Cancer Therapy & Oncology
International Journal
ISSN: 2473-554X

Juniper Publishers
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Editorial
Volume 28 Issue 1 - December 2024
DOI: 10.19080/CTOIJ.2024.28.556228

Cancer Ther Oncol Int J

Progress in Myeloma in 2024

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Submission: November 23, 2024; **Published:** December 10, 2024

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Abstract

Multiple myeloma (MM) is a hematologic neoplasm with heterogeneous outcomes. It is associated with survival rates ranging from a few months to more than a decade. The treatment of myeloma continues to evolve rapidly. In the last decade, carfilzomib, pomalidomide, ixazomib, elotuzumab, daratumumab, isatuximab, selinexor, belantamab mafodotin, teclistamab, talquetamab, elranatamab, and chimeric antigen receptor T (CAR-T) cell therapies have been approved by the Food and Drug Administration (FDA) and have improved outcomes further. Numerous combinations have been developed using drugs that have shown activity in multiple myeloma.

Abbreviations: NDMM: Newly Diagnosed Multiple Myeloma; CA: Chromosomal Abnormalities; PFS: Progression-Free Survival; R2-ISS: The Second Revision of the ISS; MRD: Minimal Residual Disease; NCCN: National Comprehensive Cancer Network; BCMA: B-cell Maturation Antigen; GPRC5d: G-protein Coupled Receptor Class C group 5 member D; BsAbs: Bispecific Antibodies; CRS: Cytokine Release Syndrome

Introduction

There is significant progress in diagnosis and treatment of multiple myeloma (MM). The median survival of myeloma patients has doubled as a result of discovery of several new drugs. Myeloma definition was also modified to include the diagnosis of myeloma bone disease using CT and PET-CT. This will allow early diagnosis and initiation of effective therapy as well as prevent the development of end-organ damage in the highest risk patients. A new staging system that incorporates standard laboratory markers of prognosis and high-risk cytogenetic abnormalities has been developed [1]. High-risk MM is defined as those having one of the following mutations del(17p), t(4;14), t(14;16), t(14;20), gain 1q, del 1p, or p53 mutation. Having any two of these high-risk factors is defined as double-hit myeloma; while having any three or more high risk factors is considered triple-hit myeloma [2].

Update in diagnosis and therapy of MM in 2024?

Diagnostic perspective

The use of PET/CT at baseline is strongly recommended in initial diagnostic workup of patients suspected of having MM or solitary plasmacytoma. The presence of extramedullary myeloma will modify the outcome of myeloma patients [3].

Risk stratification

Three risk groups were identified by the R-ISS: R-ISS I includes ISS I without high-risk chromosomal abnormalities (CA) or high LDH levels; R-ISS III includes ISS III and high-risk CA or high LDH levels, while R-ISS II includes all other possible combinations [4].

The main limitations of the R-ISS are:

- 62% of myeloma patients were classified into the intermediate-risk category (R-ISS II), possibly including patients with different risk levels of progression/death.
- 1q gain (3 copies of 1q) or amplification (≥ 4 copies of 1q), were not included in the R-ISS. Both are recently proved to be independent poor prognostic factors in newly diagnosed multiple myeloma (NDMM).
- Diagnosis of high-risk chromosomal abnormalities (CA) requires presence of at least one of these CA t(4;14), del(17p), or t(14;16). Emerging data showed that having more than one of these three previously mentioned high-risk CA predicted poorer outcomes [4].

