Role of Consolidation and Maintenance

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KEYWORDS

• Multiple myeloma • Consolidation • Maintenance • Minimal residual disease
• High-risk

KEY POINTS

- Consolidation therapy after transplant: After a stem cell transplant in multiple myeloma, there is a short-term treatment called consolidation therapy. It is like a boost to the transplant.
- Mixed results from trials: Some important tests about consolidation therapy had different outcomes. This made doctors unsure if it is always needed after a transplant, so they have different ways of treating patients.
- Maintenance therapy for long term: After the transplant, there is also long-term treatment called maintenance therapy. It can last for a fixed time or even longer.
- Different treatments for different risks: Patients with a regular risk usually get one medicine, whereas those with higher risk might need two or more medicines together.
- Side effects and quality of life: Doctors need to think about side effects and how patients feel during treatment. They are still studying to find out the best time for patients to stop maintenance therapy.

INTRODUCTION

Consolidation in multiple myeloma refers to a limited duration of systemic therapy given after autologous stem cell transplant (ASCT) and before maintenance therapy. The goal of consolidation therapy is to improve the frequency and depth of response without unacceptable toxicity.[1] Modern consolidation therapy typically consists of a triplet or even quadruplet regimen, often but not always identical to the regimen used during induction therapy. Clinical trials often include consolidation in their study schema, but trials specifically examining the role of consolidation have shown mixed results, which may be explained by variable drugs and duration of induction ahead of ASCT. As a result, clinical practice on the use of consolidation post-ASCT is not standardized. Here, the authors review the existing evidence on the role of consolidation therapy after ASCT.

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Although some definitions include ASCT within the category of consolidation, this topic is discussed in depth in our previous article titled, "Is There Still a Role for Stem Cell Transplant in Multiple Myeloma?" However, it is important to note here that ASCT itself extends progression-free survival (PFS) and, variably, overall survival (OS). The Intergroupe Francophone du Myélome (IFM) published in 1996 the first randomized trial comparing conventional chemotherapy alone to ASCT in myeloma and demonstrated improved OS in the ASCT arm (not reached in ASCT arm after median follow-up of 41 months vs 37.4 months in the chemotherapy arm after median follow-up of 37 months).[2] A subsequent trial by the British Medical Research Council similarly demonstrated that ASCT improved survival by nearly 1 year compared with conventional chemotherapy alone.[3] These trials provide historical perspective on the benefit of ASCT without consolidation as we include some phase 2 consolidation trials without a comparator arm.

Maintenance therapy involves long-term therapy after the completion of upfront induction, ASCT in eligible patients, and consolidation. The single-agent maintenance therapy is typically used in standard-risk disease, whereas a doublet is considered in higher risk individuals. Given the anticipated prolonged duration of maintenance therapy over years, factors such as adverse events (AEs) (including the dreaded long-term risk of secondary malignancy), quality of life, route of administration, and cost must be considered. Here, the authors highlight pivotal trials examining the evidence behind various maintenance strategies.

DISCUSSION

Consolidation

Various consolidation strategies have been studied in multiple myeloma; here, the authors discuss key phase 2 and 3 trials and summarize study regimens and outcomes (**Table 1**). The first of such trials is the 2013 Nordic Myeloma Study, a phase 3 trial in 370 patients that assessed the efficacy of single-agent bortezomib consolidation in bortezomib-naïve patients.[4] Patients received variable induction, most commonly cyclophosphamide and dexamethasone (89%), with others receiving thalidomide and steroids or vincristine, doxorubicin, and dexamethasone (VAD). Data on duration of induction were not provided. Bortezomib-exposed individuals were excluded from the trial. Patients underwent ASCT and then were randomized 1:1 to receive 20 doses of single-agent bortezomib consolidation or no consolidation. The bortezomib consolidation arm experienced longer PFS (27 months vs 20 months, $P = .05$), increased rate of very good partial response (VGPR) or better (71% vs 57%, $P<.01$), and a trend toward increased complete response (CR) or near CR (45% vs 35%, $P = .055$). OS and health-related quality of life were unchanged between the treatment arms. Not surprisingly, peripheral neuropathy rates were increased in the bortezomib consolidation group (57% vs 24%). Although this trial is not applicable in the era of novel therapies as most patients are bortezomib-exposed during induction, it sets the groundwork for further consolidation trials in the subsequent decade.

The Italian PETHEMA/GEM2012 trial was a randomized phase 3 clinical trial comparing bortezomib, thalidomide, and dexamethasone (VTd) induction and consolidation to thalidomide, dexamethasone (Td) induction and consolidation in 408 participants with newly diagnosed multiple myeloma (NDMM).[5] All participants received double ASCT after induction and dexamethasone maintenance after consolidation. The trial demonstrated a PFS advantage at 3 years (60% vs 48%, $P = .042$) favoring the VTd group. The investigators note that the CR and near-CR rates were equivalent in both arms after induction but significantly improved after consolidation in the VTd

Table 1
Clinical trials examining the role of consolidation therapy in multiple myeloma

