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ORIGINAL ARTICLE

The impact of induction regimen on transplant outcome in newly diagnosed multiple myeloma in the era of novel agents

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We compared overall survival (OS) of 1017 patients with newly diagnosed multiple myeloma (MM) who were treated with different novel agent-based induction regimens and who underwent early autologous stem cell transplant (ASCT). Subgroups were defined by type of induction therapy: cyclophosphamide–bortezomib–dexamethasone (CyBorD; $n = 193$), bortezomib–dexamethasone (Vd; $n = 64$), lenalidomide–dexamethasone (Rd; $n = 251$), bortezomib–lenalidomide–dexamethasone (VRd; $n = 126$), thalidomide–dexamethasone (Td; $n = 155$) and vincristine–doxorubicin–dexamethasone or dexamethasone alone (VAD/Dex; $n = 228$). The median follow-up of the surviving patients was 66.7 months. The 5-year OS rates with CyBorD, Vd, Rd, VRd, Td and VAD/Dex were 79.2%, 72.3%, 79.2%, 79.0%, 57.4% and 63.4%, respectively (log-rank, $P < 0.001$). In a multivariate analysis, after controlling for important patient and disease variables, VRd had a superior OS compared with CyBorD (hazard ratio (HR), 0.32; 95% confidence interval (CI), 0.10–0.88; $P = 0.03$) and Vd (HR, 0.16; 95% CI, 0.04–0.52; $P = 0.002$). In conclusion, our study demonstrates that among patients completing induction therapy and continuing to early transplant, VRd induction leads to improved OS compared with CyBorD and Vd regimens.

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INTRODUCTION

Multiple myeloma (MM) is a malignant plasma cell neoplasm, characterized by monoclonal plasma cells in bone marrow (BM), and constitutes ~10% of all hematologic malignancies. In 2012, ~90 000 people were living with MM in the United States.[1] In 2015, an estimated 26 850 new cases of MM (1.6% of all new cancer cases) were diagnosed in the United States,[1] and the most recent data (2005–2011) from the Surveillance, Epidemiology and End Results Program showed the 5-year relative survival rate for MM to be 46.6%.[1] In the past decade, novel agent induction therapy has been incorporated with autologous stem cell transplant (ASCT) as therapy for MM that has improved the relative survival rate of patients with newly diagnosed MM, with young adults (20–59 years) improving more after treatment than older adults (⩾60 years).[2] For transplant-eligible patients, ASCT has been the standard of care since the 1990s,[3] when trials showed it to be associated with improved response rates and superior overall survival (OS).[4,5] Early ASCT was shown to significantly improve progression-free survival (PFS) at first and second relapse (PFS1 and PFS2) and demonstrated a nonsignificant tendency toward improvement of OS compared with delayed ASCT in newly diagnosed MM.[6] Early ASCT had the added benefits of lower cost and more quality-adjusted life years gained.[7]

Novel agents, including proteasome inhibitors and immunomodulatory drugs, have been introduced into the therapeutic armamentarium of MM in the past decade, prompted by studies showing impressive response rates and superior survival with these agents when they were compared with conventional cytotoxic chemotherapy. Guidelines from the National Comprehensive Cancer Network, the European Society for Medical Oncology and the IMWG (International Myeloma Working Group) unanimously recommend novel agents, including bortezomib, lenalidomide, thalidomide or a combination as first-line induction chemotherapy for transplant and nontransplant candidates.[5,8–10] Although several doublet and triplet combinations of novel agents are used for induction chemotherapy, few prospective studies have compared these novel regimens. To the best of our knowledge, this is the largest retrospective study to compare survival outcomes of multiple novel induction regimens in patients who underwent early ASCT.

PATIENTS AND METHODS

Patients

This is a retrospective study (1 January 2000 through 31 May 2015) from the institutional database of Mayo Clinic (Rochester, MN, USA). The study was approved by the Mayo Clinic institutional review board. All patients gave written informed consent to have their medical records reviewed and used for research. Patients were included if they underwent early ASCT (within 12 months of diagnosis), did not receive more than 1 regimen of induction chemotherapy before ASCT, did not relapse before ASCT and had never received treatment for smoldering MM. Because Mayo Clinic is a tertiary care center, most patients were referred for ASCT, and their referring physicians usually determined the type of induction therapy to be used. Stem cell mobilization was done either by using growth factor (with or without plerixafor) or by using cyclophosphamide plus growth factor. Conditioning was done with high-dose melphalan (200 mg/m^2), and most patients were treated as outpatients.[11]