The Second Revision of the ISS (R2-ISS)

R2-ISS is a revision of the current R-ISS proposed by the European Myeloma Network (EMN), under the umbrella of the European Union–funded HARMONY project, to improve risk stratification in young and elderly patients with NDMM. R2-ISS calculates the prognostic significance of each baseline risk parameter including 1q gain/amplification in an additive fashion [4]. The R2-ISS identifies four risk groups by assigning a numerical

value to each risk factor based on their influence on overall survival (OS): ISS-III is 1.5 points, ISS-II is 1 point, del(17p) is 1 point, t(4;14) is 1 point, 1q+ is 0.5 points, and serum LDH > the upper limit of normal is 1 point. In R2-ISS, the intermediate-risk group has been further divided into low- and high-risk groups. The low-risk group is 0 points, low-intermediate-risk group is 0.5-1 point; intermediate high-risk group is 1.5-2.5 points, and high-risk group is 3–5 points. The limitation of R2-ISS is that it has only been validated in NDMM [3].

Quadruplets combinations and their role in myeloma treatment

The quadruplet regimen D-VRd has been added by the new version v.1.2025 of National Comprehensive Cancer Network (NCCN) guidelines as the primary therapy of NDMM fit patients proceeding to autologous stem cell transplant. The quadruplet regimen D-VRd consists of daratumumab (Darzalex), lenalidomide (Revlimid), bortezomib (Velcade), and dexamethasone. It becomes the preferred sole regimen for these patients population (category 1 recommendation) while triplets regimen have been moved to the category of other recommended regimens [3].

The combination of Sarclisa® (Isatuximab-irfc) + Kyprolis® (carfilzomib) + Revlimid® (lenalidomide) + dexamethasone [Isa-KRd] is recommended under the category of useful in certain circumstances for the primary therapy of NDMM both ASCT-eligible and non-transplant -eligible candidates. In non-transplant -eligible MM candidates, the combination has to be continued until progression with de-escalation of therapy (modification of dose and duration) as required (category 2B) [3]. These recommendations are based on the data from PERSEUS clinical trial and ISKIA phase III clinical trial. PERSEUS phase III clinical trial demonstrated significant improvement of increased depth of response and progression-free survival (PFS) of [D-VRd] compared to VRd alone in ASCT-eligible NDMM patients across relevant subgroups. Accordingly, the use of D-VRd followed by Darzalex + Revlimid [D-R] maintenance therapy as a new standard-of-care in ASCT-eligible NDMM patients is further supported [5]. The ISKIA study demonstrated that the [Isa-KRd] combination significantly increased the rates of minimal residual disease (MRD)-negativity when used as pre-ASCT induction therapy and post-ASCT consolidation therapy compared to KRd alone in every treatment phase, including patients with high-risk disease [5].

Maintenance therapy for transplant candidates

Carfilzomib plus lenalidomide combination, and daratumumab with or without lenalidomide, were moved to category of other recommended regimens in NCCN guidelines version 1.2025 instead of the category useful in certain circumstances. A regimen in the category of useful in certain circumstances was also modified to include bortezomib with or without lenalidomide [3].

Chimeric antigen receptor (CAR) T-cell therapy

CAR T-cell therapy is a promising new immunotherapy option in late-line relapsed refractory MM patients. Three B-cell maturation antigen (BCMA)–directed CAR-T cell therapy have been approved to date. Idecabtagene vicleucel (Abecma or ide-cel) and ciltacabtagene autoleucel (cilta-cel), are approved by the US FDA, the European Medicines Agency, Health Canada (ide-cel only), and Brazil ANVISA (cilta-cel only); and equecabtagene autoleucel (eque-cel), is approved by the Chinese National Medical Products Administration. Ide-cel is the first one to be approved. It targets only one epitope of the BCMA antigen while cilta-cel binds to two epitopes of BCMA antigen. This makes cilta-cel have a higher avidity of binding to the target cells [6]. Ciltacabtagene autoleucel is used after one prior line of therapy including IMiD and a PI, and refractory to lenalidomide. Idecabtagene vicleucel used after two prior lines of therapy including an IMiD, an anti-CD38 monoclonal antibody and a PI [3]. The response rates to CAR-T cell therapy range from 73 to 98% [6].