Year	Study	*N*	Treatment Regimen	Outcome
2011	IFM 2008[7]	31	*I*: VRd × 3 cycles q21 days ↓ ASCT ↓ *C*: VRd × 2 cycles q21 days ↓ *M*: lenalidomide 15 mg × 1 year	Non-randomized, but promising ORR (94%) and sCR (39%)
2013	Mellqvuist et al[4]	370	*I*: variable (bortezomib not permitted) ↓ ASCT ↓ *C*: bortezomib × 4 cycles (two 21 day cycles, four 28 days cycles), vs none ↓ *M*: None	Improved PFS, VGPR rate in bortezomib arm, trend toward significance for CR/near-CR, OS unchanged
2017	IFM 2009[8]	700	*I*: VRd × 3 cycles q21 days ↓ ASCT + VRd × 2 cycles q21 days vs VRd × 5 cycles q21 days ↓ *M*: lenalidomide 10 mg daily × 3 months, followed by possible increase to 15 mg daily; maximum duration of maintenance: 1 year	Improved PFS, CR rate, MRD negativity with ASCT arm; no change in OS
2012	PETHEMA/GEM2012[5]	480	*I*: VTd × 3 cycles q21 days vs Td × 3 cycles q21 days ↓ double ASCT (Td between transplants) ↓ *C*: VTd × 2 cycles q35 days (in VTd-induced) vs Td × 2 cycles q35 days (in Td induced) ↓ *M*: dexamethasone 40 mg d1-4/28 until PD	Improved CR/near-CR rate post-consolidation with VTd compared with Td

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Table 1
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Year	Study	*N*	Treatment Regimen	Outcome
2018	BMT CTN 0702 (STaMINA)[10]	758	*I*: Variable ↓ ASCT vs double ASCT vs ASCT + VRd × 4 cycles q21 days ↓ *M*: lenalidomide 10 mg daily × 3 months then 15 mg daily until PD	No difference in PFS and OS in ASCT vs double ASCT vs ASCT + VRd
2019	CASSOPEIA[17]	1085	*First randomization,* I: DVTd × 4 cycles q28 days vs VTd × 4 cycles q28 days ↓ ASCT ↓ *C*: DVTd × 2 cycles q28 days (in DVTd-induced) vs VTd × 2 cycles q28 days (in VTd-induced) ↓ *Second randomization,* M*:* daratumumab × 2 years vs observation	Improved PFS, response, MRD negativity with DVTd, deepened response in each after consolidation
2020	GRIFFIN[16]	207	*I*: DRVd × 4 q21 days vs VRd × 4 q21 days ↓ ASCT ↓ *C*: DRVd × 2 cycles q21 days (in DRVd-induced) vs VRd × 2 cycles q21 days(in VRd-induced) ↓ *M*: DR (in DRVd-induced) vs lenalidomide 10 mg d1-21/28 × 3 cycles then 15 mg d1-21/28 (in VRd-induced); maximum duration of either maintenance treatment: 2 year	Improved PFS, response, MRD negativity with DRVd, deepened response in both arms after consolidation

2021	EMN02/HOVON95[11]	878	*I*: VCd × 3–4 cycles q21 days ↓ *First randomization:* VMP × 4 cycles q6weeks vs single ASCT vs double ASCT (in participating centers) ↓ *Second randomization, C:* VRd × 2 cycles q28 days vs no consolidation ↓ *M*: Lenalidomide 10 mg d1-21/28 until PD	Improved PFS, CR + rate with VRd consolidation compared with no consolidation in lenalidomide-naïve patients
2021	IFM KRd[14]	46	*I*: KRd × 4 cycles q28 days ↓ ASCT ↓ *C*: KRd × 4 cycles q28 days ↓ *M*: Lenalidomide 10 mg d1-21/28 × 13 cycles	Improved ORR, VGPR + rate, CR + rate, sCR rate, MRD rate from post-ASCT to post-consolidation

Abbreviations: ASCT, autologous stem cell transplant; C, consolidation; CR, complete response; I, induction; M, maintenance; MRD, minimal residual disease; ORR, overall response rate; PD, progressive disease, sCR, stringent complete response.

arm only, supporting the added benefit of VTd consolidation. Like in the 2013 Nordic Myeloma Study, an increased rate of peripheral neuropathy (8.1% vs 2.4%) was seen in the participants treated with bortezomib consolidation. This was the first phase 3 clinical trial to compare a triplet vs doublet regimen in both induction and consolidation. There were no arms without consolidation therapy altogether.

The single-arm phase 2 IFM 2008 trial evaluated the combination of bortezomib, lenalidomide, and dexamethasone (VRd), a regimen then known to be effective in the induction setting, as consolidation therapy.[6,7] Thirty-one symptomatic NDMM patients were treated with VRd for 3 cycles, followed by ASCT, 2 cycles of VRd consolidation, and ultimately 1 year of lenalidomide maintenance. The trial demonstrated that the overall response rate (ORR) was 91% after the completion of ASCT and 94% after VRd consolidation and that the stringent CR rate deepened from 36% after ASCT to 39% after VRd consolidation. Expected toxicities including peripheral neuropathy (23%), grade 3 to 4 neutropenia (17%), and thrombocytopenia (10%) were observed, and no treatment-related mortalities occurred. The subsequent IFM 2009 trial, which sought to evaluate the necessity of ASCT in the era of modern therapies, also used VRd consolidation.[8] Patients were randomized after VRd induction to ASCT with 2 cycles of VRd or no ASCT and 5 cycles of VRd. Although no OS difference was detected, transplant followed by consolidation was associated with a PFS advantage and a higher CR and minimal residual disease (MRD) negativity, at the cost of increased toxicity.

