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Review Article

The Future of Post-Autologous Stem Cell Transplant Therapy for Multiple Myeloma

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Abstract

Multiple myeloma is a plasma cell malignancy characterized by lytic bone disease, monoclonal protein production, and immune dysregulation. For patients eligible for high-dose chemotherapy, the standard of care has been induction therapy with immunomodulatory drugs and/or proteasome inhibitor-based therapy followed by autologous stem cell transplant (ASCT). Despite this approach, nearly all patients eventually relapse and there has therefore been interest in the use of post-ASCT maintenance therapy to prolong disease control and improve survival. Phase III randomized studies have demonstrated that lenalidomide post-ASCT results in improved outcomes. There are less robust data available for the use of bortezomib. Here we review the current literature as well as the ongoing clinical trials pertaining to the use of post-ASCT maintenance therapies for myeloma. We also discuss a variety of novel therapeutic strategies; including monoclonal antibodies, immune checkpoint blockade, and CAR-T cell therapy, which may represent the future of post-ASCT therapy.

Keywords: Multiple myeloma; Autologous stem cell transplant; Maintenance; Consolidation; Minimal residual disease

Abbreviations

ALL: Acute Lymphoblastic Leukemia; AML: Acute Myeloid Leukemia; ASCT: Autologous Stem Cell Transplant; ASO PCR: Allele-Specific Oligonucleotide PCR; BET: Bromodomain and Extra-Terminal; BiTE: Bispecific T cell Engagers; CAR: Chimeric Antigen Receptor; CIR: Cumulative Incidence Risk; CR: Complete Response; DCEP: Dexamethasone/Cyclophosphamide/Etoposide/Cisplatin; IMiD: Immunomodulatory Drug; MDS: Myelodysplastic Syndrome; MFC: Multiparametric Flow Cytometry; MPR: Melphalan/Prednisone/Lenalidomide; MRD: Minimal Residual Disease; PI: Proteasome Inhibitor; OS: Overall Survival; PD-1: Programmed cell Death protein 1; PD-L1: Programmed Death Ligand 1; PFS: Progression Free Survival; RVD: Lenalidomide/Bortezomib/Dexamethasone; SPM: Second Primary Malignancy; TTP: Time To Progression; HTS: High-throughput Sequencing; VGPR: Very Good Partial Response.

Introduction

The outcomes of patients with multiple myeloma have markedly improved with the introduction of immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs). Induction therapy consisting of IMiD- and/or PI-based therapy followed by consolidation with high dose melphalan and autologous stem cell transplantation (ASCT) remains a standard of care for younger patients. However, as nearly all patients relapse following ASCT there has been continued interest in the use of post-ASCT therapies to delay disease recurrence and prolong overall survival (OS). One approach has been further consolidation post-ASCT followed by no further treatment or by maintenance therapy. Another approach has been initiation of maintenance therapy after a period of recovery following ASCT. Earlier studies concentrated on first interferon and then thalidomide (with or without corticosteroids) as maintenance therapy. However, prolonged use of these agents was limited by side effects and studies did not show a consistent improvement in OS. More recent studies have focused on lenalidomide and bortezomib. Here we review these studies and discuss how novel agents might become incorporated into post-ASCT therapy.

Lenalidomide maintenance

Palumbo et al. performed the first study to incorporate lenalidomide in the post-ASCT setting. In this phase II study, patients underwent induction therapy with bortezomib, doxorubicin, and dexamethasone followed by tandem ASCT (melphalan 100 mg/m^2) [1]. The post-ASCT therapy consisted of four cycles of lenalidomide plus prednisone followed by lenalidomide alone continued until disease relapse. The most frequent grade 3/4 adverse events included neutropenia, thrombocytopenia and pneumonia. Subsequently three randomized studies involving lenalidomide maintenance have been performed (Table 1).

