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Advantage of achieving deep response following frontline daratumumab-VTd compared to VRd in transplant-eligible multiple myeloma: multicenter study

Ja Min Byun[1#], Sung-Soo Park[2#], Sung-Soo Yoon[1], Ari Ahn[3], Myungshin Kim[3], Jung Yeon Lee[2], Young-Woo Jeon[4], Seung-Hwan Shin[5], Seung-Ah Yahng[6], Youngil Koh[1], Chang-Ki Min[2]

[1]Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, [2]Department of Hematology, Seoul St. Mary's Hematology Hospital, College of Medicine, The Catholic University of Korea, [3]Department of Laboratory Medicine, College of Medicine, The Catholic University of Korea, [4]Department of Hematology, Yeoido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, [5]Department of Hematology, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, [6]Department of Hematology, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Incheon, Korea

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[#]These authors contributed equally and are co-first authors.

Correspondence to
Youngil Koh, M.D., Ph.D.
Chang-Ki Min, M.D., Ph.D.
Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea (Y.K.)
Department of Hematology, Seoul St. Mary's Hematology Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea (C.K.M.)
E-mail: Y.K., go01@snu.ac.kr
C.K.M., ckmin@catholic.ac.kr

Background
The goal of induction therapy for multiple myeloma (MM) is to achieve adequate disease control. Current guidelines favor triplet (bortezomib-lenalidomide-dexamethasone; VRd) or quadruplet regimens (daratumumab, bortezomib-thalidomide-dexamethasone; D-VTd). In the absence of a direct comparison between two treatment regimens, we conducted this study to compare the outcomes and safety of VRd and D-VTd.

Methods
Newly diagnosed MM patients aged >18 years who underwent induction therapy followed by autologous stem cell transplantation (ASCT) between November 2020 and December 2021 were identified. Finally, patients with VRd (N=37) and those with D-VTd (N=43) were enrolled.

Results
After induction, 10.8% of the VRd group showed stringent complete remission (sCR), 21.6% showed complete response (CR), 35.1% showed very good partial response (VGPR), and 32.4% showed partial response (PR). Of the D-VTd group, 9.3% showed sCR, 34.9% CR, 48.8% VGPR, and 4.2% PR (VGPR or better: 67.6% in VRd vs. 93% in D-VTd, P=0.004). After ASCT, 68.6% of the VRd group showed CR or sCR, while 90.5% of the D-VTd group showed CR or sCR (P=0.016). VRd was associated with an increased incidence of skin rash (P=0.044). Other than rashes, there were no significant differences in terms of adverse events between the two groups.

Conclusion
Our study supports the use of a front-line quadruplet induction regimen containing a CD38 monoclonal antibody for transplant-eligible patients with newly diagnosed MM.

Key Words Transplant-eligible, Newly diagnosed, Quadruplet, Triplet, Multiple myeloma

INTRODUCTION

The goal of induction therapy for newly diagnosed (ND) transplant-eligible (TE) multiple myeloma (MM) is to achieve satisfactory disease control with deepest possible response. The current international guidelines favor a triplet induction regimen comprised of a bortezomib plus dexamethasone backbone with the addition of an immunomodulatory drug (IMiD) [1, 2]. Specifically, thalidomide [3, 4] and lenalidomide [5, 6] are recommended. Although there are no randomized controlled trials directly comparing bortezomib-thalido-

mide-dexamethasone (VTd) and bortezomib-lenalidomide-dexamethasone (VRd), the current consensus favors VRd over VTd because of its efficacy and lower toxicity [7].

Building on this foundation, recent studies assessed whether a quadruplet-based induction regimen can increase response rates and improve outcomes [7-10]. Based on the CASSIOPEIA phase III study [8] which proved the superiority of the addition of the CD38 monoclonal antibody daratumumab to the VTd backbone (D-VTd), the updated 2021 European Hematology Association (EHA)-European Society for Medical Oncology (ESMO) guidelines [1] and 2022 National Comprehensive Cancer Network (NCCN) guidelines [2] now include D-VTd as a front-line option for ND-TE MM patients.

