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Consolidation and Maintenance Therapies for Newly Diagnosed Multiple Myeloma in the Era of Novel Agents

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Abstract Advances in therapy in multiple myeloma have resulted in significant improvements in patient outcomes; however, relapse remains problematic. Strategies to improve outcomes following autologous stem cell transplantation (ASCT) include consolidation to intensify therapy and improve depth of response and maintenance therapy to achieve long-term disease control. Immunomodulatory drugs (IMiDs), including thalidomide and lenalidomide, are appealing as maintenance therapy given their oral administration; however, the cumulative toxicities of thalidomide have limited its efficacy in maintenance therapy. Maintenance lenalidomide is better tolerated, and multiple studies have demonstrated an improvement in progression-free survival (PFS), but its impact on overall survival (OS) remains controversial. Additional concerns regarding the risk of second primary malignancies and significant cost of long-term lenalidomide therapy have also been raised. Proteasome inhibitors, particularly, bortezomib have also been incorporated in consolidation and maintenance regimens alone or in combination with an IMiD. Preliminary studies have suggested bortezomib maintenance may benefit patients with adverse cytogenetics, including *t*(4;14) and deletion 17p. Determination of the optimal consolidation and maintenance regimen and duration of therapy post-transplantation is a focus of several ongoing randomized studies.

Keywords Consolidation · Maintenance · Multiple myeloma

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Introduction

With the advent of novel agents in multiple myeloma (MM), survival has improved considerably; however, it remains an incurable disease. Autologous stem cell transplantation (ASCT) remains a standard approach for transplant-eligible patients following induction therapy. Due to improved supportive care, ASCT is increasingly employed in fit patients over age 70. The use of novel agents including proteasome inhibitors and immunomodulatory drugs (IMiDs) as part of induction therapy prior to ASCT has led to improved depth of response and resulted in some patients opting to delay transplant until the time of disease relapse. Long-term outcomes improve by deepening response post-transplant, evidenced by the superior outcomes of patients achieving stringent complete response [1•]. Complete responses following induction with modern triplet therapy regimens are now frequent and in accordance, more sensitive techniques such as multiparameter flow cytometry and molecular sequencing to detect minimal residual disease (MRD) need to be incorporated into routine clinical practice. Patients achieving an MRD-negative status following treatment appear to have significantly improved progression-free survival (PFS) [2, 3] and, in some studies, a prolonged overall survival (OS) [4–8] compared with their MRD-positive counterparts. As more-sensitive assays become available, detection of MRD may assist in the identification of patients who will most benefit from consolidation and maintenance therapies. A second ASCT (tandem transplantation) may improve overall survival

in a subset of patients and remains a valid consolidation strategy for patients who do not achieve at least a very good partial response post-ASCT [9].

Early attempts at immunotherapy using interferon α2-b as maintenance treatment following induction chemotherapy and ASCT suggested a survival benefit, but a meta-analysis of 12 studies spanning a decade failed to demonstrate a survival benefit [10]. Immunotherapy remains an attractive option for maintenance therapy and the emergence of monoclonal antibodies including daratumumab, elotuzumab, and SAR650984 as well as novel peptide vaccines and PD-1 inhibitors has brought renewed interest to this area. Significant controversies remain regarding the optimization and benefit of post-transplantation consolidation and maintenance therapy. This review will discuss data on the use of novel agents for consolidation and maintenance therapy and will discuss future directions for post-transplantation therapy.

Consolidation Therapy

The term "consolidation" is typically used for a short duration of intensified therapy aimed at improving depth of response. Therapy with novel agents given for a limited period (2–4 cycles) following high-dose melphalan therapy has demonstrated a positive impact on depth of response in several recent trials. The Nordic Myeloma Study Group randomized 370 newly diagnosed, bortezomib naive MM patients following single ASCT to bortezomib consolidation versus no consolidation [11]. The most common induction regimen for both groups was cyclophosphamide and high-dose dexamethasone. Bortezomib was given intravenously at 1.3 mg/m^2 days 1, 4, 8, and 11 for the first 2 cycles, then days 1, 8, and 15 per 21 day cycle for the last 4 cycles. Median PFS improved to 27 months compared to 20 months with bortezomib consolidation ($p = 0.05$); however, no difference in OS was detected after median follow-up of 38 months. The study showed a significantly prolonged PFS of 27 versus 20 months in favor of the bortezomib consolidation group. The rate of VGPR also improved to 71 % with bortezomib consolidation versus 57 % in the control arm. The PFS benefit was limited to patients who attained less than a VGPR post-ASCT, suggesting patients with VGPR or better following transplant may not benefit from bortezomib consolidation. In this study, no major interference with quality of life and severe treatment related toxicities was infrequent, but the treatment period was relatively short.

Combination consolidation therapy with the goal of further cytoreduction post-transplant has been evaluated in several trials and may provide further benefit. The GIMEMA-MMY-3006 phase III study randomized induction and consolidation therapy for 2 cycles to VTD (bortezomib, thalidomide, and dexamethasone) versus TD (thalidomide, dexamethasone) in newly diagnosed MM patients undergoing double ASCT. Following the second ASCT, the rates of CR in the VTD and TD induction therapy arms were not significantly different (48.7 vs 40.4 %; $p = 0.131$) [12]. After 2 cycles consolidation with VTD, the CR and CR/near-CR rates significantly improved to 60.6 and 73.1 %, respectively, compared to 46.6 and 60.9 % following TD consolidation ($p = 0.012$). An interim update after a median follow-up of 65 months observed a median PFS of 57 months in the VTD arm compared to 42 months for patients in the TD arm (HR = 0.67; $p = 0.001$); however, no difference in overall survival at 5 years was observed (80 vs 73 %) [13].