CALGB 100104 was a phase III study which randomized 460 patients to receive lenalidomide *vs.* placebo following ASCT [2]. Treatment consisted of 10 mg/day (5-15 mg/day dose-adjusted for cytopenias) initiated at day 100 post-ASCT and continued until disease progression. The study was un-blinded early after interim analyses demonstrated that the primary endpoint of time to progression (TTP) was met (46 months *vs.* 27 months, HR = 0.48, p<0.001). At the time of un-blinding, 86 out of 128 non-progressing patients on the placebo arm chose to cross over and receive lenalidomide. At 34 months median follow-up there was an OS benefit for lenalidomide (85% *vs.* 77%, p=0.03). A recent update with a 65-month median follow-up for OS continues to show substantial improvements in both TTP (53 *vs.* 27 months, HR = 0.54, p <0.0001) and OS (median OS not reached for lenalidomide *vs.* 76 months for placebo, p=0.001) [3]. No difference in OS after disease progression has been observed

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Table 1: Randomized trials involving lenalidomide maintenance following ASCT.

Study	n	Induction therapy	Dosing schedule	Duration of Maintenance	EFS or PFS (maintenance vs. no)	OS (maintenance vs. no)
CALGB 100104 [2,3]	460	< 2 regimens; 94% received a regimen containing Thal, Len, and/or Bor	10 mg continuous, increase up to 15 mg	Until progression	Median TTP: 53 vs. 27 months (p<0.001)	Median follow-up 65 months: Not reached vs. 76 months (p=0.001)
IFM 2005-02 [4]	614	46% received vincristine, doxorubicin, Dex and 46% received Bor and Dex 21% received tandem transplant	All patients received 2 cycles of consolidation (25 mg/d, 21 out of 28 days) Maintenance: 10 mg continuous, increase up to 15 mg	Stopped due to concerns regarding second primary malignancies at a median time of 2 years (range 1-3 years)	Median PFS: 41 vs. 23 months (p<0.001) 4 year PFS: 43 vs. 22% (p<0.001)	Median follow-up 45 months: 74 vs. 76% (p=0.7) 4 year OS: 73% vs. 75% (p=0.7)
Italian tandem ASCT [6]	402	4 cycles Len/Dex followed by either tandem transplant (MEL200) or MPR	10 mg (3 weeks on, 1 week off)	Until progression	Median PFS*: 42 vs. 22 months (p<0.001)	3year OS*: 88 vs. 79% (p=0.14)

*combining MEL200 and MPR groups

Abbreviations: Bor: Bortezomib; Dex: Dexamethasone; Len: Lenalidomide; MEL200: Melphalan 200 mg/m2; MPR: Melphalan, Prednisone, Lenalidomide; PFS: Progression-free Survival; OS: Overall Survival; Thal: Thalidomide

between the two arms.

The IFM 2005-02 study included 614 patients who were randomized to receive lenalidomide *vs.* placebo maintenance following two cycles of consolidation therapy with lenalidomide (25 mg/day for days 1-21) post-ASCT (Table 1) [4]. This study was also unblinded early once the primary endpoint of PFS was met (median PFS of 41 months *vs.* 23 months, HR 0.5, p <0.001). Crossover to lenalidomide was not allowed. Of note, maintenance therapy was discontinued after 1-3 years (median 2 years) because of a concern about the development of second primary malignancies (SPMs). At 60 months post-randomization there continues to be a PFS benefit for lenalidomide (42% *vs.* 18%, p<0.0001) however, the 5-year OS rates are equivalent (68% *vs.* 67%) [5]. OS after progression was inferior on the lenalidomide arm as was median second PFS, defined as time from progression in first-line to second progression or death.