Approved bispecific antibodies (BsAbs)

Bispecific antibodies (BsAbs) are an immunotherapy that can bind to two antigens at a time, making them a viable treatment option for multiple myeloma. Viable targets for BsAbs in MM include BCMA, G-protein coupled receptor class C group 5 member D (GPRC5d), CD38, and Fc receptor homologue 5 (FcRH5). They have many advantages including dual treatment approach [7] and their rapid administration in patients with aggressive relapses unlike CAR-T cell products which require several weeks for collection, manufacture, and administration [2]. The currently approved bsAbs for MM include teclistamab and elranatamab (both binds BCMA on myeloma cells and CD3 on T cells), talquetamab (binds to GPRC5D on myeloma cells and CD3 on T cells). BsAbs are the preferred options for RRMM after at least four prior therapies.

Teclistamab, daratumumab and lenalidomide combination showed early efficacy and a promising safety profile. It showed ORR of 92.3%, and ≥CR in 73.1% of patients. All cytokine release syndrome (CRS) events resolved without teclistamab discontinuation. The bsAb Elranatamab monotherapy achieves deep durable responses and favorable long-term survival in heavily pretreated RRMM patients in the MagnetisMM-3 trial [7]. The three mentioned bsAbs carry boxed warnings for producing CRS and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS). Prophylactic tocilizumab, a biological drug that blocks interleukin-6 receptor, effectively reduced CRS [7].

More BsAb treatment options

Many bsAbs are still under investigation in heavily pretreated RRMM patients. These include ABBV-383 (targets BCMA × CD3),

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Linvoseltamab (targeting a BCMA × CD3 bsAb), and Cevostamab (targeting FcRH5 and CD3) [7].

Revisiting Belantamab Mafodotin (Belamaf):

Belantamab mafodotin is a humanized anti-BCMA antibody conjugated to the microtubule disrupting agent, monomethyl auristatin-F. It acts by inducing cell cycle arrest and antibody-dependent cellular cytotoxicity [2]. United States withdraws belantamab mafodotin in November 2022, because it did not achieve a PFS superior to that of pomalidomide plus dexamethasone combination in the DREAMM-3 trial (the primary end point of the study). However, the latest data from two phase 3 trials showed significant PFS benefits compared to standard treatments of RRMM patients. DREAMM-7 presented at ASCO, suggested that BVd has potential in RRMM, particularly those with high-risk genomic alterations (those with ≥ one of the following t [4;14], t [14;16], or del[17p13]) and in lenalidomide-refractory patients. DREAMM-8 (phase 3) study supports the use of belamaf, pomalidomide and dexamethasone (BPd) combination as it offers significant PFS benefits and deeper, more durable responses. AEs were grade 3/4 ocular AEs (blurred vision, dry eye, and foreign body sensation). AEs were more frequent in the BPd arm (43%) [8].

Iberdomide and Venetoclax: useful new agents in some MM patients:

Iberdomide, Ixazomib, and Dexamethasone in older patients

I2D protocol may be effective in treating older MM patient's refractory to prior lenalidomide and daratumumab therapy at first relapse. According to phase 2 IFM study, Iberdomide, a novel Cereblon E3 ligase modulator, was well tolerated when combined with Ixazomib, and dexamethasone in all oral I2D regimen. Common reported grade 3-4 AEs were neutropenia (46%), thrombocytopenia (9%), and infection (8%) [7].

Venetoclax-Dexamethasone

Phase 3 CANOVA study suggests that pomalidomide-dexamethasone (PomDex) may be less effective than venetoclax-dexamethasone (VenDex) in patients with either high BCL2 gene expression or gain(1q). VenDex or PomDex treatment is of no benefit in patients with amp(1q) [7].

Conclusion

Several investigational lines of therapy may be promising in the future. Several newer bispecific antibodies are in development. Other drugs such as the Cereblon E3 ligase modulator, Iberdomide are of interest. Clinical trials investigating these approaches should be considered in myeloma patients.

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