Several smaller studies have also demonstrated the potential benefit of VTD consolidation following ASCT. VTD consolidation was used in a group of 39 patients achieving at least VGPR following ASCT to assess impact on residual disease measured by an immunoglobulin heavy chain rearrangement derived PCR tumor-marker [14]. Molecular remission, defined as PCR negativity, increased from 3 % pre-consolidation to 18 % following 4 cycles of VTD. At a median follow-up of 42 months, no patients achieving molecular remission had relapsed. To evaluate the effect of VTd consolidation following single ASCT, the IFM group retrospectively evaluated 121 newly diagnosed MM patients who underwent three VTd induction and two consolidation cycles (bortezomib 1.3 mg/m^2 IV days 1, 4, 8, and 11, thalidomide 100 mg/day PO, dexamethasone 40 mg PO weekly for 21 days) following single ASCT with melphalan 200 mg/m^2. In a second cohort, 96 patients matched by baseline characteristics who underwent only VTd induction and ASCT without consolidation were identified. The rate of CR was significantly higher at 52 % in the post-VTd consolidation group compared to 30 % in the no consolidation post-ASCT group ($p = 0.001$) [15]. In summary, several studies have demonstrated improved PFS and depth of response following VTD consolidation; however, a translation to an improved overall survival has yet to be established. As long-term data mature from trials such as the GIMEMA-MMY-3006 study, the impact on overall survival may become clearer.

At the annual ASCO 2015 meeting, Straka et al. presented further evidence of a PFS benefit of consolidation post-transplant with bortezomib. Patients were randomized 1:1 to bortezomib (1.6 mg/m^2 days 1, 8, 15, 22 every 35 days) for 4 cycles versus observation post-transplant [16]. Median PFS was 34 months versus 28 months in the bortezomib and observation arms, respectively (HR 0.70, $p = 0.0089$). Subgroup analysis demonstrated that high-risk cytogenetics patients benefitted from bortezomib consolidation with an estimated 7-month improvement in PFS.

Lenalidomide, due to its improved efficacy and tolerability over thalidomide, has been evaluated for consolidation therapy either alone or in combination. An IFM phase 2 study of 31 patients evaluated RVD (lenalidomide 25 mg PO days 1–14, bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11, and

dexamethasone 40 mg on days 1, 8, and 15 per 21 day cycle) consolidation for 2 cycles following RVD induction and ASCT [17]. Stringent CR (sCR) increased to 40 % ($n=12$) from 27 % ($n=8$) after consolidation therapy and VGPR increased from 23 to 37 %, although neither the rates of sCR plus CR significantly change (47 to 50 %) nor did the MRD negative status by flow cytometry after consolidation therapy (54 to 58 %).

RVD consolidation followed by prolonged lenalidomide maintenance in the context of early versus delayed ASCT is being evaluated currently in a large randomized phase III study conducted by the IFM-Dana-Farber group. The IFM group has completed accrual, and these results were recently reported by Attal et al. at the annual ASH 2015 meeting [18]. Seven hundred newly diagnosed, transplant-eligible MM patients were equally randomized to RVD for 8 cycles followed by maintenance lenalidomide for 1 year versus RVD for 3 cycles, ASCT conditioned with melphalan 200 mg/m^2, RVD consolidation for 2 cycles, then lenalidomide maintenance. Patients in the delayed transplant arm underwent stem cell mobilization after 3 cycles, and ASCT was planned at time of relapse. After median follow-up of 39 months, upfront ASCT significantly improved PFS (HR 1.5; $p<0.0002$) and 3-year PFS rate was 61 % in the ASCT group versus 48 % in the RVD arm. The CR rate was higher in the ASCT arm at 58 versus 46 % in the RVD alone group ($p<0.01$). Median OS was similar in both arms at 3 years (88 %). The US trial using similar design but with lenalidomide until progression is ongoing. Based on current data, early ASCT in transplant-eligible patients remains the standard of care even in the era of highly active triplet regimens.

The ongoing BMT CTN 0702 (STaMINA) study is designed as a phase III trial of tandem autologous transplants plus maintenance therapy versus the strategy of single autologous transplant plus consolidation therapy with RVD followed by maintenance therapy or single autologous transplant plus maintenance therapy as part of upfront treatment of multiple myeloma (MM). Lenalidomide is used as maintenance therapy for 3 years in all arms. The primary objective is to compare 3-year PFS between the three treatments arms with secondary outcomes of rates of disease response, OS, grade ≥3 adverse events, and a comparison of quality of life. A novel, entirely oral regimen of IRD (ixazomib, lenalidomide, dexamethasone) as consolidation therapy, is also undergoing evaluation in a multisite phase II study. Following ASCT and 4 cycles of IRD consolidation, the primary endpoint of MRD negativity by next-generation sequencing will be evaluated, and an additional randomization to ixazomib versus lenalidomide maintenance will be performed. The results from these important pending studies will help answer many important questions regarding the benefit and tolerability of consolidation therapy and tandem transplantation in the era of novel agents.

Maintenance Therapy

Maintenance therapy following induction therapy or ASCT and consolidation therapy is aimed at improving long-term disease control through administration of long-term therapy. Early attempts at melphalan or cyclophosphamide-based maintenance therapy with the objective of improving survival following induction therapy or ASCT were limited by toxicities and questionable survival benefits [19]. Interferon-α-2b maintenance therapy given three times weekly to patients responding to induction chemotherapy demonstrated improved duration of response of 26 months in the interferon group compared to 14 months in untreated patients ($p=0.0002$) [20], which led to increased use of interferon for post-transplant maintenance. Conflicting results regarding survival benefits in subsequent interferon maintenance trials [21, 22] and increased incidence of significant CNS and hematologic toxicities, fever and myalgias, cardiac events, and infections limited the routine use of interferon maintenance therapy. The era of maintenance therapy with novel agents was introduced with pilot studies examining thalidomide monotherapy. Subsequent trials incorporating lenalidomide or bortezomib for maintenance therapy have demonstrated promising PFS benefits, but several concerns regarding long-term safety, financial burden, selection of treatment-resistant clones, and consistent overall survival benefit remain.