While not directly comparable to the aforementioned studies, the Italian tandem transplant study also evaluated the role of lenalidomide maintenance therapy (Table 1) [6]. All patients received 4 cycles of lenalidomide/dexamethasone induction followed by randomization to tandem ASCT (melphalan 200 mg/m^2) *vs.* six cycles of oral melphalan/lenalidomide/prednisone (MPR). Patients on both arms were then randomized to either lenalidomide maintenance (10 mg/day days 1-21) or no maintenance. An analysis which combined the tandem ASCT and MPR arms revealed that lenalidomide maintenance improved median PFS (42 months) compared with no maintenance (22 months) (HR =0.47, p <0.001). However, the 3-year OS rates were not significantly different (88 *vs.* 79%, p= 0.14).

The most common adverse events associated with lenalidomide maintenance therapy have been hematological. In the CALGB 100104 study, 69% of patients in the lenalidomide arm and 30% on the placebo arm patients developed grade 3/4 adverse events, of which 48% and 17% respectively were hematologic [2]. Ten percent of patients on the lenalidomide arm stopped therapy due to adverse events compared with 1% on the placebo arm and 6% of patients who crossed over to receive lenalidomide. In the IFM 2005-02 study, 74% of patients receiving lenalidomide and 43% receiving placebo had grade 3 or 4 events, of which 58% and 22%, respectively were hematologic [4]. The discontinuation rates on this study were 27% in the lenalidomide arm and 15% in the placebo arm.

There continues to be considerable debate regarding the reasons underlying the similar PFS benefit but disparate OS outcomes for the American and French studies [7]. It is likely that there are a number of factors which need to be considered including differences in induction regimens, presence or absence of consolidation therapy, duration of maintenance therapy, and available salvage regimens. With respect to induction therapy, three-quarters of patients in the CALGB trial received an IMiD-based regimen while no patients received an IMiD as induction therapy in the IFM 2005-02 study. It should also be noted that in the French trial, one quarter of patients received high-dose alkylator therapy DCEP (dexamethasone, cyclophosphamide, etoposide, cisplatin) and one-fifth underwent tandem ASCT. Subgroup analysis of CALGB 100104 has revealed that the hazard ratios for OS favor the lenalidomide arm for subgroups that either had received lenalidomide induction or had not received thalidomide induction, but did not reach statistical significance for patients who either had thalidomide induction or did not have lenalidomide induction [2]. All subgroups achieved PFS benefit from lenalidomide maintenance. Thus it may be hypothesized that the nature of the induction regimen influences OS but another factor may be disease responsiveness to subsequent lines of therapy following relapse. Notably, while lenalidomide was continued until progression in the American study, it was discontinued after a median of 2 years (range 1-3) in the French study. That both studies have reported comparable rates of SPMs (see below) suggests that there is not an increased risk for continuing lenalidomide beyond two years and that maintenance until progression contributes to the observed OS benefit in the US study.

An increased incidence of SPMs in patients receiving lenalidomide maintenance has been reported in both the CALGB 100104 and IFM 2005-02 studies. Initially, McCarthy et al. [8] reported a SPM incidence of 2.6% in the lenalidomide arm *vs.* 1.7% in the placebo arm while Attal et al. [9] reported rates of 2.6% and 0.04% respectively. With a median follow-up of 65 months for OS, there have now been 14 (6.1%) hematological and 11 (4.8%) solid tumors in the lenalidomide arm compared with 3 (1.3%) hematological and 7 (3.1%) solid tumors in the placebo arm of CALGB 100104 [3]. Notably, while the cumulative incidence risk (CIR) of developing a SPM is higher for lenalidomide compared with placebo (p= 0.005), the CIR of disease progression (p <0.001) or death (p <0.001) is higher for placebo.

With longer follow-up for the IFM study, there have been a total of 13 (4.2%) hematological malignancies and 10 (3.3%) solid tumors in the lenalidomide arm and 5 (1.6%) hematological malignancies and 4 (1.3%) solid tumors in the placebo arm [4].

