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Impact of Induction Therapy with VRD vs. VCD on Outcomes in Patients with Multiple Myeloma in Partial Response or Better Undergoing Upfront Autologous Stem Cell Transplantation

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Abstract

BACKGROUND: Bortezomib-based triplet regimens, specifically bortezomib, lenalidomide and dexamethasone (VRD) and bortezomib, cyclophosphamide and dexamethasone (VCD) are the two most common induction regimens used in transplant-eligible patients with NDMM, with conflicting data on comparative efficacy and outcomes in this population.

OBJECTIVES: We compared long-term outcomes of multiple myeloma (MM) patients receiving VRD vs. VCD induction prior to autologous stem cell transplant (ASCT).

STUDY DESIGN: Patients registered with Center for International Blood and Marrow Transplant Registry were included if they underwent ASCT for MM from 01/2013 to 12/2018 within 6 months of diagnosis, received VRD or VCD induction and achieved pre-transplant ≥ partial response. Of 1,135 patients, 914 received VRD and 221 received VCD.

RESULTS: Patients receiving VCD were more likely to have renal impairment and ISS stage III disease and less likely to receive full dose melphalan (200 mg/m^2) conditioning (69% vs 80%, $p<0.001$). Very good partial response rates pre-transplant, post-transplant and at best response in VRD vs. VCD were not significantly different. Maintenance use was more common after VRD (88% vs. 76%, $p<0.001$) with lenalidomide being the most common agent (80% vs 63%). Patients in the VRD group had higher rates of renal recovery, 74% vs. 43% $p<0.001$, which may be due to rapid reduction of light chains in the VRD group or improvement in renal function with VCD, which allowed switch over to VRD as patients who switched were classified in the VRD group. Patients receiving VRD had better survival on univariate analysis, with median progression-free

survival (PFS) from transplant of 44.6 vs 34.1 months, p=0.004 and 5-year overall survival (OS) of 79% and 60%, p<0.001, respectively. On multivariate analysis there was no significant survival difference, with hazard ratio (VCD vs. VRD induction) for PFS being 1.22 (95% CI: 0.96–1.55, p=0.10) and OS being 1.33 (95% CI: 0.93–1.92, p=0.12). Maintenance use was independently associated with superior PFS and OS, along with ISS stage, cytogenetics and pre-transplant response (PFS only).

CONCLUSIONS: In patients with MM undergoing upfront transplant after VRD or VCD induction, no independent survival difference was seen based on the induction therapy received after adjusting for other prognostic factors. The use of maintenance treatment was uniformly associated with superior outcomes.

INTRODUCTION:

Novel agent triplet regimens have been associated with improved progression free survival (PFS) and overall survival (OS) in patients with newly diagnosed multiple myeloma (NDMM)(1, 2) and have become standard of care treatment. Amongst the triplet regimens, bortezomib-based triplet regimens, specifically bortezomib, lenalidomide and dexamethasone (VRD) and bortezomib, cyclophosphamide and dexamethasone (VCD) are the two most common induction regimens used in transplant-eligible patients with NDMM. (1, 3–6) VCD is often used in patients with renal failure, given the challenges with use of lenalidomide in patients with fluctuating renal function.(7) Published data comparing outcomes with VCD and VRD induction in phase II trials (8, 9) and retrospective studies (6, 10–12) have shown variable results. It is unclear whether VRD induction has any significant advantage over VCD induction in patients receiving upfront ASCT.

A phase III randomized clinical trial comparing these two regimens is unlikely to be planned and no definitive conclusion can be made regarding the comparative efficacy of VCD vs VRD from current data. Therefore, a larger study is needed to compare these two regimens. The objective of this study was to compare outcomes of patients receiving VRD vs. VCD induction prior to transplant using the CIBMTR (Center for International Blood and Marrow Transplant Research) database. We also aimed to account for key confounding variables that may impact choice of induction regimen or impact survival outcomes, such as renal failure and post-transplant maintenance. (13–15).

METHODS:

The Center for International Blood and Marrow Transplant Research® (CIBMTR®) registry was used to identify patients and collect data. The CIBMTR registry is a prospectively maintained registry of patients undergoing autologous and allogeneic stem cell transplant. (16) For a sub-group of patients obtained using a weighted randomization algorithm,(17) detailed case report forms are reported to CIBMTR, which capture demographics, co-morbidities, laboratory data, disease characteristics, treatment details (including induction and maintenance therapy) and outcomes. Studies using CIBMTR registry data are conducted under approved by the Institutional Review Boards of the Medical College of Wisconsin, Milwaukee and National Marrow Donor Program, Minneapolis.

Patients were included in this study if they underwent upfront ASCT for MM from January 2013 to December 2018 and within six months of myeloma diagnosis, received VRD or VCD induction therapy and achieved at least a partial response prior to transplant. Induction therapy was coded in a hierarchical manner, and any patients who started on VD or VCD and switched to VRD induction before transplant were included in the VRD group. Additional inclusion criteria included use of melphalan only conditioning for ASCT and at least 3 months of follow-up for alive patients. Overall, 1,135 patients met inclusion criteria (Supplementary data: consort flow diagram), of which 914 patients received VRD induction and 221 patients received VCD induction. Two-year follow-up data were available in over 90% of patients.

