

Perspective

Major advances in the treatment of multiple myeloma in American Society of Hematology annual meeting 2020

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Abstract

Treatment of multiple myeloma (MM) has advanced dramatically in the past two decades. However, under the conditions of the COVID-19 pandemic, treatment strategies have been modified accordingly. Numerous novel agents, updated trials, and major advances in myeloma have been reported in the American Society of Hematology 2020 annual meeting, either for transplant-eligible or ineligible patients. Hot topics such as the significance of autologous stem cell transplantation (ASCT), development of novel agents, and chimeric antigen receptor-T (CAR-T) cells have been widely discussed. The triplet regimen bortezomib, lenalidomide, and dexamethasone (VRd) is recommended as the standard first-line treatment, and the addition of a fourth drug improves efficacy and survival. The value of ASCT remains undoubtful, even in the era of quadruplet induction. Dual-drug maintenance, including proteasome inhibitors and immunomodulatory drugs, overcomes unfavorable outcomes in high-risk patients. For relapsed/refractory myeloma (RRMM) patients, novel agents such as selinexor and venetoclax are superior. CAR-T cells and other cell-surface-targeted therapies also appear promising.

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Introduction

Multiple myeloma (MM) is the second most prevalent hematological malignancy, characterized by the

proliferation of monoclonal plasma cells and overproduction of monoclonal immunoglobulins. Although MM remains incurable and fatal, overall survival has been prolonged dramatically in the past two decades,¹ which has largely contributed to in-depth research of the relevant mechanisms and widespread use of novel agents. Considering the significant changes in the clinical settings due to the COVID-19 pandemic, including inconsistencies in injection chemotherapy, difficulties in hospital accessibility, and irregular evaluation of the treatment response, treatment strategies in MM have been modified accordingly. This

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review aimed to illustrate the major updates of the American Society of Hematology (ASH) 2020 annual meeting in MM.

First-line regimens in transplant-eligible MM patients

The triplet regimen bortezomib, lenalidomide, and dexamethasone (VRd) has been widely used as the first-line treatment for transplant-eligible myeloma patients.¹ The overall response rate (ORR) of the VRd regimen after induction is up to 97%, while the overall survival (OS) is approximately 10 years, when VRd is followed by autologous transplantation and lenalidomide maintenance.² Other proteasome inhibitors such as carfilzomib or ixazomib did not show superior efficacy when combined with lenalidomide.^{3,4} However, ixazomib, lenalidomide, and dexamethasone (IRd) is an all-oral regimen, which is advantageous especially when it is essential to avoid exposure to COVID-19.⁵ The FORTE study⁶ randomized participants into three arms: carfilzomib with cyclophosphamide and dexamethasone (KcD) followed by transplantation was the first arm; carfilzomib with lenalidomide and dexamethasone (KRd) followed by transplantation was the second arm; and KRd without transplantation was the third arm. KRd was more effective than KcD as a first-line regimen.

Daratumumab, an anti-CD38 monoclonal antibody, was widely discussed in ASH 2020, including key studies such as GRIFFIN.⁷ Kumar et al⁸ also updated the data on Dara-IRd for newly diagnosed myeloma (NDMM) patients. It appears that the addition of daratumumab improves ORR and/or survival in almost all regimens. Since subcutaneous injection of daratumumab is available, IRd with Dara is a promising regimen.

Autologous stem cell transplantation (ASCT) in the era of novel agents

During the past three decades, ASCT has played an irreplaceable role in consolidation treatment for transplant-eligible MM patients.⁹ In ASH this year, the IFM/DFCI 2009 study¹⁰ acquired new data showing that salvage ASCT had similar OS to VRd + ASCT when patients relapsed from VRd and lenalidomide maintenance. Furthermore, melphalan induced more clonal mutations than VRd alone. It has been debated for decades whether transplantation can be replaced with other therapies. To date, ASCT still remains

indispensable. VRd alone cannot obviate or prevent the need for transplantation in the majority of patients. The FORTE study⁶ indicated that KRd followed by transplantation was more beneficial than KRd without transplantation, suggesting that transplantation still plays a vital role in myeloma treatment.

