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Research Article

Multiple Myeloma Boretzomibe-Thalidomide-Dexamethasone Treatment Comparison with other Regimens: A systematic Review

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Abstract

Among hematologic cancers, multiple myeloma (MM) is the second most prevalent type. Proteasome inhibitors (PIs) and other immunomodulatory medications have significantly improved the prognosis for patients with recently diagnosed multiple myeloma (NDMM). Our research strives to offer a comprehensive examination of the literature. Regardless of whether the patients were transplant candidates, our goal was to assess the effectiveness of the VRd regimen in the treatment of patients with recently diagnosed multiple myeloma. A thorough investigation of Pubmed, Embase, the Wiley Cochrane Library, Scopus, Web of Science, CINAHL, and ClinicalTrials.gov MM. The period of the searches ended in April 2023. Only 25 studies were discovered to be relevant to our research question out of the 1139 publications that the literature search yielded. After reading the whole texts of these papers, another 17 publications were disregarded due to the following factors: review article, unavailable full text, duplicate study, absence of requisite efficacy and safety outcomes, or observational study. A systematic literature review was only deemed appropriate for eight investigations.

The eight articles had 2532 patients in total, including the RRMM and NDMM groups. The studies assessed and compared the efficiency of the drugs, such as bortezomib-lenalomide-dexamethasone (VRd) bortezomib-lenalodomide-dexamethasone-daratumumab (D-RVd), carfilzomide-lenalodimed-dexamethasone (KRd), and bortezomib-thalidomide-dexamethasone-daratumumab (D-VTd), ixazomibe-cyclophosphamide-dexamethasone (ICd), daratumumab-bortezomib-cyclophosphamide-dexamethasone (D-VCd). A total of (242 + 235) 477 people received the VRd regimen in the two trials that used it. PFS (progression-free survival), HR (hazard ratio), 0.73(0.58-0.92), 95% CI, p = 0.007. Survival rate overall (OS): HR 95% CI 0.74(0.55-1.00), p = 0.048. One trial was the only one that largely utilized a KRd regimen. 545 patients received this treatment regimen in total, with 95% HR, CI 1.04(0.83-1.31) for PFS, p = 0.74; p = 0.92; CI = 0.98(0.71-1.36); and 95% HR for OS.

Phase 1 and 2 clinical trials were conducted on two ICd regimens. These regimens were given to 48,70 patients in total, and neither trial was able to attain OS for the full research. Not assessed (NE), PFS, HR, and OS HR 95% CI. The phase 3-trial of the +_D-VTd regimen included a total of (542+543=1085) patients, but the target PFS and OS were not met. A total of 70 individuals received the D-VCd regimen in a phase 2 clinical trial. PFS was 23.5 months, and OS was NE for the duration of the research, according to the findings. The phase 2 clinical trial for the D-RVd regimen included 207 patients in total, but neither the PFS nor OS objectives for the entire study were met. This systematic literature review indicated that, VRd regimen associated with significantly improved OS, PFS, and ORR, compared with other regimens trials.

Keywords: *Multiple Myeloma, treatment, bortezomibe, clinical trials, NDMM, PRMM*

Introduction

Multiple myeloma (MM), which makes up roughly 1% of all cancers and is the second most prevalent hematologic malignancy, is defined by the monoclonal proliferation of plasma cells in the bone marrow [1]. Recent improvements in therapy regimens and a deeper comprehension of illness pathogenesis have resulted in a notable improvement in patient outcomes. However, there is evidence of an increase in the incidence of MM, which may be due, among other factors, to better identification as well as an increase in the aging population [2].

According to recently published data, 10% of MM cases and 33% of MM cases in patients over the age of 75 have MM [3]. Treatment-related side effects, particularly in senior patients, frequently result in dose adjustments and pauses, which may reduce the sustained response required for long-term remission and better quality of life [4]. The prognosis of patients with genetically high-risk diseases, such as del (17p), t(4;14), t(14;16), t(14;20), gain 1q, or p53 mutations, are worse in both newly diagnosed multiple myeloma (NDMM) and relapsed and refractory multiple myeloma (RRMM) [5].

