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FOUR-DRUG REGIMENS FOR TREATMENT OF MULTIPLE MYELOMA: A SYSTEMATIC REVIEW ON THEIR EFFICACY AND SAFETY

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ABSTRACT

Introduction: Despite multiple treatment options available for the treatment of Multiple myeloma (MM), the disease remains incurable and disease relapse ultimately occurs after a period of disease control. Our review aims to measure the efficacy and safety of four-drug regimens in terms of progression-free survival and disease responses. **Methods:** A comprehensive literature search yielded a total of 36429 articles. Our search strategy included the following MeSH terms: "multiple myeloma" and "antineoplastic agents". Ten studies met the inclusion criteria: phase I/II trials, phase III trials, studies published after 2010, and use of four-drug regimens with clear documentation of outcomes such as overall response rates (ORR), progression-free survival (PFS), and overall survival (OS). **Results:** A total of ten studies with 2,416 patients were included. 2,275 patients had relapsed refractory MM (RRMM), and 141 patients had newly diagnosed MM (NDMM). Seven studies demonstrated a comparison between three-drug and four-drug regimens. Six studies reported four-drug regimens to be significantly superior to three-drug regimens in terms of ORR. Two of the three studies that did not make any such comparison, showed an ORR of more than 90% with four-drug regimens whereas one study reported an ORR of about 67%. Other parameters such as PFS and OS also showed the four-drug regimen as an effective MM strategy. **Conclusion:** Four-drug antineoplastic regimens significantly improve the responses in both newly diagnosed and relapsed/refractory multiple myeloma. However, data on survival is awaited. The cost and associated synergism in the toxicity profile need further analysis and follow-up.

KEYWORDS: "multiple myeloma" and "antineoplastic agents".

INTRODUCTION

Multiple myeloma (MM) is characterized by neoplastic plasma cell proliferation and accounts for 2% of all cancers. Long-term survival of myeloma patients is improving, and current median survival is reported around 5 years.[1] In the United States, the incidence of multiple myeloma in African Americans is more than twice the incidence among Caucasians. The exact cause of MM is unclear but it seems to be related to spontaneous acquired mutations, ionizing radiation, and agricultural exposures.[2] Overall survival (OS) is based mainly on the patient's characteristics and the tumor's biology. The most notable favorable factors are age < 65 years, initial mode of presentation of monoclonal gammopathy of unknown significance (MGUS), and standard-risk cytogenetic abnormalities. Short OS

depends on the presence of poor prognostic factors such as renal failure at initial presentation, the presence of extramedullary disease, high-risk cytogenetic abnormalities, and biologically aggressive disease associated with short remission and multiple relapsed disease.[3]

The absence of curative therapy for MM has prompted the advent of newer drug combination regimens such as protease inhibitors, immunomodulatory drugs, and monoclonal antibodies (daratumumab, siltuximab) along with dexamethasone to improve responses and prolong progression-free survival. Autologous hematopoietic stem cell transplant (ASCT) with high dose chemotherapy (HDCT) consolidation is still the mainstay treatment for transplant-eligible patients after induction treatment. Four drug combinations have demonstrated significant improvement in overall response rates (ORR), progression-free survival (PFS), minimal residual disease (MRD), and overall survival (OS). The addition of monoclonal antibodies to the standard two or three-drug regimens has proven to improve the outcomes without worsening of safety or toxicity profile.[4,5,6] As the duration of response decreases with every successive relapse, four-drug regimens may activate more profound responses and lead to longer PFS in newly diagnosed and relapsed/refractory cases. Currently, only a few phase II and phase III trials are ongoing with the four-drug regimens in all groups of patients including transplant eligible NDMM, transplant-ineligible NDMM, and RRMM. We conducted a systematic review of prospective trials on the efficacy and safety of four drug regimens in NDMM as well as RRMM.

MATERIAL AND METHODS

Literature search

We conducted a comprehensive literature search by using methods specified in the preferred reporting items for systematic reviews and meta-analysis (PRISMA). We searched four literature search engines including PubMed, Cochrane Library, Embase, and Clinicaltrials.gov, the last updated search was performed on December 25, 2020. We did not limit our search strategy to any geographical area or language. Non-English-language articles were not included. Our sample search strategy included the following MeSH terms: "multiple myeloma" and "antineoplastic agents". We also included relevant articles from the following professional organizations' conference proceedings: European Hematology Association (EHA), American Society of Hematology (ASH), European Society of Medical Oncology (ESMO), and American Society of Clinical Oncology (ASCO).

