Observational Study

Disease biology alters the response to frontline bortezomib, lenalidomide and dexamethasone in Multiple Myeloma

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Abstract

Background: Achievement of the best initial response to induction regimen in multiple myeloma is a prognostic factor for disease outcome. The triplet regimen bortezomib, lenalidomide, and dexamethasone, VRd, is the preferred induction regimen in newly diagnosed Multiple Myeloma (MM) due to its favorable impact on overall survival. However, recent studies showed a deeper response and superior progression-free survival with quadruplet regimen, daratumumab-VRd, when compared to VRd. Yet, the quadruplet regimen also comes with additional toxicities. Balancing efficacy and toxicity in selecting an induction regimen is a challenge due to advanced age and comorbidities in the multiple myeloma population.

The purpose of this study is to identify biological markers that could potentially affect the response rate to upfront VRd.

Patients and methods: For this cross-sectional study, we included patients with MM treated with frontline VRd starting April 2011 through May 2018. We analyzed the correlation between patient demographics, disease biology, disease burden and stage at diagnosis, and response to therapy.

Results: After four cycles of VRd, we analyzed the response rate on 120 subjects. The overall response rates to VRd were 50% of patients achieved Very Good Partial Response (VGPR) or better, 43% achieved Partial Response (PR), 5% did not respond to treatment. We showed a statistically significant difference in treatment outcomes between myeloma subtypes particularly involved immunoglobulin, IgA, and IgG myeloma. We report an increased incidence of VGPR or better in IgA myeloma (79%) as compared to IgG myeloma (37%) (P-Value < 0.0006).

Conclusion: We conclude that IgG subtype multiple myeloma is associated with a suboptimal response to frontline VRd.

Abbreviations

MM: Multiple Myeloma; VRd: Velcade Revlimid and dexamethasone; CR: Complete Remission; VGPR: Very Good Partial Response; PR: Partial Remission

Introduction

Multiple Myeloma (MM) is a heterogeneous incurable disease. While majorities of patients have indolent courses with good response to upfront induction, some patients progress rapidly despite treatment. No consistent correlation between the intensity of therapy and long-term disease outcome currently exists [1]. Complete response has been demonstrated to strongly correlate with improved progression-free survival [2,3].

Despite identifying multiple prognostic markers in multiple myeloma, which include tumor burden (stage), performance status and tolerability to anti-myeloma therapy (fitness), the aggressiveness of disease (biology), and susceptibility of neoplastic plasma cells to anti-myeloma agents (responsiveness) [4], there is no predictor-guided algorithm...
that can be utilized in selecting regimens to achieve the best response.

Current standard initial therapy for patients with MM depends on the cytogenetic risk of disease [5,6] and eligibility for Autologous Stem Cell Transplantation (ASCT) [7]. However, there is no general agreement as to the standard induction regimen.

A three-drug regimen has been demonstrated to be more effective as compared to doublet regimens. The addition of bortezomib to lenalidomide and dexamethasone (VRD) as compared to lenalidomide and dexamethasone (Rd) in the SWOG S0777 trial resulted in significantly improved Progression-Free Survival (PFS) and Overall Survival (OS) [8]. Approximately 525 patients were included in phase 3 multicenter study; they were randomly assigned to VRd or lenalidomide and dexamethasone (Rd) only. VRd resulted in higher rates of overall response (82 versus 72 %) [8,9]. Moreover, VRd continues to represent an appropriate standard of care based on the longer-term follow-up data [8].

Similarly, the risk of disease progression or death was significantly lower with daratumumab plus lenalidomide and dexamethasone than lenalidomide and dexamethasone alone [10]. Herein, three-drug regimens are the mainstay of initial therapy for MM while two-drug regimens may still be of importance in frail patients who may not tolerate standard three-drug regimens [11].

Over the last 20 years, several new agents, such as Immunomodulatory agents (IMiDs), Proteasome Inhibitors (PIs), monoclonal Antibodies (mAbs), have been FDA-approved. These agents have been incorporated into clinical guidelines and have transformed our approach to the treatment of MM patients [12].