Since the introduction of proteasome inhibitors (PIs) and other immunomodulatory medications, outcomes in individuals with NDMM have significantly improved [6].

Significant hematological adverse events (AEs) and peripheral neuropathy (PN) are linked to combination regimens such bortezomib-melphalan-prednisone (VMP) and melphalan-prednisone-thalidomide (MPT) [7]. The first-generation PI, bortezomib, was initially approved for NDMM in 2003 but was later shown to be linked to severe neuropathy. A proteasome inhibitor called bortezomib lowers proliferation and reduces chemoresistance. Lenalidomide is an immunomodulatory drug that has direct anti-myeloma cell effects in addition to its multimodal anti-myeloma activity in improving immune function and disrupting aberrant stromal cell support [8]. When combined, bortezomib and lenalidomide have greater pro-apoptotic effects because they both suppress NF-B. Dexamethasone further improves antimyeloma action [9].

The goal of our study is to perform an extensive literature review. We aimed to assess whether the VRd regimen improves outcomes compared with the other regimens in the treatment of newly diagnosed multiple myeloma in patients regardless transplant eligible or ineligible. Additionally, in the long term, we aim to compare overall survival (OS), progression free survival (PFS) and objective response rate (ORR). Analysis of the applicability of these treatment regimens to the frontline scenario is our secondary goal.

Materials and Methods

Literature Search

The following databases were used for the thorough literature search: PubMed, EMBASE, Wiley Cochrane Library, Scopus, Web of Science, CINAHL, and Clinicaltrials.gov. Studies that were published between January 2015 and April 2023 were included in the search; search criteria were not restricted to any particular region or language other than English. Additionally included were all pertinent articles from the conference proceedings. Additionally, we looked through the conference proceedings from the European Hematology Association, American Society of Hematology, American Society of Clinical Oncology, and American Society of Bone Marrow Transplantation.

Eligibility Criteria

1. Phase I, II, or III clinical trials.

2. Clinical trials from January 2015 till April 2023.

3. Studies that evaluated the OS, PFS and ORR.

4. Studies focusing on NDMM as a primary drug therapy.

Study Selection

Based on study titles and abstracts, two impartial reviewers looked over the studies. Potential studies were then examined after irrelevant articles were eliminated by reading the entire texts. Discussion helped to settle disputes between reviewers.

Data Extraction and Analysis

Author, year, research design, patient count, NDMM principal treatment regimens, and efficacy outcomes including overall response rate (ORR), overall survival (OS), and progression-free survival (PFS) were all included in the data that were extracted into pre-specified Microsoft Excel tables. We noted it as "not available (NA)" if the desired information wasn't reported in a particular study. The median or percentage of the data were recorded. The study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) reporting guidelines.

Results

Search Results

A total of 1139 articles were found throughout the literature search. After removing duplicate articles, relevancy was checked based on titles and abstracts. 25 studies were discovered to have the ability to help us answer our research question once the references were taken out. After reading the complete texts of these papers, another 17 articles were disregarded for the following reasons: review article, unavailable full text, duplicate study, lack of required efficacy and safety outcomes, or observational study. The requirements for inclusion were met by a total of 8 articles.

Study demographics

Along with the RRMM and NDMM groups, there were 2532 patients from eight articles. The studies involved clinical trials phase 1,2&3 that assessed and compared the efficiency of the drugs, such as bortezomibe-lenalomide-dexamethasone (VRd) bortezomib-lenalodomide-dexamethasone-daratumumab (D-RVd), carfilzomide-lenalodimed-dexamethasone (KRd), and bortezomib-thalidomide-dexamethasone-daratumumab (D-VTd), ixazomibe-cyclophosamide-dexamethasone (ICd), daratumumab-bortezomib-cyclophosphamide-dexamethasone (D-VCd).