Thalidomide Maintenance

Multiple thalidomide maintenance trials have been published in the last decade, most extending the duration of therapy until time of progression [23–28]. In the largest phase III study reported to date, the MRC IX trial randomized 820 patients with newly diagnosed myeloma to thalidomide maintenance until progression versus placebo. Thalidomide maintenance resulted in an improvement in median PFS to 23 months versus 15 months ($p<0.001$) but no significant difference in median OS ($p=0.4$). Subgroup analysis by interphase FISH showed that thalidomide maintenance in patients with adverse cytogenetics was associated with no PFS benefit and worse median OS ($p=0.009$). In the IFM 99–02 phase III study, 597 patients following tandem ASCT were randomized to no maintenance, pamidronate, or pamidronate plus thalidomide until progression [23]. Initial 4-year post-diagnosis survival was improved with thalidomide maintenance; however, this benefit was no longer evident after median follow-up of 5.7 years, underscoring the risks involved with premature interpretation of data [29]. The National Cancer Institute of Canada MY.10 study compared thalidomide-prednisone maintenance to no maintenance following ASCT in 332 patients. Similar to prior results, 4-year PFS was improved to 32 vs 14 % with maintenance. Although this study failed to demonstrate an improvement in survival (HR = 0.77; $p=0.18$), it did show reduction in health-related quality of life

metrics. A recent meta-analysis including six post-transplantation thalidomide studies confirmed similar findings of the clear PFS benefit of thalidomide maintenance (HR = 0.67; $p < 0.001$) but did not translate into an OS benefit (HR = 0.90; $p = 0.343$) [30].

In contrast to the inconsistent overall survival benefits of thalidomide across randomized controlled trials, the increased toxicities and high rates of treatment discontinuation were demonstrated across all trials. Treatment discontinuation rates varied between 30 and 76 % due to side effects that were primarily related to peripheral neuropathy. In the HOVON-50 study of thalidomide versus interferon maintenance, grade 2–4 peripheral neuropathy incidence was 50 % and treatment discontinuation or dose reduction was required in 58 % [25]. Additional treatment-limiting side effects included constipation, mood disturbances, fatigue, and venous thromboembolism, and longer duration of therapy and higher doses of thalidomide were associated with increasing toxicity.

Lenalidomide Maintenance

Lenalidomide maintenance therapy following ASCT has been explored in several phase III trials, and many ongoing trials continue to evaluate its benefit and safety post-transplant.

The phase III IFM 2005–02 study involved 614 patients up to age 65 at multiple European sites that were randomized to lenalidomide maintenance (10 mg/day for 3 months followed by 15 mg daily if tolerated) versus placebo following single ASCT, until disease progression [31]. The PFS was significantly longer in favor of the lenalidomide arm (41 versus 23 months), but 4-year overall survival was similar. It was notable that prior to maintenance, participants received 2 cycles of consolidation with lenalidomide. In a follow-up analysis after median follow-up of 70 months from diagnosis, lenalidomide maintenance 10–15 mg/day improved 5-year PFS post-randomization to 42 vs 18 % with placebo ($p < 0.0001$) [32]. Overall survival at 5 years was not significantly different in the lenalidomide maintenance group at 68 vs 67 %. Of concern, the incidence of second primary malignancies (non-melanoma skin cancers excluded) was significantly higher with lenalidomide maintenance at 2.3 per 100 patient years compared to 1.3 in the control arm ($p = 0.03$). Important distinctions of the IFM 2005–02 study include the rare IMiD exposure with induction therapy in addition to the lenalidomide consolidation (25 mg/day, days 1–21 per 28-day cycle) for 2 cycles prior to randomization to a maintenance arm.

The phase 3 CALGB 100104 study involved fewer ($n = 460$) patients up to age 70 at multiple US sites. Patients with stable disease or response at day 100 post-ASCT were randomized to lenalidomide versus placebo until disease progression [33]. In contrast to the IFM 2005–02 trial, 74 % of patients received induction therapy with an IMiD-based regimen. A planned interim analysis showed a significantly longer time to progression in the lenalidomide group, at which time the study was unblinded, and patients on the placebo arm who had not progressed were allowed to cross over. Median time to progression was significantly improved to 46 months in the lenalidomide arm versus 27 months in the placebo group ($p < 0.001$). Initial results after a median of 34 months follow-up demonstrated 15 % of patients in the lenalidomide arm had died compared to 23 % in the placebo arm ($p = 0.03$). In a follow-up analysis presented at the 2013 International Myeloma Workshop, McCarthy et al. reported that after a median follow-up of 48 months, the OS benefit remained present with 80 % survival in the lenalidomide group versus 70 % in the placebo group [34]. The incidence of second primary malignancies was also higher with lenalidomide maintenance, including 6 new diagnoses of acute leukemia (1 ALL, 5 AML) and 1 MDS in the 231 lenalidomide patients compared to no acute leukemia or MDS diagnoses in the placebo group. The incidence of solid-tumor second primaries was also higher with lenalidomide use at 4.3 % compared to 2.2 % with placebo. A subsequent meta-analysis associated oral melphalan plus lenalidomide to increased risk of second primary malignancies (HR 4.86; $p < 0.0001$) [35].

A randomized phase III study conducted by the Italian group compared ASCT with melphalan-prednisone-lenalidomide (MPR) and lenalidomide maintenance versus no maintenance in newly diagnosed patients under age 65 [36•]. Both PFS (43 versus 22 months) and 4-year OS (81.6 % versus 65.3 %) were significantly prolonged in favor of the ASCT group. Median PFS was significantly prolonged (41.9 versus 21.6 months) in favor of the lenalidomide maintenance group, but 3-year overall survival was similar. A meta-analysis of four randomized controlled trials comparing lenalidomide maintenance therapy (IFM 05–02, CALGB 100104, MM-015, RV-MM-PI209) involved 1935 patients and demonstrated significant improvement in PFS (HR 0.49, 95 % CI 0.41–0.58; $p < 0.0001$), but only a trend towards OS improvement in the lenalidomide maintenance arms (HR 0.77, 95 % CI 0.57–1.02; $p = 0.07$) [37].

Lenalidomide continuous maintenance for 1 year using 10 mg/day for 3 months then escalated to 15 mg/day as tolerated was included as part of the IFM VRD induction and consolidation transplantation study of 31 patients [17]. Due to frequent grade 3/4 neutropenia or pancytopenia, only 37 % of patients received lenalidomide at the planned full dose. The trial demonstrated increasing depth of response across treatment sequences and the authors concluded the 1 year of lenalidomide may function as a prolonged consolidation. During lenalidomide maintenance, response category was upgraded in four patients and five patients changed from MRD positive to MRD negative (68 vs 58 %). At a median follow-up of 39 months, 3-year PFS was 77 % and OS was 100 % with none of the MRD negative patients demonstrating

disease relapse. This study highlights that attaining an MRD negative state is feasible and that maintenance therapy plays an important role towards achieving that goal.