Unfortunately, to date, no direct comparisons have been made between VRd and D-VTd. Although a recent matching-adjusted indirect comparison (MAIC) of progression-free survival (PFS) and overall survival (OS) [11] between D-VTd versus other standard of care treatments estimated significant improvements in PFS and OS with D-VTd treatment, many unanswered questions remain, including the depth of response and relative adverse events (AE) rates. It should also be considered that while the D-VTd group's data was obtained from a recent CASSIOPEIA study, the VRd group's data was obtained from the IFM2009 study conducted 2010–2012 [5]. To close these gaps, we conducted this study to compare the treatment outcomes and toxicity profiles of 4-weekly VRd versus 4-weekly D-VTd in homogeneous East Asian patients with ND TE MM during the same period.

MATERIALS AND METHODS

Patients

This was a retrospective cohort study of ND patients with MM aged 18–65 years who required treatment according to the International Myeloma Working Group (IMWG) criteria [12] between November 2020 and December 2021. Patients with extramedullary disease (EMD) were included. EMD is defined as 1) soft tissue masses in extraosseous locations and 2) bone-related plasmacytomas that extend via the disruption of cortical bones into contiguous soft tissues. Conversely, patients with plasma cell leukemia and amyloidosis were excluded. Finally, a total of 37 patients undergoing VRd induction and 43 patients undergoing D-VTd induction were identified (Fig. 1). Subsequently, their medical records were reviewed for demographic information, baseline disease characteristics, treatment outcomes, adverse event (AE) incidence, and survival outcomes.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of each participating hospital (Seoul National University Hospital and Seoul St. Mary's Hospital).

Induction

The VRd regimen was based on the phase 3 PETHEMA/GEM2012 study [6] and consisted of 1.3 mg/m^2 subcutaneous bortezomib on days 1, 4, 8, and 11 of each cycle, 25 mg/day lenalidomide on days 1–21, and 40 mg dexamethasone on days 1–4 and 9–12 at 4-week intervals for up to six cycles. Meanwhile, D-VTd induction followed the phase 3 CASSIOPEIA study [8] and all patients received up to four cycles at 28-day intervals. The regimen consisted of 1.3 mg/m^2 subcutaneous bortezomib on days 1, 4, 8, and 11 of each cycle; 100 mg/day thalidomide on days 1 to 28; and dexamethasone (40 mg on days 1, 2, 8, 9, 15, 16, 22, and 23 during induction cycles 1 and 2 and days 1 and 2 during induction cycles 3 and 4; and 20 mg on days 8, 9, 15, and 16 of induction cycles 3 and 4). Daratumumab was administered intravenously at a dose of 16 mg/kg body weight once weekly in induction cycles 1 and 2 and once every two weeks during induction cycles 3 and 4.

Post-induction treatment

Upon achieving partial response (PR) or better response, stem cell mobilization was carried out using granulocyte colony-stimulating factor (G-CSF) ± plerixafor. Chemomobilization with cyclophosphamide or etoposide was performed in selected patients as determined by the attending physician. When white blood cell count reached ≥10/μL, apheresis

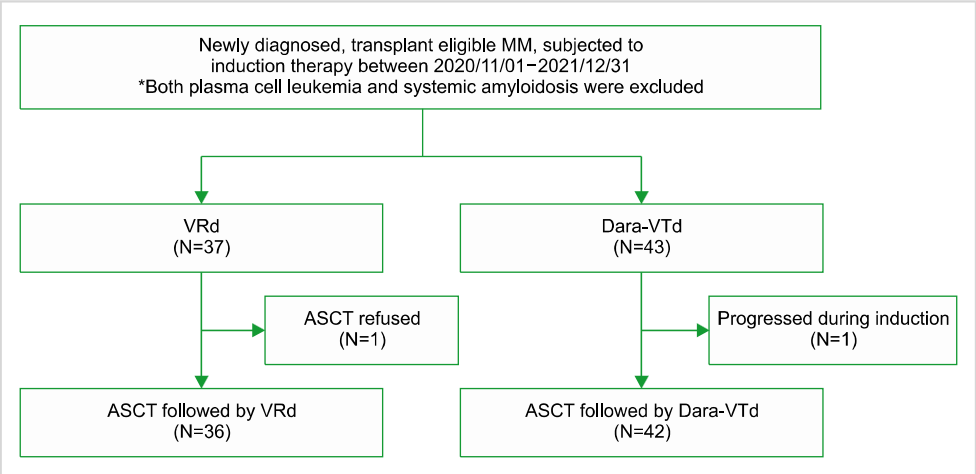

Fig. 1. Study flow.

began with the goal of collecting at least 2×10^6 CD34+ cells/kg peripheral blood stem cells.