Electronic health records were reviewed to abstract data about age, sex, International Staging System (ISS) stage at diagnosis, presence of high-risk

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Table 1. Patient baseline demographic and clinical characteristics at diagnosis

Characteristic	*Induction regimen*							P-*value*
	Overall (N = *1017*)	*CyBorD* (N = *193*)	*VRd* (N = *126*)	*Vd* (N = *64*)	*Rd* (N = *251*)	*Td* (N = *155*)	*VAD/Dex* (N = *228*)	
Median age (range), years	60.3 (24.4–76.1)	61.9 (34.2–76.1)	60.8 (24.4–75.6)	62.2 (38.0–74.1)	60.8 (29.0–75.9)	59.3 (32.4–75.5)	58.6 (35.5–75.8)	0.004
Men, %	58.4	56.0	61.9	57.8	56.6	57.4	59.6	0.90
ISS stage, %[a]								< 0.001
I	23.8	22.9	25.0	22.9	25.2	19.6	25.5	
II	49.8	42.0	49.0	33.3	59.7	45.7	53.9	
III	26.4 (*n* = 709)	35.0 (*n* = 157)	26.0 (*n* = 104)	43.8 (*n* = 48)	15.0 (*n* = 206)	34.8 (*n* = 92)	20.6 (*n* = 102)	
Serum creatinine > 1.5 mg/dL at transplant, %	8.0 (*n* = 1016)	14.1 (*n* = 192)	2.4 (*n* = 126)	10.9 (*n* = 64)	1.2 (*n* = 251)	9.7 (*n* = 155)	9.6 (*n* = 228)	< 0.001
LDH level, median (range), U/L	186 (3–2244) (*n* = 1,010)	190 (3–454) (*n* = 191)	184 (105–411) (*n* = 126)	198 (4–420) (*n* = 63)	180 (3–2244) (*n* = 250)	177 (85–853) (*n* = 153)	189 (83–699) (*n* = 227)	< 0.001
β_2-microglobulin, median (range), mg/L	3.6 (1.0–100.0) (*n* = 771)	4.5 (1.3–100.0) (*n* = 158)	3.4 (1.2–48.3) (*n* = 105)	4.6 (1.2–31.2) (*n* = 48)	3.2 (1.1–96.3) (*n* = 207)	3.7 (1.0–44.3) (*n* = 106)	3.3 (1.0–25.5) (*n* = 147)	< 0.001
High-risk cytogenetic abnormality, FISH,[b,c] %	12.3 (*n* = 432)	11.5 (*n* = 157)	25.3 (*n* = 91)	0 (*n* = 31)	7.0 (*n* = 129)	13.3 (*n* = 15)	11.0 (*n* = 9)	< 0.001
Deletion (17p), %	9.7	7.7	22.8	0	6.2	6.7	0	
t(14;16) or t(14;20), %	5.1	5.8	6.5	0	3.1	6.7	11.0	
t(4;14), %	8.8	14.2	9.8	6.4	2.3	1.3	0	
Pretransplant response rates, %								< 0.001
sCR	8.0	12.4	17.5	12.5	7.6	3.2	0.9	
CR+VGPR	28.5	40.4	41.3	39.1	23.1	21.3	17.2	
⩽PR	63.5	47.2	41.3	48.4	69.3	75.5	81.9	
BMPCs, median, (range), %	42 (0–99) (*n* = 994)	50 (0–95) (*n* = 192)	50 (1–95) (*n* = 122)	50 (1–95) (*n* = 63)	31 (0–95) (*n* = 240)	45 (3–99) (*n* = 153)	35 (0–95) (*n* = 224)	< 0.001
LI, median (range)	0.6 (0–10.0) (*n* = 369)	1.1 (0–10.0) (*n* = 58)	1.2 (0–5.3) (*n* = 21)	1.0 (0–4.8) (*n* = 14)	0.6 (0–4.5) (*n* = 102)	0.6 (0–4.0) (*n* = 61)	0.4 (0–4.6) (*n* = 113)	< 0.001

Abbreviations: BMPC = bone marrow plasma cell; CR = complete response; CyBorD = cyclophosphamide–bortezomib–dexamethasone; ISS = International Staging System; LDH = lactate dehydrogenase; Rd = lenalidomide–dexamethasone; sCR = stringent complete response; Td = thalidomide–dexamethasone; VAD/Dex = vincristine–doxorubicin–dexamethasone or dexamethasone; Vd = bortezomib–dexamethasone; VGPR = very good partial response; VRd = bortezomib–lenalidomide–dexamethasone. [a]Not all percentages sum to 100% because of rounding. [b]High-risk cytogenetics was defined by updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Guidelines (http://www.msmart.org/) that included del (17p), t (14;16) and t(14;20). [c]*n*, number of patients with available data.