Thalidomide Versus Lenalidomide: Where Do We Stand Today?

The role of maintenance with IMiDs was evaluated in a large meta-analysis of 18 randomized trials involving a total of 7730 patients [30]. Meta-analysis of six studies involving thalidomide maintenance [23–28] showed unequivocal prolongation of PFS, but the OS benefit remains controversial. The three pivotal trials of lenalidomide maintenance post-ASCT [31, 33, 36•] all demonstrated significantly prolonged PFS in favor of lenalidomide maintenance. The OS benefit, however, remains controversial. The CALGB 100104 study [33] did show an OS benefit in favor of the lenalidomide maintenance arm, but the IFM 2005–02 study [31] did not. This may be due to differences in study design including lenalidomide consolidation administered and a low rate of IMiD-based induction in the IFM study compared to the CALGB study, leading to selection of patients responsive to IMID induction in the latter study. The more recent study by the Italian group [36•] did not show a survival benefit either, and the authors suggested that a longer follow-up duration may be required. Due to need for prolonged follow-up, study crossover, and the availability of increasingly effective salvage regimens, the OS benefit of lenalidomide maintenance therapy is likely to remain difficult to establish. The concept of PFS2, or the time to disease progression or death after second-line therapy has been proposed to evaluate for possible adverse effects of maintenance therapy on the next line of therapy and is likely to be increasingly used in future study designs.

Besides the increased financial costs of maintenance therapy, the adverse event profile needs careful examination. Thromboembolism is well described, it is more common with thalidomide than lenalidomide, and prophylactic use of aspirin, warfarin, or low molecular weight heparin is routinely recommended. In the IFM lenalidomide study, the incidence of thromboembolic events was significantly more common in the lenalidomide (6 %) versus placebo group (2 %). Grade 3 and 4 hematologic events, most notably neutropenia, were significantly more common in the lenalidomide group in all three studies. The incidence of second primary malignancy with lenalidomide maintenance was significantly higher, whereas in the IMiD maintenance meta-analysis study by Wang et al., thalidomide was not associated with an increased risk of second primary malignancy [30]. Whereas more hematologic adverse events were seen with lenalidomide, thalidomide is much more likely to require treatment discontinuation due to non-hematologic toxicities such as peripheral neuropathy, constipation, fatigue, and mood disturbances.

Bortezomib Maintenance

The strategy of bortezomib maintenance has also been tested in several post-transplantation trials. Eight hundred twenty-seven newly diagnosed myeloma patients [38] were studied in the randomized phase III HOVON-65/GMMG-HD4 trial where induction with vincristine, doxorubicin and dexamethasone (VAD) or bortezomib, doxorubicin and dexamethasone (PAD) followed by ASCT with high-dose melphalan conditioning was administered. Maintenance therapy was planned for 2 years for all patients with the VAD group receiving thalidomide, while the PAD group received bortezomib. There was significant improvement in PFS and OS in favor of the PAD induction group that also received bortezomib maintenance. In high-risk patients presenting with a creatinine greater than 2 mg/dL and/or deletion 17p13, bortezomib significantly improved both PFS and OS. The benefit of maintenance is difficult to interpret in this trial due to the differing induction regimens. Peripheral neuropathy grades 2 to 4 were more common in the PAD (40 %) versus VAD (18 %) arm. Grade 3 to 4 peripheral neuropathy developed in 8 % of patients receiving thalidomide maintenance compared to 5 % in the bortezomib maintenance group.

A randomized phase III study conducted by the Spanish Myeloma Group [39] compared VTD (bortezomib, thalidomide, and dexamethasone) versus TD (thalidomide, dexamethasone) versus VBMCP/VBAD/B (vincristine, BCNU, melphalan, cyclophosphamide, prednisone/vincristine, BCNU, doxorubicin, dexamethasone/bortezomib) followed by ASCT with high-dose melphalan conditioning. Three months post-ASCT, patients were randomized to maintenance for 3 years with interferon alpha-2b versus thalidomide versus thalidomide plus bortezomib. The pre- and post-transplantation CR rate was significantly higher in the VTD group, and PFS was significantly longer, but it was unable to overcome the adverse effect of high-risk cytogenetics. PFS was significantly longer with combination thalidomide-bortezomib maintenance compared with thalidomide alone, but this study was again difficult to interpret, since all patients did not receive induction with bortezomib; therefore, it is unclear whether the survival benefits observed are due to bortezomib induction or maintenance.

Ixazomib is the first available oral proteasome inhibitor and has demonstrated durable responses and manageable safety profile as part of a phase II maintenance study [40]. A total of 21 patients underwent induction therapy with oral ixazomib 4 mg on days 1, 8, and 15, lenalidomide 25 mg on days 1–21, and dexamethasone 40 mg on days 1, 8, 15, and 22 every 28 days for up to 12 cycles followed by maintenance ixazomib at the same dose. During maintenance, 33 % of patients demonstrated deepening response and only 10 % developed a grade 3 treatment-related adverse event (thrombocytopenia, hypokalemia) and only 1 patient required ixazomib dose

reduction (neuralgia). Importantly, no treatment-related peripheral neuropathy was reported. At a median follow-up of 16.9 months from start of maintenance therapy, 52 % of patients remained on ixazomib maintenance and median duration of response was 26.5 months (5.6–26.6 months ongoing). A phase III study of ixazomib maintenance vs. placebo following ASCT is currently ongoing (NCT02181413).

Current Approaches to Consolidation and Maintenance for Transplant-Eligible Patients

Based on current limitations in the available data regarding post-transplantation consolidation and maintenance therapy, participation in ongoing clinical trials is encouraged. At Mayo Clinic, a FISH-based risk stratification model termed mSMART (Mayo Stratification of Myeloma and Risk-Adapted Therapy) has been developed to individualize treatment based on tumor biology. In intermediate risk [t(4;14) or 1q gain] VRd for 4 cycles followed by ASCT then bortezomib-based maintenance for 1 year or greater is currently recommended. In high-risk patients [t(14;16), t(14;20), 17p deletion, or high-risk gene expression profile], bortezomib or carfilzomib-based maintenance following KRd (carfilzomib, lenalidomide, dexamethasone) induction for a minimum of 1 year after ASCT is currently recommended by the Mayo Clinic group. Neben et al. evaluated the effect of bortezomib-based induction and maintenance compared to treatment without bortezomib in the HOVON-65/GMMG-HD4 trial and concluded that long-term bortezomib treatment could improve outcomes in this high-risk group [41]. Specifically, patients with del(17p) treated with bortezomib induction and maintenance had a median PFS of 26.2 months versus 12 months in patients treated without bortezomib.