Eligibility Criteria

Inclusion criteria: (1) Studies in which four-drug regimens were used for the treatment of MM; (2) Phase II or III clinical trials also including the phase I clinical trials that were eventually expanded into phase II; and (3) Trials that were conducted in last ten years (from January 1st, 2011 to December 25, 2020).

Exclusion criteria: We excluded review articles, opinions, pre-clinical studies, editorials, case reports/series, non-English studies, observational studies, and older studies (before 2011).

Study Selection and Data Extraction

The comprehensive literature search retrieved 36,429 articles. After removing 2733 duplicate references, two reviewers performed the first screening by reviewing the titles and abstracts of the articles. A total of 32,185 articles were excluded in the first screening leaving behind 1,511 articles. After assessing the full-length papers of 1,511 articles, 1501 articles were further excluded. A total of 10 studies were finally selected for our systematic review. The study's selection process of articles is laid out in Figure 1. For data extraction, we used an excel sheet to add the following information about studies: author, publication year, study design, the total number of patients included in the study, median age, the median number of prior therapies, treatment regimens, response rates, median PFS, OS, and adverse events (AE).

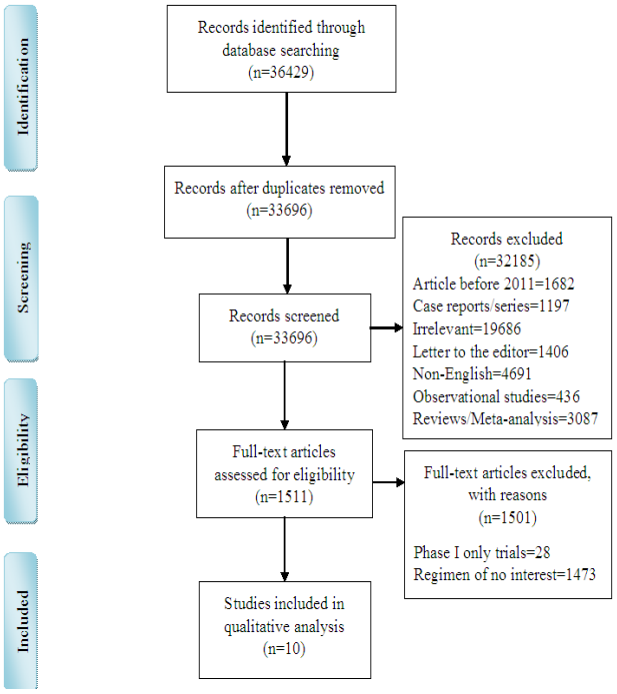

Figure 1 PRISMA flow chart outlining study selection procedure.

RESULTS

The eight phase II and two phase III trial results were included in our study. Out of 2416 included patients in our study, 2275 patients had NDMM, and 141 patients had RRMM. There were 673 and 1791 patients in phase II and phase III trials, respectively.

Phase III trial results

Moreau et al. (2019) studied the efficacy of daratumumab (D), bortezomib (V), thalidomide (T), and dexamethasone (d) (Dara-VTd) vs VTd in NDMM patients in the CASSIOPEIA trial. There were 1085 patients included in the study. Dara-VTd group showed better progression-free survival (PFS) of 93% vs 85% in VTd group at 18 months (mo) (hazard ratio (HR) 0.42 [0.34-0.51]; p<0.0001), and there was an overall response rate (ORR) of 92.6% in Dara-VTd group and 89.9% in VTd group. Minimal residual disease (MRD) negative status in bone marrow was 64% in Dara-VTd vs 44% in the VTd group (p<0.0001).

Mateos et al. (2018) reported the role of Dara-V+ melphalan (M) + prednisone (P) (Dara-VMP) vs VMP in NDMM patients (ALCYONE trial). There were 706 patients in the trial with a median age of 71 years. Dara-VMP showed better PFS: 63% vs 36% at 24 mo (HR: 0.47, 95% CI 0.33-0.67, p<0.0001), ORR: 90.9% vs 73.9%, and MRD negative status: 28% vs 7% (p<0.0001).