cytogenetic abnormalities by FISH, follow-up, relapse, use of maintenance or consolidation therapy after transplant, best response achieved both before and after transplant according to the IMWG uniform response criteria and mortality. To identify patients who had a stringent complete response (sCR), we evaluated the data for involved/uninvolved free light chain (FLC) ratio and determined the presence of clonal BM plasma cells as assessed by immunohistochemistry or immunofluorescence.

Statistical analyses

Characteristics of patients in the different induction groups were compared by using the Wilcoxon test for continuous variables and the χ^2 test for categorical variables. All time-to-event (PFS and OS) distributions were estimated by the Kaplan–Meier method,[12] and comparisons between curves were made with a two-sided log-rank test. Hazard ratios (HRs) for univariate and multivariate analyses were computed by using the Cox proportional hazards regression model. The analysis was spanned over a long period of time and a large cohort of patients to ensure statistical power. Response rates were divided into three categories for statistical analysis: sCR, complete response or very good partial response (CR/VGPR) and partial response (PR) or less. The PFS was calculated from the date of diagnosis to the date of progression or of death, whichever was earlier. Data for patients who were alive and free of progression were censored at the last known follow-up visit. The OS was calculated from the date of diagnosis to the date of death or from when the patient was last known to be alive. The following prognostic factors were evaluated on univariate analysis: induction regimen, age (>70 years vs ⩽70 years), sex, transplant period (2000–2007 vs 2008–2015), ISS stage (III vs I and II) and high-risk cytogenetics by FISH. Factors significantly prognostic for PFS and OS in the univariate model ($P < 0.05$) were studied in a multivariate analysis. A *P*-value of < 0.05 was considered to be statistically significant. All statistical analyses were done by using JMP 10.0.0 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient characteristics

A total of 1086 patients were initially included in the study and categorized according to the induction regimen they received before ASCT. After we excluded induction groups with < 50 patients, data from 1017 patients in 6 induction regimen categories remained available for analysis, namely, cyclophosphamide–bortezomib–dexamethasone (CyBorD), bortezomib–lenalidomide–dexamethasone (VRd), lenalidomide–dexamethasone (Rd), thalidomide–dexamethasone (Td), bortezomib–dexamethasone (Vd) and vincristine–doxorubicin–dexamethasone or dexamethasone alone (VAD/Dex). Baseline characteristics of the 1017 patients included in the retrospective analysis are listed by induction regimen received before ASCT in Table 1. The median age of patients at diagnosis was 60.3 years (range, 24.4–76.1 years), and the median follow-up of surviving patients was 66.7 months (Table 2). Patients received a median of 4 cycles (range, 1–12) of induction chemotherapy before ASCT. Of the 1017 patients, 212 received maintenance or consolidation therapy after ASCT. Of the 212 patients receiving post-transplant maintenance or consolidation therapy, 206 (97.2%) underwent transplant during

Table 2. Post transplant response and survival rates by induction regimen

Outcome	*Induction regimen*							P-*value*
	Overall (N = *1017*)	*CyBorD* (N = *193*)	*VRd* (N = *126*)	*Vd* (N = *64*)	*Rd* (N = *251*)	*Td* (N = *155*)	*VAD/Dex* (N = *228*)	
sCR rate, %	317 (31.2)	66 (34.2)	58 (46.0)	20 (31.2)	76 (30.4)	40 (26.1)	55 (24.1)	< 0.001
⩾VGPR rate,[a] %	717 (70.5)	150 (77.7)	104 (82.5)	51 (79.7)	164 (65.2)	105 (67.5)	141 (62)	< 0.001
PFS, median (95% CI), months	32.4 (30.7–34.2)	32.6 (30.2–38.2)	32.6 (30.3–42.5)	40.4 (30.7–49.2)	40.7 (33.3–45.1)	28.4 (24.6–31.0)	28 (25.0–33.3)	0.001
OS, median (95% CI), months	96.1 (85.7–103.4)	NR	NR	97.1 (66.5–NR)	111.6 (99.0–124.2)	80.1 (57.8–99.0)	77.1 (64.9–92.3)	< 0.001
5-Year OS rate (95% CI), %	69.0 (65.5–72.3)	79.2 (65.3–88.5)	79.0 (65.7–88.1)	72.3 (58.5–82.9)	79.2 (72.9–84.4)	57.4 (49.5–65.0)	63.4 (57.0–69.4)	< 0.001
Follow-up of surviving patients, median duration (95% CI), months	66.7 (60.4–74.7)	26.9 (23.1–29.6)	32.1 (29.1–35.7)	54.3 (48.6–63.4)	63.3 (59.8–71.3)	132.2 (124.6–138.2)	143.4 (138.5–157.1)	NA

