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MULTIPLE MYELOMA- AN OVERVIEW OF CURRENT AND NOVEL TREATMENT IN 2024

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ABSTRACT

Multiple myeloma is a malignant neoplasm that builds up in the bone marrow, leading to renal failure, hypercalcemia, bone destruction, and anemia. It is slightly more common in men than in women and twice as common in African Americans. Clinical manifestations include bone abnormalities, low blood counts, nerve damage, hyper viscosity, renal insufficiency, and more. Although there have been numerous recent advances in the paradigm of multiple myeloma therapy, long term efficacy of current therapies is limited, and the likelihood of eventual relapse is quite high. Clonal evolution and changes to cellular signaling pathways are common methods in which myeloma cells acquire resistance, to drugs. This review provides an overview of evaluation of transplant eligibility, frailty score and recommendation of quadruplet and triplet regimens approved by National Comprehensive Cancer Network (NCCN) and European Hematology Association (EHA) and European Society for Medical Oncology clinical practice guidelines to transplant eligible and ineligible patients. In order to avoid drug resistance, overcome treatment limiting toxicities, and improve outcomes for patients with this incurable illness, further research on novel targets in multiple myeloma is necessary.

KEYWORDS: Multiple myeloma, Quadruplet regimen, Triplet regimen, Maintenance therapy, CAR T-cell therapy.

1. INTRODUCTION

Multiple myeloma (MM) is a malignant neoplasm of the plasma cells that builds up in the bone marrow, leading to renal failure, hypercalcemia, bone destruction, and anemia due to

marrow failure. MM accounts for approximately 1.8% of all cancers and 10% of hematologic malignancies.[1] Multiple myeloma is slightly more common in men than in women, and is twice as common in African Americans as compared to Caucasians. The median age of patients at the time of diagnosis is about 65 years.[2] Multiple myeloma can cause bone abnormalities, low blood counts, nerve damage, hyper viscosity, renal insufficiency, and more. Bone pain, weakness, and broken bones are common symptoms. Low blood counts can lead to weakness, reduced ability to exercise, and dizziness. Leukopenia and thrombocytopenia can lower resistance to infections. High blood levels of calcium can cause extreme thirst, kidney failure, and coma. Spinal cord compression can cause sudden severe back pain, numbness, and muscle weakness. Hypo viscosity can slow blood flow to the brain, causing confusion, dizziness, and symptoms of a stroke. Kidney problems can cause weakness, shortness of breath, itching, and leg swelling. Removing the protein from the blood using plasmapheresis can rapidly reverse these symptoms.[3] The diagnosis requires ≥10% clonal bone marrow plasma cells or a biopsy proven plasmacytoma with evidence of one or more multiple myeloma defining events (MDE): CRAB (hypercalcemia, renal failure, anemia, or lytic bone lesions) attributable to the plasma cell disorder, bone marrow clonal plasmacytosis ≥60%, serum involved/uninvolved free light chain (FLC) ratio ≥100 (provided involved FLC is ≥100 mg/L and urine monoclonal protein is ≥200 mg/24 h), or >1 focal lesion on magnetic resonance imaging.[4] In order to identify trisomies, del(17p), t(11;14), t(4;14), t(14;20) and other abnormalities, bone marrow tests should include fluorescence in situ hybridization (FISH) probes at the time of initial diagnosis, Standard karyotyping is useful for identifying hypodiploidy and deletion 13, but the added benefit in preliminary risk stratification diminishes if FISH investigations are conducted. If it is accessible, gene expression profiling (GEP) can offer more prognostic information.[5] The FDA has approved the use of bortezomib in conjunction with cyclophosphamide and dexamethasone as a first therapy for multiple myeloma. Additionally, it is FDA-approved for use in treating multiple myeloma in patients who responded to bortezomib in the past but relapsed at least six months following the end of the last course of treatment.[6] To minimize toxicity as a bridge to transplant and to achieve good disease management and deep response rates, adequate induction is necessary. According to current worldwide standards, triplet or quadruplet induction regimens centered around the proteasome inhibitor bortezomib and dexamethasone (Vd) are preferred over doublet induction regimens, which have significantly lost their popularity. Actually, lenalidomide-Vd (VRd) or daratumumab-thalidomide-Vd (Dara-VTd) are the preferred first-line treatments for transplant-eligible newly diagnosed multiple

myeloma patients, with thalidomide-Vd (VTd) or cyclophosphamide-Vd (VCd) serving as acceptable backups when available. These recommendations come from the updated 2021 European Hematology Association (EHA) and European Society for Medical Oncology clinical practice guidelines. Promising quadruplet regimens using anti-CD38 monoclonal antibodies are still being studied extensively, as is the use of more modern proteasome inhibitors such carfilzomib.[7]