Additional frontline regimens for MM include daratumumab, lenalidomide, Dexamethasone (DRd) [10], bortezomib, Cyclophosphamide, Dexamethasone (CyBorD) [13] and carfilzomib, lenalidomide, dexamethasone (KRd) [14]; have demonstrated tolerability and efficacy with significant improvement in overall response rates [9,10,13,14]. In addition, when comparing VRd to KRd at the Endurance E1A11 trial, it showed similar PFS and OS [14]. VRd remains to be the preferred regimen given the potential overall survival benefit and lower toxicity profile [8,9].

More recently, the benefit of adding a fourth drug is being evaluated in several clinical trials. The phase 2 trial (GRIFFIN) randomized 207 patients to VRd with or without daratumumab (D–VRd versus VRd). It showed that D–VRd resulted in a higher overall response rate (99 versus 92 percent) and deeper response (63% reached stringent Complete Remission (sCR) and CR). However, toxicity was greater with D–VRd with higher rates of neutropenia and upper respiratory tract infections [15].

The association between depth of response and the long-term outcome remains a debated topic in MM, however, the relationship between a complete response and progression-free survival has been more consistent [16]. A significant correlation between the achievement of Complete Response (CR) or Very Good Partial Response (VGPR) and improved PFS, and thus OS has been demonstrated in eight out of ten studies included in a meta-analysis [3].

Additionally, the achievement of response less than a Very Good Partial Response (VGPR) after initial induction is an adverse prognostic factor for Progression-Free Survival (PFS) in MM [2]. Therefore, achieving CR or VGPR is a valid surrogate marker of the treatment efficacy [2].

While debating between three-drug regimens versus four-drug regimens aiming to achieve the deepest response to induction regimen for newly diagnosed MM, balancing efficacy and toxicity is a challenge due to advanced age and comorbidities associated with the myeloma population.

Biomarkers that can guide the selection of frontline therapy based on prediction for efficacy would be clinically useful in determining the best approach to achieve maximal benefit in an individualized approach rather than a trial-and-error approach.

In this study, we hypothesized that a selective subgroup of patients with newly diagnosed MM, which share common biological markers, may not benefit from frontline treatment with VRd.

Material and methods

Study aims

Based on previous studies demonstrating the best initial response to be strongly correlated with survival outcomes [2,3,16], this study aims at evaluating the initial response rate to 3–6 cycles of frontline VRd as a surrogate marker for treatment efficacy. Additionally, we aimed to evaluate whether disease burden, biology, or presenting clinical picture impact response to VRd.

The primary outcome of this study was to identify if certain characteristics of myeloma are associated with higher or lower initial response rates to VRd. Results from our study may become a future platform in selecting an induction regimen through a personalized approach.

Study design

This is a cross-sectional study including participants with newly diagnosed MM. Participants were selected from the cohort of patients with newly diagnosed MM treated in our institution from April 2011 until May 2018, and, followed for at least the first 6 months after initiation of therapy.

We classified our cohort according to response to therapy [17] into 3 groups: participants who achieved a) Complete Response (CR) or Very Good Partial Response (VGPR) b) Partial Response (PR) c) less than partial response (<PR) or progression of the disease.

To measure the effect of disease burden, biology, and patients’ fitness on the responsiveness to therapy, we identified
several variables that could potentially affect response to therapy and analyzed the correlation between different variables and response to therapy.

We classified our cohort based on gender, age at diagnosis, stage of disease [5], disease biology in terms of Free Light Chain analysis (FLC), and immunofixation (IgG, IgA, or IgM monoclonality). We also classified our patients by their risk strata using Fluorescence in Situ Hybridization (FISH) and cytogenetics (standard versus high risk) [5].

Disease burden defined as the percent of bone marrow involvement with malignant plasma cells. CRAB criteria, hypercalcemia defined as serum calcium >11 mg/dL, renal insufficiency defined as serum creatinine >2 mg/dL, anemia defined as hemoglobin level < 10 g/dl, presence of bone lesions defined as one or more osteolytic lesions ≥5 mm in size by PET–CT or MRI, and the presence or absence of extramedullary disease.