High-risk cytogenetics were defined as presence of at least one of the following abnormalities: t(4;14), t(14;16), t(14;20), deletion 17p, gain or amplification of 1q (18) on FISH and/or conventional cytogenetics. Patients were categorized by International Staging System (ISS) as previously described.(19) Hematopoietic Cell Transplant Comorbidity Index (HCT-CI) scores were evaluated.(20) Renal-adjusted HCT-CI scores were used as described before,(7) which excluded renal co-morbidity as renal insufficiency was studied separately as a covariate. Renal insufficiency was defined based on estimated glomerular filtration rate (eGFR). Patients were categorized as having moderate to severe renal impairment if eGFR was < 60 ml/min/1.73 m^2 or normal renal function/mild impairment if eGFR was ≥ 60 ml/min/1.73 m2. Response and disease progression were defined per International Myeloma Working Group criteria. (21)

Univariable analysis for categorical variables were carried out using chi-square tests and for continuous variables using Wilcoxon rank-sum test/Kruskal Wallis test. Survival analysis was done using Kaplan Meier method, and log-rank test was used to compare survival curves. The cumulative incidence of relapse/progression was estimated using the cumulative incidence function and tested using Gray's test, accounting for death without preceding relapse/progression as competing risk. Estimates of outcomes were reported with 95% confidence interval (CI). PFS was defined as time from ASCT to progression or death and OS was defined as time from ASCT to death or last follow-up. Cox proportional hazards models were created for multivariable survival analysis. Hazard ratios (HR) with 95% confidence intervals (CI) are reported. The following covariates were considered in the multivariable models: induction regimen (main effect), age, sex, race, performance score, renally adjusted HCT-CI score, eGFR at diagnosis, immunoglobulin subtype, cytogenetics, ISS stage, response status at transplant, conditioning melphalan dose, and maintenance therapy. A step-wise approach was used to identify the variables to be included in the final model. All p-values were 2-sided and the difference between two variables was consider significant if $p<0.05$.

RESULTS:

Amongst patients who met the inclusion criteria, 914 patients received VRD induction and 221 patients received VCD induction prior to undergoing upfront ASCT. As shown in Table 1, patients in the VRD and VCD cohorts had similar age (median age: 60.3 and 61.4 years) and sex distribution (males: 55% and 54%). Patients in the VRD group were

more likely to be African American (30% vs 19%, p=0.004). Patients in both groups had a similar performance status at diagnosis. Karnofsky performance status ≥ 90 was seen in 51% and 59% of patients in the VRD and VCD cohorts, p=0.09. There was no difference in renal-adjusted HCT-CI scores (score of ≥ 2: 55% and 49%, p=0.74), and distribution of high-risk cytogenetics (37% and 35%, p=0.89) amongst patients in VRD and VCD groups, respectively. Patients in the VCD group were more likely to have renal impairment, ISS stage III disease and light chain myeloma. Moderate to severe renal insufficiency at diagnosis with an eGFR < 60 mL/min/1.73m^2 was seen in 26% of patients receiving VRD vs. 48% of patients receiving VCD induction, p=<0.001. Similarly, ISS stage III was seen in 17% vs. 34% (p=<0.001) of patients, respectively. Light chain myeloma was seen in 19% of patients in the VRD group and 27% patients in the VCD group, p=0.07. We also observed a change over time, with use of VRD therapy becoming more frequent from 2013 to 2018 compared to VCD therapy. (Supplementary Table 1) Black or African American patients were more likely to receive VRD therapy, likely related to the fact that Black/African American patients in our cohort were younger and less likely to have renal impairment. (Supplementary Table 2)

Treatment and Response:

Median cycles of induction therapy was similar in both groups at 4, p=0.30. (missing in n=138). As shown in Table 1, pre-transplant response in the VRD cohort was: complete response (CR)- 17%, very good partial response (VGPR)- 48% and partial response (PR)- 35%. Response in the VCD cohort was: CR- 17%, VGPR- 42% and PR- 41%. Rates of VGPR or better response pre-transplant in the VRD vs VCD group were 65% vs. 59%, p=0.11. Table 2 describes transplant and post-transplant differences between the two groups. A higher proportion of patients in the VRD group received full dose melphalan conditioning (melphalan 200 mg/m^2) compared to the VCD group, 80% vs. 69%, p=<0.001. Rates of VGPR or better response post-transplant in the VRD and VCD group at day 100 and best response were similar at 74% vs. 75%, p=0.47 and 85% vs. 89%, p=0.17, respectively. Post-transplant CR rates in the VRD and VCD groups were 63% vs. 57%, p=0.07, respectively.

Maintenance Therapy:

The majority of patients received maintenance therapy, though maintenance was more common in patients receiving VRD induction (VRD: 88%, VCD: 76%, p <0.001), with lenalidomide based maintenance being most frequently used regimen. The median time from transplant to start of maintenance therapy was 4 months (inter-quartile range 2.99–4.34 months) in both groups. Maintenance in the VRD group was as follows- lenalidomide based (+/− bortezomib): 80% (n=732), bortezomib based: 5% (n=50), other: 3% (n=24) and no maintenance in 12% of patients. In the VCD group, maintenance was as follows- lenalidomide based: 63% (n=139), bortezomib based: 11% (n=25), other- 1% (n=4) and no maintenance: 24% (n=52). Response to maintenance therapy in the VRD vs. VCD group was VGPR or better in 68% vs. 56% of patients, p 0.66, respectively. In the no maintenance group, 18 patients reported progression before the first 4 months after transplant.

