Highlights in Multiple Myeloma from the Annual ASCO and EHA 2022 Meetings

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Learning Objective:

- Identify novel approaches to the management of newly diagnosed and relapsed/refractory multiple myeloma

Overview:

Join Dr. Richter as he reviews new and noteworthy data on newly diagnosed and relapsed/refractory multiple myeloma from the American Society of Clinical Oncology (ASCO) and European Hematology Association (EHA) 2022 annual meetings

What are the current challenges and unmet needs associated with managing multiple myeloma (MM)?

To date, MM is considered an incurable disease, so the global unmet need is to eventually find a cure. At a more pragmatic, day-to-day level, the unmet needs generally encompass management strategies for people with multiple treatment relapses. Once patients have relapsed on several lines of therapy (eg, immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies), they advance to a level of functionally higher risk, even in the absence of high-risk mutations. So this clinical challenge is currently an area where we are focusing our research efforts to maximize outcomes, as these patients have very few treatment options.

What are some new and notable findings relevant to transplant-eligible newly diagnosed MM (NDMM)?

One of the most important findings to come out of the 2022 season has been data from the phase 3 DETERMINATION trial, which sought to determine whether early autologous stem cell transplant (ASCT) enhances efficacy in patients with NDMM receiving triplet induction therapy of bortezomib (V), lenalidomide (R) and dexamethasone (d) followed by long-term lenalidomide maintenance therapy.[1] This study, which has been continuing for over a decade, has shown that patients who receive ASCT experience a deeper response on average, and also have longer progression-free survival (PFS), but do not experience improvement in overall survival (OS) compared to those who do not receive ASCT. In addition, among patients who have achieved measurable residual disease (MRD) negativity with VRd induction therapy, the true benefit of ASCT has been negligible. This data is the first to suggest that ASCT may not be necessary for all patients who receive induction therapy.

What are the highlights of studies in transplant-ineligible NDMM?

There are several interesting studies that have evaluated treatment modalities in this patient population. One study, called the REST study, evaluated the effects of isatuximab (Isa)VR without standard dexamethasone therapy.[2] This study is important because steroids impart some of the greatest morbidity burden in the day-to-day management of MM, especially in older, frailer patients who may have comorbidities such as hypertension, diabetes, and cataracts. While the results are early, the outcomes are quite promising, with an overall response rate (ORR) of 100% (15/15) and a ≥ very good partial response (VGPR) rate of 53.3% (8/15).

A similar trial evaluating the effects of daratumumab (Dara), ixazomib (Ixa) and dexamethasone was the phase 2 HOVON 143 study.[3] This trial, which included older, frail patients with NDMM, showed that maintenance therapy resulted in improvement of response in 19% of patients and a rate of ≥ VGPR that increased from 41% to 50% over the study period. One of the benefits offered by this drug regimen is the infrequent dosing schedule of daratumumab, which may be prolonged to a monthly or every-other-month dosing regimen in the maintenance setting.

What are the data surrounding new approaches to maintenance therapy for MM?

Maintenance therapy is an exciting topic for research at this time because it represents a shift from previous approaches, which typically involved administration of ASCT with no continuous follow-up therapy. Now that studies have confirmed the benefit of maintenance regimens following transplant, researchers are now focusing on modifying these regimens based on disease risk. For example, the ATLAS study was a phase 3 randomized trial comparing carfilzomib (K)Rd to R monotherapy after ASCT.[4] What was interesting about this study design was that MRD was assessed after 8 cycles of either therapy; those who were MRD negative went on to R maintenance, but those who were MRD positive continued on KRd. This 'MRD/risk-adapted' post-ASCT approach is helping to refine how MRD information is used to guide treatment selection and duration in the maintenance setting.

What are the notable trials in relapsed/refractory MM (RRMM)?

There is an overwhelming number of investigational agents being evaluated in RRMM, but two types of therapies that are demonstrating especially good efficacy are bispecific antibodies and the CAR T-cell therapies. The bispecific antibody teclistamab was recently evaluated in the phase 1/2 MajesTEC trial and was found to be associated with response rates of 60%-70% in patients who have received multiple prior lines of therapy.[5] Similarly, the bispecific antibody REGN5458 was shown to confer an ORR of 51%, a ≥ VGPR rate of 86%, and a ≥ complete response (CR) rate of 43% in RRMM patients in a phase 1/2 trial.[6] Talquetamab is an off-the-shelf bispecific antibody that recently was granted Breakthrough Therapy designation by the FDA after findings from the phase 1/2 MonumenTAL-1 trial, which showed that RRMM patients treated with talquetamab experienced an ORR of 70.0% and a ≥ VGPR rate of 56.8%.[7] Other bispecific antibodies such as elranatamab and talquetamab are demonstrating comparable efficacy for RRMM.[8,9] Bispecific therapies are also being combined with other MM drugs. Data on combination talquetamab/daratumumab and teclistamab/daratumumab are early but promising.[10,11] The safety data associated with these bispecific antibodies is also exciting. While T-cell engagers are typically associated with high rates of cytokine release syndrome (CRS), these bispecific

antibodies are associated with low or no rates of grade ≥3 CRS, suggesting that they will be widely applicable in the community setting.

Finally, additional data on CAR T-cell therapies were recently presented. One notable study involved a dual-targeting CAR T-cell therapy that was associated with a rapid production rate and manufacturing times.[12] One limitation of CAR T-cell therapies is the extended 'vein-to-vein' time, or the time necessary to procure T-cells through apheresis, develop the CAR T-cells, and replace the cells in the patient. This process typically requires 4-6 weeks, so a manufacturing process that requires only a few days would be a significant advancement.

T-cell redirection therapies represent a new era in MM treatment, where the patient's own immune system is harnessed to effectively treat, and perhaps even cure, MM. The future of MM treatment is exciting, and we are eagerly awaiting the development and approval of even more efficacious drugs for this challenging condition.

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