For response assessment, we use the International Myeloma Working Group (IMWG) response definition [17]. For MM staging, we used the International Staging System [18,19]. Our Institutional Review Board (IRB) approved the research protocol.

Selection of participants

This observational study included participants with newly diagnosed MM who were 18 years or older and eligible for treatment with a bortezomib–based regimen (VRd or Vd) in the frontline setting. Participants had an Eastern Cooperative Oncology Group (ECOG) 0–2 at the time of diagnosis, and no evidence of organ dysfunctions unrelated to MM such as cardiac, hepatic, pulmonary, and/or central nervous system dysfunction.

We excluded patients who had evidence of other malignancies that required active treatment.

VRd regimen followed the SWOG-S0777 study protocol [9] was given as 21–day cycle. Bortezomib was given at 1.3 mg/m² intravenously on days 1, 4, 8, and 11, combined with oral lenalidomide 25 mg daily on days 1–14 plus oral dexamethasone given as either (20 mg daily on days 1, 4, 5, 8, 9, 11, and 12) or (40 mg weekly) [9]. All participants received 3–6 cycles of therapy. The standard protocol for dosage adjustments for toxicity was utilized [9].

Statistical analysis

Data were analyzed using Statistical Analysis Software (SAS) 9.4.

Among the cohort of patients treated in our institution at the selected period, we included in our analysis only the patients who received the bortezomib–based regimen, and the cohort who received VRd for at least 3–6 cycles.

Data collected included age at diagnosis, gender, presence of CRAB at the initial presentation, presence of extramedullary disease at the time of diagnosis, ISS stage, and percent of bone marrow involvement at diagnosis, albumin level at diagnosis, FLC restriction, FLC ratio, and risk classification for each participant.

We classified our cohort based on response status into three groups (responders, partial responders, and non-responders). We analyzed the correlation between each different variable and response status. For categorical dichotomous variables, we used Chi-Square (Fisher’s Exact) test. For continuous variables, we used logistic regression analysis model.

A subgroup analysis was performed on the subgroup of patients who showed a significant difference in response to therapy.

Results

Patients’ characteristics

Starting April 2011 through May 2018, 175 patients were treated in our institution for newly diagnosed MM. A hundred and twenty patients received bortezomib–based regimen, 80% (96 subjects) received VRd and 20% (24 subjects) received Vd due to intolerance and fragility. All participants included in this study were able to finish 3–6 cycles of VRd.

The median age at diagnosis was 60.5 (ranging from 39–73 years), 62% of participants were males and 38% were females. Thirty–seven percent were lambda restricted and 63% were kappa restricted. The majority of our cohort had IgA or IgG monoclonality on immunofixation, 31% were IgA and 68% were IgG. 41% had > 60% bone marrow involvement by malignant plasma cells. Response to therapy evaluated after the third cycle for all patients with 50% achieved VGPR or better, 45% achieved PR, and five patients had disease progression (Table 1).

Analysis of VRd treated cohort

We had 96 subjects who received at least 3 cycles of frontline VRd. Thirty–six subjects had high–risk disease and 45 had standard risk with missing risk strata on 15 subjects. In regards to response assessment, 50% (48 of 96 subjects) were responders, 45% (43 of 96 subjects) were partial–responders and 5% were non–responders.

When analyzing response status by gender in our VRd treated cohort, the 96 subjects were 36 females and 60 males. Despite having a numerically higher response rate in females with 56% responders, it was not statistically significant (P-value 0.31).

In addition, there was no statistically significant difference in the mean age at diagnosis among the three outcomes (P-value 0.114).

Analyzing disease biology and its correlation with response to VRd, we showed that neither FLC restriction (Kappa or lambda) nor the FLC ratio (involved /uninvolved FLC) showed a statistically significant difference in the response to VRd (P-value 0.88 and 0.81 respectively). Molecular risk of disease also failed to show a difference in response to VRd (p-value =0.52).
partial-responders were in the IgG group, and all five non-responders in the VRd cohort were IgG subtypes (Table 2).