Renal function recovery kinetics:

We evaluated recovery of renal function from diagnosis to ASCT as shown in Table 3. This was defined as improvement of renal function at diagnosis from moderate/severe renal dysfunction (eGFR < 60 ml/min/1.73m^2) to mild impairment/normal renal function (eGFR ≥ 60 ml/min/1.73m^2) before transplant. Paired data on renal function was available in 1,040 patients, of whom 344 patients had at least moderate renal impairment (eGFR<60) at baseline. Median (range) eGFR at diagnosis in the VRD and VCD groups was 75.7 (2.2–56.5) ml/min and 56.5 (2.3–167.3) ml/min (p<0.001), while eGFR prior to transplant in the two cohorts was 95.6 (7.8–276.7) ml/min and 82.0 (5.2–191.7) ml/min, respectively (p<0.001). Amongst patients with renal dysfunction (eGFR < 60) at diagnosis, median eGFR in the VRD vs. VCD group was 45 ml/min and 22 ml/min, respectively, p <0.001. Overall, 64% (222/344) of patients experienced improvement in renal function, including 74% in the VRD group and 43% in the VCD group, p=<0.001. There was no difference in receipt of maintenance therapy based on renal function recovery. Maintenance therapy was given in 86% (191/222) of patients with renal function improvement (eGFR increased from < 60 to ≥ 60 ml/min), which was similar to rates of maintenance in patients who had eGFR ≥ 60 at both time points (86%, 602/696), p=0.86. Amongst patients who did not recover renal function, maintenance was given in 81% (99/122) of patients.

Survival:

Median follow-up of survivors in the VRD group was 25 months (range: 3–82) and that in the VCD group was 38 months (range: 3–77). On unadjusted analysis, patients receiving VRD induction had superior outcomes compared to VCD induction, with median PFS from transplant of 44.6 (95% CI: 38.0–55.8) months vs 34.1 (95% CI: 25.8–44.7) months, p=0.004 respectively. (Figure 1) Median OS was not reached in either group, with 5-year OS being 79% in the VRD cohort and 60% in the VCD cohort, p <0.001. Univariable PFS and OS outcomes at 2 and 5 years by induction regimen are shown in Table 4. We further evaluated survival outcomes after excluding 52 patients who were initially started on VD/VCD and switched to VRD. Outcomes after excluding these patients were similar to that observed in the entire group, with better PFS and OS observed in the VRD group on unadjusted analysis, as shown in Supplementary Table 3. We also analyzed survival outcomes based on renal function at diagnosis, as shown in Table 5 and Figure 2. In patients with eGFR ≥ 60, patients in the VRD group had a longer PFS than those receiving VCD. Median PFS from transplant in the VRD vs. VCD group for patients with eGFR ≥ 60 was: 42.1 vs 31.6 months, p=0.003. Median OS was not reached in either group, p=0.075. At 5 years, OS in the VRD vs VCD patients with eGFR > 60 was 78% vs 61%, p=0.017. In patients with eGFR < 60, there was no difference in the median PFS in the VRD vs VCD group, : 48.7 vs 38.5 months, p=0.555. OS was superior in patients with eGFR < 60 who received VRD (p=0.042). 5-year OS was 84% vs 60%, p=0.008.

Multivariable survival analysis is shown in Table 6. Variables considered in the multivariable analysis are described under the methods section. Using a step-wise approach, the following variables were included: induction regimen, ISS stage, cytogenetics, maintenance therapy and pre-transplant response. After adjusting for these variables in this model, there was no statistically significant difference between the two induction regimens, with hazard ratio

(HR) for PFS in the VCD vs VRD group being 1.20 (95% CI: 0.95–1.53, p=0.13). ISS stage, cytogenetics and maintenance were independent prognostic factors for PFS. Similarly, on multivariable analysis for OS, there was no statistically significant difference in the two groups, with HR for OS in the VCD vs. VRD group being 1.33 (95% CI: 0.92–1.9, p=0.13). ISS stage, cytogenetics and maintenance were independent prognostic factors for OS. Specifically, hazard ratio for maintenance no vs. yes was as follows, PFS: 1.74, 95% CI: 1.33–2.28, p<0.001 and OS: 2.28, 95% CI: 1.53–3.38, p <0.0001. We also conducted a sub-group analysis in patients receiving full dose melphalan 200 mg/m2 conditioning (N=821). (Table 7) Results were similar, and there was no statistically significant difference between the two induction regimens with HR for PFS in the VCD vs VRD group being 1.20 (0.91–1.57), p=0.19 and HR for OS in the VCD vs VRD group being 1.24 (0.81–1.88), p=0.32.

DISCUSSION

In patients with MM undergoing upfront transplant, VRD induction was associated with longer PFS and OS on univariable analysis. Importantly, however, there was no difference in VGPR or better response rates in both groups pre- or post-transplant and survival outcomes were similar after adjusting for key prognostic factors. The use of maintenance treatment was uniformly associated with superior outcomes.

