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Maintenance therapy after Autologous Stem Cell Transplantation in Multiple Myeloma – currents and perspectives

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ABSTRACT

MM is non-curable cancer that arises from plasma cells and is the second most common type of blood cancer. Drug-refractory relapses are inevitable, making it essential to sustain long-lasting remissions as part of therapy. Lenalidomide maintenance until progression is a standard of care for transplant-eligible newly-diagnosed patients. However, poor outcomes of high-risk patients and the risk of secondary primary malignancies associated with maintenance underline the need for novel approaches. Significant changes in frontline treatment maintenance are expected, with the increasing importance of minimal residual disease monitoring and the development of novel drug combinations for maintenance. This article explores current standards and prospects for maintaining response after upfront in ASCT in MM.

Introduction

Multiple Myeloma (MM) is a type of cancer that arises from plasma cells and is the second most common hematological neoplasm. The disease is incurable, and drug-resistant relapses are common, narrowing the applicable therapeutic portfolio with each relapse [1]. Therefore, maintaining durable remissions is one of the crucial points of the therapy. These thousand words describe current standards and perspectives in the remission maintenance strategies in MM after ASCT.

Current standards

An upfront quadruplet-inducing regimen followed by high-dose chemotherapy, autologous stem

cell transplant (ASCT), and lenalidomide maintenance therapy is a standard for transplant-eligible newly diagnosed (ND) MM patients. Lenalidomide is the only drug approved for maintenance after ASCT. The current strategy involves treatment until progression, which has been shown to increase progression-free survival (PFS) compared to observation [2–5]. McCarthy et al.'s meta-analysis showed that lenalidomide maintenance post-ASCT resulted in better overall survival and confirmed the progression-free survival benefit for patients with NDMM compared to those on placebo or observation [5]. The median PFS was 52.8 months for the lenalidomide group and 23.5 months for the placebo or observation group. This was confirmed by the phase III Myeloma XI trial, in which patients eligible for transplantation had a median PFS of 57 months, compared to the observation group, which had a median PFS of 30 months [2].

Proteasome inhibitors (PIs) are, alongside immunomodulatory drugs (IMIDs), the core of MM treatment and aspire to establish their position in maintenance therapy. Ixazomib is a promising option for maintenance among PIs due to its low toxicity profile and once-weekly oral dosing. According to the phase III TOURMALINE-MM3 study, there was a 28% decrease in the risk of progression or death with ixazomib compared to placebo. This result was obtained with a median follow-up of 31 months [6]. The combination of immunomodulatory drugs and PI is another strategy. According to the FORTE trial, adding carfilzomib to lenalidomide maintenance led to a 3-year PFS of 75%, higher than the 65% achieved using lenalidomide alone [7]. The superiority of the triplet maintenance was reported by Dytfeld et al. in an ATLAS study of KRd (carfilzomib, lenalidomide, and dexamethasone) versus lenalidomide alone. KRd reduced death and progression by 44% compared to lenalidomide alone, providing an 18-month longer PFS without significantly increasing toxicity [8]. Contrary to these findings, Rosinol et al. reported that adding ixazomib did not improve maintenance with lenalidomide and dexamethasone [9].

Daratumumab, an anti-CD38 antibody, is being studied for maintenance therapy alone or with other agents. The CASSIOPEIA study showed that daratumumab maintenance therapy was effective in improving outcomes for patients with NDMM who received VTd (bortezomib, thalidomide, dexamethasone) induction/consolidation treatment. However, no benefits were observed compared with observation in patients who received daratumumab-VTd. [10]. The GRIFFIN study revealed that adding daratumumab to RVd (lenalidomide, bortezomib, dexamethasone) induction and consolidation, followed by daratumumab plus lenalidomide maintenance, resulted in deep and lasting responses in transplant-eligible NDMM patients. The study showed a positive trend towards improved PFS, with 4-year progression-free survival of 87.2% for D-RVd compared to 70.0% for RVd. [11]. The results of the PERSEUS trial align with these findings, supporting the use of daratumumab in combination with RVd for transplant-eligible NDMM, followed by daratumumab-lenalidomide maintenance. D-RVd showed a significant improvement in PFS compared to RVd, with estimated 48-month PFS rates of 84.3% for D-RVd, versus 67.7% for RVd. [12]. Based on these findings, adding daratumumab to lenalidomide maintenance has the potential to become a new standard of care.

Maintenance duration

The duration of maintenance therapy is still a research subject, mainly because of the risk of secondary primary malignancies (SPM). SPM post-ASCT for myeloma leads to lower PFS and overall survival (OS), but MM remains the leading cause of death [13]. Therefore, there is a need to discuss how to avoid unnecessary patient treatment, and the measurement of Minimal Residual Disease (MRD) may significantly address this issue. MRD is a powerful PFS and OS predictor and emerges as a tool for monitoring disease and could, in the future, guide therapeutic decisions [14]. The MASTER trial showed that most patients who achieved MRD negativity did not experienced progression without maintenance therapy [15]. There is growing interest in researching the role of MRD in post-ASCT maintenance and identifying which individuals can benefit from MRD-guided maintenance cessation [16]. Rosinol et al. suggested that patients who achieve MRD-negativity can undergo limited maintenance therapy for up to two years [9]. In the PERSEUS trial, Patients who achieve MRD negativity

for 12 months can stop receiving daratumumab but continue with lenalidomide maintenance. In a recent report, 64% of patients discontinued daratumumab maintenance after achieving sustained MRD-negativity [12]. In the KRd arm of the ATLAS study, patients with standard-risk cytogenetics achieved superior PFS and MRD-free survival. Patients with sustained MRD-negativity in the KRd arm confirmed in 78% of patients who received de-escalated therapy from KRd to lenalidomide. Only 25% had progressive disease or MRD resurgence, compared to 47% in the lenalidomide arm [17].