Since sub-analyses of the IFM 2009 study showed that patients with or without transplantation had the same outcomes as those with minimal residual disease (MRD) negativity, possible recommendations can be either VRd or VRd + daratumumab in patients with standard-risk myeloma. Once patients are able to achieve complete remission (CR) and MRD negativity, hematopoietic stem cells can be harvested and lenalidomide maintenance can start, or autologous transplantation can be performed. Patients treated with this regimen with sustained CR after many years can be defined as having an operational cure. However, current techniques are not effective enough to categorize patients eligible for this approach. On the other hand, in patients that do not achieve CR and MRD negativity, transplantation is necessary. Data from numerous studies show that for patients with high-risk disease, continuous ASCT after induction, even a tandem ASCT for further consolidation, can be beneficial.^{11,12} Finally, high-dose melphalan is still a very cost-effective therapy compared with expensive novel agents. Therefore, in many places where resources are still restricted, high-dose melphalan and ASCT rescue remain part of the standard therapy, at least for the immediate future.

First-line regimens in transplant-ineligible MM patients

Over the past decades, lenalidomide and dexamethasone (Rd) have become standard first-line regimens for transplant-ineligible NDMM patients.¹ Various agents such as proteasome inhibitors or monoclonal antibodies are added to enhance efficacy (i.e. daratumumab + Rd¹³ or VRd-lite¹⁴). Thus, patients now have more efficacious options, while the decision of therapy is becoming more complicated. All transplant-ineligible patients should receive a triplet regimen when possible, unless they have other comorbidities. Moreover, if the decreased performance of the patients is not related to myeloma, a doublet such as Rd or bortezomib and dexamethasone (Vd) are very reasonable options. In the ASH 2020 meeting, updated data from the TOURMALINE-MM2 study¹⁵ were shown; for example, oral ixazomib, lenalidomide,

and dexamethasone (IRd) have been examined in transplant-ineligible patients. Compared with Rd, IRd showed prolonged progression-free survival (PFS) from 21.8 months to 35.3 months. However, the difference was not statistically significant, possibly due to the inclusion of two patient cohorts in the study arm. One cohort benefited from IRd, while the other did not respond as well. Subpopulation analysis of the IRd group is expected. Currently, within Southwest Oncology Group (SWOG), there is a United States-wide phase III study (NCT03652064) proposed to investigate whether VRd-lite or Dara-Len-Dex is the best triplet for transplant-ineligible patients. In this older and frailer patient cohort, it will be more challenging to obtain a quadruplet regimen, in terms of tolerability and toxicity.

Updates of maintenance strategies

Although MM is still incurable, the intensity of treatments in whole process management, including induction, consolidation, and maintenance, is enhanced. Several studies have reported data on dual drug maintenance after ASCT, such as elotuzumab plus lenalidomide,¹⁶ ixazomib plus lenalidomide,⁴ and carfilzomib plus lenalidomide.⁶ A non-randomized study (NCT02619682) of ixazomib and lenalidomide as a combination maintenance is ongoing, and preliminary results indicated great advantages in PFS in the dual-drug maintenance group. As an oral doublet, it is convenient for administration to patients, and ixazomib was well tolerated. Another non-randomized trial (NCT02420860) investigated dual-drug maintenance of elotuzumab and lenalidomide, and the results also confirmed the superiority of the combination. In these studies, both standard- and high-risk patients benefited from the therapy, although high-risk patients relapsed sooner. Therefore, for patients who are at standard risk at baseline and acquire MRD negativity after ASCT, lenalidomide as a single agent is sufficient. However, for high-risk or MRD-positive patients after transplantation, doublet therapy is necessary.

To further investigate whether the duration of maintenance could be determined by MRD negativity, a SWOG study (NCT04071457) is being conducted in the United States, where patients were randomized into two arms. One arm was the current standard lenalidomide treatment, and the other was lenalidomide with daratumumab. After a 2-year maintenance, patients with MRD negativity will be randomized again, either to continue the assigned maintenance or to stop maintenance and monitor the PFS. Although the results

may not be finalized for several years, it is possible that MRD may play a role in the decision of maintenance duration. Mass spectrometry,¹⁷ as an MRD assay on peripheral blood, is more sensitive and can bypass the challenges of monoclonal antibody treatment.

Regarding the timing to start maintenance, the TOURMALINE maintenance study¹⁵ revealed the benefit of the proteasome inhibitor ixazomib. For patients on induction, as long as their tumor load decreases, primary therapy should be continued. Once they reach a plateau, they can switch to maintenance therapy, during which ixazomib may be an option. Because the MRD assay has sensitivity limitations, continuous treatments are still required, especially in patients without transplantation.