It has been well documented that plasma cell dyscrasias, even without therapy, are associated with an increased risk of other hematological malignancies [10-12]. There is also an increased risk of SPM following ASCT. In a retrospective cohort study, the overall cumulative incidence of SPMs was 5.3% at 5 years and 11.2% at 10 years following ASCT [13]. It appears likely that the combination of lenalidomide and alkylator therapy contributes to the risk of SPMs, particularly hematological SPMs. A recent meta-analysis of 3254 newly diagnosed patients from seven randomized phase III studies revealed a 5-year incidence of SPMs of 6.9% in those receiving lenalidomide vs. 4.8% in those who did not receive lenalidomide (p-0.037) [14]. An increased risk was observed for hematological malignancies (3.1% *vs.* 1.4%, p=0.029) but not for solid tumors. Lenalidomide and low dose oral melphalan was associated with an increased risk of hematological SPMs but this was not observed with lenalidomide and higher dose intravenous melphalan. The cumulative incidences of death due to myeloma or treatment-related events were higher than those due to SPMs. In another report, a pooled analysis of 2459 newly diagnosed patients from 9 European Myeloma network trials was performed. This study showed a cumulative incidence of SPM at three years of 2.0% in patients receiving lenalidomide and alkylator therapy compared with 1.1% for those who were not treated with lenalidomide [15]. This analysis also demonstrated that the cumulative incidence of death from myeloma was lower for those who had received lenalidomide (13.8% *vs.* 26.1%).

While the majority of hematological SPMs reported on CALGB 100104 and IFM 05-02 have been myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), it is worth noting that there have also been cases of acute lymphoblastic leukemia (ALL) (5 on CALGB 100104 and 3 on IFM 05-02). Whether the risk factors for developing ALL on lenalidomide post-ASCT are different from those contributing to a myeloid disorder is not known. It is interesting that deletions in the gene for the transcription factor IKZF1, which gets degraded following IMiD binding to cereblon and has been shown to be necessary for lenalidomide sensitivity, [16-18] have been associated with B-ALL [19-21]. Further studies are needed to determine the mechanisms underlying the association between lenalidomide maintenance therapy and development of ALL as an SPM.

Thus lenalidomide maintenance is associated with a decreased risk of progression and death from myeloma but also carries a small but measurable increased risk of SPMs, primarily hematological. We would recommend that patients be counseled about this risk of SPMs and continue to undergo age-appropriate cancer screening. Blood counts should be monitored closely and there should be a low threshold for performing a bone marrow biopsy if unexpected cytopenias develop.

Bortezomib maintenance

To date, there have not been any placebo-controlled randomized studies with bortezomib in the post-ASCT setting. The HOVON-65/GMMG-HD4 trial is most frequently cited as the basis for use of bortezomib maintenance [22]. This study involved 827 newly diagnosed patients who were randomized to receive either VAD (vincristine, doxorubicin, and dexamethasone) or PAD (bortezomib, doxorubicin, and dexamethasone) induction therapy followed by either single or tandem ASCT. Patients on the VAD arm received thalidomide maintenance while those on the PAD arm received bortezomib maintenance given every other week for two years. Given this study design, it is not possible to directly compare the two maintenance regimens. However, it was noted that bortezomib maintenance improved the nCR + CR rate and was better tolerated than thalidomide. In addition when PFS was calculated from time of transplant, a statistically significant benefit was seen with bortezomib. When adjusted for the International Scoring System (ISS), the OS was superior on the PAD arm (HR= 0.80, p= 0.047) and the PAD arm also demonstrated improved PFS and OS for patients in renal failure. Thus this study forms the basis of the practice of every other week dosing of bortezomib as post-ASCT maintenance therapy. Prolonged use of bortezomib can be limited by the development or worsening of existing peripheral neuropathy.

The Nordic Myeloma Study Group performed a randomized consolidation study in which 370 patients received no consolidation vs. bortezomib consolidation (days 1, 4, 8, 11 out of a three week cycle for 2 cycles then once weekly days 1, 8, 15 in a 4-week cycle for 4 cycles) [23]. There was no difference in OS but the PFS favored bortezomib consolidation (27 mos *vs.* 20 mos, p=0.05). More patients achieved at least a very good partial response (VGPR) with bortezomib (71 *vs.* 57%, p<0.01).