The conditioning regimen for autologous stem cell transplantation (ASCT) was at the discretion of the attending physician. Patients undergoing busulfan-melphalan (BUMEL) conditioning received 3.2 mg/kg busulfan on days -6 to -4, followed by 70 mg/m^2/day melphalan on days -3 and -2 [13]. Patients undergoing high dose melphalan (HDMEL) conditioning received 100 mg/m^2/day melphalan on days -3 and -2 [14]. The melphalan dose was reduced to 70 mg/m^2/day in some patients (i.e. MEL140), based on their condition.

After ASCT, consolidation and maintenance therapies were administered at the attending physician's discretion. Up to two cycles of consolidation were allowed in both the VRd and D-VTd groups. VRd consolidation was performed in the same manner as induction. D-VTd consolidation was performed according to the CASSIOPEIA study [8]. For patients receiving maintenance treatment, either 10 mg/day lenalidomide or 100 mg/day thalidomide was administered.

Minimal residual disease

Multiparametric flow cytometry was performed using the DuraClone method [15] according to the manufacturer's instructions and the principles outlined by the European Myeloma Network [16]. Fresh EDTA (ethylenediaminetetraacetic acid) anticoagulated bone marrow aspirate samples were collected. Red blood cells were lysed using Versafix solution (VersaLyse supplemented with IOTest 3 Fixative Solution, Beckman Coulter, Brea, CA, USA) and cell suspensions containing 5×10^6 nucleated cells were transferred to a premixed, dry reagent cocktail (DuraClone RE PC antibody panel) and CD117 ECD (Beckman Coulter, Marseille, France). The DuraClone RE PC antibody panel was composed of CD81-FITC, CD27-PE, CD19-PC5.5, CD200-PC7, CD138-APC, CD56-APC-A750, CD38-Pacific blue, and CD45-Krome orange. After 15 min of incubation at room temperature, the cells were washed with phosphate-buffered saline (PBS) and centrifuged at 3,000 rpm for 3 min. The final pellet was resuspended in 500 μL PBS and data acquired using the predefined settings of a 9-color, 3-laser DxFLEX flow cytometer (Beckman Coulter). All acquired data files were analyzed using the Kaluza analysis software, version 2.1 (Beckman Coulter) by manual serial gating, according to the consensus guidelines of minimal residual disease (MRD) reporting [17]. According to the guidelines for MRD detection in patients with MM, we defined 30 and 50 cells as the limit of detection (LOD) and lower limit of quantitation (LLoQ), respectively. In our study, the LOD and LLoQ were set to 6×10^{-6} and 1×10^{-5}, respectively.

Statistical analysis

Response evaluation was performed according to the

Table 1. Baseline characteristics.

N (%)		VRd (N=37)	D-VTd (N=43)	*P*
Age at diagnosis	Median, years (range)	55 (35–65)	58 (39–70)	0.010
Sex	Male	21 (56.8)	22 (51.2)	0.617
ECOG	0	5 (13.5)	5 (11.6)	0.096
	1	29 (78.4)	26 (60.5)	
	2	1 (2.7)	9 (20.9)	
	3	2 (5.4)	3 (7.0)	
ISS	I	15 (40.5)	14 (32.6)	0.272
	II	17 (45.9)	17 (39.5)	
	III	5 (13.5)	11 (25.6)	
	Missing	0	1 (2.3)	
R-ISS	I	9 (24.3)	9 (20.9)	0.453
	II	19 (51.4)	20 (46.5)	
	III	5 (13.5)	5 (11.6)	
	Missing	4 (10.8)	9 (20.9)	
Type	IgG	24 (64.9)	22 (51.2)	0.032
	IgA	10 (27.0)	6 (14.0)	
	Light chain disease	3 (8.1)	14 (32.6)	
	Non-secretory	0	1 (2.3)	
Risk group	High-risk[a)]	16/34 (47.1)	11/34 (32.4)	0.128
	Missing	3	9	
CrCl	<50 mL/min	1 (2.7)	14 (32.6)	0.001
EMD	Present	9 (24.3)	10 (23.3)	0.911
Induction cycles	Median (range)	5 (1–6)	4 (2–5)	<0.001

