Managing Myeloma

Recent Developments in the Treatment of Newly Diagnosed Multiple Myeloma

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Overview: Join Dr. Sagar Lonial as he reviews recent developments in the treatment of newly diagnosed multiple myeloma (NDMM). Included in this discussion are findings from the DETERMINATION, GRIFFIN, CASSIOPEIA, ALCYON, and COLUMBA trials, among others, that may inform treatment for both transplant-eligible and transplant-ineligible NDMM.

What is the overall therapeutic picture for NDMM?

Treatment for multiple myeloma (MM) has advanced considerably in recent years. Today, the treatment paradigm for NDMM involves two primary treatment paths based on transplant eligibility. Transplant-eligible patients typically receive front-line induction therapy, followed by consolidation therapy with autologous stem cell transplant (ASCT) and maintenance therapy. Alternately, non-transplant-eligible MM patients will receive initial therapy followed by maintenance therapy. In both cases, re-emergence of disease during maintenance therapy necessitates a relapsed/refractory (RR) treatment approach.

Because NDMM patients may receive different therapies based on suitability for transplant, researchers have been investigating new approaches to these very different treatment routes. Much of this research has been published very recently, and some findings may potentially change established treatment paradigms for these patients.

What are some notable findings related to transplant-eligible NDMM?

There have been multiple studies searching for the best treatment approach for transplant-eligible NDMM.

The benefits of early high-dose therapy and ASCT in transplant-eligible patients were recently confirmed in the phase 3 DETERMINATION trial, which demonstrated a progression-free survival (PFS) rate of 65 months in association with induction with bortezomib (V), lenalidomide (R), and dexamethasone (d), ASCT, and maintenance lenalidomide -- the longest PFS ever reported in a randomized phase 3 trial.[1] VRd induction followed by ASCT is also supported by

updated data from the SWOG777 trial.[2] This induction regimen is currently recommended (Category 1) by the National Comprehensive Cancer Network (NCCN).[3]

To further improve upon outcomes obtained with VRd, investigators have included the addition of anti-CD30 antibodies to this regimen. The GRIFFIN study was a phase 2 study evaluating the addition of daratumumab (dara) to VRd in transplant-eligible NDMM patients.[4] This trial compared a regimen of dara-VRd induction as well as dara-VRd consolidation and dara-R maintenance to VRd transplant, VRd consolidation, and R alone for maintenance therapy. In all, the addition of dara to VRd produced a significantly deeper response, with 82% achieving a greater than complete response (CR) versus just 61% in those taking dara-free regimens. Importantly, the rate of minimal residual disease (MRD) negativity was also significantly higher among those taking dara-VRd, which not only emphasizes the efficacy of this regimen, but also is suggestive for the possibility of treatment discontinuation. While no difference in overall survival (OS) was observed, it is likely that the length of time of this study precluded changes in this extremely long-term outcome.

Dara was also added to thalidomide (T)Vd induction and consolidation therapy in the phase 3 CASSIOPEIA study.[5] This regimen was followed by a second randomization of either dara monotherapy or observation. This trial showed that rates of CR and MRD negativity were significantly higher among patients in the dara-VTd arm versus VTd alone, both in the post-induction and consolidation period. Sustained CR plus MRD negativity rates at one year were also higher in the dara-VTd group (50.1%) versus the VTd group (30.1%), and two-year findings continued to favor the dara-VTd arm (35.5% vs. 18.8%). Interestingly, those within the dara-VTd treatment group who achieved MRD negativity also had a longer PFS compared to those who did not receive dara but also achieved MRD negativity. This indicates that MRD alone should not necessarily be an endpoint; instead, the treatments used to achieve sustained MRD negativity also can impact outcomes.

Finally, dara-carfilzomib (K)Rd was evaluated in NDMM patients in the phase 2 MASTER trial.[6] In this trial, MRD status as assessed by next-generation sequencing (NGS) at a depth of 10^{-5} was used to determine eligibility for potential treatment discontinuation with MRD surveillance (referred to as 'MRD-SURE'). Overall, 80% of patients achieved MRD negativity at 10^{-5} and 71% achieved treatment-free surveillance. In this study, the number of high-risk cytogenetic abnormalities (HRCAs) significantly impacted outcomes. The two-year PFS was 91%, 97%, and 58% for patients with 0, 1, and 2+ HRCAs, respectively, and the cumulative incidence of MRD resurgence or progression at 12 months after cessation of therapy was 4%, 0%, and 27%, respectively.

What are some notable findings in transplant-ineligible NDMM?