Phase II trial results

NDMM

San et al. (2014) studied the role of siltuximab (S) with a standard VMP regimen (S-VMP) in NDMM patients. 98 patients were randomized to either S-VMP (49) or VMP alone (49). The median time to complete response (CR) was shorter for S-VMP (3 mo) vs VMP (5.6 mo). S-VMP also showed better ORR of 88% (95% CI, 75-95) vs 80% (95% CI, 66-90) in VMP group. On the other hand, 1-year PFS was the same for both the arms, i.e. 88%. However, the median survival was not reached in either arm after a median follow-up of 23.3 months in the SVMP and 21.9 months in the VMP arm.

Laubach et al. (2017) studied the role of elotuzumab (E) + lenalidomide (R) + VP in NDMM patients. 41 patients with a median age of 60 yrs were enrolled in the study, and the response data of 29 patients were evaluated. After the completion of four cycles of treatment, there was 100% ORR.

Vorhees et al. (2019) reported the effects of Dara, lenalidomide (R) + V + d (Dara-RVd) vs RVd in GRIFFIN study in transplant eligible NDMM patients. A total of 207 patients were included. The PFS at 24 months was noted to be 95.8% (95% CI, 89.2-98.4) in the Dara-RVd arm vs 89.8 (95% CI, 77.1-95.8) in the RVd arm. ORR of 99% was reported in Dara-RVd arm vs 91.8% in RVd arm (p=0.0160) and MRD negative status in Dara-RVd and RVd arms was 51% and 20.4% respectively.

Yimer et al. (2019) studied the role of daratumumab (D) plus cyclophosphamide (C), bortezomib, and dexamethasone (Dara-CyBorD) in patients with NDMM (n=86) and RRMM (n=14). A total of 100 patients were evaluated for response with a median age of 64 (41-82) yrs. 35% of patients had high-risk cytogenetics defined as del(17p), t(4;14), t(14;16). The ORR was 81.4% (95% CI, 71.6-89) and 71.4% (95% CI, 41.9-91.6) for NDMM and RRMM groups respectively. After a median follow up of 7.9 mo, the median PFS and the median OS were not reached in NDMM patients. 12 mo PFS rate and OS rate were 87% (95% CI, 57.1-96.6) and 98.8% (95% CI, 92-99.8) respectively. In the RRMM group, the median PFS was 13.3 mo (95% CI, 6.8-13.3). 12 mo PFS rate and OS rate were 66.2% (95% CI, 32.4–86.0) and 54.5% (95% CI, 8.6–86.1) respectively.

RRMM

Michael et al. (2015) studied the role of carfilzomib (K) + CTd (k-CTd) in NDMM pts. A total of 64 patients (M: 34, F: 30) were enrolled in the trial with a median age of 62.5 (27-82) yrs. 45 patients were of the intermediate or high-risk category. After a median follow-up of 17.5 mo, there was an ORR of 91%. The PFS rate was 85% (95% CI, 71-93) and 76% (95% CI, 59-87) at 12 and 24 mo respectively.

Popat et al. (2016) reported the role of panobinostat + VTD in RRMM patients. There were 57 patients included in this study with a median age of 61(52-66) yrs, and 46 patients were selected as modified intention to treat population. Thirty-seven patients had 1 previous line of treatment, and nine patients had >1 prior line of treatment. After a median follow-up of 15 months, ORR was 91% (80% CI, 83.4-96.2). Median PFS was 15.6 mo, and the PFS rate at 12 mo was 75.4% (95% CI, 56.7-86.8). However, the median OS was not reached after a median follow-up of 15 months.

Waldschmidt et al. (2018) studied the role of vorinostat, bortezomib, doxorubicin, and dexamethasone in RRMM patients. 33 patients were part of the trial. After a median follow-up of 30.8 months, ORR was 67%. The PFS and OS were 9.6 mo and 33.8 mo respectively.

Bahlis et al. (2019) compared the efficacy and safety of venetoclax (VEN) + DVd with VEN-Dd in RRMM patients. A total of 48 patients were enrolled in this study (24 in each group). The median age of patients treated with VEN-DVd was 64 (41-80) yrs and the median age of patients treated with VEN-Dd was 63 (51-76) yrs. The ORR for VEN-DVd and VEN-Dd groups was 88% and 92% respectively.

Adverse events

Adverse events were categorized into two parts, hematological and non-hematological parts. Among the hematological adverse events, neutropenia was most commonly reported. Other grade 3 or higher hematological adverse events included thrombocytopenia, lymphopenia, anemia, and leucopenia. Common non-hematological grade 3 or higher adverse events were infections, hypophosphatemia, and pneumonia.

