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CLINICAL TRIALS AND OBSERVATIONS

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Maintain maintenance in multiple myeloma?

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In this issue of *Blood*, Rosiñol et al describe that adding ixazomib to lenalidomide-dexamethasone maintenance therapy following autologous stem cell transplantation does not improve disease control. Furthermore, the authors show that maintenance therapy may be limited to 2 years in patients who reach minimal residual disease (MRD) negativity.[1]

Lenalidomide following autologous stem cell transplantation (autoSCT) is currently the only approved maintenance treatment resulting in improved progression-free survival (PFS) and overall survival (OS) compared with observation. However, there are still unanswered questions about maintenance therapy.

One important question is whether intensifying maintenance therapy could further enhance outcomes by decreasing relapses. To address this, Rosiñol et al investigated whether the addition of ixazomib to lenalidomide-dexamethasone (RD) maintenance therapy after therapy with 6 cycles of bortezomib-lenalidomide-dexamethasone (VRD), an autoSCT, and 2 consolidation cycles with VRD could improve PFS. The results showed impressive 6-year PFS rates following maintenance randomization, but they were similar between ixazomib-lenalidomide-dexamethasone versus RD, 55.6% and 61.3%, respectively.

However, these findings do not indicate that the strategy of intensifying maintenance therapy should be abandoned. Recent results from the randomized phase 3 Forte trial demonstrated that the addition of carfilzomib to lenalidomide significantly improved PFS, regardless of MRD status.[2] Accordingly, carfilzomib-lenalidomide-dexamethasone (KRD) maintenance therapy following autoSCT improved PFS compared with lenalidomide maintenance.[3] Unfortunately, Rosiñol et al used RD as the control arm instead of lenalidomide (R) alone, which may have obscured the additional value of ixazomib to just lenalidomide and hinders comparisons with other trials. Therefore, the results from ongoing (registration) trials investigating intensification of lenalidomide maintenance therapy by the addition of anti-CD38 monoclonal antibodies (clinicaltrials.gov NCT02874742), a bispecific antibody (clinicaltrials.gov NCT05243797), or a combination of monoclonal and bispecific antibodies (clinicaltrials.gov NCT05695508) are eagerly awaited.

Many patients on long-term maintenance therapy have no evidence of disease progression. After achieving sustained disease control, continuing maintenance therapy may have drawbacks in terms of adverse effects and quality of life, raising the question whether the duration of maintenance therapy can be limited. However, data from the Intergroupe Francophone du Myelome (IFM) 2009 and the Determination trial do not support this concept.[4,5] In both trials, patients received the same treatment (VRD induction, autoSCT, and VRD consolidation), except for lenalidomide maintenance, which was given for either 1 year or until disease progression. The median PFS was 20.2 months longer in the Determination trial as compared to the IFM 2009 trial, supporting long-term maintenance treatment until progression. Accordingly, a recent retrospective post hoc analysis of the myeloma XI trial showed that lenalidomide maintenance beyond 3 years is associated with improved PFS, compared with observation. However, the results also suggested that the benefit may diminish between 4 and 5 years.[6] Especially in MRD-negative patients, continuation beyond 3 years appeared to be of limited value.

Therefore, the predefined analysis of the randomized phase 3 study by Rosiñol et al is revealing. Maintenance therapy resulted in an increase in MRD negativity in bone marrow to ≈70% after 2 years of maintenance therapy, regardless of the treatment arm. More important, per protocol, MRD-negative patients discontinued maintenance after 2 years. Subsequently, only 17.2% of patients progressed in the 4 years after discontinuation, which was independent of cytogenetic risk at diagnosis. Similarly, in the MASTER trial, only 6.4% disease recurrence was observed within the first 12 months after discontinuation of maintenance therapy with daratumumab-KRD. However, the success of discontinuation was lower (27% recurrence) in patients with ≥2 high-risk cytogenetic abnormalities.[7] In a prospective phase 2 trial investigating MRD dynamics, no disease progression was observed in patients who reached sustained MRD negativity for 2 years, although the follow-up is shorter. However, the maintenance strategy in this study differed from that of Rosiñol et al, as it continued maintenance irrespective of MRD status, whereas the latter discontinued maintenance in MRD-negative patients after 2 years.[8]

These 2 approaches reflect the ongoing debate of whether sustained MRD negativity is sufficient to discontinue maintenance therapy, considering the low rate of progression, or if a clinical trial randomizing MRD-negative patients between continuation and discontinuation of maintenance therapy is required before discontinuation at sustained MRD negativity becomes standard of care? From a methodological perspective, the latter is certainly necessary. Currently, there is a limited number of phase 3 trials directly comparing maintenance strategies in MRD-negative patients. The Radar trial directly compares discontinuation of isatuximab maintenance therapy with continuation in standard-risk patients with sustained MRD negativity (Eudract 2019-001258-25). The Drammatic study (clinicaltrials.gov NCT04071457) explores discontinuation of daratumumab and/or lenalidomide maintenance therapy.