2. EVALUATION OF TRANSPLANT ELIGIBILITY AND FRAILITY SCORE

The age range at which patients with cancer can have an ASCT has been increased to 70-75 years old. ASCT has been rising among the geriatric population, in European nations, the rate was 3% between 1991 and 1995 and 18% between 2006 and 2010.[8] The usefulness of aHSCT in geriatric patients is difficult to assess given the effectiveness of novel combinations with immunomodulatory drugs, second generation proteasome inhibitors, and monoclonal antibodies. For instance, the addition of daratumumab with standard regimens in transplant-ineligible population was significantly reduce the risk of death or progression and increase the rates of minimal residual disease (MRD) negativity (25%), as demonstrated by the MAYA and ALCYONE trials (Daratumumab plus lenalidomide-Dexamethasone-DaraRd and Daratumumab plus Bortezomib-Melphalan-Prednisone-DaraVMP).[9] The frailty of elderly patients is now categorized by the International Myeloma Working group (IMWG) using a scoring system that takes into account age, comorbidities (Charlson comorbidity index) and patient evaluated assessment of household management and self-care using the Lawton Instrumental Activity of Daily Living (IADL) scales and Kartz Activity of Daily Living. Patients with NDMM were categorized as fit, moderate or frail using the IMWG frailty scale, and these classifications were able to predict survival and the likelihood of treatment related toxicity. Some transplant-ineligible individuals were treated with lenalidomide and dexamethasone in the IMWG trial.[10]

3. CURRENT TREATMENT PARADIGM FOR NEWLY DIAGNOSED MYELOM

The Food and Drug Administration (FDA) has approved Bortezomib, carfilzomib, pomalidomide, ixazomib, elotuzumab, daratumumab, isatuximab, selinexor, belantamab, mafo-dotin, teclistamab, talquetamab, elranatamab, and chimeric antigen receptor T (CAR-T) cell therapies for the treatment of multiple myeloma. These treatments have further improved patient outcomes.[11][12][13][14] Many mechanisms underlie the actions of approved myeloma medications, some of which are still poorly understood. Immunomodulatory drugs (IMiDs)

include thalidomide, lenalidomide, and pomalidomide. Two distinct B cell transcription factors, Ikaros (IKZF 1) and Aiolos (IKZF3), are rapidly transformed and degraded as a result of IMiDs binding to cereblon and activating cereblon E3 ligase activity.[15],[16],[17] While isatuximab and daratumumab target CD38, elotuzumab targets SLAMF7. Belantamab mafodotin is a humanized antibody that targets the microtubule-disrupting drug monomethyl auristatin-F, also known as the B cell maturation agent (BCMA).[18] The recently approved CAR-T therapies idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel), which target BCMA, are effective in treating relapsed refractory myeloma.[19],[20] Bispecific antibodies such as teclistamab and elranatamab bind to CD3 on T cells and BCMA on myeloma cells, respectively, to generate an immunotherapeutic effect.[21],[22] Another novel bispecific antibody is Talquetamab, which binds to CD3 on T cells and G protein-coupled receptor class C group 5 member D (GPRC5D) on myeloma cells.[23]

Table 1: Current treatment regimen for patients with newly diagnosed multiple myeloma.

Regimens	Recommended dosing schedule
Bortezomib-thalidomide-dexamethasone (VTd)[24]	Bortezomib 1.3 mg/m^2 subcutaneous days 1, 8, 15, 22 Thalidomide 100–200 mg oral days 1–21 Dexamethasone 20 mg oral on day of and day after bortezomib (or 40 mg days 1, 8, 15,22) Repeated every 4 weeks×4 cycles as pre-transplant induction therapy
Bortezomib-cyclophosphamide-dexamethasone (VCd or CyBord)[25]	Cyclophosphamide 300 mg/m^2 orally on days 1, 8, 15 and 22 Bortezomib 1.3 mg/m^2 subcutaneous on days 1, 8, 15, 22 Dexamethasone 40 mg oral on days on days 1, 8, 15, 22 Repeated every 4 weeks
Bortezomib-lenalidomide-dexamethasone (VRd)[26]	Bortezomib 1.3 mg/m^2 subcutaneous days 1, 8, 15 Lenalidomide 25 mg oral days 1–14 Dexamethasone 20 mg oral on day of and day after bortezomib (or 40 mg days 1, 8, 15,22)
Carfilzomib-cyclophosphamide-dexamethasone (KCd)[27]	Carfilzomib 20 mg/m^2 (days 1 and 2 of Cycle 1) and 27 mg/m^2 (subsequent doses) intravenously on days 1, 2, 8, 9, 15, 16 Cyclophosphamide 300 mg/m^2 orally on days 1, 8, 15 Dexamethasone 40 mg oral on days on days 1, 8, 15, 22 Repeated every 4 weeks