DISCUSSION

Novel combinations of drugs such as monoclonal antibodies as front-line agents especially in triplet and quadruplet treatment regimens are emerging. Front-loaded 4-drug induction versus sequential therapy with the aim for better OS and organ toxicity need to be tested. Transplant is still a cost-effective treatment in NDMM.[7] Adding a fourth drug to already established triplet regimens can add to the overall cost of treatment, thus the significance of 4-drug regimens needs to be determined. Clinical trials have shown promising results with daratumumab (anti CD-38 antibody) in transplant-eligible (TE) patients. CASSIOPEIA Study, a phase 3 trial [(daratumumab added to bortezomib (V), thalidomide (T), dexamethasone (d) (VTd)] and GRIFFIN Trial, a phase 2 trial [(daratumumab added to lenalidomide (R), bortezomib (V), dexamethasone (d) (RVd)] are two noteworthy trials in NDMM transplant eligible patients where daratumumab is added to standard triplet regimens for both pre-transplant induction as well as post-transplant consolidation.[8,9] The overall response continues to be higher and responses are deeper in both studies with significant improvement in PFS and OS. Since median OS was not reached in both trials, this is a very encouraging sign indicating a high probability of improved OS, with ongoing long-term follow-ups. The use of four drugs in TE patients did not adversely impact the mobilization of stem cells. There is no increase in overall toxicity with the addition of daratumumab as it has a good tolerability profile. Most common grade 3 or 4 adverse events (AE) with the addition of daratumumab are hematological (thrombocytopenia, leukopenia, and anemia). Infusion-related reactions (IRR) are common with the first dose but do not lead to discontinuation of treatment (similar rates of discontinuation when compared to corresponding triplet regimens). Patients with high-risk cytogenetic abnormalities and International Staging System (ISS) stage 3 disease did not prove to have any statistically significant benefit in both GRIFFIN and CASSIOPEIA trials from the addition of Dara to already established triplet regimens. Carfilzomib (a proteasome inhibitor) was added to cyclophosphamide (C), thalidomide (T) and dexamethasone (d) (CTd).[12] This study was significant with 91% of patients showing partial or better response. 5 out of 64 (8%) patients also demonstrated complete response (CR). 24 months PFS and OS was 76% and 96% respectively. The response also deepened with continued treatment.

It is challenging to treat transplant-ineligible NDMM patients since transplant exclusion criteria including advanced age, comorbidities, and other poor prognostic factors make it very likely that the patients would not be able to tolerate standard doses in combination regimens. ALCYONE trial studied the addition of daratumumab to the standard regimen of bortezomib (V), melphalan (M), and prednisone (P) (VMP). PFS, the primary endpoint, was significantly longer with daratumumab-VMP combination over 3 years follow-up.[5] Daratumumab-VMP combination was found to be superior across all groups with improved OS along with a 50% decrease in risk of progression and death. It showed twice as high rates of Stringent complete response (sCR) and three times as high negative status of MRD. Adverse events included a higher rate of infections especially pneumonia and IRR, but rates of regimen discontinuation and mortality were no higher compared to VMP alone.

San et al. reported improvement in very good partial response (VGPR) only with Siltuximab (anti IL-6) in combination with VMP but did not find any statistically significant improvement in CR, PFS, or OS. There was also 7% increase in serious adverse events mostly hematological (neutropenia, thrombocytopenia) and peripheral neuropathy.[13] 17% of patients in this study had high-risk cytogenetic abnormalities, thus explaining why no mortality benefit was observed.

RRMM poses significant additional challenges since every relapse and successive treatment are known to increase the resistance to future salvage treatments. LYRA study introduced daratumumab to bortezomib, cyclophosphamide, and dexamethasone (Dara-VCd) in both NDMM and RRMM.[14] The regimen induced a deep and durable response with >50% reduction in progression and mortality risk and >90% VGPR. Other newer agents being studied include venetoclax (a highly selective oral BCL-2 inhibitor), which when added to Dd or DVd seems to have better ORR but the relevant study is currently on partial clinical hold and might prove to be promising.[15]

Another approach to decrease toxicity profile in RRMM is attempted by decreasing dose of thalidomide and frequency of bortezomib by introducing maximal tolerated dose of panobinostat (Pan-deacetylase inhibitor) to standard VTd regimen at first relapse. ORR achieved was 91.3%, while a CR of 6.5% and VGPR of 39.1% were reported.[16] The majority of AEs associated with this drug are grade 1 or 2 only and are well tolerated. Vorinostat (an oral class I/II histone deacetylase inhibitor) is mostly out of favor due to high incidence of cardiac toxicity and arrhythmias. Acceptable cardiac toxicity profile was found in the VERUMM study, focusing on the lower dose of vorinostat 300 mg (4 days on and off schedule) in combination with bortezomib, doxorubicin, and dexamethasone.[17]