Severe or moderate renal impairment at diagnosis was more common in the VCD group compared to patients receiving VRD induction, which aligns with a higher proportion of patients with ISS stage III in this group due to decreased renal clearance of beta-2-microglobulin and a higher proportion of patients with light chain myeloma, which increases the likelihood of cast nephropathy.(22, 23) This is similar to findings seen in a comparativeness effective study of VRD vs. VCD induction in NDMM patients, where patients in the VCD group were more likely to have renal dysfunction.(24) While dose adjusted lenalidomide can be given with renal dysfunction,(25, 26) it can be challenging to administer lenalidomide with fluctuating renal function and therefore physicians may elect to start VCD in such patients. It has been previously shown that PFS and OS outcomes in patients with moderate to severe renal dysfunction undergoing ASCT are similar to that observed in patients with normal renal function, and other factors such as maintenance can independently impact survival outcomes in this population.(7) We noted higher renal improvement rates in the VRD group compared to the VCD group. This could be due to two reasons. The first being that patients who show improvement on VCD are often transitioned to VRD therapy, and such patients were categorized in the VRD group in our study. Second, it is possible that achieving a rapid response with VRD therapy can result in higher likelihood of renal recovery. Significant out of pocket costs for lenalidomide for some patients can also play a role in treatment selection and that may have contributed to choice of triplet induction in some patients.

Previous studies comparing VRD and VCD induction or similar regimens have found differing results. In the IFM 2014–04 trial comparing four cycles of VTD (bortezomib, thalidomide and dexamethasone) induction to VCD induction, rates of VGPR or better response were higher in the VTD arm, 66% vs 56%, p=0.05.(8) Post-transplant response

or survival data from this trial are not yet available. The EVOLUTION trial was a randomized phase II trial of VCD, VRD and VCRD quadruplet therapy in both transplant-eligible and ineligible patients.(9) In contrast to findings from the IFM 2013–04 trial, there was no difference in response rates or one year PFS in the VRD or VCD groups. (9) Some institutional retrospective studies have demonstrated similar response rates and survival outcomes with VCD vs. VRD induction, while others have demonstrated that VRD induction is associated with deeper response and survival.(6, 10–12, 24) It is important to note that maintenance use was infrequent in studies reporting superior outcomes with VRD over VCD induction therapy. Uttervall *et al.* reported superior outcomes with VRD therapy, however, only 8% patients received maintenance in their cohort.(12) Chakraborty *et al.* observed that VRD induction may be associated with superior OS after controlling for baseline prognostic factors. However, only 20% of patients received maintenance therapy in that study(10), likely because the role of maintenance was not established in the era during which most patients were treated. Kumar *et al.* reported data from a randomized trial of 125 patients receiving VRD or VCD induction conducted in India.(27) The primary endpoint was VGPR rate after 4 cycles of treatment and there was a trend towards superiority in the VRD arm (61.5 vs 48.3%, p=0.09). CR rates were also higher in the VRD arm (35.4 vs 18.3, p<0.02). Survival data was not reported.

In this current study, VGPR or better response rates after induction were similar in the VRD and VCD cohorts. (65% vs 59%, p=0.11). Response rates in our study are comparable to prior reports where VRD induction has been associated with VGPR rates of 45% to 70%.(3, 4, 10, 28, 29) Similarly, VCD induction has been associated with VGPR rates of 40% to 61%.(5, 8–10, 24, 30) Patients with MM spend the longest therapeutic period in the maintenance phase. Therefore, it is not surprising to see that maintenance was more prognostic than choice of induction therapy. Our findings of greater impact of maintenance therapy over induction therapy are in line with previous reports. In a CIBMTR study evaluating impact of doublet or triplet novel induction regimens in patients undergoing transplant from 2008 to 2013, post-transplant maintenance was noted to have a greater impact on disease outcomes than doublet vs. triplet induction therapy.(31) Paquin *et al.* also reported that choice of induction therapy did not impact OS in patients with NDMM. (6) Prospective trials have demonstrated that maintenance therapy with lenalidomide is associated with improved PFS and OS in MM.(15) A recent long-term follow-up update of the STAMINA trial, a BMT CTN multicenter phase 3 trial, demonstrated inferior PFS in patients who discontinued lenalidomide maintenance at 38 months post-transplant, underlining the role of long-term continuous maintenance.(32) It is reassuring to see that VCD induction was not an independent predictor of inferior PFS in our study, likely due to the eventual transition to maintenance therapy in the majority of patients. Renal function improved in two-thirds of patients following induction therapy and lenalidomide-based therapy was most common maintenance therapy. We did not observe a difference in rates of maintenance based on recovery of renal function. Our findings are different from that seen in the FORTE trial, where the cohort of patients receiving KRD + transplant had superior outcomes compared to the group receiving KCD + transplant, including deeper response rates and better PFS.(33) There could be several reasons why our results differ from the FORTE trial, including (i) exclusion of patients in our study who had primary refractory

disease i.e those who did not achieve at least a partial response and (ii) inclusion of only fit, younger patients with normal renal function in the FORTE trial, whereas our 'real-world' study population included all patients, including those with impaired renal function.