[a)]High-risk multiple myeloma: presence of del(17p) and/or t(4, 14) and/or t(14, 16) translocations.
Abbreviations: CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; EMD, extramedullary disease; ISS, International Staging System; NA, not applicable; R-ISS, Revised International Staging System.

IMWG criteria [12]. Post-induction response evaluation was performed after the completion of induction therapy prior to ASCT. Post-ASCT response evaluation was performed within 30 days of ASCT. The MRD was assessed 100 days post-ASCT. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Renal impairment and assessments were performed according to the IMWG criteria (CRrenal, PRrenal, MRrenal and no response) [18]. Creatinine clearance (CrCl) was calculated using the Cockcroft-Gault formula.

Differences between groups were assessed using Student's t-test or one-way analysis of variance for continuous variables and Pearson's chi-square test for categorical variables, as indicated. PFS was defined as the time from stem cell infusion to relapse or death of any cause. The PFS curves were estimated using the Kaplan-Meier method. If patients survived without death or progression, then survival was censored at the latest follow-up date. Binary logistic regression was used to identify significant prognostic indicators of post-induction response. Data available before to July 1, 2022, were used. *P*-values of <0.05 were considered statistically significant. These data were analyzed using the Statistical Package for the Social Sciences software (SPSS, IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics and treatment schema

The baseline characteristics of the patients are shown in Table 1. Patients in D-VTd tended to be older than those in the VRd group (P=0.010); however, there were no significant differences between the two groups regarding sex, ECOG performance, disease stage, risk stratification, or EMD presence. Two patients had concurrent amyloidosis and both underwent D-VTd induction. Owing to lenalidomide nephrotoxicity, there were more patients with renal insufficiency, defined as serum creatinine (Cr) >2 mg/dL, in D-VTd group (2.7% in VRd vs. 18.6% in D-VTd, P=0.033).

Since VRd induction was allowed for up to six cycles, while D-VTd was allowed for up to four cycles, patients in the VRd group were subjected to more cycles of induction therapy than those in the D-VTd group (median five cycles vs. four cycles, $P<0.001$). Accordingly, the time to ASCT was longer in the VRd group (median, 183 vs. 148 days; $P<0.001$).

One patient in the VRd group refused to undergo ASCT, while one patient in the D-VTd group progressed during induction. ASCT was carried out in 36/37 patients in the VRd group and 42/43 patients in the D-VTd group (Table 2). There were no differences in mobilization yield and failure rates between the two groups. BUMEL conditioning was used more frequently in the VRd group than in the D-VTd group.

Post-induction treatment outcomes

Post-induction response evaluation was performed in all 37 patients who underwent VRd (Fig. 2A). Four patients (10.8%) achieved stringent complete response (sCR), eight (21.6%) achieved complete response (CR), 13 (35.1%) achieved very good partial response (VGPR), and 12 (32.4%) achieved PR. In the D-VTd group, a post-induction response evaluation was performed in all 43 patients. Four patients (9.3%) achieved sCR, 15 (34.9%) achieved CR, 21 (48.8%) achieved VGPR, and two (4.7%) achieved PR. One patient progressed after two cycles of D-VTd after initially achieving VGPR with one cycle of D-VTd.

Table 2. ASCT and post-ASCT treatment details.