Bortezomibe-Based Regimens

Bortezomibe-based triplet regimens (VRd) were employed in two trials, and a total of (242+235) 477 individuals received these regimens. The progression-free survival (PFS) was 43 months in one study and 41 months in the other. The OS was 75 months in the first trial, however it wasn't reached (NR) in the second trial. The objective response rate (ORR) for the first study was 82 percent, while the ORR for the second study was 90.2 percent. Progression-free survival, HR, 0.73(0.58-0.92), 95% confidence interval, p = 0.007. Overall survival rate: HR 95% confidence interval 0.74(0.55-1.00), p = 0.048. (Tables,1&2).

Carfilzomide-Based Regimens

In the Phase 3 clinical trial investigation of the carfilozomide-based triplet regimen (KRd), only one study was primarily included. A total of 545 patients got this regimen; PFS was 34.4 months; OS was not fulfilled; and ORR was not reported. 95% HR, CI 1.04(0.83-1.31) for progression-free survival, p = 0.74. p = 0.92; CI = 0.98(0.71-1.36); HR 95% for overall survival. (Tables,1&2).

Source	Journal	Clinical Trial phase	Drug Treatment	No. Of Patients	PFS, No.	OS, No.	ORR, No.
Brian G M Durie, et al,2016[19]	The Lancet	3	Bortezomibe+lenalodomide+ Dexatmethasone	242	43 mo,	75 mo,	82%
Brian G M Durie et al, 2020 [20]	Blood Cancer Journal	3	Bortezomibe+lenalodomide+ Dexatmethasone	235	41 mo,	NR	90.2%
Shaji K Kumar et al,2020 [21]	The Lancet	3	Carfilzomide+lenalodimed+Dexamethasone	545	34.4	NR	NA
Shaji K Kumar et al,2020 [22]	Blood Cancer Journal	1/2	Ixazomib+cyclophosphamide+Dexamethasone	48	NR(18 mo81%)	NR(18 mo96%)	77%
Philippe Moreau et al,2019 [23]	The Lancet	3	Bortezomibe+Thalidimide+ Dexatmethasone-±Daratumumab	(542+543)=1085	NR	NA	
Habte Yimer et al,2018[24]	British Journal of Heamatology	2	Daratumumab+bortezomib+cyclophosphamide+Dexamethasone	100	13.3(12 Mo87.0 %)	NA(12Mo98.8%)	71.4%
Meletios A. Dimopoulos et al,2018[25]	European Journal of Cancer	2	Ixazomib+cyclophosphamide+dexamethasone	70	23.5	NA	73%
Peter M. Voorhees et al,2020[26]	American Society of Hematology	2	Bortezomibe+lenalodomide+ Dexatmethasone±Daratumumab	207	NR	NR	98% vs 89%

Table:1

Not Available=NA, Not Reached= NR, Months=Mo, overall survival=OS, Progression free survival=PFS, Objective Response rate=ORR

Authors	Regimens	Number of Patient	Progression free survival	Overall survival
			HR (95%CI) p Value	HR (95%CI) p Value
Brian G M Durie et al 2016 [19]	VRd	242	0.73(0.58-0.92) 0.007	0.74(0.55-1.00) 0.048
Brian G M Durie et al, 2020 [20]	VRd	235	0.77(0.62-0.95) 0.013	0.75(0.58-0.98) 0.033
Shaji K Kumar et al,2020 [21]	KRd	545	1.04(0.83-1.31) 0.74	0.98(0.71-1.36) 0.92
Shaji K Kumar et al,2020 [22]	ICd	48	NE	NE
Philippe Moreau et al,2019 [23]	±D-VTd	(542+543)= 1085	0.47(0.33-0.67) 0.0001	
Habte Yimer et al,2018 [24]	D-VCd	100	(57.196.6%) 12 Month	(92.0-99.8) 12 Month
Meletios A. Dimopoulos et al,2018 [25]	ICd	70	NE	NE
Peter M. Voorhees et al,2020[26]	D-RVd	207	NE	NE