At present, VRD induction remains the standard of care induction choice in patients with NDMM, and its role was further cemented with the findings from the ENDURANCE randomized clinical trial,(34) which demonstrated similar PFS in patients receiving VRD vs. KRD (carfilzomib, lenalidomide and dexamethasone) induction therapy, despite deeper responses in the KRD group. Daratumumab-based quadruplets are being investigated in clinical trials.(8, 35) It remains to be seen whether daratumumab-VRD will become a standard of care over VRD in the future based on long term follow-up data. Taken together with available evidence, our findings suggest that lenalidomide exposure is important in optimizing survival outcomes in NDMM. If patients are started on VCD therapy, maintenance therapy, typically lenalidomide based maintenance should be considered following transplant.

Our study has the advantage of comparing outcomes with VRD and VCD induction in large cohort of patients undergoing transplant in the current era. However, given the retrospective design, there are inherent limitations. We observed clear confounding differences between the two groups, with impaired renal function and lower rates of maintenance therapy being the most obvious differences. We attempted to account for these through multivariable analysis incorporating known prognostic variables. Our analysis was not intention to treat and patients who switched from initial VCD during inpatient hospitalization or initial cycle to VRD were analyzed in the VRD group. We excluded patients not achieving at least a partial response before transplant {4% of patients meeting other eligibility criteria (Supplementary data, consort flow diagram)}. However, it is impossible to know whether sub-optimal response in a particular treatment group excluded patients from proceeding to transplant in a timely manner since our data are limited to transplanted patients only and results of our study should be interpreted in that context.

In conclusion, we did not observe any difference in VGPR or better response rates with VRD or VCD induction therapy amongst patients who achieved at least a partial response and proceeded to stem cell transplant. In patients who proceed to stem cell transplant, the two regimens were found to have associated with comparable survival outcomes after adjusting for maintenance therapy and other known prognostic variables. Similar findings were observed in the subset of patients receiving full dose melphalan conditioning. Maintenance use was more important than the choice of bortezomib-based triplet induction in patients with MM undergoing upfront transplant. As the CIBMTR data does not capture patients who do not proceed to transplant, these results do not indicate the superiority or equivalence of one induction regimen over another for all newly diagnosed patients with MM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CIBMTR supports accessibility of research in accord with the National Institutes of Health (NIH) Data Sharing Policy and the National Cancer Institute (NCI) Cancer Moonshot Public Access and Data Sharing Policy. The CIBMTR only releases de-identified datasets that comply with all relevant global regulations regarding privacy and confidentiality.

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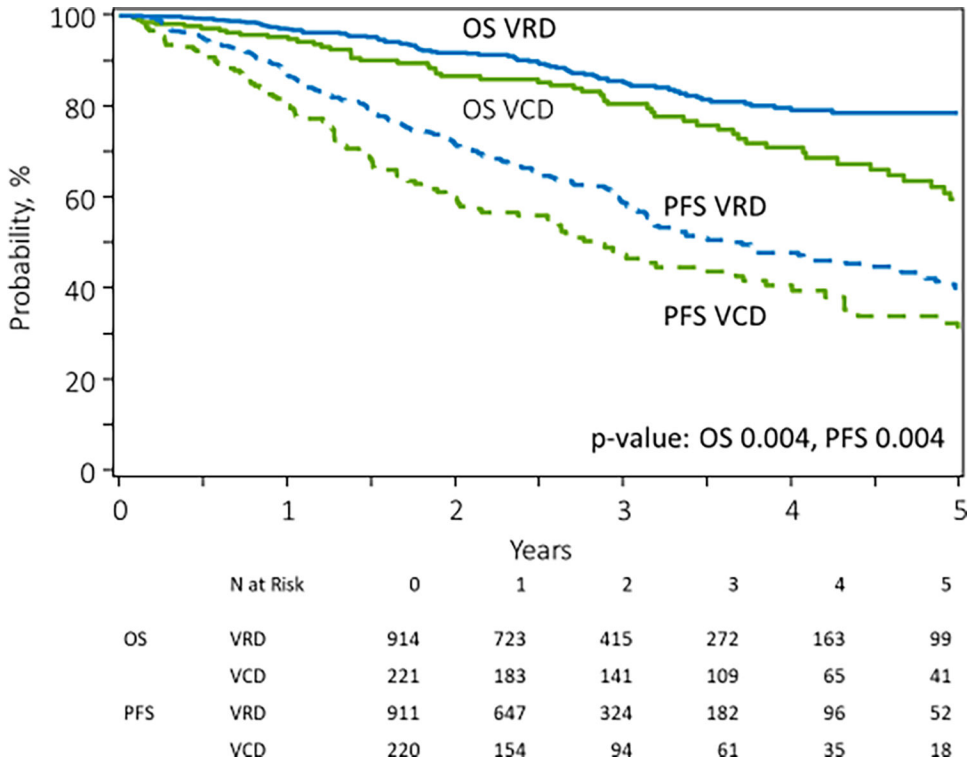

	N at Risk	0	1	2	3	4	5
OS	VRD	914	723	415	272	163	99
	VCD	221	183	141	109	65	41
PFS	VRD	911	647	324	182	96	52
	VCD	220	154	94	61	35	18

Figure 1:

Unadjusted progression free survival and overall survival in patients receiving VRD (N=914, 80.5%) vs VCD (N=221, 19.5%) induction therapy for newly diagnosed multiple myeloma.