The BMT CTN 0702 (STaMINA)[9] trial was a phase 3 clinical trial across 54 centers in the United States. Patients undergoing induction were enrolled on trial, and any induction regimen was permitted. Bortezomib, lenalidomide, dexamethasone (VRd) was most commonly used, composing 57% of the study populations, but others received cyclophosphamide, bortezomib, and dexamethasone; lenalidomide and dexamethasone; bortezomib and dexamethasone; or other regimens. Patients were required to receive at least 2 cycles of any systemic therapy without progression and to be within 2 to 12 months of first dose of initial therapy, resulting in considerable variation in therapy duration before trial enrollment. Participants were randomized to single transplant, single transplant followed by 4 cycles of VRd consolidation, or double transplant. All participants then received maintenance lenalidomide. There was no PFS or OS benefit at 38 months with the addition of VRd consolidation or second ASCT, leading the investigators to conclude that single ASCT without consolidation followed by lenalidomide maintenance should remain the standard of care to avoid unnecessary toxicities. Six-year follow-up data showed similar PFS and OS across all three arms in the intention-to-treat analysis ($P = .6$ for PFS, $P = .8$ for OS).[10] In high-risk patients using as-treated analysis, 6-year PFS was prolonged in the double ASCT arm (43.6%) compared with single ASCT without consolidation ($P = .03$); 6-year PFS for high-risk patients in the ASCT with VRd consolidation arm was not provided.

The European Myeloma Network (EMN) conducted the prospective, open-label phase 3 EMN02/HOVON95 clinical trial to understand the utility of VRd consolidation.[11] They enrolled 1197 participants with untreated multiple myeloma. All patients received induction with vincristine, cyclophosphamide, and dexamethasone (VCd) for 3 to 4 cycles. Importantly, lenalidomide, which was later used in consolidation and maintenance, was absent from the induction regimen. Patients were first randomized to ASCT vs bortezomib, melphalan, and prednisone (VMP) intensification. ASCT demonstrated a PFS benefit over VMP.[12] A second randomization was done for 878 eligible participants to VRd consolidation for 2 cycles followed by maintenance lenalidomide vs maintenance lenalidomide alone. There was a PFS benefit (59.3 months vs 42.9 months, hazard ratio [HR] = 0.81, $P = .016$) favoring the VRd consolidation arm at

a median follow-up of 74.8 months. This result was upheld in most subgroups, except in the high-risk deletion *17p* patients. There was also an improvement in CR or better (59% vs 46%, $P<.001$) in the VRd consolidation arm. This trial established the benefit of VRd consolidation in NDMM who are lenalidomide naïve and received 3 to 4 cycles of VCd. OS was not reached in either arm, indicating the need for longer follow-up.

Given that the STaMINA trial and the EMN02/HOVON95 trial yielded contradictory results on the role of VRd consolidation, it is important to highlight key differences. Of note, in the STaMINA trial, the induction regimen was heterogenous and patients were predominantly lenalidomide-exposed, whereas all patients received VCd induction in the EMN02/HOVON95 trial and were not exposed to lenalidomide until consolidation. The STaMINA investigators suggest that VRd induction, an accepted standard in the United States, is superior to VCd, obviating the need of consolidation or double ASCT. The STaMINA trial had a high rate of nonadherence (up to 32%) with the second intervention, although this may be in line with natural patterns of patient behavior. Another possible interpretation of STaMINA is that the heterogeneity in the drugs and cycles before induction therapy blunted the ability of post-SCT therapies to show a difference.

In more recent years, carfilzomib, a second-generation proteosome inhibitor, has been studied in combination with carfilzomib, lenalidomide, and dexamethasone (KRd), initially in the relapsed/refractory setting and now in the upfront NDMM setting.[13–15] The phase II IFM KRd study administered 4 cycles of KRd induction and ASCT, 4 cycles of KRd consolidation, and 1 year of lenalidomide maintenance to 46 participants.[14] Responses deepened at every step in the treatment regimen, with CR+ rate improving from 41.5% post-ASCT to 64.3% post-consolidation. Notable AEs include two cases of heart failure: a toxicity associated with carfilzomib and five pulmonary embolisms/deep vein thromboses, which may be due to lenalidomide. The most common grade 3 and 4 AEs were cytopenias (74%) and infection (22%). The FORTE trial done across 42 centers in Italy also included an arm with KRd consolidation after KRd induction and ASCT; the comparator arms were 12 cycles of KRd without ASCT and carfilzomib, cyclophosphamide, and dexamethasone (KCd) induction/ASCT/KCd consolidation.[15] The KRd/ASCT/KRd arm had superior responses overall (4-year PFS 69%, compared with 56% in the KRd12 arm and 51% in the KCd/ASCT/KCd arm). In all arms, responses deepened after consolidation. For example, in the KRd/ASCT/KRd arm, VGPR+ rate improved from 82% to 89% and sCR improved from 25% to 46%.

In the ever-evolving field of myeloma, quadruplet regimens have recently been studied in the front line in NDMM; both the GRIFFIN and CASSOPEIA trials included consolidation post-ASCT in their study schema.[16,17] The GRIFFIN trial randomized patients to daratumumab, lenalidomide, bortezomib, and dexamethasone (DRVd) vs RVd. Patients received 4 induction cycles of their assigned regimen, ASCT, then 2 consolidation cycles, followed by maintenance daratumumab and lenalidomide (DR) in the DRVd arm vs lenalidomide alone in the RVD arm for up to 2 years. DRVd proved to have better PFS, response, and MRD negativity rate. With regard to consolidation, response deepened after consolidation therapy in both arms (sCR improved from 21.2% to 42.4% and VGPR+ improved from 86.9% to 90.9% in the DRVd arm; sCR improved from 14.4% to 32%; and VGPR+ improved from 66% to 73.2% in the RVd arm). The CASSOPEIA trial similarly randomized 1085 patients to a quadruplet of daratumumab VTd (DVTd) or VTd induction, followed by ASCT, then DVTd or VTd consolidation. DVTd improved PFS, depth of response, and MRD negativity much like the GRIFFIN trial; consolidation deepened responses in both arms (sCR 13.4% to 28.9% and VGPR+ 76.7% to 83.% in the DVTd arm; sCR 9.4% to 20.3%; and

VGPR+ 67.4% to 78% in the VTd arm). Both trials did not include treatment arms without consolidation, making it difficult to make definitive conclusions about the added utility of consolidation.