VTd consolidation has been studied the most thoroughly and has promising PFS benefit; however, the high rates of peripheral neuropathy and treatment discontinuation remain a limitation. A consolidation/maintenance VRd strategy following ASCT for high-risk patients also resulted in promising results with a low rate of grade 3/4 neuropathy [42]. In this retrospective study of 45 high-risk patients at Emory University, VRd was administered after ASCT on a 28-day cycle up to 3 years, then lenalidomide 10 mg/day single agent therapy thereafter. Median PFS was 32 months with a 3-year OS of 93 %, which significantly exceeds the median overall survival of 3 years in many studies of high-risk patients.

In standard-risk patients by mSMART classification (trisomies, t(11;14), t(6;14)), current recommendations support 2 cycles of Rd (lenalidomide and dexamethasone) consolidation followed by lenalidomide maintenance of limited duration (12–24 months) if VGPR has not been achieved following consolidation. More data are needed before quality consensus guidelines can be proposed, and with the available data, we suggest individualization of recommendations based on patient treatment tolerance, risk profile, and preferences. Given the concerns of increased second primary malignancy with lenalidomide maintenance, we favor a limited duration course of therapy (1–2 years) rather than indefinite therapy until progression in hopes of reducing this risk.

Evolving Treatment Paradigms in Transplant-Ineligible Patients

Fixed duration therapy historically has been the standard of care for elderly or transplant-ineligible MM patients; however, several recent trials incorporating continuous therapy with novel agents suggest durable benefit. The FIRST trial compared Rd until progression, Rd for 18 cycles, and MPT for 18 cycles in 1623 newly diagnosed transplant-ineligible patients. Continuous Rd was better tolerated than MPT while also demonstrating superior PFS, OS, and time to second therapy. At a median follow-up of 37 months, median PFS was 25.5, 20.7, and 21.2 months in the continuous Rd, Rd18, and MPT arms, respectively (HR 0.72; $p < 0.001$) [43]. At the interim analysis, 4-year OS was 59 % for Rd, 56 % for Rd18, and 51 % for MPT. In a subsequent analysis of the FIRST trial, Hulin et al. stratified patients aged ≤75 and >75 years to compare the impact of continuous Rd vs. MPT on older patients. In patients >75, continuous Rd compared to MPT showed a trend toward improved PFS (21.2 vs 19.4 months; HR 0.81; $p = 0.11$), significantly increased response rates (71 vs 55 %), and increased duration of response (31 vs 24 months). In patients 75 or younger, continuous Rd demonstrated a more profound PFS benefit (HR 0.68; $p < 0.01$) with a median PFS of 27.4 vs. 21.8 months in the MPT group [44].

Transplant-ineligible patients were randomized to nine cycles of MPR-R (melphalan, prednisone, lenalidomide followed by lenalidomide maintenance) versus MPR without maintenance therapy in the MM-015 study. Median PFS was significantly improved with MRP-R compared to MPR without maintenance at 31 vs 14 months (HR 0.49; $p < 0.001$). Patients between ages 65–75 benefitted the most from lenalidomide maintenance [45]. The time to third-line therapy (estimate of PFS2) was also improved with MPR-R at 39.7 months compared to MRP at 27.8 months. In frail patients or age ≥75, continuous Rd is better tolerated than MPR and is our preferred regimen for standard-risk patients.

Several European studies have evaluated bortezomib maintenance following VMPT (bortezomib, melphalan, prednisone, thalidomide) or VMP induction therapy and have shown potential survival benefits. Palumbo et al. [46] randomized 511 transplant-ineligible patients to either VMPT for 9 cycles followed by bortezomib 1.3 mg/m^2 every 2 weeks and thalidomide 50 mg/day for 2 years or standard VMP. Estimated 5-year OS was 61 % in the VMPT-VT group compared to 51 % in the

VMP patients (HR 0.52; $p<0.001$). The median PFS in the VMPT-VT group was 35 versus 25 months (HR 0.58, $p<0.001$). A higher rate of patients in the VMPT-VT group required treatment interruption (25 %) and 35 % of patients age >75 discontinued treatment due to adverse effects. Grade 3/4 non-hematologic adverse events occurred in 54 % of the VMPT-VT group, including a 19 % incidence of sensory neuropathy and/or neuralgia. Next-generation combinations of IMiDs and proteasome inhibitors such as KRd (carfilzomib, lenalidomide, dexamethasone) may offer improved tolerability and efficacy. In a phase II study of KRd (carfilzomib lenalidomide, dexamethasone) for 8 cycles followed by lenalidomide with 45 newly diagnosed MM patients, no patients experienced grade 3 or 4 peripheral neuropathy and 62 % of patients achieved CR or stringent CR [47] following 8 cycles. PFS at 18 months was 92 %, and no deaths have been observed.

Novel Strategies for Maintenance/Continuous Therapy

Agents capable of harnessing the power of cellular immunity have long been sought; however, allogeneic hematopoietic stem cell transplantation has remained the only proven therapy capable of long-term disease eradication through a graft-vs-myeloma effect. The development of innovative treatment approaches including monoclonal antibodies, chimeric antigen receptor T-cell therapy, checkpoint blockade, and novel vaccine therapies has led to a new era of immunotherapy in multiple myeloma, and many therapies have entered clinical testing. Immune checkpoint blockade with monoclonal antibodies against PD-1/PD-L1 aims to prevent T-cell anergy induced by the tumor microenvironment. Contrary to the results seen in some solid and hematologic malignancies, few objective responses have been observed with checkpoint blockade alone in multiple myeloma. In a phase I study including 27 relapsed MM patients, no patients achieved PR or better, and by 24 weeks, only 15 % remained progression-free [48].