### Subgroup analysis

An unplanned subgroup analysis was performed on the IgG and IgA group to analyze the correlation between risk stratification and response outcomes in those subgroups. We also analyzed the correlation between FLC restriction and the presence of bone lesions at the time of diagnosis. We selected to do subgroup analysis for those variables due to a discordance of prevalence in the study cohort, the majority of our cohort had osteolytic bone lesions at diagnosis and about two-thirds had kappa restriction.

Among subjects with IgG type myeloma, neither risk of disease (P-value = 0.52), FLC restriction (P-value = 1.0), nor presence of osteolytic bone lesions at diagnosis (P-value = 0.51) correlated with treatment response.

Additionally, in the IgA type myeloma, our data did not show a statistically significant difference between risk strata, FLC restriction, or osteolytic lesions at diagnosis and treatment outcomes (P-values = 1.0, 1.0, and 0.56 respectively).

Other variables including disease burden, percent of bone marrow involvement with malignant plasma cells, presence of CRAB criteria at diagnosis, presence of extramedullary disease, and ISS stage failed to show a statistically significant correlation with treatment outcomes.

In conclusion, our results showed an association between immunoglobulin monoclonality in MM and initial response to VRd. IgG type myeloma showed to have a less optimal response to frontline VRd, characterized by a higher rate of partial response and a lower rate of VGPR or CR in comparison to IgA myeloma patients.

### Discussion

Multiple myeloma is an incurable disease [20,21], achieving complete response is the goal of therapy as it correlates with improved overall survival and progression-free survival [2,3,16]. VRd is the preferred frontline induction regimen to date due to its tolerability and its ability to induce a deep response in patients with newly diagnosed MM regardless

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**Table 1: Patient characteristics.**

| Variable | Level | N = 96 | % |
|----------|-------|--------|---|
| Age at diagnosis | Mean | 59.69 | - |
| | Median | 60.45 | - |
| | Minimum | 39.33 | - |
| | Maximum | 73.50 | - |
| Sex | Female | 36 | 38 |
| | Male | 60 | 62 |
| Hypercalcemia (Serum calcium ≥ 11 mg/dL at diagnosis) | Yes | 14 | 16 |
| | No | 74 | 74 |
| Anemia (Hemoglobin < 10 at diagnosis) | Yes | 25 | 27 |
| | No | 68 | 73 |
| Osteolytic bone lesions at diagnosis | Yes | 70 | 75 |
| | No | 23 | 25 |
| Extra medullary disease (including plasma cell leukemia) | Yes | 22 | 24 |
| | No | 71 | 76 |
| Bone marrow involvement with malignant plasma cell > 60% | Yes | 41 | 45 |
| | No | 51 | 55 |
| Albumin level ≥ 3.5 | Yes | 45 | 57 |
| | No | 34 | 43 |
| Stage | ISS III | 10 | 19 |
| | ISS I or II | 43 | 81 |
| Immunoglobulins | IgA | 29 | 31 |
| | IgD | 1 | 1 |
| | IgG | 63 | 68 |
| | IgM | 0 | 0 |
| | Missing | 3 | - |
| Free Light Chain (FLC) Restriction | Yes | 27 | 33 |
| | No | 54 | 67 |
| FLC Ratio >100 | Yes | 15 | - |
| | No | 36 | 44 |
| Risk stratification | High | 36 | 44 |
| | Standard | 45 | 56 |
| | Missing | 15 | - |
| Response to VRd after Cycle 3 | CR or VGPR | 48 | 50 |
| | PR | 43 | 45 |
| | Disease progression | 5 | 5 |

*ISS: International Staging System; *VRd: bortezomib, lenalidomide and dexamethasone; *CR: Complete Response; *PR: Partial Response; *VGPR: Very Good Partial Response

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**Table 2: Response Status by Immunoglobulin classification among VRd treated cohort.**

| Immunoglobulin (lg) Status | CR or VGPR | Partial Response | Disease progression | Total |
|----------------------------|-------------|-------------------|---------------------|-------|
| IgA                        | 23 (79%)    | 6 (21%)           | 0                   | 29 (31%) |
| IgD                        | 1 (100%)    | 0                 | 1 (100%)            | 1 (100%) |
| IgG                        | 23 (37%)    | 35 (56%)          | 8 (13%)             | 66 (68%) |
| IgM                        | -           | -                 | -                   | -     |
| Total                      | 47 (51%)    | 41 (44%)          | 5 (5%)              | 93    |

Chi Square (Fisher’s Exact) P-value 0.0006

*CR: Complete Response; *VGPR: Very Good Partial Response; *VRd: Bortezomib, lenalidomide and dexamethasone

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of if followed by autologous stem cell transplantation or not (9,23). We studied several factors that might affect the initial response to VRd. We summarized potential factors into patient demographics, disease burden at diagnosis, disease stage, and biology.