A novel approach in recent trials has been using a response-adapted fixed treatment duration strategy to administer consolidation to certain patients. The MASTER trial treated patients with daratumumab KRd (DKRd), ASCT, followed by 0, 4, or 8 cycles of KRd consolidation based on MRD status (assessed after induction, after ASCT, and every 4 weeks during consolidation).[18] Once MRD negativity was attained for two consecutive time points, all therapy was discontinued. Eighty percent of patients were able to reach MRD negativity with this approach, and 2-year PFS was 87%. Extended follow-up data demonstrated that patients with two or more high-risk cytogenetic abnormalities (HRCAs) had worse 3-year PFS (51% compared with 91% and 97% in individuals with 0 or 1 high-cytogenetic features, $P < .001$) and OS (75% compared with 96% and 91%, $P = .004$), suggesting that alternative strategies are necessary for ultra-high-risk patients.[19] The ongoing open-label, single-arm CONPET trial (NCT03314636) instead uses an imaging-guided approach and aims to administer KRd consolidation to PET-CT positive patients after induction (VRd, VTd, or VCd) and ASCT.[20]

Maintenance

Numerous maintenance trials have investigated different maintenance regimens, as single-agent therapy or multi-agent combinations and as fixed-duration, indefinite, or response-adapted. The authors review here pivotal trials and provide details on study drugs, therapy duration, and adverse effects (**Table 2**).

Thalidomide, an immunomodulatory agent (IMiD), is rarely used in the United States since the advent of lenalidomide. However, thalidomide is still widely used in many parts of the world and has been studied at doses of 50 to 200 mg.[21] The MMC Myeloma IX trial compared indefinite thalidomide maintenance at up to 100 mg if tolerated to observation after induction (with either intensive therapy including transplant or non-intensive therapy based on patient performance status).[22] Thalidomide maintenance prolonged PFS (23 vs 15 months, HR = 1.45, log-rank $P < .001$) but did not impact OS. Fifty-two percent of patients discontinued the trial early due to AEs, including paresthesias, drowsiness, constipation, skin conditions, hematological events, infection, thrombosis, and tremor. Owing to the early discontinuation of maintenance, median time on therapy was only 7 months despite intended indefinite therapy until progression. There was an equal rate of secondary malignancy between the maintenance and observation arms. The investigators conducted a meta-analysis of five existing thalidomide maintenance trials including their own, when pooling data, thalidomide significantly prolonged OS ($P = .047$) and had a late survival benefit (4% survival benefit at 3 years and 12.3% survival benefit at 7 years).

Single-agent lenalidomide is a mainstay of maintenance therapy in the United States and increasingly around the world and has been evaluated in numerous trials. The IFM investigators evaluated 614 patients treated with lenalidomide, administered as consolidation 25 mg on day 1 to 21 (out of a 28 day cycle) for 2 cycles followed by maintenance 10 mg daily for 3 months with dose escalation to 15 mg, vs placebo for a fixed duration of 2 years.[23] The trial demonstrated an improvement in PFS in the lenalidomide arm (41 vs 23 months, HR = 0.50, $P < .001$) with no difference in OS at long-term 5 year follow-up.[23,24] Thromboembolic events (6% vs 2%, $P = .01$), grade 3 to 4 cytopenias, and secondary malignancy (3.1 vs 1.2 per 100 patient-year, $P = .002$) were more common in the lenalidomide group. Lenalidomide was stopped early in January 2011 after a median duration of 27 months in 119

Table 2
Clinical trials examining the maintenance therapies in multiple myeloma

Year	*N*	Study	Maintenance	Induction, ASCT, Consolidation	Outcomes	AEs
THALIDOMIDE						
2012	820	MMC Myeloma IX[22]	Thalidomide 50 mg × 4 weeks, then 100 mg until PD vs observation	*If intensive pathway:* *I*: CVAD × 4–6 cycles q28 days vs CTD × 4–6 cycles q28 days ↓ ASCT *If non-intensive pathway:* *I*: MP q28 days vs attenuated CTD q28 days	Maintenance prolonged PFS, no change in OS	Increased infection in thalidomide maintenance arm (intensive pathway), increased rate of any serious AE in thalidomide maintenance arm (both intensive and non-intensive pathway)
LENALIDOMIDE						
2012	614	IFM 2005–02[23,24]	Lenalidomide 10 mg daily × 3 months, then 15 mg vs placebo. Stopped early in 119 participants, after median 27 months) due to increased secondary cancers	*I*: variable ↓ ASCT ↓ *C*: Lenalidomide 25 mg d1-21/28 × 2 cycles	Maintenance prolonged PFS, 5-year OS unchanged	Increased cytopenias, thromboembolic events, and secondary malignancy in lenalidomide maintenance arm
2014	251	RV-MM-209[26]	Lenalidomide 10 mg d1-21/28 until PD vs observation	*I*: Rd × 4 cycles q28 days ↓ *C*: MP × 6 cycles q28 days vs ASCT (with melphalan 200 mg/m^2 monthly × 4 doses prior)	Maintenance prolonged PFS, OS improvement not statistically significant	Increased rate of neutropenia and skin reactions in lenalidomide maintenance arm