Abbreviations: CI = confidence interval; CyBorD = cyclophosphamide–bortezomib–dexamethasone; NA = not applicable; NR = not reached; OS = overall survival; PFS = progression-free survival; Rd = lenalidomide–dexamethasone; sCR = stringent complete response; Td = thalidomide–dexamethasone; VAD/Dex = vincristine–doxorubicin–dexamethasone or dexamethasone; Vd = bortezomib–dexamethasone; VGPR = very good partial response; VRd = bortezomib–lenalidomide–dexamethasone. [a] ⩾ Indicates sCR, CR and VGPR.

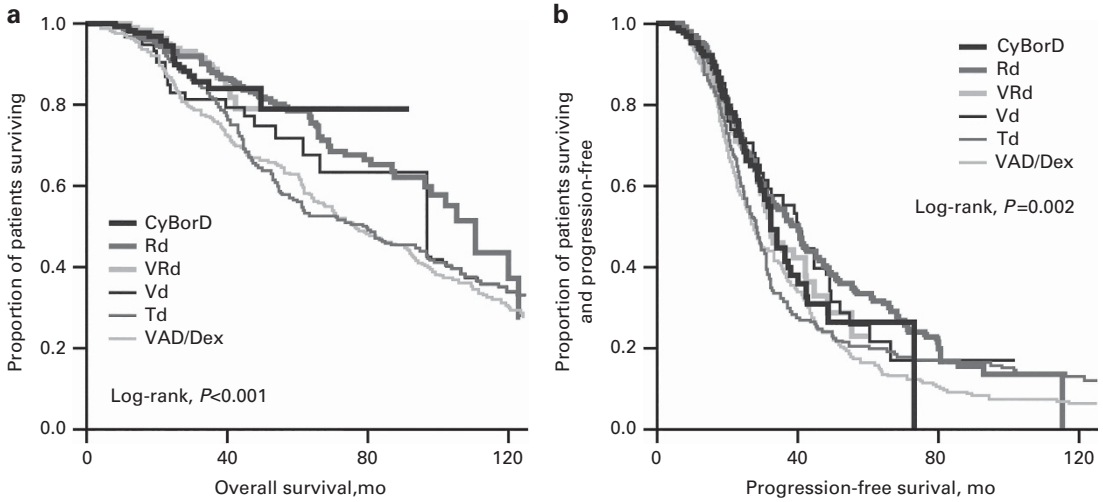

Figure 1. Kaplan–Meier curves from the time of diagnosis stratified by the different induction groups. (**a**) Overall survival. (**b**) Progression-free survival.

2008 to 2015. Patients receiving VRd induction therapy had a disproportionately high presence of high-risk cytogenetic signatures by FISH (25.3% of patients with available data), compared with those receiving CyBorD (11.5%), Vd (0%), Rd (7.0%), Td (13.3%) and VAD/Dex (11.1%). The CyBorD induction group had a higher proportion of patients with serum creatinine levels of >1.5 (14.1%) as compared with the VRd (2.4%), Vd (10.9%), Rd (1.2%), Td (9.7%) and VAD/Dex (9.6%) groups.

Impact of induction regimens on response rates, PFS and OS

The rate of post-transplant sCR in VRd, CyBorD, Vd, Rd, Td and VAD/Dex was 46.0%, 34.2%, 31.2%, 30.4%, 26.1% and 24.0%, respectively ($P < 0.001$).