In ASH 2020, although the final results of a real-world community-based US-MM6 Study¹⁸ have not been published yet, positive updates have been reported. The bortezomib-based combination can rapidly reduce the tumor load after a few cycles, and when maximum benefits are reached, bortezomib can be switched to ixazomib. To maintain proteasome inhibitor (PI)-based continuous treatment for MM patients, the in-class transition from the 3-cycle bortezomib-based parenteral treatment to oral ixazomib-based triplet regimen can significantly relieve the burden of expense, travel, and COVID exposure.

Anti-CD38 antibodies

In ASH 2020, various studies reported updated data on the anti-CD38 monoclonal antibody daratumumab in both newly diagnosed and relapsed/refractory MM patients. One optimal situation considering cost-effectiveness can be the so-called response adapted approach, which uses VRd or other preferred triplets when the reduction of myeloma disease burden decreases rapidly, or to add daratumumab or isatuximab when reduction is gradual. Although currently there are no data on this approach, it can be applied to patients who cannot use daratumumab at the start of the therapy. Another approach is to define the treatment regimen according to the molecular risk. Currently, there is still a debate over whether anti-CD38 antibodies can benefit high-risk myeloma patients,¹⁹ but a regimen that improves the reduction of disease burden and the accomplishment of MRD negativity can be beneficial. Therefore, standard-risk patients can start with the triplet without anti-CD38, but high-risk patients should consider using anti-CD38 therapy.

Other anti-CD38 monoclonal antibody therapies have also been developed. In this ASH meeting, the

interim analysis of the IKEMA study²⁰ was reported, which combined isatuximab with carfilzomib and dexamethasone (Isa-Kd) in RRMM. Another one was a subgroup analysis of the Icaria-MM study²¹ with isatuximab, pomalidomide, and dexamethasone in RRMM. Although there is still no randomized direct comparison between daratumumab and isatuximab, the current data indicate that the two drugs are largely equivalent in activity. However, some differences have also been observed; for example, the infusion reaction of intravenous daratumumab is more severe. Other anti-CD38 antibodies have also been developed, such as MOR 202.²² Moreover, in relapse and refractory myeloma, the first B-Cell Maturation Antigen (BCMA) antibody–drug conjugate (ADC), belantamab mafodotin,²³ has been developed. An anti-CD38 antibody–drug conjugate may also be developed.

Advances in relapsed and refractory multiple myeloma

With the progressive understanding of the molecular mechanisms of myeloma, numerous innovative drugs have been studied in RRMM patients, such as BCMA ADC belantamab,²³ the XPO-1 inhibitor selinexor,^{24,25} a BRAF/MEK co-inhibitor,²⁶ and the Bcl-2 inhibitor venetoclax,²⁷ as reported this year. Venetoclax is a well-studied drug, which shows excellent superiority in patients with t (11; 14).²⁸ In these patients, a venetoclax-based regimen can be used as early as the second-line treatment and even as part of the first-line therapy. In relapsed patients, the best results have been observed with bortezomib-venetoclax-dexamethasone.²⁷ However, the BELLINI trial²⁹ does not support the application of venetoclax in a non-t (11; 14) cohort. Belantamab has been approved by FDA in patients with very advanced disease and is currently under investigation (NCT04802356, NCT04091126). The major adverse events are thrombocytopenia and keratopathy, which require careful evaluation at baseline and before each therapy. According to the BOSTON trial,²⁴ once-weekly selinexor combined with bortezomib and dexamethasone showed better results than twice-weekly bortezomib and dexamethasone. Each step towards less dosing and reduced toxicity results in a significant improvement in myeloma treatment.

Regarding the BRAF/MEK co-inhibitor, according to a laboratory-based study published in 2019,³⁰ the activating mutations of RAF/NRAS/KRAS conferred resistance to proteasome inhibitors. In contrast, the bortezomib and BRAF/MEK co-inhibitor combination had a synergistic effect when activating mutations were

present. The results indicate that the BRAF/MEK co-inhibitor and bortezomib combos are used only in patients with activation BRAF, NRAS, or KRAS mutations, which account for approximately 50% of all myeloma patients. In addition, the study group at the University of Arkansas³¹ has also reported that MEK inhibitors or combinations have positive effects on patients with upregulated P44/42 MAPK pathway. Therefore, mutations in key oncogenes, such as BRAF/NRAS/KRAS, will guide decision-making on therapeutic strategies. An international effort is required to define a certain category of patients that could benefit from certain therapies based on molecular rationale and to avoid empirical treatments.