Would it be justified to discontinue maintenance therapy in certain patients while awaiting such data? Data support considering this in patients who received maintenance for at least 2 to 3 years and have sustained MRD negativity, especially in those experiencing adverse effects that negatively impact their quality of life. Whether this approach applies to patients with high-risk cytogenetic disease at diagnosis is questionable. Goicoechea et al demonstrated in the same patient population as enrolled in the trial reported here that the superior PFS and OS in MRD-negative patients compared with MRD-positive patients was independent of high-risk status.[1,9] The MASTER trial supports discontinuation in MRD-negative patients with ≤1 high-risk cytogenetic abnormality only. In contrast, maintenance therapy should be continued in ultra–high-risk patients with ≥2 high-risk abnormalities, even in those with sustained MRD negativity, given the high rate of MRD recurrence and progressive disease after discontinuation.[7]

Rosiñol et al add important data to the recent MASTER trial, providing initial evidence that discontinuation of maintenance therapy in patients with sustained MRD negativity may be safe and worthy of consideration while awaiting results of randomized trials in MRD-negative patients. However, using MRD-based maintenance guidance still has limitations. The currently available MRD techniques are bone marrow (BM) based, which limits sequential use and may yield false-negative results because of multifocal disease or poor quality of the BM sample. Therefore, there is a need for a minimally invasive technique, better reflecting residual disease, such as blood-based targeted mass spectrometry assays.[10] In the near future, such sensitive blood-based MRD techniques may provide improved and more dynamic guidance on which patients may safely discontinue maintenance treatment. This is especially important given the dismal outcome of patients who convert to MRD positivity. Equally important, it should help identify patients who may benefit from alternative, intensified maintenance approaches.

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REFERENCES

1. Rosiñol L, Oriol A, Rios R, et al. Lenalidomide and dexamethasone maintenance with or without ixazomib, tailored by residual disease status in myeloma. *Blood*. 2023;142(18):1518-1528.
2. 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.
3. Dytfeld D, Wróbel T, Jamroziak K, et al. Carfilzomib, lenalidomide, and dexamethasone or lenalidomide alone as maintenance therapy after autologous stem-cell transplantation in patients with multiple myeloma (ATLAS): interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2023;24(2):139-150.
4. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. *N Engl J Med*. 2017;376(14):1311-1320.
5. Richardson PG, Jacobus SJ, Weller EA, et al. Triplet therapy, transplantation, and maintenance until progression in myeloma. *N Engl J Med*. 2022;387(2):132-147.
6. Pawlyn C, Menzies T, Davies FE, et al. Defining the optimal duration of lenalidomide maintenance after autologous stem cell transplant - data from the Myeloma XI Trial [abstract]. *Blood*. 2022;140(suppl 1):1371-1372.
7. 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.
8. Diamond B, Korde N, Lesokhin AM, et al. Dynamics of minimal residual disease in patients with multiple myeloma on continuous lenalidomide maintenance: a single-arm, single-centre, phase 2 trial. *Lancet Haematol*. 2021;8(6):e422-e432.
9. Goicoechea I, Puig N, Cedena MT, et al. Deep MRD profiling defines outcome and unveils different modes of treatment resistance in standard- and high-risk myeloma. *Blood*. 2021;137(1):49-60.
10. Langerhorst P, Noori S, Zajec M, et al. Multiple myeloma minimal residual disease detection: targeted mass spectrometry in blood vs next-generation sequencing in bone marrow. *Clin Chem*. 2021;67(12):1689-1698.

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HEMATOPOIESIS AND STEM CELLS

Comment on Wu et al, page 1529

After DNA damage, AREG-ular niche it's not

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In this issue of *Blood*, Wu et al[1] have demonstrated that leptin receptor-expressing (LepR$^+$) bone marrow (BM) stromal cells upregulate and secrete amphiregulin (AREG) in mice during aging and in mice deficient in the DNA repair gene *Brca2*. This increase in AREG promotes a decline in