The Kaplan–Meier method curves for PFS and OS are shown by different induction regimen groups in Figure 1. The median PFS, median OS and 5-year OS rates of the different groups are shown in Table 2. The HRs for PFS and OS on univariate and multivariate analysis are shown in Table 3. The median PFS for all 1017 patients was 32.4 months (95% confidence interval (CI), 30.7–34.2 months). The median PFS for the different induction groups was 32.6 months (95% CI, 30.2–38.2 months) for CyBorD, 32.6 months (95% CI, 30.3–42.5 months) for VRd, 40.4 months (95% CI, 30.7–49.2 months) for Vd, 40.7 months (95% CI, 33.3–45.1 months) for Rd, 28.4 months (95% CI, 24.6–31.0 months) for Td and 28 months (95% CI, 25.0–33.3 months) for VAD/Dex. On univariate analysis, VRd was shown to have superior PFS compared with VAD/Dex (HR, 1.37; 95% CI, 1.02–1.88; $P = 0.04$). There was no significant difference in PFS among regimens on multivariate analysis (Table 3).

The median OS for all 1017 patients was 96.1 months (95% CI, 85.7–103.4 months), with a 5-year OS rate of 69.0% (95% CI, 65.5–72.3%). The 5-year OS rates for the different induction groups were 79.2% (95% CI, 65.3–88.5%) for CyBorD, 79.0% (95% CI, 65.7–88.1%) for VRd, 72.3% (95% CI, 58.5–82.9%) for Vd, 79.2% (95% CI, 72.9–84.4%) for Rd, 57.4% (95% CI, 49.5–65.0%) for Td and 63.4% (95% CI, 57.0–69.4%) for VAD/Dex. On multivariate analysis, VRd was shown to have significantly superior OS compared with CyBorD (risk ratio, 3.11; 95% CI, 1.14–9.96; $P = 0.03$) and Vd (risk ratio, 6.16; 95% CI, 1.92–21.79; $P = 0.002$).

Impact of best response after ASCT on PFS and OS

Response rates for the novel induction regimens following ASCT are summarized in Table 2. The median PFS (Kaplan–Meier method) was 49 months (95% CI, 42.2–55.6 months) in patients

Table 3. Univariate and multivariate analyses of progression-free survival and overall survival

Variable	*Progression-free survival*				*Overall survival*			
	Univariate Analysis		*Multivariate Analysis*		*Univariate Analysis*		*Multivariate Analysis*	
	Risk ratio (95% CI)	P-*value*	*Risk ratio (95% CI)*	P-*value*	*Risk ratio (95% CI)*	P-*value*	*Risk ratio (95% CI)*	P-*value*
Induction regimen								
VRd (reference; $N = 126$)	1		1		1		1	
CyBorD ($N = 193$)	1.06 (0.74–1.51)	0.76	1.42 (0.91–2.26)	0.13	1.14 (0.56–2.36)	0.72	3.11 (1.14–9.96)	0.03
Vd ($N = 64$)	1.01 (0.67–1.52)	0.95	1.21 (0.61–2.28)	0.57	1.51 (0.74–3.16)	0.25	6.16 (1.92–21.79)	0.002
Rd ($N = 251$)	0.93 (0.68–1.28)	0.64	0.93 (0.60–1.48)	0.76	1.13 (0.64–2.16)	0.68	1.87 (0.71–5.88)	0.22
Td ($N = 155$)	1.24 (0.91–1.72)	0.18	0.69 (0.26–1.88)	0.46	1.85 (1.07–3.48)	0.03	1.98 (0.43–10.49)	0.39
VAD/Dex ($N = 228$)	1.37 (1.02–1.88)	0.04	0.43 (0.13–1.35)	0.15	2.06 (1.20–3.84)	0.007	1.93 (0.36–11.05)	0.45
Age ($\geqslant$70 vs $<$ 70)	1.24 (0.96–1.57)	0.09	NA	NA	1.48 (1.07–1.99)	0.02	1.26 (0.60–2.39)	0.53
Sex (male vs female)	1.31 (1.12–1.53)	$<$ 0.001	1.51 (1.11–2.06)	0.008	1.31 (1.07–1.61)	0.008	1.40 (0.81–2.44)	0.23
Transplant period (2000–2007 vs 2008–2015)	1.42 (1.22–1.66)	$<$ 0.001	2.21 (1.00–4.38)	0.05	1.70 (1.33–2.18)	$<$ 0.001	1.69 (0.47–5.07)	0.40
High-risk cytogenetics by FISH (present vs absent) ($n/N^a = 432/1017$)	1.73 (1.11–2.59)	0.02	1.88 (1.18–2.89)	0.009	2.48 (1.21–4.65)	0.01	3.69 (1.72–7.35)	0.001
ISS stage (III vs I and II) ($n/N^a = 709/1017$)	1.20 (0.97–1.48)	0.09			1.31 (0.98–1.74)	0.07	NA	NA