There have been several studies which have assessed the combination of bortezomib with thalidomide post-ASCT. The Spanish Myeloma Group performed a trial in which patients were randomized to thalidomide *vs.* bortezomib plus thalidomide *vs.* interferon as maintenance therapy [24]. Although the bortezomib-thalidomide arm had an improved PFS, no differences were observed amongst the arms with respect to OS. In addition, the bortezomib-thalidomide arm did not overcome the poor prognosis associated with high-risk cytogenetics. A study by Cavo et al. compared thalidomide/dexamethasone (TD) to TD plus bortezomib (VTD) as induction therapy followed by tandem ASCT and then two cycles of TD or VTD consolidation [25]. Higher response rates were observed in the bortezomib-containing arm but this was accompanied by a higher incidence of adverse events which included peripheral neuropathy. The VTD arm had a higher PFS but there was no OS benefit.

As yet, data have not emerged that bortezomib maintenance is associated with SPMs. Although not a transplant study, the VISTA trial which compared melphalan/prednisone (MP) to bortezomib-MP (VMP) reported equivalent numbers of SPMs in both arms (hematological and solid tumor) [26].

Adverse risk cytogenetics

Although the use of induction therapies with novel agents and ASCT has improved myeloma patient outcomes in general, those with adverse risk cytogenetics such as del 17p, monosomy 13, t(4;14) and t(14;16) continue to have inferior outcomes. Bortezomib has been shown to partially overcome the adverse prognosis associated with t(4;14) and chromosome 13 deletion [25,27,28]. While patients with del17 had improved OS rates in the bortezomib-containing arm of the HOVON trial, those with other high risk abnormalities did not

Table 2: Ongoing or not yet reported consolidation/maintenance studies post-ASCT.

Study	Induction	Consolidation s/p ASCT	Maintenance	Primary Endpoint
BMT CTN 0702 NCT01109004	Not specified	Arm A) second ASCT with MEL200 Arm B) none Arm C) RVD x 4	Len until progression for all arms	PFS
NCT02181413	Not specified	None	Ixa vs. placebo for 2 years	PFS
NCT02253316	Not specified	IRD x 4	Ixa up to 3 years -or- Len up to 3 years	Improvement in MRD
NCT01936532	IRD x 3	IRD x 2 followed by IR x 6	Ixa for 1 year	sCR rate
NCT02406144	RVD x 6 (Patients on GEM2012MENOS65 (NCT01916252), randomized to receive MEL200 vs. BUMEL conditioning)	RVD x 2 (Patients on GEM2012MENOS65)	Len + Dex for 2 yrs -or- Len + Dex + Ixa for 2 yrs After 2 yrs of therapy, those with MRD-negativity will discontinue maintenance while those with MRD-positivity will continue Len + Dex for another 3 yrs	PFS
GMMG-HD6 NCT02495922	RVD x 4 RVD x 4 RVD + Elo x 4 RVD + Elo x 4	RVD x 2 RVD x 2 RVD x 2 RVD + Elo x 2	Len + Dex for 2 yrs Len + Dex + Elo for 2 yrs Len + Dex for 2 yrs Len + Dex + Elo for 2 yrs	PFS
NCT02420860	Not specified	None	Len + Dex + Elo	PFS
HOVON 131 MM/ IFM 2015-01 (planned)	VTD x 4 VTD-Dara x 4	VTD x 2 VTD-Dara x 2	Both arms randomized to Dara vs. observation	sCR rate