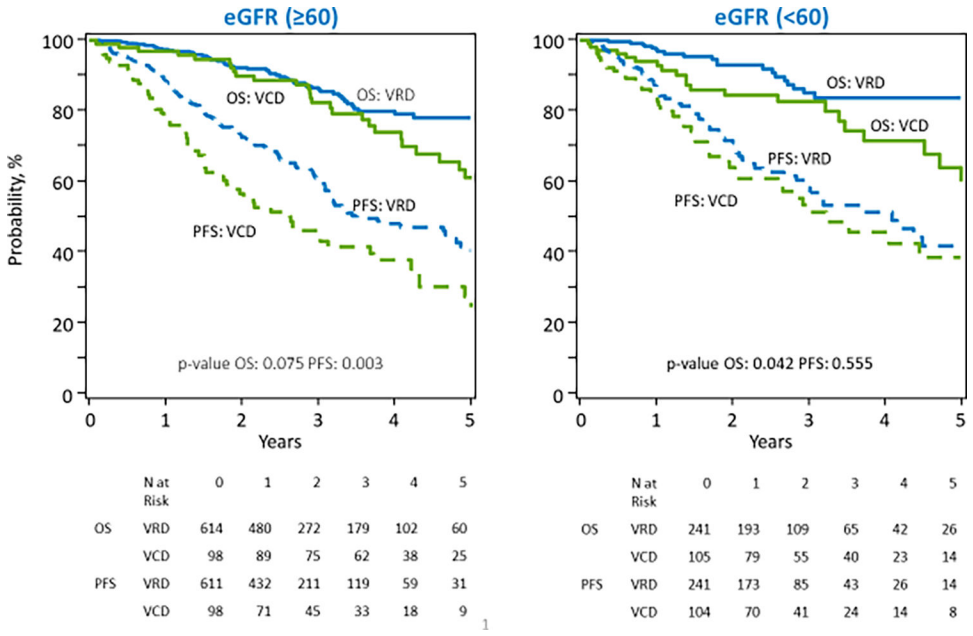

Figure 2:

Unadjusted progression free survival and overall survival in patients receiving VRD vs VCD induction therapy by eGFR at diagnosis for newly diagnosed multiple myeloma.

Table 1.

Patient and disease related characteristics in patients receiving VRD and VCD induction therapy before autologous transplant for newly diagnosed multiple myeloma

Variable	VRD(N=914; 80.5%) Median (range) or N (%)	VCD (N=221;19.5%) Median (range) or N (%)	P-value
Age, years	60 (30 – 82)	61 (32 – 79)	0.06
Sex, Male	503 (55)	119 (54)	0.75
Self-reported race			0.004
Caucasian	576 (63)	162 (73)	
African-American	278 (30)	41 (19)	
Other/Missing	60 (6)	18 (8)	
Karnofsky performance score, ≥90%	470 (51)	131 (59)	0.09
Renal adjusted HCT-CI Score #			0.74
0	279 (31)	77 (35)	
1	136 (15)	35 (16)	
2+	498 (55)	109 (49)	
International Staging System (ISS)			<0.001
I	296 (32)	49 (22)	
II	309 (34)	52 (24)	
III	158 (17)	76 (34)	
Missing	151 (17)	44(20)	
Cytogenetics	337 (37)	78 (35)	0.89
High-risk [t(4;14), t(14;16), t(14;20), del17p, +1q, HR2]			
Standard risk, including normal	544 (60)	134 (61)	
Missing/not done	33 (4)	9 (4)	
Myeloma subtype			0.07
IgG	515 (56)	106 (48)	
IgA	210 (23)	52 (24)	
Light chain myeloma	172 (19)	60 (27)	
Non-secretory/other	17 (2)	3 (1)	
eGFR at diagnosis, <60 mL/min/1.73m^2: ##	241 (26)	105 (48)	<0.001
Serum creatinine at diagnosis, ≥ 2 mg/dl	74 (8)	64 (29)	<0.001
eGFR prior to HCT, < 60 mL/min/1.73m^2 ##	78 (9)	67 (30)	<0.001
Serum creatinine prior to transplant, ≥ 2 mg/dl	14 (2)	26 (12)	<0.001
Pre-transplant response			0.21

Variable	VRD(N=914; 80.5%) Median (range) or N (%)	VCD (N=221;19.5%) Median (range) or N (%)	P-value
CR	152 (17)	38 (17)	
VGPR	438 (48)	92 (42)	
PR	324 (35)	91 (41)	
Pre-transplant response, ≥ VGPR	590 (65)	130 (59)	0.11

Table Abbreviations: CR: complete response, eGFR: estimated glomerular filtration rate, PR: partial response, VCD: bortezomib, cyclophosphamide and dexamethasone, VGPR: very good partial response, VRD: bortezomib, lenalidomide and dexamethasone.

[#]Renal HCT-CI score missing in one patient in the VRD group.

[##]eGFR at diagnosis missing in 59 patients (6%) in VRD group and 18 (8%) in VCD group. eGFR prior to HCT missing in 1 patient in VRD group (0%) and 3 patients in VCD group. Therefore numbers do not add to 100%.