Preclinical data suggest potential synergy of PD-1 blockade in combination with other immunotherapies. San Miguel et al. presented early-phase clinical data pairing lenalidomide with pembrolizumab in heavily pretreated patients (41 % IMiD-refractory, 18 % double refractory) demonstrated objective response in 76 % of patients, including the refractory patients [49]. Personalized dendritic-cell vaccines including a dendritic cell/myeloma fusion vaccine created from the patient's intact tumor cells have been developed with the objective of enhancing antigen presentation and both humoral and cellular responses [50]. Increased PD-1 expression is present in T cells of patients with active multiple myeloma, and PD-1 blockade enhances T cell activation of cytotoxicity following DC/tumor vaccine administration [51]. A pilot study of PD-1 blockade with DC/myeloma vaccine following ASCT is anticipated to complete enrollment in 2016 (NCT01067287), and an additional study of a MAGE-A3 tumor-specific antigen vaccine for consolidation in patients undergoing ASCT is ongoing (NCT01380145).

Chimeric antigen receptor (CAR) T cell therapy uses engineered T cells that express CARs capable of target antigen recognition on cancer cells. This approach is also area of active research in multiple myeloma. CAR T cells targeting CD19 have been highly successful in treating B-cell ALL and CLL and have also been explored for the treatment of myeloma. In a study of patients with early relapse post-ASCT, anti-CD19 CAR T cells were infused following a second transplant [52]. Follow-up data is limited to less than 1 year; however, early data demonstrated three of five patients achieved in CR and had not progressed at last follow-up. Ongoing trials also include CAR T cells targeting kappa light chain, CD138, and B-cell maturation antigen (BCMA) CAR. Early trials have primarily focused on the relapsed/refractory MM population; however, in the future, CAR T cells could be employed in a number of settings including consolidation therapy or in combination with other immunotherapies.

Monoclonal antibodies capable of targeting myeloma-specific antigens are now available in the clinic and given their excellent safety profile and potential synergy with IMiDs may contribute to an improvement over the currently available consolidation and maintenance strategies. Two recent FDA approvals in the relapsed/refractory MM population for elotuzumab, an anti-CS-1/SLAM7 antibody, and daratumumab, an anti-CD38 antibody, demonstrate the promise on therapeutic antibody therapy in MM. The MMY-3006 study led by the IFM/HOVON groups plans to enroll 1080 patients and will add daratumumab to VTD during induction and consolidation after single ASCT, and will then randomize patients to continued daratumumab maintenance (NCT02541383). The GMMG-HD6 study is a randomized phase III trial in newly diagnosed patients undergoing ASCT evaluating the efficacy elotuzumab in VRD induction and consolidation therapy and in lenalidomide maintenance (NCT02495922).

Conclusions

Debate continues about the optimal consolidation approach, which patients most benefit from maintenance, and the duration of therapy. Both thalidomide and lenalidomide maintenance following ASCT prolongs PFS and lenalidomide is generally well tolerated, but questions remain about its ability to impact long-term survival. Due to problematic rates of peripheral neuropathy and poor quality of life with thalidomide, lenalidomide is now primarily used in ongoing maintenance studies despite the slight increased risk of second primary malignancies. Bortezomib maintenance may lead to significant improvement in post-ASCT outcomes in patients with

high-risk cytogenetic abnormalities and renal failure as shown in the HOVON-65/GMMG-HD4 data. Studies evaluating next-generation proteasome inhibitors including carfilzomib and the recently approved oral agent ixazomib will also provide further insight about maintenance therapy and its impact on quality of life and survival outcomes.

Early results from the IFM portion of the IFM/DFCI study of RVD consolidation and lenalidomide maintenance in the context of early versus delayed transplant demonstrate that upfront ASCT will continue to remain the standard of care for newly diagnosed transplant eligible MM patients although no OS benefit was observed with early ASCT. Further results are anticipated. The BMT CTN 0702 (STaMINA) phase III multicenter trial evaluating the three approaches of either ASCT followed by maintenance lenalidomide, RVD consolidation and lenalidomide maintenance, or tandem transplantation plus lenalidomide maintenance will help define the risks and benefits of tandem transplantation in the era of novel agents. Given the heterogeneity of tumor biology and differing responses post induction and ASCT, more data are needed to define which patient subgroups need routine consolidation and maintenance therapy and who may be observed post-ASCT. Detection of MRD with flow cytometry-based or molecular methods post-ASCT may help guide an individualized consolidation and maintenance approach in the future.

Compliance with Ethical Standards

Conflict of Interest Nitya Nathwani and Jeremy T. Larsen each declare no potential conflicts of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- Of importance