N (%)	VRd (N=36)	D-VTd (N=42)	*P*
Mobilization			0.625
G-CSF	22 (61.1)	30 (71.4)	
Chemotherapy	14 (38.9)	12 (28.6)	
Collected cell, CD34×10^6/kg, mean	6.9	6.4	0.556
Additional mobilization required	7 (19.4)	14 (33.3)	0.168
Induction to ASCT, days, median	183	148	<0.001
ASCT conditioning regimen			
HDMEL	27 (75.0)	27 (64.3)	0.036
BUMEL	9 (25.0)	8 (19.0)	
MEL140	0	7 (16.7)	
Infused cell, CD34×10^6/kg, mean	4.3	4.1	0.449
Consolidation after ASCT	29/35 (82.9)	5/42 (11.9)	<0.001
Tandem ASCT	0 (0.0)	1/42 (2.4)	0.351
Maintenance	9/35 (25.7)	22/42 (52.4)	0.014
Lenalidomide	9/9 (100)	18/22 (81.8)	
Thalidomide	0	4/22 (18.2)	

Abbreviations: ASCT, autologous stem cell transplantation; BUMEL, busulfan plus melphalan; G-CSF, granulocyte colony-stimulating factor; HDMEL, high-dose melphalan or melphalan 200 mg/m^2; MEL140, melphalan 140 mg/m^2.