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Year	*N*	Study	Maintenance	Induction, ASCT, Consolidation	Outcomes	AEs
2017	460	CALGB 100104[25]	Lenalidomide 10 mg daily × 3 months, then 15 mg daily until PD vs placebo	*I*: Variable ↓ ASCT	Maintenance prolonged time to progression, OS	Increased cytopenias and secondary cancers in lenalidomide maintenance arm
2019	1917	Myeloma XI[28]	Lenalidomide 10 mg d1-21/28, until PD vs observation	*If intensive pathway:* *I*: CTD × 4+ cycles vs CRD × 4+ cycles vs KCRd × 4+ cycles ↓ ASCT *If non-intensive pathway:* *I*: attenuated CTD × 6+ cycles vs attenuated CRD × 6+ cycles	Maintenance prolonged PFS, 3-year OS improvement was not statistically significant	Most common grade 3–4 AE in maintenance arm were neutropenia (33%), thrombocytopenia (7%), and anemia (4%)
BORTEZOMIB						
2012	827	HOVON-65/GMM-HD4[32]	Bortezomib 1.3 mg/m^2 every 2 weeks in PAD arm vs thalidomide 50 mg daily in VAD arm	*I*: PAD × 3 cycles q28 days vs VAD × 3 cycles q28 days ↓ ASCT	CR, PFS, OS prolonged in bortezomib arm	Peripheral neuropathy increased (40% vs 18%) in bortezomib arm
IXAZOMIB						
2018	656	TOURMALINE-MM3[33]	Ixazomib 3 mg d1, 8, 15/28 × 5 cycles, then 4 mg vs placebo. Maintenance up to 2 years	*I*: Variable, must include PI or IMiD ↓ ASCT	5.2 month PFS benefit with ixazomib	Equal rate of secondary malignancy

CARFILZOMIB						
2022	168	CARFI[34]	Carfilzomib 27 mg/m^2 every other weeks × 4 weeks, then 56 mg/m^2 + dexamethasone 20 mg every other week vs observation	*I*: KCd × 4 cycles q28 days ↓ ASCT	Improved PFS with maintenance, OS benefit not statistically significant	Increased thrombocytopenia anemia, dyspnea, and bacterial infection in the Kd maintenance arm
DARATUMUMAB						
2021	886	CASSOPEIA	Daratumumab 16 mg/kg q8 weeks × 2 years vs observation	*First randomization, I*: DVTd × 4 cycles q28 days vs VTd × 4 cycles q28 days ↓ ASCT ↓ *C*: DVTd × 2 cycles q28 days (in DVTd-induced) vs VTd × 2 cycles q28 days (in VTd-induced)	Improved PFS in daratumumab-naïve patients	Increased lymphopenia in daratumumab maintenance arm, 2 fatalities (sepsis, NK-lymphoblastic leukemia) due to daratumumab
LENALIDOMIDE + BORTEZOMIB						
2013	45, high-risk	Nooka et al[37]	Lenalidomide 10 mg d1-21/28, bortezomib 1.3 mg/m^2 weekly, dexamethasone 40 mg weekly (VRd) × 3 years followed by lenalidomide maintenance	*I*: Variable ↓ ASCT	PFS 32 months, 3-year OS 93%	Dose modification in 40% patients, no early cessation of therapy due to AE, no new grade 3–4 neuropathy
2020	1000	Joseph et al[38]	Variable; 1000 patients with RVD induction followed, 107 received IMiD + PI	*I*: RVd ↓ Non-randomized: Upfront or deferred ASCT	PFS 40.3, OS 78.2 in IMiD + PI group	Not described in article

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Year	*N*	Study	Maintenance	Induction, ASCT, Consolidation	Outcomes	AEs
LENALIDOMIDE + DARATUMUMAB						
2020	207	GRIFFIN[16]	Daratumumab 16 mg/kg IV q4-8 weeks + lenalidomide 10 mg d1-21/28 × 3 cycles then 15 mg vs lenalidomide alone. DR or R up to 2 years	*I*: DRVd × 4 q21 days vs VRd × 4 q21 days ↓ ASCT ↓ *C*: DRVd × 2 cycles q21 days (in DRVd-induced) vs VRd × 2 cycles q21 days (in VRd-induced)	Improved PFS, response, MRD negativity with DRVd, deepened response at each stage of therapy	Increased grade 3-4 hematological AE and infections with DRVd vs RVd, similar grade 3–4 infection in both arms
LENALIDOMIDE + CARFILZOMIB						
2021	356	FORTE[15]	Lenalidomide 10 mg d1-21/28 + carfilzomib 70 mg IV d1, 15 vs lenalidomide alone. Carfilzomib up to 2 years, lenalidomide until progression	*First randomization:* *I*: KRd × 4 cycles[a] → ASCT → C: KRd × 4 cycles[a] vs *I*: KRd × 12 cycles[a] vs *I*: KCd × 4 cycles[a] → ASCT → C: KCd × 4 cycles[a] [a]All cycles q28 days	Improved 3-year PFS, MRD conversion in doublet arm	Most common grade 3-4 AEs were neutropenia (20% in KR vs 23% in R), infection (5% vs 7%), and vascular events (7% vs 1%)
2023	180	ATLAS[42]	Carfilzomib 36 mg/m^2 d1, 2, 8, 9, 15, 16/28 during cycle 1–4, then carfilzomib 36 mg/m^2 on d1, 2, 15, 16/28 from cycle 5–36, lenalidomide 25 mg d1-21/28, dexamethasone 20 weekly (KRd) × 36 cycles then lenalidomide alone until PD vs lenalidomide 10 mg daily for 3 cycles, then 15 mg daily until PD	*I*: Variable ↓ ASCT	Improved PFS in triplet maintenance arm	Most common grade 3-4 AE were neutropenia (48% in KRd vs 60% in R), thrombocytopenia (13% vs 7%), and lower respiratory tract infection (8% vs 1%)