1.• Kapoor P, Kumar SK, Dispenzieri A, Lacy MQ, Buadi F, Dingli D, et al. Importance of achieving stringent complete response after autologous stem-cell transplantation in multiple myeloma. J Clin Oncol : Off J Am Soc Clin Oncol. 2013;31(36):4529–35. **This study showed that depth of response results in improved long term outcome**.
2. Paiva B, Gutierrez NC, Rosinol L, Vidriales MB, Montalban MA, Martinez-Lopez J, et al. High-risk cytogenetics and persistent minimal residual disease by multiparameter flow cytometry predict unsustained complete response after autologous stem cell transplantation in multiple myeloma. Blood. 2012;119(3):687–91.
3. Rawstron AC, Child JA, de Tute RM, Davies FE, Gregory WM, Bell SE, et al. Minimal residual disease assessed by multiparameter flow cytometry in multiple myeloma: impact on outcome in the Medical Research Council Myeloma IX Study. J Clin Oncol. 2013;31(20):2540–7.
4. Martinez-Lopez J, Lahuerta JJ, Pepin F, Gonzalez M, Barrio S, Ayala R, et al. Prognostic value of deep sequencing method for minimal residual disease detection in multiple myeloma. Blood. 2014;123(20):3073–9.
5. Rawstron AC, Gregory WM, de Tute RM, Davies FE, Bell SE, Drayson MT, et al. Minimal residual disease in myeloma by flow cytometry: independent prediction of survival benefit per log reduction. Blood. 2015;125(12):1932–5.
6. Paiva B, Vidriales MB, Cervero J, Mateo G, Perez JJ, Montalban MA, et al. Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation. Blood. 2008;112(10):4017–23.
7. Ludwig H, Greil R, Masszi T, Spicka I, Shpilberg O, Hajek R, et al. Bortezomib, thalidomide and dexamethasone, with or without cyclophosphamide, for patients with previously untreated multiple myeloma: 5-year follow-up. Br J Haematol. 2015;171(3):344–54.
8. Ferrero S, Ladetto M, Drandi D, Cavallo F, Genuardi E, Urbano M, et al. Long-term results of the GIMEMA VEL-03-096 trial in MM patients receiving VTD consolidation after ASCT: MRD kinetics' impact on survival. Leukemia. 2015;29(3):689–95.
9. Attal M, Harousseau JL, Facon T, Guilhot F, Doyen C, Fuzibet JG, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med. 2003;349(26):2495–502.
10. The Myeloma Trialists' Collaborative Group. Interferon as therapy for multiple myeloma: an individual patient data overview of 24 randomized trials and 4012 patients. Br J Haematol. 2001;113(4):1020–34.
11. Mellqvist UH, Gimsing P, Hjertner O, Lenhoff S, Laane E, Remes K, et al. Bortezomib consolidation after autologous stem cell transplantation in multiple myeloma: a Nordic Myeloma Study Group randomized phase 3 trial. Blood. 2013;121(23):4647–54.
12. Cavo M, Pantani L, Petrucci MT, Patriarca F, Zamagni E, Donnarumma D, et al. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma. Blood. 2012;120(1):9–19.
13. Tacchetti P, Pantani L, De Stefano V, Zamagni E, Peccatori J, Pezzi A, et al. Superior PFS2 with VTD Vs TD for newly diagnosed, transplant eligible, Multiple Myeloma (MM) patients: updated analysis of Gimema MMY-3006 study. ASH Ann Meet Abstr. 2014;124(21):196.
14. Ladetto M, Pagliano G, Ferrero S, Cavallo F, Drandi D, Santo L, et al. Major tumor shrinking and persistent molecular remissions after consolidation with bortezomib, thalidomide, and dexamethasone in patients with autografted myeloma. J Clin Oncol. 2010;28(12):2077–84.
15. Leleu X, Fouquet G, Hebraud B, Roussel M, Caillot D, Chretien ML, et al. Consolidation with VTd significantly improves the complete remission rate and time to progression following VTd induction and single autologous stem cell transplantation in multiple myeloma. Leukemia. 2013;27(11):2242–4.
16. Straka C, Vogel M, Muller J, Kropff M, Metzner B, Langer C, et al. Results from two phase III studies of bortezomib consolidation vs observation post-transplant in patients with newly diagnosed multiple myeloma. J Clin Oncol. 2015;33(suppl):Abstr 8511.
17. Roussel M, Lauwers-Cances V, Robillard N, Hulin C, Leleu X, Benboubker L, et al. Front-line transplantation program with