Table 2:

Transplant and maintenance in patients receiving VRD and VCD induction therapy before autologous transplant for newly diagnosed multiple myeloma

Variable	VRD(N=914, 80.5%) Median (range) or N (%)	VCD (N=221,19.5%) Median (range) or N (%)	P-value
Conditioning melphalan dose, 200 mg/m2	732 (80)	152 (69)	<0.001
Post-transplant response (day 100)##			0.07
CR	404 (45)	81 (38)	
VGPR	277 (31)	85 (39)	
PR	181 (20)	38 (18)	
SD or worse	40 (5)	12 (6)	
Post-transplant response, ≥ VGPR	681(76)	166 (77)	0.68
Best response to transplant##			0.07
CR	571 (63)	125 (57)	
VGPR	213 (23)	70 (32)	
PR	101 (11)	21 (10)	
SD or worse	26 (3)	4 (2)	
Best response, ≥ VGPR	784 (86)	195 (89)	0.31
Maintenance Therapy, Yes	806 (88)	169 (76)	<0.001
Maintenance Regimen#			<0.001
Lenalidomide based (+/−bortezomib)	732 (80)	139 (63)	
Bortezomib (+/− other)	50 (5)	25 (11)	
Other (including carfilzomib)	24 (3)	4 (1)	
None	108 (12)	52 (24)	
Response to Maintenance###			0.46
CR	455 (60)	84 (54)	
VGPR	166 (22)	40 (25)	
PR	73 (10)	15 (10)	
SD or worse	59 (8)	16 (11)	

Table Abbreviations: CR: complete response, PR: partial response, SD: stable disease, VCD: bortezomib, cyclophosphamide and dexamethasone, VGPR: very good partial response, VRD: bortezomib, lenalidomide and dexamethasone.

Data missing for one patient in the VCD group

Missing response (best response: 4 patients, day 100 response: 17patients, maintenance response: 67 patients)

Not applicable (no maintenance): 160 patients

Table 3:

Renal Function Recovery Kinetics (Renal recovery is defined as improvement in eGFR at diagnosis from < 60 ml/min to > = 60 ml/min at pre-transplant)

	VRD N=845 N (%)	**VCD N=195 N (%)**	**Overall N=1040 N (%)**
Diagnosis eGFR ≥ 60 ml/min and pre-transplant eGFR ≥ 60 ml/min (Normal Renal Function)	604 (71.5%)	92 (47%)	696 (67%)
Diagnosis eGFR < 60 ml/min and pre-transplant eGFR ≥ 60 ml/min (**Recovered Renal Function**)	178 (21%)	44 (23%)	222 (21%)
Diagnosis eGFR < 60 ml/min and pre-transplant eGFR < 60 ml/min (**Non-recovered Renal Function**)	63 (7.5%)	59 (30%)	122 (12%)

Table Abbreviations: eGFR: Estimated glomerular filtration rate

Table 4.

Univariate survival outcomes in patients receiving VCD and VRD induction. Probabilities with 95% confidence intervals are shown

	VRD, (n=914;80.5%)	VCD, (n=221; 19.5%)	p-value
PFS (%)			0.004
2-year	72 (68–75)	60 (53–67)	0.004
5-year	40 (34–46)	32 (24–41)	0.152
OS (%)			0.004
2-year	92 (90–94)	87 (81–91)	0.056
5-year	79 (74–83)	60 (50–69)	<0.001

Table Abbreviations: OS: overall survival, PFS: progression free survival, VCD: bortezomib, cyclophosphamide and dexamethasone VRD: bortezomib, lenalidomide and dexamethasone.

Multi-variate Z test based on the pointwise estimates and standard errors was used to calculate P-value at each timepoint. Overall P-value for PFS and OS calculated using Log Rank Test

Table 5.

Univariate survival outcomes in patients receiving VCD and VRD induction, stratified by eGFR. Probabilities with 95% confidence intervals are shown

	VRD, eGFR≥60 (n=614)	VRD, eGFR<60 (n=241)	VCD, eGFR≥60 (n=98)	VCD, eGFR<60 (n=105)	p-value
PFS (%)					0.021
2-year	73 (68–77)	71 (64–78)	57 (46–67)	64 (53–74)	0.033
5-year	41 (33–48)	39 (27–51)	28 (17–40)	39 (25–53)	0.342
OS (%)					0.053
2-year	92 (89–95)	93 (89–96)	90 (83–95)	85 (76–92)	0.250
5-year	78 (72–84)	84 (76–90)	61 (48–73)	60 (44–75)	0.003

Table Abbreviations: OS: overall survival, PFS: progression free survival, VCD: bortezomib, cyclophosphamide and dexamethasone VRD: bortezomib, lenalidomide and dexamethasone.

Table 6.