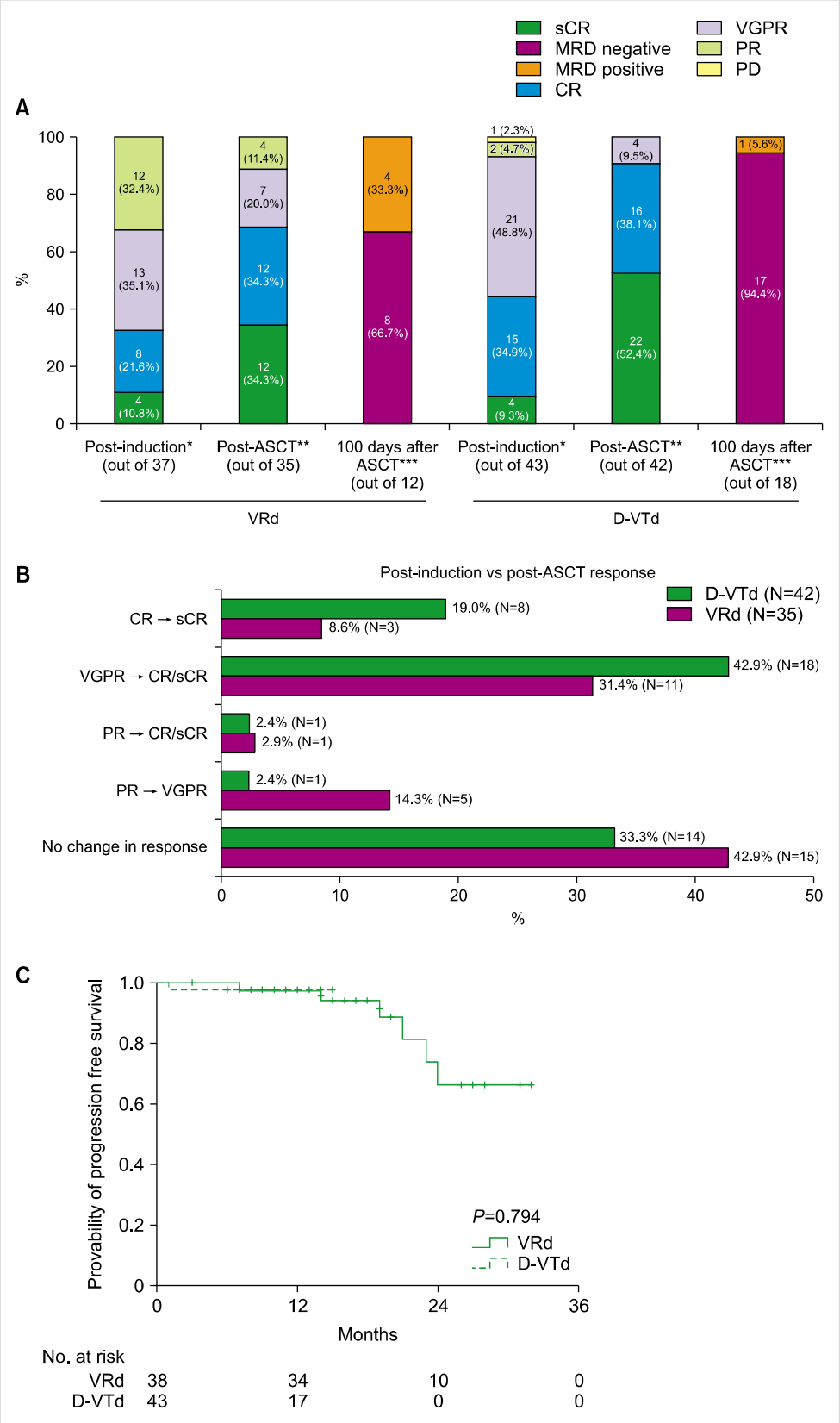

Fig. 2. Summary of responses and subgroup analysis **(A)** response throughout the treatment, *VGPR or better rate post induction, 67.6 % vs. 93% (P=0.004); **CR or better rate post ASCT, 68.6% vs. 90.5% (P=0.016); ***MRD negativity at 100 days post ASCT, 66.7% vs. 94.4%, P=0.046, respectively **(B)** change in response, **(C)** progression free survival.
Abbreviations: ASCT, autologous stem cell transplantation; CR, complete response; D-VTd, daratumumab-bortezomib-thalidomide-dexamethasone; MRD, minimal residual disease; PD, progressive disease; PR, partial response; sCR, stringent complete response; VGPR, very good partial response; VRD, bortezomib-lenalidomide-dexamethasone.

A higher number of patients achieved CR/sCR in D-VTd group than the VRd group (12 patients or 32.4% in VRd vs. 19 patients or 44.2% in D-VTd, P=0.282), but the difference did not reach statistical significance. When VGPR or a better response was considered, the D-VTd group showed a significantly better response than VRd (P=0.004, Fig. 2A).

D-VTd showed superior response regardless of high-risk status. Among high-risk patients, the D-VTd group was more likely to achieve CR or sCR post-induction compared to the VRd group [odds ratio, 5.322; 95% confidence interval (CI), 1.275–22.225; *P*=0.022]. Also, age did not alter the D-VTd response. For patients older than 55 years of age, the D-VTd group was more likely to achieve CR or sCR compared to VRd group (odds ratio, 4.215; 95% CI, 1.662–10.693; *P*=0.040). Finally, patients with CrCl <50 mL/min in the D-VTd group were more likely to achieve CR or sCR post-induction compared to patients with normal CrCl in VRd group (odds ratio, 4.453; 95% CI, 1.716–11.552; *P*=0.002). Among the 14 patients with initial renal insufficiency (Table 1) in the D-VTd group, eight fully recovered (CRrenal), one showed PRrenal, four showed MRrenal, and one showed no response.

Post-ASCT treatment outcomes

Post-ASCT response evaluation was carried out in 35 patients in the VRd group because one patient refused ASCT and one patient died during ASCT (transplant-related mortality). Twelve patients (34.3%) achieved sCR and same number of patients achieved CR after ASCT. Post-ASCT response evaluations were available for 42 patients in the D-VTd group. Twenty-two patients (52.4%) achieved sCR and 16 (38.1%) achieved CR after ASCT. When CR+sCR was considered, the D-VTd group showed a significantly better response than VRd (*P*=0.016, Fig. 2A).

Changes in response from post-induction to post-ASCT occurred more often in the D-VTd group (Fig. 2B). More specifically, 19% of D-VTd patients went from CR to sCR, and 42.9% went from VGPR to CR or sCR.

Post-ASCT D+100 MRD data were available for selected patients (Fig. 2A). D-VTd was associated with higher rates of MRD negativity than was VRd (*P*=0.046).

Survival outcomes

Although this study was not powered to compare survival outcomes, during the median 13 months of follow-up (18 mo for VRd group vs. 11 mo for D-VTd group), there were more relapses in VRd group (N=6, 16.2%) compared to D-VTd group (N=1, 2.3%) (*P*=0.028). However, this did not translate into an increase in PFS (Fig. 2C).