Abbreviations: CI = confidence interval; CyBorD = cyclophosphamide–bortezomib–dexamethasone; ISS = International Staging System; NA = not applicable; Rd = lenalidomide–dexamethasone; Td = thalidomide–dexamethasone; VAD/Dex = vincristine–doxorubicin–dexamethasone or dexamethasone; Vd = bortezomib–dexamethasone; VRd = bortezomib–lenalidomide–dexamethasone. [a]*n*, number of patients with available data for the parameter; *N*, total number of patients in the study cohort.

who achieved sCR; 29.4 months (95% CI, 27.6–32.5 months) in those with CR/VGPR; and 25.0 months (95% CI, 22.4–27.7 months) in those with PR or less (log-rank, $P < 0.001$). On multivariate analysis (Cox model), the HRs for progression or death, after controlling for age ($\geqslant$70 vs $<$ 70 years), sex, induction regimen and transplant period (2000–2007 vs 2008–2015) for categories sCR, CR/VGPR and PR or less were 1, 1.79 (95% CI, 1.39–2.30; $P < 0.001$) and 2.03 (95% CI, 1.50–2.75; $P < 0.001$), respectively.

The median OS (Kaplan–Meier method) of patients with sCR was 129.5 months (95% CI, 121.3–not reached); CR/VGPR, 82.6 months (95% CI, 70.8–95.0); and PR or less, 73.6 months (95% CI, 63.9–92.9) (log-rank, $P < 0.001$). Kaplan–Meier curves are shown in Figure 2. Using sCR response as reference, the HRs (multivariate analysis) for all-cause mortality of categories CR/VGPR and PR or less were 1.90 (95% CI, 1.46–2.51; $P < 0.001$) and 2.12 (95% CI, 1.61–2.82; $P < 0.001$), respectively. On subgroup analysis, patients achieving sCR were shown to have superior OS compared with those who had a conventional CR (HR (multivariate analysis), CR/sCR, 1.96; 95% CI, 1.41–2.73; $P < 0.001$). Survival analysis (PFS and OS) was also done using 4 months as a post-transplant landmark (Figure 3).

The impact of best response to induction regimen before ASCT on PFS and OS was also evaluated by using the Kaplan–Meier method. The median PFS in patients achieving a CR ($n = 130$) and in patients achieving less than a CR ($n = 887$) to induction therapy was 42.5 months (95% CI, 32.6–51.9 months) and 30.8 months (95% CI, 28.9–32.6 months), respectively (log-rank $P < 0.001$). The median OS in patients achieving a CR and in those achieving less than a CR to induction therapy was 124.2 months (85% CI, 94.7–not reached) and 92.5 months (95% CI, 82.6–99.2), respectively (log-rank $P = 0.01$).

DISCUSSION

In this study, the VRd induction regimen was shown to have superior response rates and survival benefit over CyBorD and Vd in patients successfully completing induction therapy and undergoing early transplant, after controlling for important host and tumor characteristics. Furthermore, achieving sCR post transplant was shown to translate into superior PFS and OS.

In the past decade, management of MM has changed dramatically because of the availability of novel therapeutic agents, including proteasome inhibitors and immunomodulatory drugs. First-line use of proteasome inhibitors and immunomodulatory drugs for transplant and nontransplant patients has yielded higher response rates, PFS and OS.[5] A phase 3 randomized controlled trial conducted by Harousseau *et al.*[13] in France compared the novel regimen Vd with VAD and showed that patients who had Vd therapy achieved a deeper response, with an absolute increase in PFS of ~6 months ($P = 0.06$). The incidence of hematologic toxicity and death because of serious adverse events was more common with VAD, whereas grade 3 to 4 peripheral neuropathy was more common with Vd. The phase 2 EVOLUTION study compared bortezomib and dexamethasone with either cyclophosphamide or lenalidomide (CyBorD or VRd) and showed similar pretransplant response rates, 1-year PFS rates and 1-year OS rates at a median follow-up of 20 months.[14] A meta-analysis of studies testing CyBorD or bortezomib–thalidomide–dexamethasone (VTd) as induction therapy in patients with newly diagnosed MM showed higher rates of VGPR (or better) with VTd (67 vs 27%; $P < 0.001$)[15] but did not report differences in survival outcomes. In a meta-analysis of randomized controlled trials, bortezomib-based induction regimens before ASCT were shown to be superior to non-bortezomib-based regimens for response, PFS and OS rates.[16] However, lenalidomide was not a part of the non-bortezomib-based regimens in this meta-analysis. Earlier studies also showed that triplet regimens containing bortezomib and thalidomide given before ASCT achieved superior response