Many patients with NDMM are not considered suitable candidates for high-dose induction therapy and ASCT due to age, frailty, comorbidities, or other contraindications. These patients are typically treated with combination therapy including steroids, alkylators, and novel agents. The NCCN currently recommends VRd, dara-Rd, or dara-V with melphalan (M) and prednisone (P) (Category 1) for transplant-ineligible NDMM,[3] but researchers are searching for more effective regimens for this patient population.

VRd-lite is a regimen that includes weekly VR with dose-reduced dexamethasone administered over a 35-day cycle.[7] In a small phase 2 trial consisting of 53 transplant-ineligible MM patients, the overall response rate (ORR) to VRd-lite was 86% and the median PFS was 35.1 months. These outcomes were similar to that of the SWOG S0777 trial of VRd,[2] but this regimen was better tolerated; 62% of patients reported peripheral neuropathy and only one patient experienced grade 3 symptoms.

VRd was also compared to KRd for transplant-ineligible patients in the phase 3 ENDURANCE study.[8] At a median follow-up of 9 months (representing a second planned interim analysis), the median PFS was similar between treatment arms: 34.6 months in the KRd group and 34.4 months in the VRd group. There was a notable difference, however, in the toxicities associated with these regimens. KRd was associated with cardiac, pulmonary, and renal toxicity, while VRd was associated with peripheral neuropathy. Due to the greater toxicity associated with KRd, VRd remains the standard of care for induction therapy in patients with standard-risk, transplant-ineligible NDMM.

In patients with high-risk NDMM, the phase 2 SWOG1211 study compared standard VRd with elotuzumab-VRd for induction and maintenance without transplant (of note, ASCT is now recommended for high-risk MM).[9] Unfortunately, the addition of elotuzumab to VRd did not significantly improve PFS or OS in these individuals, reinforcing the need for ASCT in high-risk patients, particularly in first remission.

Alternately, the addition of dara to VMP in transplant-ineligible NDMM patients successfully improved outcomes in the phase 3 ALCYONE study.[10] At a median follow-up of 16.5 months, the 18-month PFS rate was 71.6% in the dara-VMP group and 50.2% in the VMP group. The ORRs for these treatment arms were 90.9% and 73.9% respectively. Likewise, achievement of MRD negativity occurred in 22.3% and 6.2% of the groups, respectively. However, dara-VMP was associated with more grade 3 or 4 infections (particularly pneumonia) compared with VMP.

Dara has also been added to Rd in transplant-ineligible NDMM patients. The phase 3 MAIA study compared dara-Rd to Rd in 737 individuals with NDMM.[11] This trial included a significant

number of patients over the age of 75, which is a more accurate representation of patients who are ineligible for ASCT. As with other dara-containing regimens, dara-Rd was associated with a greater ORR of 93% versus 81% at 28 months, and superior rates of CR and very good partial response (VGPR) achievement. Updated results of this trial, which were presented in 2021, revealed a significant and clinically meaningful OS and PFS improvement in association with dara-Rd versus Rd, representing a 32% reduction in the risk of death and a 47% reduction in the risk of disease progression or death.[12] These outcomes support the use of front-line dara-based regimens to maximize PFS and extend OS, particularly in older, frailer patients.

The route of administration of dara has also been evaluated. Because intravenous (IV) administration of dara negatively affects quality of life and is associated with infusion reactions, subcutaneous (SC) dara has been developed to reduce treatment burden. SC dara was compared to IV dara in the phase 3 COLUMBA trial which included 533 patients, almost all of whom had relapsed/refractory multiple myeloma (RRMM).[13] SC dara was found to be non-inferior to IV dara in terms of efficacy and pharmacokinetics, and also had an improved safety profile. These findings have been particularly noteworthy since the advent of the COVID-19 pandemic, where clinicians have made efforts to reduce patient time spent in infusion centers. In a real-world analysis of RRMM patients, 84% of whom received SC dara in combination with other antimyeloma agents, there were no cases of administration-related reactions, irrespective of previous exposure to IV dara.[14]

Finally, belantamab mafodotin (belamaf) is a novel B-cell maturation antigen-binding antibody-drug conjugate that is being evaluated in the ongoing phase 1 DREAMM-9 study in combination with standard care (ie, VRd) in patients with transplant-ineligible NDMM.[15] In a preliminary analysis, 100% of patients achieved ≥VGPR; at data cutoff, 42% achieved CR, and 25% achieved stringent CR. In addition, 7 out of 9 patients achieved MRD negativity. No new safety signals were observed. While early, these findings are promising for a potentially superior alternative to Rd in older, frail MM patients.

With so many recent developments in NDMM, the future of this disease is more promising than ever. As scientific study continues to identify optimal treatment combinations and approaches, it is likely that significant gains in PFS and OS will be achieved in the near future. Healthcare professionals should continue to keep their fingers on the pulse of NDMM research to ensure that their patients are receiving the very best therapy.

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