Addition of daratumumab to various combinations that can be Dara-RVd (GRIFFIN Trial) or Dara-VTd (CASSIOPEIA Study) for NDMM TE patients or addition of daratumumab to VMP for NDMM transplant-ineligible or RRMM (ACYONE Trial) seems to be the most promising. None of these studies reached median OS and that is an encouraging sign, thus necessitating long-term follow-ups.

Limitations

At this point, we are missing long-term follow-up on OS. Language bias also needs to be considered since only studies in English were included in this systematic review.

CONCLUSION

Significant improvement in survival of multiple myeloma patients is seen with combinations of antineoplastic agents. However, the mortality rate still remains high. Adding a fourth drug to well-established triple regimens is a promising ground. Quadruplet drug regimens can be used as front-line treatment for both NDMM and RRMM but require further cost-benefit and tolerability analyses.

REFERENCES

1. Łopuch, S., P. Kawalec, and N. Wiśniewska, *Effectiveness of targeted therapy as monotherapy or combined therapy in patients with relapsed or refractory multiple myeloma: A systematic review and meta-analysis.* Hematology, 2015; 20(1): 1-10.
2. Riedel, D.A. and L.M. Pottern, *The epidemiology of multiple myeloma.* Hematol Oncol Clin North Am, 1992; 6(2): 225-47.
3. Smith, D. and K. Yong, *Advances in understanding prognosis in myeloma.* Br J Haematol, 2016; 175(3): 367-380.
4. Kumar, S., et al., *Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma.* Blood, 2012; 119(19): 4375-4382.
5. Mateos, M.V., et al., *Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial.* Lancet, 2020; 395(10218): 132-141.
6. Palumbo, A., et al., *Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma.* New England Journal of Medicine, 2016; 375(8): 754-766.
7. Fu, S., et al., *Cost Effectiveness of Transplant, Conventional Chemotherapy, and Novel Agents in Multiple Myeloma: A Systematic Review.* Pharmacoeconomics, 2019; 37(12): 1421-1449.
8. Moreau, P., et al., *Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study.* Lancet, 2019; 394(10192): 29-38.
9. Voorhees, P.M., et al., *Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial.* Blood, 2020; 136(8): 936-945.
10. Scott, K., et al., *Bortezomib for the treatment of multiple myeloma.* Cochrane Database Syst Rev, 2016; 4: Cd010816.
11. Kekre, N. and J.M. Connors, *Venous thromboembolism incidence in hematologic malignancies.* Blood Reviews, 2019; 33: 24-32.
12. Mikhael, J.R., et al., *Phase Ib/II trial of CYKLONE (cyclophosphamide, carfilzomib, thalidomide and dexamethasone) for newly diagnosed myeloma.* British Journal of Haematology, 2015; 169(2): 219-227.
13. San-Miguel, J., et al., *Phase 2 randomized study of bortezomib-melphalan-prednisone with or without siltuximab (anti-IL-6) in multiple myeloma.* Blood, 2014; 123(26): 4136-42.
14. Yimer, H., et al., *Daratumumab, bortezomib, cyclophosphamide and dexamethasone in newly diagnosed and relapsed multiple myeloma: LYRA study.* British Journal of Haematology, 2019; 185(3): 492-502.
15. Bahlis, N., et al., *First Analysis from a Phase 1/2 Study of Venetoclax in Combination with Daratumumab and Dexamethasone, +/- Bortezomib, in Patients with Relapsed/Refractory Multiple Myeloma.* Blood, 2019; 134(Supplement_1): 925-925.
16. Popat, R., et al., *Bortezomib, thalidomide, dexamethasone, and panobinostat for patients with relapsed multiple myeloma (MUK-six): a multicentre, open-label, phase 1/2 trial.* The Lancet Haematology, 2016; 3(12): e572-e580.
17. Johannes, M.W., et al., *Safety and efficacy of vorinostat, bortezomib, doxorubicin and dexamethasone in a phase I/II study for relapsed or refractory multiple myeloma (VERUMM study: vorinostat in elderly, relapsed and unfit multiple myeloma).* Haematologica, 2018; 103(10): e473-e479.