Managing Myeloma

Advances and Evolving Standards of Care in Transplant-eligible NDMM

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Welcome to this issue entitled *Advances and Evolving Standards of Care in Transplant-eligible Newly Diagnosed Multiple Myeloma (NDMM)*. This edition will outline practical strategies for implementing new and evolving standards of care into the treatment of transplant-eligible patients with NDMM. We will summarize clinical data that supports the use of triplet and quadruplet regimens in transplant-eligible patients. We will also consider the factors when developing an optimized treatment sequencing strategy for an individual transplant-eligible NDMM patient. Many themes in this newsletter will be similar to ***Newsletter 1***, emphasizing that transplant eligible and non-eligible are merging together.

Myeloma is not one disease and every patient's disease is different. Disease pace varies with some patients remaining in remission for 10-15 years, while others continue to relapse. More research to better characterize disease risk in each individual is needed since cytogenetics are not the sole indicator of disease risk. The immune microenvironment also impacts progression of NDMM, and hence T-cell-based therapies have shown efficacy in relapsed disease. New ideas around clonal evolution of myeloma are important when it comes to the use of targeted therapies, especially when we focus on relapse post B-cell maturation antigen (BCMA) targeted therapies. Is the relapse due to a new clone? Is it a BCMA-resistant clone? Or immune mediated T-cell exhaustion?

Stratification of NDMM patients may provide data on prognosis, aid in therapeutic decisions such as the use of quadruplet versus triplet induction therapy, and guide maintenance therapy intensity. Proteasome inhibitors and CD38 antibodies are already used in high-risk populations. Biomarker driven strategies such as the use of B-cell lymphoma-2 (BCL-2) inhibitors in patients with translocation t(11;14) and even in the frontline setting are under study and show promising results. Patients with p53 deletion, and especially those with more than one high-risk chromosome abnormality remain a challenge. Current therapeutic strategies, such as quadruplet induction, upfront transplant consolidation, and aggressive maintenance are improving outcomes but overall survival of these patients is still poor. Aggressive initial induction therapy is important since many patients do not make it to later lines of therapy.[1] The goal of initial therapy is to get a rapid, deep, and long response.

Clinical Studies

The phase III DETERMINATION study comparing delayed versus early transplant highlights an evolving NDMM subgrouping of early versus delayed transplant, instead of transplant-ineligible versus transplant-eligible. This study compared early versus delayed transplant trial using RVd (lenalidomide + bortezomib + dexamethasone) induction and randomization to further RVd versus consolidation with transplant, then followed by RVd consolidation, and finally both arms received lenalidomide maintenance until disease progression. The primary endpoint of the DETERMINATION study was progression-free survival (PFS), which was 67 months in the autologous transplant arm versus 46 months in the RVd-alone arm. High-risk patients benefited most after transplant with a PFS of 55 months compared to only 17 months in the non-transplant group.[2] Minimal residual disease (MRD)-negative patients had the longest PFS, regardless of transplant status, although patients in the transplant arm had a higher rate of MRD-negativity; 54% of patients were MRD negative in the transplant arm versus 40% of patients in the non-transplant group at the start of maintenance.[2] The DETERMINATION trial met its primary endpoint of an overall PFS benefit with an early transplant. Lenalidomide was given as maintenance therapy until disease progression. After a median follow up of 76 months, there was no overall survival (OS) difference. Survival of myeloma patients continues to improve and evolve and demonstrating OS benefits remains challenging and is often driven by access to therapies at relapse, which varies worldwide. There was no difference in the overall rate of second primary malignancies in both arms of the DETERMINATION study. The transplant arm had a higher incidence of acute myeloid leukemia or myelodysplastic syndromes, but this did not reach statistical significance; 10 patients (2.7%) in the transplant arm versus none in the RVd-alone group developed acute myeloid leukemia or myeloid syndromes.[2] Clonal hematopoiesis of indeterminate potential (CHIP) at baseline may aid our understanding of who is at risk of getting second malignancies and guide our therapy choices.