Adverse events

There were no significant differences in hematologic AE between the two groups (Table 3), although there were more patients with grade 3–4 neutropenia in the D-VTd group. The most common non-hematologic AE in VRd group was constipation (32.4%), followed by skin rash (29.7%) and peripheral neuropathy (29.7%). In the D-VTd group, the most common non-hematologic AE was also constipation

Table 3. Adverse events.

N (%)	VRd (N=37)		D-VTd (N=43)		*P*[a]
	Any	Grade ≥3	Any	Grade ≥3	
Hematologic AE					
Neutropenia	1 (2.7)	1 (2.7)	4 (9.3)	4 (9.3)	0.224
Thrombocytopenia	0	0	0	0	NA
Lymphopenia	1 (2.7)	0	1 (2.3)	0	0.914
Non-hematologic AE					
Peripheral neuropathy	11 (29.7)	0	9 (20.9)	0	0.365
Constipation	12 (32.4)	1 (2.7)	12 (27.9)	0	0.660
Skin rash[b]	11 (29.7)	3 (8.1)	5 (11.6)	1 (2.3)	0.044
Pruritis[c]	8 (21.6)	1 (2.7)	3 (7.0)	0	0.058
Edema	5 (13.5)	0	2 (4.7)	0	0.162
Nausea	4 (10.8)	0	6 (14.0)	0	0.672
Documented infection	4 (10.8)		2 (4.7)		0.297
Viral	2		1		
Bacterial	2		1		
Fungal	0		0		
Daratumumab IRR	NA		19 (44.2%)	0	NA
Cycle 1			18	0	
Cycle 2			0	0	
Cycle 3			0	0	
Cycle 4			1	0	
IMiD dose reduction					NA
Lenalidomide	6 (16.2)		NA		
Thalidomide	NA		6 (13.6)		

[a] *P*-value for adverse events. [b] *P*-value for grade ≥3 skin rash, *P*=0.237. [c] *P*-value for grade ≥3 pruritis, *P*=0.278.
Abbreviations: AE, adverse events; IMiD, immunomodulatory drug; IRR, infusion-related reaction; NA, not applicable.

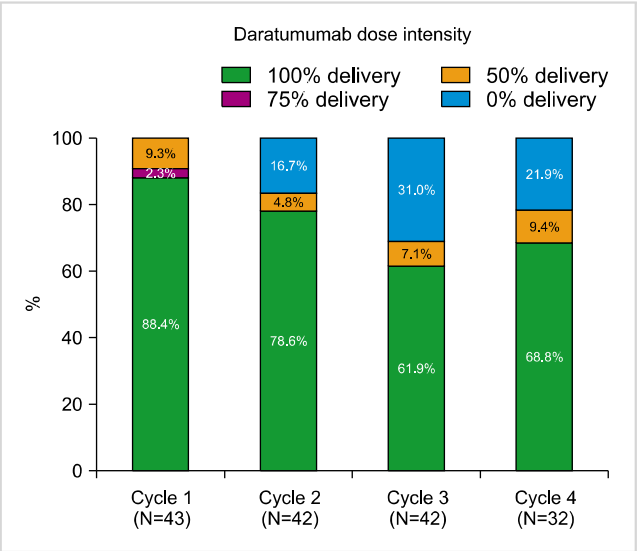

Fig. 3. Daratumumab dose intensity per cycle.

(27.9%), followed by peripheral neuropathy (20.9%) and nausea (14.0%). Patients in VRd group experienced more frequent skin rashes (P=0.044), but the rates of grade 3–4 skin rash were similar between the two groups (P=0.237).

The patients in the VRd group had a higher rate of infection. Four patients had documented infections: one with sepsis, one with blepharitis, and two with HSV infection. Two patients in the D-VTd group had an HSV infection.