Table 02

Bortezomib-lenalodomide-dexamethasone=VRd, Carfilzomide-lenalodomide-dexamethason=Krd, Ixazomib-cyclophosphamide-dexamethasone=ICd, Daratumumab-thalidimide-bortezomib-dexamethasone=D-VTd, Daratumumab-bortezomib-cyclophosphamide-dexamethasone=D-Vcd, Bortezomib-lenalodomide-dexamethasone-daratumumab=D-RVd. Hazard ratio=HR, Confidence Interval= CI, Not evaluated= NE

Two Ixazomib-Cyclophosphamide-Dexamethasone (ICd) based triplet regimens were the subject of phase 1 and 2 clinical trials. A total of 48,70 patients received these regimens; PFS was not achieved for the entire study, but PFS at 18 months was (81%-23.5 months). OS for the entire study was also not achieved for either trial, but OS at 18 months was 96%, and ORR was (77%-73%). Survival without progression, HR, 95% CI (NE). Survival rate overall HR 95% CI (NE). (Tables,1&2).

Bortezomibe -Thalidomide -Daratumumab Based Regimens

A total of (542+543=1085) patients participated in the phase 3-trial of bortezomib, thalidomide, dexamethasone, and daratumumab (+_D-VTd), but the target PFS and OS were not achieved. Survival without progression, HR, 95% CI, 0.47(0.33-0.67), p-value 0.0001. Survival rate as a whole HR 95% CI (NA). (Tables,1&2).

Daratumumab-Bortezomib-Cyclophosamide- Based Regimens

In a phase 2 clinical trial, daratumumab-bortezomib-cyclophosamide-dexamethasone (D-VCd) was administered to 70 patients in total. The results showed a PFS of 23.5 months, an OS that was not evaluable for the entire study, and an ORR of 73%. Progression free survival, HR 95% CI (0.57-196.6%) 12 Month. HR 95% CI (92.0-99.8) 12 Month Overall Survival. (Tables,1&2).

Daratumumab-Bortezomibe-Lenalodimde- Based Regimens

A total of 207 patients participated in the phase 2 clinical trial for daratumumab-bortezomibe-lenalodimde-dexamethasone (D-RVd), but neither the PFS nor OS goals for the entire study were met. However, the ORR was (98%-89%). Progression-free survival, HR, 95% CI (NE). HR 95% CI (NE) for overall survival. (Tables,1&2).

Discussion

After adding bortezomib to lenalidomide and dexamethasone, patients with previously untreated multiple myeloma enjoyed noticeably better outcomes. Overall Survival rose by 11 months, whereas progression-free survival rose by 13 months [10]. This is the first prospective randomized experiment to assess the efficacy of the three-drug regimen VRd versus the two-drug regimen Rd in the absence of front-line transplantation. The improved progression-free survival and overall survival rates attained with deeper responses (i.e., very excellent partial response or better) further support the efficacy of the three-drug regimen [11]. There is precedent for the added benefit of a three-drug, proteasome inhibitor, immunomodulatory agent, and steroid combination as a first therapy when using bortezomib with thalidomide plus dexamethasone for induction. Regardless of age or intended transplant, VRd remains an appropriate standard of care with a respectable safety and tolerability profile [12].

Our trial's findings indicate that the KRd regimen is not superior to the VRd regimen for the initial treatment of patients with newly diagnosed standard-risk or intermediate-risk multiple myeloma who are ineligible for ASCT or who did not wish to undergo ASCT right away. Long-term monitoring of patients' overall survival will continue. At three years, the two regimens had comparable rates of progression-free survival and overall survival. Although overall response rates were comparable between the regimens, more patients in the KRd group had a very excellent partial response or better than those in the VRd group [13].