The FORTE study compared (1:1:1) KRd (carfilzomib + lenalidomide + dexamethasone) with transplant (KRd+SCT) versus 12 weeks of KRd without transplant (KRd12) versus KCd (carfilzomib + cyclophosphamide + dexamethasone) with transplant (KCd). FORTE showed KRd to be superior to KCd.[3] A second randomization in this study to KR (carfilzomib + lenalidomide) versus R (lenalidomide) showed no difference in OS, but the KR arm showed a PFS benefit. Patients with amplification of 1q did not show a PFS benefit from KR versus R maintenance, though patients with 17p deletion and 1q gain did, suggesting we still need newer therapies for certain high-risk patients.

The GRIFFIN study, a phase II randomized study, looked at quadruplet induction therapy, daratumumab-RVd versus RVd, in the transplant setting.[4] The quadruplet therapy arm had a higher response rate and greater depth of response, and showed a PFS benefit of 87% compared to the 70% PFS benefit in the triplet RVd arm.[4] This study revealed that high-risk subgroups benefit with quadruplet therapy, including those with 1q abnormalities with a

stringent complete response (sCR) rate of 42% in the daratumumab-RVd arm versus 32% in the RVd arm by the end of post-autologous stem cell transplant consolidation.[5,6]

In the Phase III GMMG-HD7 study, an anti-CD38 antibody, isatuximab plus RVd was compared to RVd alone.[7] GMMG-HD7 showed higher response rates and deeper responses in the quadruplet arm, with 50% of the quadruplet arm being MRD negative versus 35% being MRD negative in the RVd alone arm at the end of induction therapy.[7]

The CONCEPT trial used isatuximab plus KRd in both a transplant arm and a non-transplant arm using an intensive induction, intensive consolidation, and intensive maintenance. Results showed a 100% response rate with 90% of patients getting a very good partial response (VGPR) or better.[8,9] This trial's initial PFS was a promising 79% at 12 months for these high-risk patients.[9] The abstract revealed that the transplant cohort had a 68% MRD negative rate while the non-transplant group had a 54% MRD negative rate at the point of measurement, with an overall response rate (ORR) of 94% in the transplant-eligible population.[10] An updated PFS was presented at the ASH 2022 meeting, showing that quadruplet induction therapy gets NDMM patients closer to the goal of a deep response.

The MASTER study used MRD to guide therapy cessation through an intensive induction with daratumumab plus KRd, transplant, daratumumab plus KRd consolidation, and then lenalidomide maintenance with MRD measured at multiple time points, with MRD at a sensitivity of $<10^{-5}$.[11] This intensive regimen produced high response rates and a high depth of response. An encouraging PFS was observed with none, or one high-risk cytogenetic abnormality. Patients with two or more high-risk cytogenetic abnormalities still present a challenge while those with zero or one high-risk cytogenetic abnormality had a lower rate of MRD resurgence.[11]

Ceasing therapy is the goal in NDMM. The PERSEUS study randomized patients to lenalidomide or daratumumab with lenalidomide maintenance.[12] MRD was then assessed, and patients could cease daratumumab but maintain lenalidomide in both arms to test de-escalating therapy.[12] The primary endpoint is PFS.

In the SWOG DRAMMATIC study, patients received any induction therapies prior to getting a transplant, then were randomized post-transplant to lenalidomide plus daratumumab or lenalidomide alone. MRD was then assessed at two years and MRD negative patients were randomized to either continue or cease therapy, helping us to see if patients can cease therapy if they get to a deep response.

Newer Therapies

The last few years has seen a focus on BCMA as a target in NDMM. BCMA combination data beyond the antibody-antibody combinations and BCMA anti-CD38 immune mediated

inflammatory diseases (IMiD) combination data has laid the platform for frontline strategies for many NDMM patient populations.