Studies of CAR-T cell therapies

At the ASH 2020 annual meeting, CAR-T therapy in MM was well discussed, including CAR-T cells targeting BCMA³² (KarMMA-4), bispecific CAR-T cells,³³ or fully humanized CAR-T cells^{34,35} (CT053). The first BCMA CAR-T Ide-cel was approved by FDA on March 26, 2021, for use in RRMM patients who have received PI, IMiDs, and anti-CD38 antibodies. The Chinese have been pioneers in the field, and another BCMA CAR-T Cilta-cel is also under development. There are currently no trials directly comparing the two BCMA CAR-T therapies, but Cilta-cel may be more effective. Therapies with bispecific CAR-T cells are also advancing. Since the production of bispecifics is faster in terms of T-cell collection, manufacture, infection, and expansion, bispecifics can be used when patients progress rapidly and do not respond to bridging chemotherapy. Both CAR-T and bispecific CAR-T therapies may result in cytokine release syndrome (CRS). However, CAR-T cells are single-shot therapies, and patients do not need further treatment after recovering from CRS, while bispecific CAR-T cells are continuous therapies. Unfortunately, BCMA CAR-T therapy has not been as effective for myeloma as CD19 CAR-T was for lymphoma.³⁶ Nevertheless, fully human scFvs as part of the CAR-T construct may be more efficient.

The earlier utilization of CAR-T cells has two advantages. The first is greater drug sensitivity. Although the mechanism of immunotherapy differs from that of chemotherapy, greater drug sensitivity may imply greater immune sensitivity. The second benefit is that more functional T cells may be collected from patients who receive less treatment than from those continuously treated for many years. There are studies on both high-risk and standard-risk patients attempting to use

CAR-T cells earlier (NCT04287660, NCT04196491, NCT04133636), the possibility of which can be exciting.

Whether CAR-T cell therapy is effective in eliminating MRD is an intriguing question. A certain amount of residual disease is required for T-cell activation. In patients without myeloma, CAR-T cells are not active. However, in general, the less severe the myeloma when therapy starts, the better the outcome. Therefore, consolidation therapy with CAR-T cells will be more effective when it starts in patients with lower tumor bulk than in patients with greater disease burden.

Beyond the BCMA targeted therapies, two bispecifics were presented in ASH 2020, one targeting GPRC5D^{37,38} and the other targeting FcRH5.³⁹ The activity of both drugs is exciting, because, for patients who relapse as BCMA negative after prior BCMA targeted therapy, coming back with another BCMA targeted therapy may not be possible. With more cell surface targets discovered for follow-up therapy, the situation can be different. In the future, there may even be a combination of two bispecifics against two different cell surface targets, just as a combination of a PI and an IMiD, which may be an exciting area for the future, too. Most patients who are naïve to BCMA-targeted therapy express BCMA. However, once ADCs or bispecifics are used more commonly, the proportion of patients who relapse with BCMA negative disease may increase, and measuring the BCMA content on the surface is essential.

Conclusions

The ASH 2020 was another exciting meeting for myeloma patients, caregivers, physicians, and researchers, with abundant exciting advances. For transplant-eligible and transplant-ineligible NDMM patients, triplet regimens incorporating PI and IMiDs are the standard of care. Addition of an anti-CD38 antibody therapy is practical and will improve outcomes. Although a quadruplet regimen as an induction treatment is recommended to further improve response, autologous transplantation is still part of the standard of care and cannot be replaced. Regarding maintenance therapy, emerging data indicate that combinations of PI and IMiD are probably better and should primarily be used for high-risk patients and potentially for patients with positive MRD after transplantation, whereas single-agent maintenance with either lenalidomide or ixazomib is appropriate

for standard-risk patients. In the relapse setting, numerous novel data with small molecules, including the Bcl-2 inhibitor venetoclax for t (11; 14) patients and the XPO-1 inhibitor selinexor with bortezomib, display superiority. Furthermore, the advances in CAR-T cell therapies are inspiring, most of which target BCMA. They are being studied in earlier stages of therapy, where the benefits could be substantially better. Other cell surface targets, including GPRC5D and FcRH5, also appear promising. With the optimal combination of these novel agents, PFS and OS of myeloma patients will continue to improve. Even within the next five years, a large proportion of standard-risk patients can be cured.

Conflicts of interest

None.

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