The main finding, we report from this cross-sectional study is that disease biology in regards to immunoglobulin monoclonality (heavy chain subtypes) has a statistically significant association with response outcomes.

Although the impact of serum immunofixation was addressed in previous retrospective studies and did not show an association with disease outcomes [23–25], IgD myeloma was associated with worse outcomes due to a higher incidence of renal insufficiency [26]. In a large multicenter retrospective study, which addressed the same question of the effect of paraprotein on myeloma outcomes, no difference was observed between IgA and IgD in overall survival. However, it showed a shorter PFS for IgA type myeloma. [24] This study concluded that worse PFS was contributed to renal insufficiency and specifically higher levels of FLC excretion, which was more prominent in the IgA group. Their data showed that patients with IgD or IgA subtype with the same level of urinary FLC excretion had the same incidence of renal failure and poor survival.

We are reporting a different outcome, IgG paraprotein is associated with suboptimal response to frontline using VRd, but showed no significant difference when we stratified subjects based on FLC type in our subgroup analysis.

Our study implicates that the immunoglobulin subtype of myeloma could be another factor that needs to be taken into account as we select a preferred regimen for optimal response. Quadruplet regimen with targeted monoclonal antibodies in combination with VRd as frontline therapy in newly diagnosed multiple myeloma is superior to VRd in Overall Response Rate (ORR) and PFS, however, it may carry a higher toxicity [15,27]. Whether an upfront quadruplet regimen would provide a better response rate in the IgG subgroup as compared to triplet VRd is not known. While balancing benefits and toxicities in selecting therapeutic regimens for patients with multiple myeloma is crucial, further confirmation of our findings is critical. A subgroup analysis using the previous study to analyze the outcome in IgG and IgA myeloma, using frontline D–VRd versus VRd, or a future large randomized prospective study comparing the response to D–VRd versus VRd based on immunoglobulin subtype of multiple myeloma could help validate our findings. Our data could also potentially affect how we stratify therapeutic regimens in various individuals, preferring quadruplet regimen to VRd with IgG type MM, especially if it is in the context of molecularly high-risk disease.

There are certain limitations to our study. The small sample size in the VRd- treated cohort limits our conclusion; perhaps a more collaborative effort with additional institutions to increase our sample size would strengthen the validity of our results.

Designing the study as a cross-sectional retrospective study limits our results. Although we could evaluate the association between immunoglobulin monoclonality and treatment outcomes, we are unable to state a causal relationship between IgG type MM and poor response to frontline VRd.

We achieved the primary aim of our study which is IgG subgroup of MM patients was associated with lower response rates to frontline VRd. Our data raises awareness of the importance of disease characteristics and biology in treatment response. As we aim at personalized medicine and designing individualized treatment algorithms in MM, future studies evaluating the efficacy of various treatment regimens for MM should always incorporate disease characteristics and biology as one the important parameters in the analysis.

Conclusion

We conclude that IgG type MM was associated with suboptimal response to frontline VRd. Our limited single institutional study suggests that immunoglobulin monoclonality could be an important parameter to be considered as we stratify therapeutic regimens in multiple myeloma. Further studies would help confirm our finding. MM remains an incurable disease and a disease that occurs in older individuals who commonly carry underlying comorbidities, being able to balance treatment-related benefits and risks is crucial. Our findings could be important as we aim towards personalized medicine.

Disclosure

The data that support the findings of this study are available from the corresponding author upon reasonable request.

The research protocol has been reviewed and approved by the University of Oklahoma Health Sciences Center institutional review board (OUHSC-IRB # 11793).

Informed consent was obtained from all study participants to permit them to use their data for research purposes.

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