Carfilzomib-lenalidomide-dexamethasone (KRd)[28]	Carfilzomib 20 mg/m^2 (days 1 and 2 of Cycle 1) and 27 mg/m^2 (subsequent doses) intravenously on days 1, 2, 8, 9, 15, 16 Lenalidomide 25 mg oral days 1–21 Dexamethasone 40 mg oral days 1, 8, 15, 22 Repeated every 4 weeks
Carfilzomib-pomalidomide-dexamethasone (KPd)[29]	Carfilzomib 20 mg/m^2(days 1 and 2 of Cycle 1) and 27 mg/m^2 (subsequent cycles) intravenously on days 1, 2, 8, 9, 15, 16 Pomalidomide 4 mg oral on days 1–21 Dexamethasone 40 mg oral on days on days 1, 8, 15, 22 Repeated every 4 weeks
Daratumumab-lenalidomide-dexamethasone (DRd)[30]	Daratumumab 16 mg/kg intravenously weekly × 8 weeks, and then every 2 weeks for 4 months, and then once monthly Lenalidomide 25 mg oral days 1–21 Dexamethasone 40 mg intravenous days 1, 8, 15, 22 (given oral on days when no daratumumab is being administered) Lenalidomide-Dexamethasone repeated in usual schedule every 4 weeks
Daratumumab-bortezomib-dexamethasone (DVd)[31]	Daratumumab 16 mg/kg intravenously weekly × 8 weeks, and then every 2 weeks for 4 months, and then once monthly Bortezomib 1.3 mg/m^2 subcutaneous on days 1, 8, 15, 22 Dexamethasone 40 mg intravenous days 1, 8, 15, 22 (given oral on days when no daratumumab is being administered)
Daratumumab-pomalidomide-dexamethasone (DPd)[32]	Daratumumab 16 mg/kg intravenously weekly × 8 weeks, and then every 2 weeks for 4 months, and then once monthly Pomalidomide 4 mg oral on days 1–21 Dexamethasone 40 mg intravenous days 1, 8, 15, 22 (given oral on days when no daratumumab is being administered) Repeated every 4 weeks
Daratumumab-carfilzomib-dexamethasone (DKd)[33]	Daratumumab 1800 mg subcutaneously (or 16 mg/kg intravenously) weekly × 8 weeks, and then every 2 weeks for 4 months, and then once monthly Carfilzomib 56 to 70 mg/m^2 days 1, 8, and 15 (Cycle 1, day 1 dose is 20 mg/m^2) Dexamethasone 40 mg days 1, 8, 15, 22 Carfilzomib-Dexamethasone repeated in usual schedule every 4 weeks
Ixazomib-lenalidomide-dexamethasone (IRd)[34]	Ixazomib 4 mg oral days 1, 8, 15 Lenalidomide 25 mg oral days 1–21 Dexamethasone 40 mg oral days 1, 8, 15, 22

	Repeated every 4 weeks
Elotuzumab-pomalidomide-dexamethasone (EPd)[35]	Elotuzumab 10 mg/kg intravenously weekly × 8 weeks, and then 20 mg/kg every 4 weeks Pomalidomide 4 mg oral days 1–21 Dexamethasone per prescribing information Lenalidomide-Dexamethasone repeated in usual schedule every 4 weeks
Isatuximab-pomalidomide-dexamethasone (Isa-Pd)[36]	Isatuximab 10 mg/kg intravenously weekly × 4 weeks, and then every 2 weeks Pomalidomide 4 mg oral days 1–21 Dexamethasone per prescribing information
Isatuximab-carfilzomib-dexamethasone (Isa-Kd)[37]	Isatuximab 10 mg/kg intravenously weekly × 4 weeks, and then every 2 weeks Carfilzomib 56 to 70 mg/m^2 days 1, 8, and 15 (Cycle 1, day 1 dose is 20 mg/m^2) Dexamethasone 40 mg days 1, 8, 15, 22 Carfilzomib-Dexamethasone repeated in usual schedule every 4 weeks