Overall, 44.2% (19/43) of the D-VTd group experienced infusion related reaction Table 3. Fortunately, there were no grade 3–4 events. Fig. 3 shows the daratumumab dose intensity delivered per cycle. During cycle 1, daratumumab dose reduction was due to adverse events. However, from cycle 2 onward, dose reductions were due to financial rather than medical reasons. During a median of five cycles, six patients (16.2%) experienced lenalidomide dose reduction in VRd group. During a median of four cycles, six patients (13.6%) experienced thalidomide dose reduction in D-VTd group.

DISCUSSION

In this study, we compared the current standard triplet induction VRd to quadruplet induction D-VTd and found that D-VTd was associated with a better response post-induction and post-ASCT than VRd. The importance of our study lies in the following: 1) the study was conducted over a short time period; thus, confounding factors were minimized; 2) the study population was homogeneous; 3) induction chemotherapy schedules were synchronized in that both VRd and D-VTd were delivered on a 4-week basis; 4) we provided information on real-world D-VTd use patterns for financial reasons; and 5) we provided comparative results on response rates and toxicity profiles, which closes the gaps in recent MAIC analyses [11] thereby providing more comprehensive evidence supporting the use of quadruplet induction.

Although retrospective in nature, the response rates for both the VRd and D-VTd groups were comparable to those of previous reports, ensuring the credibility of our data. The reported VGPR or better response rates for post-induction VRd ranges from 57.1% in the IFM2009 [5] to 70.4% in the PETHEMA/GEM2012 [6] trial. Likewise, 67.6% of patients in VRd group achieved VGPR or better response post-induction. D-VTd group outcomes (VGPR or better, 93%) were better than CASSIOPEIA [8] trial (VGPR or better, 64.9%). This is especially important since only 17/43 (39.5%) patients received the full dose of daratumumab during the four cycles of induction (Fig. 3). Because there is a paucity of real-world D-VTd efficacy data, we remain conservative with the actual numbers and percentages, but our data suggest that quadruplet induction yields better and deeper responses than triplet induction.

Notably, despite the unfavorable baseline characteristics, including older age and a higher number of patients with renal insufficiency, D-VTd was associated with a deeper response than VRd both post-induction and post-ASCT. D-VTd showed a significantly better response than VRd in the high-risk group (P=0.022) and older patients (P=0.040). Additionally, D-VTd was more advantageous in patients with renal insufficiency (P=0.003). Among the IMiDs [19], it is already well-established that thalidomide is less nephrotoxic than lenalidomide. Up to 50% of patients with MM have renal insufficiency at presentation [20], thus it is important to have a potent option in the treatment arsenal for these patients.

Another important point is that quadruplet induction was not associated with increased toxicities compared to triplet induction, including hematologic AEs, peripheral neuropathy, and mobilization failure. One of the major concerns when adding daratumumab is the possibility of lymphopenia and subsequent infections. Fortunately, limited daratumumab cycles in treatment-naïve settings were not associated with increased rates of hematologic AEs or infections. Although the study was conducted during the unprecedented COVID-19 pandemic, none of the patients were infected.

One of the most obvious limitations of our study is the possibility of selection bias owing to its retrospective nature. However, it should be considered that the choice between VRd and D-VTd was arbitrary Korea because VRd is covered by the national health insurance, whereas D-VTd is not. Of course, attending physicians can recommend one regimen over another based on medical rationale, but the ultimate choice is left to the patient because of out-of-pocket charges. We believe that this “arbitrary selection” provides the same effects as randomization. Unfortunately, we did not estimate incremental cost-effectiveness ratios in this study. A longer follow-up with better powered survival outcomes are needed to determine whether the initial economic burden of quadruplet induction can translate into a total cost decrement. Another limitation is the heterogeneity of the post-ASCT treatment schema, which underpowers the survival outcome

analysis. However, our response data, including the MRD results, are relevant, as they have little to do with consolidation and maintenance treatments. Despite these shortcomings, this is the first detailed study comparing the two regimens; thus, we strongly believe that our results will be of great help to physicians navigating nuanced decision-making in a real-world clinical setting.

In conclusion, our results provide additional evidence for the favorable efficacy of D-VTd in the treatment of patients with ND TE MM and highlights the potential clinical benefit of daratumumab as front-line therapy.

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Authors' Disclosures of Potential Conflicts of Interest

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

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