Abbreviations: IMiD, immunomodulatory agent; NK, natural killer; PI, proteosome inhibitor.
[a] All cycles q28 days.

patients due to the signal for increased secondary malignancy. The CALGB 100104 trial randomized 460 post-ASCT participants to indefinite lenalidomide 10 mg daily (with dose escalation permitted at 3 months to 15 mg) vs placebo.[25] Time to progression was prolonged in the lenalidomide group (57.3 months vs 28.9 months, HR = 0.57, $P < .001$) as was median OS (113.8 months vs 84.1 months, HR = 0.61, $P < .004$). Cytopenias and secondary malignancies were increased in the maintenance arm (7.8% hematological malignancies, 6.1% solid tumors in lenalidomide arm vs 1.3% hematological malignancies, and 3.9% solid tumor in the placebo arm). The Italian RV-MM-209 used a 2-by-2 factorial design; after induction lenalidomide and dexamethasone, patients underwent first randomization to melphalan SCT or melphalan, prednisone, and lenalidomide consolidation.[26] The trial then performed a second randomization to lenalidomide 10 mg on day 1 to 21 (out of a 28 day cycle) until progression vs observation and demonstrated a PFS advantage (41.9 vs 21.6 months, HR = 0.47, $P < .001$) without a statistically significant OS benefit at 3 years (88% vs 79.2%, HR = 0.62, $P = .14$).[26] There was an increased rate of neutropenia (23.3% vs 0%) and skin reactions (4.3% vs 0%) in the lenalidomide arm. Of note, a meta-analysis of IFM 2005 to 02, CALGB 100104, and RV-MM-209 did in fact show both a PFS and OS benefit (not reached in lenalidomide maintenance vs 86.0 months in placebo/observation group, at median follow-up of 79.5 months).[27]

The Myeloma XI trial, which had not completed accrual at the time of the above meta-analysis, used an adaptive design with three potential randomizations at induction, intensification, and maintenance.[28] At the maintenance stage, the trial randomized participants to indefinite lenalidomide 10 mg on day 1 to 21 (out of a 28 day cycle) or observation and demonstrated a statistically significant PFS benefit (39 vs 20 months, HR = 0.46, $P < .001$) and 3-year OS increase (78.6% vs 75.8%, HR = 0.87, $P = .15$) that was not statistically significant. Updated long-term follow-up data indicated that the benefit of lenalidomide persisted beyond 3 years, but the magnitude of benefit diminished after 4 to 5 years in all comers and even earlier in patients who achieved MRD negativity after transplant.[29] However, caution should be used as this was a post-hoc analysis with a diminishing number of patients continued on therapy beyond 4 years.

Although these lenalidomide maintenance trials vary in terms of lenalidomide dose, schedule, duration, and presence of placebo or observation as a comparator arm, they all uniformly show a benefit of either PFS or time to progression and some demonstrate an OS advantage. However, the optimal duration remains unclear. Many patients may be unable to continue the initial maintenance lenalidomide dose of 10 to 15 mg indefinitely, particularly real-world patients that may have comorbidities. Importantly, the dose of lenalidomide during maintenance must be adjusted for renal function as per the prescribing label. The Myeloma XI trial demonstrated that 69% of patients required dose modification, and 594 of 1137 (52%) in the lenalidomide maintenance arm had discontinued therapy after a median follow-up of 31 months, due to disease progression, death, AE, patient preference, or other.[28] The RV-MM-209 trial in contrast demonstrated that 11% of patients discontinued therapy, either due to AE, withdrawal of consent, or investigator's decision after a median follow-up of 51.2 months.[26]

Until prospective, risk-adapted studies are available, physicians should consider a patient's genomic and functional risk (ie, depth of response attained) as well as long-term toxicities of lenalidomide, including cytopenias, rash, venous thromboembolism, and secondary malignancy, when determining optimal dosing and duration for individual patients. Cost is also an important consideration, though there is increasing availability of generic lenalidomide globally.

There are no data to our knowledge evaluating pomalidomide, iberdomide, or mezigdomide as maintenance after front-line SCT. There are existing data evaluating these agents for maintenance of salvage ASCTs, which are beyond the scope of this article.[21,30,31]

Thus far, the authors have discussed IMiDs, but proteasome inhibitors can also be used for maintenance therapy. The HOVON-65/GMM-HD4 trial randomized patients to a regimen VAD induction, ASCT followed by thalidomide 50 mg daily maintenance, or bortezomib, doxorubicin, dexamethasone (PAD) induction followed by ASCT and bortezomib 1.3 mg/m^2 every 2 weeks.[32] Bortezomib maintenance had superior CR/near-CR (49% vs 34%, $P < .001$). At a median follow-up of 41 months, the PAD/ASCT/bortezomib arm outperformed the VAD/ASCT/thalidomide arms in terms of PFS (35 vs 28 months, HR = 0.75, $P = .002$) and OS (per multivariate analysis, HR = 0.77, $P = .49$). This benefit persisted in high-risk patients, including those harboring a *17*p deletion. However, owing to the variable induction regimens, it is challenging to attribute the superior responses to bortezomib maintenance alone. The rate of peripheral neuropathy in the first year of therapy was increased in the bortezomib arm compared with thalidomide (40% vs 18%, HR = 1.50, $P < .001$). If considering bortezomib maintenance, providers must keep in mind the potential irreversibility of neuropathy and the fact that it can interfere with balance and ambulation, a consequence that may be particularly devasting in the elderly. Bortezomib in addition requires frequent in-person visits to an infusion center, which poses an inconvenience to patients but may be favorable if compliance is under question with oral medications.