3.1 TRANSPLANT ELIGIBLE PATIENTS

Since the introduction of vincristine Adriamycin-dexamethasone (VAd) regimen, novel agents have transformed the landscape of multiple myeloma by improving the depth of response during the induction phase, from doublet to more recent quadruplet-based regimens. Additionally, these novel agents have made it possible to transition from consolidation to maintenance during post-transplant therapy. Patients' overall survival has increased dramatically with first line therapy and the advancements made at every stage. Nevertheless, these advancements have never improved the conditioning protocol for autologous transplantation, which is still dependent on large dosage of melphalan thirty years later. Alongside heightened activity, drug combinations are currently often less hazardous than earlier therapies that primarily used cytotoxic medications.[38] The triplet induction regimen is the standard of care in the US and Europe, with bortezomib-based triplet regimens like bortezomib, cyclophosphamide, and dexamethasone (VCd), bortezomib, thalidomide, and dexamethasone (VTd), bortezomib, lenalidomide, and dexamethasone (VRd) being commonly used mentioned in table 1. VTd is the most frequently used regimen for induction, particularly in Europe. VTd has shown superiority over VCd in terms of very good partial response rates. However, there has been no direct comparison between VTd and VRd. An integrated analysis of four randomized controlled trials demonstrated that VRd is associated with an improvement in very good partial response rates compared to VTd, as well as fewer peripheral neuropathy and treatment-related adverse events.[39]

lenalidomide-Vd (VRd) or daratumumab-thalidomide-Vd (Dara-VTd) are the preferred first-line options for autologous stem cell transplant-eligible NDMM patients, with thalidomide-Vd (VTd) or cyclophosphamide-Vd (VCd) serving as acceptable backups when unavailable. This recommendation comes from the updated 2021 European Hematology Association (EHA) and European Society for Medical Oncology (ESMO) clinical practice guidelines. Promising quadruplet regimens using anti-CD38 monoclonal antibodies are still being studied extensively, as is the use of more modern proteasome inhibitors such carfilzomib.[40] Although it might be taken into consideration for patients who show insufficient response, consolidation treatment—a fixed-duration combination therapy intended to improve depth of response—is not currently regarded as standard of care.[41]

3.1.1 Quadruplet-Regimens

For newly diagnosed myeloma patients who are eligible for autologous stem cell transplant, the quadruplet regimen of daratumumab, bortezomib, lenalidomide, and dexamethasone (Dara-VRd) has recently become the standard of treatment for initial therapy. In comparison to bortezomib, lenalidomide, and dexamethasone (VRd), Dara-VRd has improved response rates, MRD negative rates, and progression free survival (PFS).[42] In newly diagnosed myeloma patients, isatuximab with VRd (Isa-VRd) has also demonstrated remarkable outcomes. The selection between the two quadruplet regimens, Isa-VRd and Dara-VRd, might be determined by availability and accessibility.[43]

3.1.2 Triplet Regimens

In cases where quadruplet regimens are not available due to insurance, regulations, or cost, VRd and daratumumab, lenalidomide, and dexamethasone (DRd) continue to be recommended options for initial treatment.[44] Other bortezomib-containing regimens, such as daratumumab-bortezomib-cyclophosphamide-dexamethasone (Dara-VCd), bortezomib-cyclophosphamide-dexamethasone (VCd), or bortezomib-thalidomide-dexamethasone (VTd), can be used as alternatives for initial therapy if lenalidomide is not available for use as initial therapy or in case of acute renal failure. When treating newly diagnosed multiple myeloma, carfilzomib has been investigated in place of bortezomib; individuals with significant preexisting neuropathy may find this to be an alternative.[45]

3.2 TRANSPLANT INELIGIBLE PATIENTS

Phase 3 FIRST (NCT00689936) was an early trial in 1623 patients considered ineligible for stem cell transplantation that compared melphalan-dexamethasone-thalidomide (MPT)

against lenalidomide-dexamethasone. Comparing the lenalidomide arm to the MPT arm, significant improvements in PFS and OS were seen.[46] Daratumumab was approved for use in conjunction with lenalidomide and dexamethasone in patients with non-differentiated myeloid mass who were not eligible for autologous stem cell transplantation, as a result of the phase 3 MAIA research.[47]

Furthermore, PFS and OS were shown to be considerably longer in patients with newly diagnosed MM who were transplant-ineligible when treated with daratumumab-bortezomib-melphalan-prednisone (D-VMP) as compared to bortezomib-melphalan-prednisone (VMP) alone in the ALCYONE study.[48],[49]

Recently individuals with NDMM who are not eligible for transplants have been studied in the TOURMALINE-MM2 trial (NCT01850524) to see if ixazomib and lenalidomide-dexamethasone work together. The addition of ixazomib was tolerated, and non-statistically significant but clinically substantial advantages were observed in PFS of 13.5 months in the ixazomib group compared to the control.[50]