Multivariate analysis of survival outcomes in patients receiving VRD and VCD induction therapy. Hazard ratios with 95% confidence intervals are shown

Outcomes	N	HR (95% CI)	P-value
Progression free survival			
Induction Therapy			0.13
VRD	852	Reference	
VCD	202	1.20 (0.95–1.53)	0.13
ISS Stage at Diagnosis			0.001
Stage I	330	Reference	
Stage II	346	1.20 (0.90–1.59)	0.22
Stage III	220	1.81 (1.34–2.46)	<0.001
Missing	158	1.41 (1.00–1.97)	0.047
Cytogenetics			<0.001
No Abnormality	180	Reference	
High Risk	393	1.45 (1.07–1.99)	0.02
Standard Risk	447	0.87 (0.64–1.18)	0.36
Missing	34	1.44 (0.86–2.42)	0.17
Disease Status Prior to Transplant			<0.001
sCR/CR	175	Reference	
VGPR	499	1.23 (0.88–1.73)	0.23
PR	380	1.79 (1.28–2.51)	0.001
Maintenance Therapy			<0.001
Yes	904	Reference	
No	150	1.74 (1.33–2.28)	<0.001
Overall survival			
Induction Therapy			0.13
VRD	852	Reference	
VCD	202	1.33 (0.92–1.9)	0.13
ISS Stage at Diagnosis			0.002
Stage I	330	Reference	
Stage II	346	1.31 (0.80–2.14)	0.29
Stage III	220	2.25 (1.36–3.72)	0.002
Missing	158	2.26 (1.31–3.89)	0.003
Cytogenetics			<0.001
No Abnormality	180	Reference	
High Risk	393	2.21 (1.33–3.66)	0.002
Standard Risk	447	0.80 (0.46–1.40)	0.44
Missing	34	2.01 (0.94–4.27)	0.07
Disease Status Prior to Transplant			0.053

Outcomes	N	HR (95% CI)	P-value
sCR/CR	175	Reference	
VGPR	499	1.12 (0.65–1.93)	0.68
PR	380	1.66 (0.97–2.84)	0.06
Maintenance Therapy			<0.001
Yes	904	Reference	
No	150	2.28 (1.53–3.38)	<0.001

The following covariates were considered in the multivariate models: induction regimen (main effect), age, sex, race, performance score, hematopoietic cell transplant-comorbidity index (HCT-CI), estimated glomerular filtration rate (eGFR) at diagnosis, immunoglobulin subtype, cytogenetics, ISS stage, response status at transplant, melphalan dose, and maintenance therapy. A step wise approach was used to narrow down the variables in the model

Table Abbreviations: CI: confidence interval, CR: complete response, HR: hazard ratio, PR: partial response, sCR: stringent complete response, VCD: bortezomib, cyclophosphamide and dexamethasone, VGPR: very good partial response, VRD: bortezomib, lenalidomide and dexamethasone.

Table 7:

Multivariate analysis in subgroup of patients receiving full dose melphalan conditioning, 200 mg/m^2 (N=821)

Outcomes	N	HR (95% CI)	p-value
Progression Free Survival			
Induction therapy			0.19
VRD	682	Reference	
VCD	139	1.20 (0.91–1.57)	0.19
ISS stage at diagnosis			0.001
Stage I	268	Reference	
Stage II	278	1.20 (0.88–1.64)	0.26
Stage III	152	1.93 (1.38–2.70)	<0.001
Missing	123	1.40 (0.97–2.03)	0.08
Cytogenetics			0.0541
No Abnormality	147	Reference	
High risk	313	1.31 (0.93–1.85)	0.12
Standard risk	334	0.92 (0.66–1.30)	0.65
Test not done/ Unknown	27	1.37 (0.78–2.39)	0.27
Disease status prior to transplant			0.001
sCR/CR	140	Reference	
VGPR	384	1.43 (0.97–2.09)	0.07
PR	297	1.99 (1.36–2.92)	<0.001
Maintenance therapy			0.001
Yes	702	Reference	
No	119	1.66 (1.23–2.22)	0.001
Overall Survival			
Induction therapy			0.32
VRD	682	Reference	
VCD	139	1.24 (0.81–1.88)	0.32
ISS Stage at diagnosis			0.006
Stage I	268	Reference	
Stage II	278	1.20 (0.69–2.09)	0.53
Stage III	152	2.34 (1.33–4.10)	0.003
Missing	123	2.09 (1.12–3.90)	0.02
Cytogenetics			0.001
No Abnormality	147	Reference	
High risk	313	2.45 (1.34–4.48)	0.004
Standard risk	334	1.05 (0.55–1.99)	0.89
Test not done/ Unknown	27	1.96 (0.82–4.65)	0.13
Disease status prior to transplant			0.009

Outcomes	N	HR (95% CI)	p-value
sCR/CR	140	Reference	
VGPR	384	1.54 (0.78–3.01)	0.21
PR	297	2.46 (1.27–4.78)	0.008
Maintenance therapy			<0.001
Yes	702	Reference	
No	119	2.44 (1.58–3.77)	<0.001

The following covariates were considered in the multivariate models: induction regimen (main effect), age, sex, race, performance score, hematopoietic cell transplant-comorbidity index (HCT-CI), estimated glomerular filtration rate (eGFR) at diagnosis, immunoglobulin subtype, cytogenetics, ISS stage, response status at transplant and maintenance therapy. A step wise approach was used to narrow down the variables in the model

Table Abbreviations: CI: confidence interval, CR: complete response, HR: hazard ratio, PR: partial response, sCR: stringent complete response, VCD: bortezomib, cyclophosphamide and dexamethasone, VGPR: very good partial response, VRD: bortezomib, lenalidomide and dexamethasone.