The TOURMALINE-MM3 trial evaluated the effectiveness of ixazomib, a second-generation oral proteosome inhibitor, in 656 participants.[33] Post-ASCT patients were randomized 3:2 to oral ixazomib 3 mg on day 1, 8, 15/28 (with increase to 4 mg at cycle 5 if tolerable) vs placebo, for a duration of 2 years. The trial met its primary endpoints, with a PFS benefit favoring ixazomib (26.5 vs 21.3 months, HR = 0.72, $P = .0023$). The rate of secondary malignancy was equal across both arms (3%), unlike results seen in many lenalidomide trials. Although generally well tolerated, ixazomib has not been taken up widely in clinical practice given that magnitude of PFS benefit is short compared to lenalidomide.

Carfilzomib, an intravenous second-generation proteosome inhibitor has been recently studied in the maintenance setting. The phase 2 CARFI trial enrolled relapsed myeloma patients and administered 4 cycles of KCd followed ASCT.[34] Of 200 patients who were enrolled, 168 patients were then randomized to carfilzomib (27 mg/m^2 every other week, dose escalated to 56 mg/m^2 after 4 weeks) and dexamethasone 20 mg every other week or observation. The median time to progression was 25.1 months in the maintenance arm and 15.7 months in the observation arm (HR = 0.46, $P = .004$). OS was not reached in the maintenance arm compared with 44.5 months in the observation arm, although this difference was not statistically significant (HR = 0.47, $P = .10$). Like other maintenance therapies previously discussed, carfilzomib most commonly caused hematological toxicity (thrombocytopenia in 29% vs 21%, anemia in 58% vs 44%). Notable non-hematological toxicities include dyspnea (24% vs 11%) and bacterial infections (41% vs 26%).

Daratumumab, an anti-CD38 monoclonal antibody now included in many upfront triplet and quadruplet regimens, was studied as maintenance therapy in the CASSOPEIA trial.[35] As discussed earlier, transplant-eligible patients were randomized to DVTd vs VTd as induction and consolidation. Next, a second randomization was performed to daratumumab maintenance at 16 mg/kg IV every 8 weeks for up to 2 years vs observation. Daratumumab maintenance prolonged PFS (not reached vs 35.4, HR = 0.53, $P < .0001$) and increased conversion to MRD negativity (44% vs 30%,

odds ratio = 1.84, nominal P = .004). However, an important caveat is that the PFS benefit only existed in the daratumumab-naïve patients who received VTd (HR = 0.32, nominal $P < .001$), not in the daratumumab-exposed patients who received DVTd (HR = 1.02, nominal P = .91). In addition, the every 8 week dosing schedule that was used is not standard; pharmacokinetic data shows that the drug should be dosed long-term at an every 4 week schedule after initial weekly then biweekly dosing.[36] Longer follow-up data are required as the highest rates of MRD negativity attained were in patients who received daratumumab before and after SCT. Lymphopenia was increased in the daratumumab arm (4% vs 2%). Two deaths were attributed to the drug (septic shock and natural killer-cell lymphoblastic leukemia).

Ongoing research in recent years has evaluated multi-agent maintenance regimens, particularly in high-risk patients who have worse prognoses. In an observational study, Nooka and colleagues at Emory reported the outcomes of 45 patients with HRCAs (deletion *17p*, deletion *1p*, t(4;14), t(14;16), or plasma cell leukemia), treated with 3 years of RVd maintenance followed by a de-escalation to lenalidomide maintenance.[37] PFS was 32 months, 3-year OS was 93%, and best response was VGPR or better in 96% of patients. No patients terminated therapy early due to AEs. In their larger observational study following 1000 patients induced with RVd, 251 had high-risk cytogenetic features and 107 received a combination of an IMiD+ proteosome inhibitor (most commonly RVd), with a median PFS of 40.3 months and OS of 78.2 months.[38] The GRIFFIN trial used a DR doublet for 2 years in the DRVd induction arm, after which daratumumab was discontinued and only lenalidomide was continued until progression.[16]

The much-awaited phase 3 AURGIA trial (NCT03901963) will compare head-to-head DR to lenalidomide alone in both standard and high-risk patients who are anti-CD38 naïve and are MRD+ after SCT.[39] The DRAMMATIC trial (NCT04071457) will include both anti-CD38 exposed and naïve patients, randomized to DR or lenalidomide alone for 2 years, with a second randomization at the 2 year mark of MRD negative patients to discontinuation of therapy or ongoing therapy up to 7 years.[40] The maintenance component of the FORTE trial randomized patients to carfilzomib and lenalidomide for 2 years or lenalidomide alone and demonstrated improved 3-year PFS (75% vs 65%, P = .023) and MRD conversation (46% vs 30%, P = .046), without a statistically significant difference in 3-year OS (94% vs 90%).[15] Preplanned cytogenetic subgroup analysis showed that patients with more high-risk features had worse 4-year PFS (71% if 0 HRCA, 60% if 1 HRCA, and 39% if 2 or more HRCAs) and 4-year OS (94%, 83%, and 63%, respectively).[41] These findings reiterate the need for refined strategies for ultra-high-risk patients with 2 or more HRCAs. Interim analysis of ATLAS trial, which compares 3 years of KRd maintenance to lenalidomide alone, demonstrated an improved median PFS with triplet therapy (59.1 vs 31.4 months, HR = 0.51, P = .01).[42]