Maintenance treatment is the current standard of care for patients who are eligible for transplantation as well as those who are not. Although lenalidomide maintenance is recommended, bortezomib or ixazomib may be an option for patients who cannot take lenalidomide or who are intolerant to it. Since bortezomib seems to be able to overcome high-risk traits like t(4;14), some centers choose a PI as maintenance treatment in high-risk patients.[51],[52] While some studies show that bortezomib may counteract the poor prognosis in these individuals, bigger studies have not duplicated these findings, leaving the significance of bortezomib in patients with del(17p) unclear.[53][54]

3.2.1 Triplet Regimens

Based on the findings of a worldwide multicenter randomized study that demonstrated advantage over lenalidomide plus dexamethasone (Rd), DRd has been approved for patients with newly diagnosed myeloma. When compared to Rd, VRd, an alternate regimen, has similarly demonstrated a decreased mortality rate. After taking VRd for around 8–12 cycles, maintenance treatment is initiated. As opposed to VRd, where the triplet regimen is utilized for a shorter period of time, DRd therapy necessitates treatment with all three medications till advancement, which results in a far more costly regimen over time.[55] Ixazomib may be explored as an alternative to bortezomib for individuals whose first therapy with DRd or VRd

is not feasible, mostly due to logistical issues (such as issues with compliance owing to parenteral delivery).[56]

3.2.2 Quadruplet Regimens

Patients considered ineligible for stem cell transplantation but who are not considered frail may seek Dara-VRd or Isa-VRd as initial therapy. Current research indicates that even in patients over 65, quadruplet regimens have better response rates, MRD negative rates and progression free survival (PFS) than triplet regimens.[57],[58]

3.2.3 Alkylating agents-based regimen

Lenalidomide and anti-CD38 monoclonal antibodies could be challenging to get, in such cases, VCd may be an option. It is not recommended to use melphalan based regimens. The VMP regimen, with the exception of the substitution of cyclophosphamide with melphalan as the alkylating agent. The advantage of this alternative is that dosage is more predictable and it has no effect on stem cell mobilization.

3.3 MAINTENANCE THERAPY

Post ASCT, maintenance treatment is recommended when patients receiving treatment without autologous stem cell transplantation have completed 8-12 cycles of initial therapy, maintenance therapy should also be taken into consideration. For most individuals, lenalidomide is the recommended maintenance medication.[59],[60] Lenalidomide maintenance was found to significantly increase PFS and OS when compared to placebo or no medication, according to a meta-analysis of randomized studies. Patients need to be checked and counselled for 2-3-fold increase in risk of second malignancies associated with lenalidomide maintenance will have on individuals with multiple myeloma at high risk. A meta- analysis revealed that these groups of high-risk patients did not significantly benefit with OS.[61]

Data on the optimal duration of maintenance are scarce despite the fact that its benefits are well recognized. In patients receiving daratumumab as part of frontline treatment, its exact function is unknown.[62],[63] Until further information on the benefit of addition of daratumumab to lenalidomide maintenance is known, daratumumab with lenalidomide maintenance is known, daratumumab with lenalidomide maintenance is not frequently advised.

3.4 CAR T-CELL THERAPY

Synthetic transmembrane receptors called chimeric antigen receptors (CAR) are made to specifically recognize certain antigens on the surface of target cells. Whereas, the intracellular activation domain is usually generated from the CD3ζ chain, which causes T-cell activation upon antigen binding, the extracellular antigen recognition domain is usually composed of a single-chain variable fragment.[64] Only mild responses were obtained from first generation CARs because they lacked a co-stimulatory domain. In contrast, Co-stimulatory endo domains like CD28, CD137 or inducible T cell co-stimulation that occurs during physiological T cell activation via TCR recognition by APC, which leads to an improvement in T-cell responses.[65] Although CAR T-cell treatment is linked with high response rates, not all patients experience sustained responses. This can be attributed to many variables relating to the tumor and the structure of CAR T-cells. Evidence suggests that low baseline B-cell maturation antigen expression levels on tumor cells negatively influence CAR T-cell effectiveness, which is not surprising given that majority of CAR T-cell products target BCMA. Furthermore, BCMA can be lost by myeloma cells, which lowers the concentration of soluble BCMA on their surfaces and increases their circulation. Preclinical research has demonstrated that soluble BCMA attaches to CAR T-cells and inhibits their ability to connect with BCMA on the surface of the malignant cells, reducing the effectiveness of CAR T-cell.[66]

Author contributions

All authors had active roles in the preparation of original manuscript and the treatment of the patient.

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