Maintenance in high-risk cytogenetics abnormalities (HRCA)

HRCAs are still a major challenge for MM treatment associated with unfavorable outcomes, especially for patients with co-existing HRCAs. MYELOMA XI trail shows that lenalidomide maintenance post-ASCT turned out to be beneficial for patients with a single HRCA [18]. How to manage co-existing HRCAs needs to be clarified. The addition of PIs could be beneficial. A phase II trial by Nooka and colleagues found that combining carfilzomib, pomalidomide, and dexametha-

Table 1. Outcomes of key completed and ongoing studies evaluating maintenance treatment in newly-diagnosed transplant-eligible multiple myeloma. ASCT: Autologous Stem Cell Transplantation; CR: Complete Response; DR: Daratumumab and Lenalidomide; D-RVd: Daratumumab, Lenalidomide, Bortezomib, and Dexamethasone; D-VTd: Daratumumab, Bortezomib, Thalidomide, and Dexamethasone; IRd: Ixazomib, Lenalidomide, and Dexamethasone; Kd: Carfilzomib, and Dexamethasone; KRd: Carfilzomib, Lenalidomide, and Dexamethasone; MRD: Minimal Residual Disease; OS: Overall Survival; PFS: Progression-Free Survival; R: Lenalidomide; Rd: Lenalidomide and Dexamethasone; RVd: Lenalidomide, Bortezomib, and Dexamethasone; VTd: Bortezomib, Thalidomide, and Dexamethasone.

Trial Name and status	Phase	Treatment Arms	Key Findings	MRD Status Impact
PERSEUS NCT03710603 Active	3	D-RVd induction and consolidation with daratumumab and lenalidomide maintenance vs. RVd induction and consolidation therapy and lenalidomide maintenance	Estimate 48-month PFS: 84.3% D-RVd vs. 67.7% RVd, 87.9%; CR in D- RVd group vs 70.1%, in RVd; MRD-negative status in D-RVd 75.2% vs 47.5%	Patients who achieve MRD negativity for 12 months can stop receiving daratumumab but continue with lenalidomide maintenance
ATLAS NCT02659293 Active	3	KRd vs. lenalidomide maintenance	Median PFS: 59.1 months KRD vs. 41.4 months lenalidomide	Switch to lenalidomide maintenance if MRD-negative after cycle six
CASSIOPEA NCT02541383 Completed	3	D-VTd induction and consolidation vs. VTd induction and consolidation; with further re-randomization to maintenance arm of daratumumab vs observation	At a median follow-up of 35.4 months, median PFS was not reached in the group receiving daratumumab, compared to 46.7 months in the observation group	–
GRIFFIN NCT02874742 Completed	2	D-RVd or RVd induction, ASCT, D-RVd or RVd consolidation, and lenalidomide maintenance with or without daratumumab	Higher stringent CR and 4-year PFS in D-RVd	–
GEM2012MENOS65 NCT01916252 Completed	3	RVd induction, ASCT, RVd consolidation and maintenance with Rd vs. IRd	6-year PFS: 61.3% for RD and 55.6% for IRD	Discontinuation for MRD-negative patients after 24 cycles
MYELOMA XI NCT01554852 Completed	3	Lenalidomide maintenance vs. observation	Median PFS: 39 months lenalidomide vs. 20 months in observation arm; 3-year OS: 78.6% R vs. 75.8% in observation arm; Transplantation-eligible 3-year OS: 87.5% R vs. 80.2% in observation arm	–
TOURMALINE-MM3 NCT02181413 Active	3	Ixazomib maintenance vs. placebo	28% reduction in the risk of progression or death with ixazomib	–
FORTE NCT02203643 Active	2	Carfilzomib and lenalidomide maintenance vs. lenalidomide maintenance	3-year PFS was 75% with carfilzomib and lenalidomide vs. 65% with lenalidomide alone	–

sone was effective and safe in treating high-risk multiple myeloma. The study showed significant improvement in patient responses, with 80% achieving MRD negativity. However, the study also found that patients with a double-hit MM still had poor PFS and OS outcomes [19]. In a single-center retrospective study, Joseph et al. underlined the benefits of risk-adapted maintenance. Standard-risk patients received single-agent maintenance therapy, mostly lenalidomide (76%). High-risk patients received PI and IMID combination. PFS and OS were shorter in this group, however, with the benefit of the risk-adapted algorithm, achieving a median PFS of 40.3 months and a median OS of 78.2 months. Patients with 17p deletion in this study had a median PFS of 37.2 months and a median OS of 68.5 months. Most of them received triple-drug maintenance therapy with IMID and PI [20].

Conclusion

This article provides an overview of the latest developments in maintenance treatment for NDMM following ASCT (**Table 1**). While significant progress has been made in this area, many questions remain regarding maintenance therapy. The challenges include establishing the optimal duration of maintenance to avoid SPM and therapy-related toxicities. On the other hand, there is still a need for new approaches for high-risk patients. Novel drugs, combinations, and MRD guidance are expected to improve maintenance outcomes soon.

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Conflict of interest statement
The authors declare no conflict of interest.

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