To boost response and depth rates, as well as sCR and MRD-negativity (10-5) rates, daratumumab was added to RVd for NDMM patients who were transplant-eligible. As therapy progressed, responses in both groups were more intense, according to earlier observations. These findings confirm the benefit shown in CASSIOPEIA, in which the addition of daratumumab to bortezomib, thalidomide, and dexamethasone raised the frequencies of sCR and MRD negative (10-5) in transplant-eligible NDMM. The odds ratios for sCR were nearly equal in the studies GRIFFIN and CASSIOPEIA (1.57 and 1.60, respectively), demonstrating that the addition of daratumumab to a standard-of-care regimen containing an immunomodulatory drug, a proteasome inhibitor, and dexamethasone leads to deeper responses. Improved long-term OS and PFS results have previously been reported in MM patients who obtained sCR following ASCT [14,15].

The combination of ixazomib, cyclophosphamide, and dexamethasone in patients with recently diagnosed myeloma is described for the first time in this study, to the best of our knowledge. Additional potential combinations are quite intriguing because of ixazomib's activity and long-term tolerability when given to patients with newly diagnosed as well as relapsed myeloma. Given the success of bortezomib, cyclophosphamide, and dexamethasone (VCd) as induction therapy in patients with recently diagnosed MM, further research was required for the cyclophosphamide component in particular. For the first-line therapy of newly diagnosed myeloma, ixazomib, cyclophosphamide, and dexamethasone are an oral combination that is effective and well-tolerated. The efficacy is on par with regimens based on bortezomib, but with significantly less neurotoxicity. Due to its simplicity and tolerability, this regimen is particularly important for elderly, transplant-ineligible patients who are considering longer-term treatment. If qualified and requested, stem cell harvest and autologous transplantation can still be done using cyclophosphamide, which is less expensive than the lenalidomide-based combination without reducing efficacy. To further boost effectiveness without incurring the cost of utilizing three additional drugs at once, monoclonal antibodies can be added to ICd as a basis [16,17].

Daratumumab plus these medications demonstrated a significant and clinically meaningful impact when compared to bortezomib, thalidomide, and dexamethasone alone. In the second phase of the study, it is being investigated whether patients who show a partial response or improved in both groups should receive daratumumab or observation. Giving patients with NDMM an IMiD-sparing regimen, D-VCd can be delivered safely and induces VGPR or better in the community setting. This study demonstrates that the first daratumumab dose can be given over the course of two days, resulting in a shorter initial infusion without an increase in IRs and making it simpler to provide the first daratumumab dose on a weekly basis in the community [18].

Limitations

It is important to acknowledge the limitations of our study. First of all, no literature in other languages on the same issue was included in our search because all the research that were included were in English. Second, no individual patient data were used in this investigation; all data were taken from published literature. The literature review's findings could be skewed.

Third, not all of the research in the subgroup analysis in our literature review contained randomized clinical trials. For instance, some research utilized 40 years as the cut point in the age subgroup analysis, while other studies chose 65 years. In light of this, it is possible that our results do not accurately reflect the disease-development features of all patients, which may have an impact on how our results should be interpreted. On the other hand, we think that the bias was somewhat constrained by our statistical techniques and the thoroughly aggregated data we used. However, our findings suggested that the VRd regimen was linked to specific and significant benefits to OS, PFS, and ORR, providing crucial clinical practice guidance.

Conclusion

Our research shown that the adoption of various alternative regimens, in comparison to the VRd regimen, was associated with significant improvements in multiple myeloma patients' PFS, ORR, and OS. The majority of the research, despite other regimens' clinical evidence to the contrary, have not reached a conclusion since they are still being investigated. Physicians can choose an efficient regimen for Multiple Myeloma patients with the help of this study's findings.

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