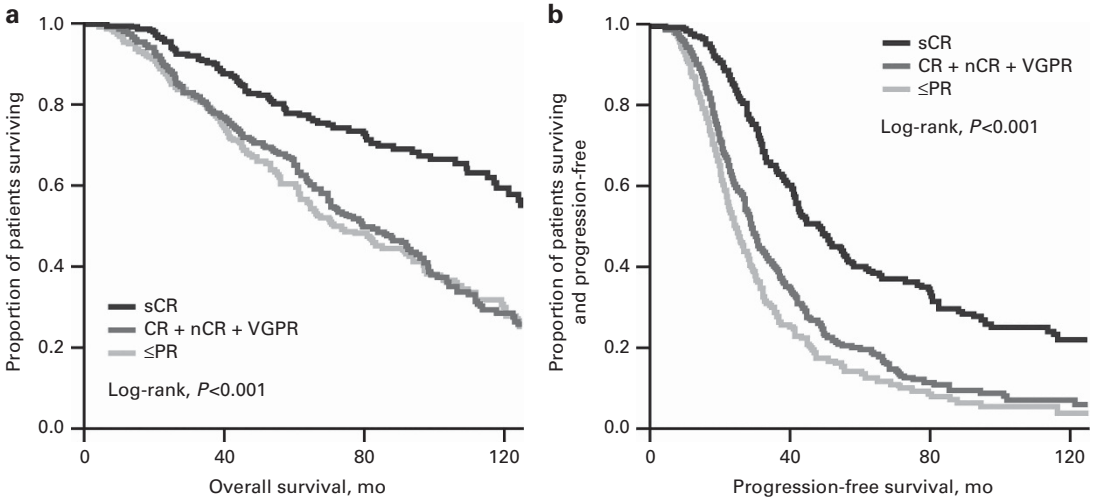

Figure 2. Kaplan–Meier curves from the time of diagnosis stratified by depth of response. (**a**) Overall survival. (**b**) Progression-free survival.

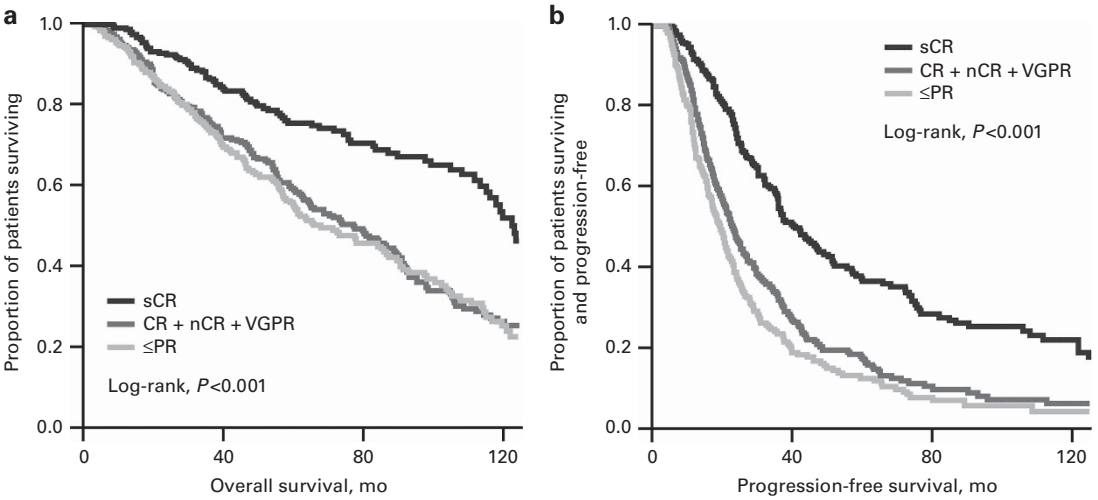

Figure 3. Kaplan–Meier curves for different response rates stratified by time since the 4-month, post-transplant landmark. (**a**) Overall survival. (**b**) Progression-free survival.

rates with manageable toxicity compared with novel agent-containing doublets.[17,18]