Data presented at ASH 2022 of a phase I study of cevostamab, an FcRH5xCD3 T-cell engaging bispecific monoclonal antibody that promotes death of myeloma cells, given every three weeks for 1 year (17 cycles) raised the possibility of treatment-free periods. Results indicate that after a year-long treatment with cevostamab, a long-lasting response of ≥6 months is possible, moving us to potential longer treatment-free periods after fixed-duration treatment. We will need to optimize how we sequence bispecific T-cell engagers, along with optimizing how we sequence CAR T.[13]

The NDMM landscape is currently quite dynamic but getting patients into as good a response as possible through an optimal treatment strategy is still the goal, regardless of their transplant eligibility status. Distinguishing NDMM as transplant eligible or non-eligible will fall away soon as CAR T-cell therapies and bispecific antibodies become frontline treatment. The first bispecific T-cell engager was approved in October 2022 and trials to use it in the frontline setting are already being discussed. We also expect to move to more tailored treatment between standard and high-risk patients, and even defining duration of treatment for patients. Ceasing therapy after a fixed duration will enable patients to maximize benefit and minimize risk.

References:

1. Yong K, Delforge M, Driessen C, et al. Multiple myeloma: patient outcomes in real-world practice. *Br J Haematol*. 2016;175(2):252-264. doi:10.1111/bjh.14213
2. Richardson PG, Jacobus SJ, Weller EA, et al. Triplet therapy, transplantation, and maintenance until progression in myeloma. *N Engl J Med.* 2022; 387:132-147. DOI: 10.1056/NEJMoa2204925
3. Gay F, Musto P, Rota-Scalabrini D, et al. Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): a randomised, open-label, phase 2 trial. *Lancet Oncol*. 2021;22(12):1705-1720. doi:10.1016/S1470-2045(21)00535-0
4. Johnson & Johnson website. Latest News. Final Analysis of Phase 2 GRIFFIN study Presented for DARZALEX (daratumumab)-based Investigational Quadruplet Regimen in Patients with Newly Diagnosed, Transplant-Eligible Multiple Myeloma. Date updated August 2022. Date accessed February 2023. https://www.jnj.com/final-analysis-of-phase-2-griffin-study-presented-for-darzalex-daratumumab-based-investigational-quadruplet-regimen-in-patients-with-newly-diagnosed-transplant-eligible-multiple-myeloma

5. Chari A, Kaufman JL, Laubach JP, et al. Daratumumab Plus Lenalidomide, Bortezomib, and Dexamethasone (D-RVd) in Transplant-Eligible Newly Diagnosed Multiple Myeloma (NDMM) Patients (Pts): Final Analysis of Griffin Among Clinically Relevant Subgroups. *Blood.* 2022;140(1):7278–7281. doi.org/10.1182/blood-2022-162339
6. Voorhees PM, Kaufman JL, Laubach J, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. *Blood.* 2020; 136 (8): 936–945. doi: https://doi.org/10.1182/blood.2020005288
7. Goldschmidt H. Abstract #463. Presented at the 2021 American Society of Hematology Annual Meeting, December 12, 2021 (ASH 2021).
8. Weisel K, Asemissan AM, Besemer B, et al. Depth of response to isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) in front-line treatment of high-risk multiple myeloma: Interim analysis of the GMMG-CONCEPT trial. *J Clin Oncol*. 2020;38(15):8508. DOI: 10.1200/JCO.2020.38.15_suppl.8508
9. Leypoldt LB, Besemer B, Asemissen, AM, et al. Isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) in front-line treatment of high-risk multiple myeloma: interim analysis of the GMMG-CONCEPT trial. *Leukemia*. 36:885–888(2022). doi.org/10.1038/s41375-021-01431-x
10. Weisel K, et al. Abstract #759. Presented at the 2022 American Society of Hematology Annual Meeting, December, (ASH 2022). https://ash.confex.com/ash/2022/webprogram/Paper156309.html
11. Costa LJ, Chhabra S, Medvedova E, et al. Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone With Minimal Residual Disease Response-Adapted Therapy in Newly Diagnosed Multiple Myeloma. *J Clin Oncol*. 2022;40(25):2901-2912. doi:10.1200/JCO.21.01935
12. Sonneveld P, et al. ASCO 2019. Poster presentation. Abstract TPS8055. NCT03710603.
13. American Society of Hematology website. 64th ASH Annual Meeting and Exposition. 1924 Enduring Responses after 1-Year, Fixed-Duration Cevostamab Therapy in Patients with Relapsed/Refractory Multiple Myeloma: Early Experience from a Phase I Study. Date accessed February 2023. https://ash.confex.com/ash/2022/webprogram/Paper157547.html

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