SUMMARY

The authors demonstrate that many consolidation therapies have been used in multiple myeloma, including single-agent bortezomib, VRd, VTd, KRd, KCd, DVRd, and DVTd. As illustrated, many trials include consolidation in their study schema and demonstrate that response and MRD negativity deepen from post-ASCT values to post-consolidation values. However, in these studies, it is difficult to definitely ascertain whether such improvements are directly a result of the consolidation or due to lasting effects of potent induction therapy and ASCT. Two recent pivotal trials that directly compared consolidation to no consolidation were the EMN02/HOVON95 and BMT

CTN 0702 (STaMINA) trials.[10,12] EMN02/HOVON95 found improved PFS and response rates with VRd consolidation compared with no consolidation in lenalidomide-naïve patients but used VCd induction which arguably is inferior to VRd induction. The STaMINA trial did not standardize induction regimens but demonstrated no added benefit to VRd consolidation post-ASCT and risk of added toxicity. In the present day, clinical practice on the routine use of consolidation varies, based on geographic region of practice, patient fitness, and response after induction and ASCT.

The authors show that there are many options for maintenance therapy in multiple myeloma, including single agents which generally are acceptable for standard-risk patients and doublets which are of interest particularly in high-risk patients. The authors demonstrate that maintenance therapy prolongs PFS or time to progression, with mixed results regarding OS. Debate still exists as to the optimal duration of therapy, as the magnitude of benefit seems to diminish with time and maintenance can lead to drug-resistance and long-term toxicities including secondary malignancies.

SUMMARY AND FUTURE DIRECTIONS

Given that high-risk individuals have worse outcomes despite advances in therapy, myeloma researchers need to first refine the definition of high-risk disease. Genomic high risk must be segregated into no risk factors, single-hit, or double-hit characteristics. Functional high risk, defined as patients who relapse within 12 months or have persistent disease based on dynamic assessments MRD testing and imaging, must be considered as well. Although there has been much excitement about MRD testing, currently this test primarily has prognostic and not predictive value. The authors anticipate that this will evolve over the coming years, as trials use MRD and other dynamic assessments to guide treatment intensity and duration.[40]

The authors eagerly await data from randomized prospective genomic and functional risk-stratified studies to guide practice. Until then, if a patient is lenalidomide- or daratumumab-naïve and/or is functionally-high risk with measurable or MRD-positive disease and/or received induction therapy for 3 to 4 cycles without attaining a CR, then 2 cycles of triplet/quadruplet consolidation may be considered. In the absence of these features, the benefit of consolidation is unclear based upon current data. When clinicians use more than single-agent maintenance therapy, they need to consider both AEs and quality of life concerns, including time commitment to receiving IV/SC therapy in an infusion center and cost. Avoiding overtreatment in patients who do not benefit from additional therapy is important. The authors suggest that single-agent maintenance therapy is sufficient in standard-risk MRD-negative myeloma. The longer such patients remain MRD-negative, the more any AEs experienced by the patient should drive a discussion with the patient about the pros/cons of continued therapy. For high-risk patients and possibly standard-risk MRD-positive patients, more-intensified doublet maintenance approaches until progression should be considered.

Drug refractoriness should also be considered when determining the optimal duration of maintenance therapy. Lenalidomide refractoriness has been associated with worse outcomes including OS compared with lenalidomide-exposed non-refractory patients; however, this is offset by the OS benefit even in CALGB 100104 study where lenalidomide was used until progression.[25,43] Now, the long-term impact of anti-CD38 refractoriness is unknown and caution should be used with using these agents in the maintenance setting until progression.

Novel therapies, including bi-specific T-cell engagers and chimeric antigen receptor (CAR) T-cells, have been an exciting new development in relapsed myeloma.

Preliminary data for ciltacabtagene autoleucel in functional high-risk patients are already encouraging.[44] The role of these agents in consolidation and maintenance is an area of active investigation with several trials ongoing, including the following: NCT05846737 BCMA CAR-T Cell Therapy in High-risk NDMM Patients With Positive MRD After First-line ASCT evaluating BCMA-directed CAR-T in MRD positive patients post-ASCT, NCT05632380 ASCT in Combination With C-CAR088 for Treating Patients With Ultra High-risk Multiple Myeloma (MM) investigating a BCMA-directed CAR-T 3 days post-ASCT in ultra-high risk patients, CARTITUDE-5 (NCT04923893) comparing DRVd followed by ASCT and DRVd followed by ciltacabtagene autoleucel, and MagnestisMM-7 (NCT05317416) studying elranatamab monotherapy vs lenalidomide monotherapy as maintenance post-ASCT. Of particular interest will the ability of these highly potent therapies, after a fixed duration of therapy, to provide a treatment-free interval after frontline therapy is completed.

CLINICS CARE POINTS

- Clinical trials evaluating the role of short-duration consolidation therapy after autologous stem cell transplant have shown mixed results. EMN02/HOVON95 showed a progression -free survival (PFS) advantage with bortezomib, lenalidomide, and dexamethasone (VRd) consolidation in lenalidomide-naïve patients, whereas STaMINA did not show an added benefit for VRd consolidation.
- Single-agent lenalidomide is the mainstay for maintenance therapy for standard-risk myeloma in the United States.
- Doublet maintenance strategies are being investigated, particularly for high-risk patients.
- The optimal duration of maintenance therapy is unknown. Adverse events, secondary malignancy, drug resistance, quality of life, cost, PFS and overall survival endpoints need to be considered.

DISCLOSURE

A. Chari: Consulting: Abbvie, Adaptive, Amgen, Antengene, Bristol Myers Squibb, Forus, Genetech/Roche, Glaxo Smith Klein, Janssen, Karyopharm, Millenium/Takeda, Sanofi/Genzyme. Research: Janssen. *A. Kumar*: Research: Janssen, BMS.

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