lenalidomide, bortezomib, and dexamethasone combination as induction and consolidation followed by lenalidomide maintenance in patients with multiple myeloma: a phase II study by the Intergroupe Francophone du Myelome. J Clin Oncol. 2014;32(25):2712–7.
18. Attal M, Lauwers-Cances V, Hulin C, Facon T, Caillot D, Escoffre M, et al. Autologous transplantation for multiple myeloma in the era of new drugs: a phase III study of the intergroupe francophone du myelome (IFM/DFCI 2009 Trial). Blood. 2015;126(23):Abstr 391.
19. Belch A, Shelley W, Bergsagel D, Wilson K, Klimo P, White D, et al. A randomized trial of maintenance versus no maintenance melphalan and prednisone in responding multiple myeloma patients. Br J Cancer. 1988;57(1):94–9.
20. Mandelli F, Avvisati G, Amadori S, Boccadoro M, Gernone A, Lauta VM, et al. Maintenance treatment with recombinant interferon alfa-2b in patients with multiple myeloma responding to conventional induction chemotherapy. N Engl J Med. 1990;322(20):1430–4.
21. Drayson MT, Chapman CE, Dunn JA, Olujohungbe AB, Maclennan IC. MRC trial of alpha2b-interferon maintenance therapy in first plateau phase of multiple myeloma. MRC Working Party on Leukaemia in Adults. Br J Haematol. 1998;101(1):195–202.
22. Salmon SE, Crowley JJ, Balcerzak SP, Roach RW, Taylor SA, Rivkin SE, et al. Interferon versus interferon plus prednisone remission maintenance therapy for multiple myeloma: a Southwest Oncology Group Study. J Clin Oncol. 1998;16(3):890–6.
23. Attal M, Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benboubker L, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood. 2006;108(10):3289–94.
24. Barlogie B, Pineda-Roman M, van Rhee F, Haessler J, Anaissie E, Hollmig K, et al. Thalidomide arm of Total Therapy 2 improves complete remission duration and survival in myeloma patients with metaphase cytogenetic abnormalities. Blood. 2008;112(8):3115–21.
25. Lokhorst HM, van der Holt B, Zweegman S, Vellenga E, Croockewit S, van Oers MH, et al. A randomized phase 3 study on the effect of thalidomide combined with adriamycin, dexamethasone, and high-dose melphalan, followed by thalidomide maintenance in patients with multiple myeloma. Blood. 2010;115(6):1113–20.
26. Morgan GJ, Gregory WM, Davies FE, Bell SE, Szubert AJ, Brown JM, et al. The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis. Blood. 2012;119(1):7–15.
27. Stewart AK, Trudel S, Bahlis NJ, White D, Sabry W, Belch A, et al. A randomized phase 3 trial of thalidomide and prednisone as maintenance therapy after ASCT in patients with MM with a quality-of-life assessment: the National Cancer Institute of Canada Clinicals Trials Group Myeloma 10 Trial. Blood. 2013;121(9):1517–23.
28. Maiolino A, Hungria VT, Garnica M, Oliveira-Duarte G, Oliveira LC, Mercante DR, et al. Thalidomide plus dexamethasone as a maintenance therapy after autologous hematopoietic stem cell transplantation improves progression-free survival in multiple myeloma. Am J Hematol. 2012;87(10):948–52.
29. Barlogie B, Attal M, Crowley J, van Rhee F, Szymonifka J, Moreau P, et al. Long-term follow-up of autotransplantation trials for multiple myeloma: update of protocols conducted by the intergroupe francophone du myelome, southwest oncology group, and university of arkansas for medical sciences. J Clin Oncol. 2010;28(7):1209–14.
30. Wang Y, Yang F, Shen Y, Zhang W, Wang J, Chang VT, et al. Maintenance therapy with immunomodulatory drugs in multiple myeloma: a meta-analysis and systematic review. J Natl Cancer Inst. 2016 Mar;108(3).
31. Attal M, Lauwers-Cances V, Marit G, Caillot D, Moreau P, Facon T, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366(19):1782–91.
32. Attal M, Lauwers-Cances V, Marit G, Caillot D, Facon T, Hulin C, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma: follow-up analysis of the IFM 2005–02 Trial. ASH Annual Meeting Abstracts. 2013;122(406).
33. McCarthy PL, Owzar K, Hofmeister CC, Hurd DD, Hassoun H, Richardson PG, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366(19):1770–81.
34. McCarthy P, Owzar K, Hofmeister C. Analysis of overall survival (OS) in the context of cross-over from placebo to lenalidomide and the incidence of second primary malignancies (SPM) in the phase III study of lenalidomide versus placebo maintenance therapy following autologous stem cell transplant (ASCT) for multiple myeloma (MM) CALGB (Alliance) ECOG BMTCTN. Clin Lymphoma Myeloma. 2013;Suppl 1:S28.
35. Palumbo A, Bringhen S, Kumar SK, Lupparelli G, Usmani S, Waage A, et al. Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data. Lancet Oncol. 2014;15(3):333–42.
36.• Palumbo A, Cavallo F, Gay F, Di Raimondo F, Ben Yehuda D, Petrucci MT, et al. Autologous transplantation and maintenance therapy in multiple myeloma. N Engl J Med. 2014;371(10):895–905. **Showed both PFS and OS benefit with ASCT, and PFS benefit with lenalidomide maintenance, but no OS benefit**.
37. Singh PP, Kumar S, Laplant B, Gertz M, Dispenzieri A, Bergsagel PL, et al. Lenalidomide maintenance therapy in multiple myeloma: a meta-analysis of randomized trials. Blood. 2013;122(21):407.
38. Sonneveld P, Schmidt-Wolf IG, van der Holt B, El Jarari L, Bertsch U, Salwender H, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. J Clin Oncol : Off J Am Soc Clin Oncol. 2012;30(24):2946–55.
39. Rosinol L, Oriol A, Teruel AI, Hernandez D, Lopez-Jimenez J, de la Rubia J, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. Blood. 2012;120(8):1589–96.
40. Kumar S, Berdeja JG, Niesvizky R, Lonial S, Laubach J, Hamadani M, et al. Long-term Ixazomib maintenance is tolerable and improves depth of response following Ixazomib-Lenalidomide-Dexamethasone induction in patients with previously untreated multiple myeloma: phase 2 study results. Blood. 2014;124(21):Abst 82.
41. Neben K, Lokhorst HM, Jauch A, Bertsch U, Hielscher T, van der Holt B, et al. Administration of bortezomib before and after autologous stem cell transplantation improves outcome in multiple myeloma patients with deletion 17p. Blood. 2012;119(4):940–8.
42. Nooka AK, Kaufman JL, Muppidi S, Langston A, Heffner LT, Gleason C, et al. Consolidation and maintenance therapy with lenalidomide, bortezomib and dexamethasone (RVD) in high-risk myeloma patients. Leukemia. 2014;28(3):690–3.
43. Benboubker L, Dimopoulos MA, Dispenzieri A, Catalano J, Belch AR, Cavo M, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med. 2014;371(10):906–17.
44. Hulin C, Facon T, Shustik C, Belch A, Petrucci MT, Duhrsen U, et al. Effect of age on efficacy and safety outcomes in patients with newly diagnosed multiple myeloma receiving Lenalidomide and low-dose Dexamethasone (Rd): the first trial. Blood. 2014;124(21):81.
45. Palumbo A, Hajek R, Delforge M, Kropff M, Petrucci MT, Catalano J, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med. 2012;366(19):1759–69.

46. Palumbo A, Rajkumar SV, San Miguel JF, Larocca A, Niesvizky R, Morgan G, et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. J Clin Oncol. 2014;32(6):587–600.
47. Korde N, Roschewski M, Zingone A, Kwok M, Manasanch EE, Bhutani M, et al. Treatment with Carfilzomib-Lenalidomide-Dexamethasone with Lenalidomide extension in patients with smoldering or newly diagnosed multiple myeloma. JAMA Oncol. [Research Support, Non-U.S. Gov't]. 2015 Sep;1(6):746–54.
48. Lesokhin A, Ansell S, Armand P, Scott EC, Halwani A, Gutierrez M, et al. Preliminary results of a phase i study of Nivolumab (BMS-936558) in patients with relapsed or refractory lymphoid malignancies. ASH Ann Meet Abstr. 2014;124(21).
49. San Miguel J, Mateos M, Shah J, Ocio E, Rodriguez-Otero P, Reece D, et al. Pembrolizumab in combination with Lenalidomide and low-dose Dexamethasone for Relapsed/Refractory Multiple Myeloma (RRMM): Keynote-023. ASH Ann Meet Abstr. 2015;126(23).
50. Vasir B, Borges V, Wu Z, Grosman D, Rosenblatt J, Irie M, et al. Fusion of dendritic cells with multiple myeloma cells results in maturation and enhanced antigen presentation. Br J Haematol. 2005;129(5):687–700.
51. Rosenblatt J, Glotzbecker B, Mills H, Vasir B, Tzachanis D, Levine JD, et al. PD-1 blockade by CT-011, anti-PD-1 antibody, enhances ex vivo T-cell responses to autologous dendritic cell/myeloma fusion vaccine. J Immunother. 2011;34(5):409–18.
52. Garfall AL, Valderrama M, Lacey SF. Safety and efficacy of anti-CD19 chimeric antigen receptor (CAR)-modified autologous T cells (CTL019) in advanced multiple myeloma [ASCO abstract 8517]. J Clin Oncol. 2015;33(15).