is effective in prolonging survival for MM [27]. We hypothesized that tumor reduction before ASCT achieved mainly by bortezomib-based treatment and a lower dose of thalidomide as maintenance therapy might result in a sustained response and prevent the negative impact on survival after relapse.

The results of the current study should be used in a limited manner to provide novel therapies in the context of ASCT. One caveat in this small study is that bortezomib or thalidomide was administered as an initial induction therapy in some patients, while bortezomib was administered as second-line treatment for those who obtained suboptimal response to high-dose dexamethasone or VAD. In addition, thalidomide was the only post-transplantation treatment modality and lenalidomide was not used at all.

In summary, NA-based induction regimens administered before the high-dose melphalan provide further improvement in treatment response following ASCT, but without an increase in PFS or OS. Instead, high activity is shown by thalidomide after ASCT as maintenance therapy, suggesting that NAs may be more beneficial as post-transplantation therapies rather than pre-transplantation treatments. A larger trial is required to explore the survival outcomes of ASCT after induction treatments using NAs stratified by the impact of NA maintenance in the current era of novel therapies.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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