Novel induction regimens were also compared in the phase 3, randomized SWOG S0777 trial[19] and the prospective IFM 2013–2014 trial.[20] SWOG S0777 compared VRd with Rd in patients with newly diagnosed MM who were not receiving early ASCT and showed improved PFS (median PFS: VRd, 43 months; Rd, 31 months; $P = 0.002$) and OS (median OS: VRd, 75 months; Rd, 64 months; $P = 0.01$) in the VRd arm across age groups and ISS stages.[19] The IFM 2013-2014 trial, which compared VTd and CyBorD before ASCT in newly diagnosed MM, showed a higher VGPR (66.7 vs 56.2; $P = 0.04$) rate with VTd after a median of 4 induction cycles in both groups, with a low incidence (4%) of grade 3/4 peripheral neuropathy.[20] Similarly, another randomized phase 3 study from the Spanish Myeloma Group showed a higher post-ASCT CR rate with VTd compared with Td (46% vs 24%, $P = 0.004$).[21]

With a large sample size and long follow-up, our study provides a broad overview of the comparative effectiveness of novel induction regimens in patients who have early ASCT. Not surprisingly, patients who received bortezomib- and lenalidomide-containing regimens had a shorter median duration of follow-up compared with those who received thalidomide or non-novel regimens (VAD/Dex). Furthermore, patients who received VAD/Dex or Td were not contemporaneous with those receiving proteasome inhibitor or lenalidomide-based regimens, and hence did not have equal access to novel agent-based maintenance and salvage therapy, which was addressed by controlling for transplant period in the multivariate analysis.

Use of novel induction regimens for patients with newly diagnosed MM has increased the depth of response, with more patients achieving CR and VGPR when they were compared with patients treated with the older regimens. CR and VGPR have been associated with prolonged OS and PFS.[22–24] A study of 1175 elderly patients newly diagnosed with MM who received novel agent-based induction therapy containing bortezomib and thalidomide showed higher 3-year PFS and OS rates in patients who had CR compared with those who had VGPR or PR.[24] Another study of patients who had transplants between 1989 and 1998 showed significantly higher OS and PFS for patients who had CR after transplant compared with those who had near complete response, VGPR or PR.[25] However, sCR was not distinguished from conventional CR in these studies.

Stringent CR is defined as conventional CR with normalization of serum FLC (sFLC) ratio and complete absence of clonal plasma cells in BM, indicating restoration of polyclonality. In 2006, this

definition was incorporated by the IMWG into the response criteria for MM defined earlier by the European Group for Blood and Marrow Transplantation.[26] In a retrospective study, improved OS and PFS were reported for patients who had sCR after ASCT; the 5-year OS was 80% for patients with sCR, 53% for CR and 47% for near complete response ($P < 0.001$).[27] In the era of novel agents, our study reaffirms the importance of identifying and differentiating sCR from conventional CR after ASCT and of routinely documenting sCR in clinical trials and in general practice. Regardless of the induction regimen used, sCR after ASCT was independently associated with superior OS and PFS. We did not note any significant differences in OS among our patients who had CR, VGPR or PR after sCR was separated from conventional CR, consistent with a previous report by Kapoor *et al.*[27] Interestingly, VRd induction yielded impressive sCR rates (46%) after ASCT and translated into improved OS on multivariate analysis. Martinez-Lopez *et al.*[28] further analyzed sCR to determine the relative prognostic significance of the sFLC ratio and BM clonality in 69 patients with MM who achieved sCR after therapy. They reported that persistent, clonal BM disease identified by traditional, 4-color, multiparameter flow cytometry had maximal prognostic significance, followed by BM clonal disease identified by immunohistochemistry. The investigators did not find that an abnormal sFLC ratio identified CR patients at high risk. In the Medical Research Council Myeloma IX trial, minimal residual disease negativity (as shown by flow cytometry) was predictive of superior OS and PFS regardless of the choice of induction regimen before ASCT.[29] With prospective studies reporting sFLC ratio and the presence of minimal residual disease after therapy, the sCR category might undergo further refinement to better identify its impact on patient survival.

In recent years, maintenance or consolidation therapy with novel agents has been used after transplant, with the aim of improving depth of response and subsequently survival.[30] However, there is no uniform consensus regarding the selection of patients for maintenance therapy and the agent or regimen to be used. In our study, 97% of patients who received maintenance or consolidation therapy underwent transplant during the 2008 to 2015 period. Therefore, we included a transplant cohort in the multivariate analysis to evaluate the effect of various induction regimens on survival.

In conclusion, our study showed that among patients completing induction therapy and having an early transplant, use of the VRd induction regimen led to superior OS compared with CyBorD and Vd. However, further prospective randomized trials that directly compare novel induction regimens for patients with newly diagnosed MM who have early ASCT are needed to validate these findings.

CONFLICT OF INTEREST

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