Abbreviations: Dara: Daratumumab; Dex: Dexamethasone; Ixa: Ixazomib; Elo: Elotuzumab; Len: Lenalidomide; IRD: Ixazomib, Lenalidomide, Dexamethasone; IR: Ixazomib, Lenalidomide; MEL200: Melphalan 200 mg/m2; MRD: Minimal Residual Disease; PFS: Progression-free Survival; sCR: Stringent CR; RVD: Lenalidomide, Bortezomib, Dexamethasone; VTD: Bortezomib, Thalidomide, Dexamethasone

benefit [22,29,30]. CALGB 100104 did not report outcomes based on cytogenetics [2]. The IFM 2005-02 study reported that the hazard ratio for progression or death favored the lenalidomide arm for patients with 13q deletion, without 13q deletion, and without (t4;14) or 17p deletion, but did not reach significance for patients with either t(4;14) or 17p deletion [9].

One strategy which has been reported to try to overcome adverse risk cytogenetics is the use of multi-agent chemotherapy as maintenance or extended consolidation treatment. Nooka et al. reported the outcomes of high-risk patients treated with up to three years of lenalidomide/bortezomib/dexamethasone (RVD) therapy followed by single agent lenalidomide [31]. This therapy was noted to be feasible and a 3-yr OS rate of 83% was achieved. The Arkansas 2006-66 study incorporated three years of post-ASCT RVD therapy [32]. When compared with the Total Therapy 3 regimen, which had three years of VTD, there was no improvement in the outcomes of patients with high-risk disease based on gene expression profiling.

Overall, there are not yet sufficient data to support the practice of choosing a maintenance therapy based on cytogenetics or gene expression profiling. Results from the BMT CTN 0702 study (Table 2) are eagerly awaited. This study randomized patients to three arms: tandem ASCT followed by lenalidomide maintenance, single ASCT followed by 4 cycles of RVD consolidation and then lenalidomide maintenance or single ASCT followed by lenalidomide maintenance. Patients were stratified into high-risk (high beta-2 micro globulin, t(4;14), t(14;20), t(14;16), del17p, del13 detected by standard cytogenetics, or aneuploidy) or standard-risk (beta-2 micro globulin <5.5 mg/L, del13 detected only by FISH).

Ongoing consolidation/maintenance studies

Table 2 summarizes consolidation/maintenance trials which are either currently in progress or for which results have yet to be reported. Table 3 summarizes studies which are evaluating upfront ASCT *vs.* continued treatment with multi-agent chemotherapy and which incorporate post-ASCT consolidation and/or maintenance therapy. Many of these studies include two-to-four cycles of multi-agent consolidation therapy prior to initiating maintenance therapy. As noted above, BMT CTN 0702 will provide the most direct comparison between lenalidomide maintenance alone *vs.* RVD consolidation followed by maintenance and should help guide clinical practice.

Several ongoing studies are focused on the use of the novel proteasome inhibitor ixazomib. Unlike the currently available proteasome inhibitors, ixazomib is an oral agent and can be administered on a weekly basis [33,34]. Although chemically similar to bortezomib, this agent does not appear to be associated with as much peripheral neuropathy as bortezomib and is therefore a reasonable candidate for maintenance therapy. A previously reported study demonstrated the feasibility of ixazomib maintenance therapy for up to 1.5 years following ixazomib-lenalidomide-dexamethasone induction therapy [35]. Adverse events of ixazomib maintenance included diarrhea, nausea, and cytopenias but notably, no peripheral neuropathy was reported. Although CALGB 100104 supports continuation of lenalidomide until disease progression, it is not known whether ixazomib should be similarly continued until progression and there are varying durations of treatment in the ongoing studies. It will be interesting to determine whether ixazomib can overcome poor-risk cytogenetics.

The other novel agent which is currently under investigation is the monoclonal antibody elotuzumab. This antibody targets CS1, a member of the signaling lymphocyte activating molecule family

Table 3: Transplant vs. no transplant studies which incorporate post-ASCT therapy.

Study	Induction	ASCT/Consolidation	Maintenance	Primary Endpoint
Palumbo et al. [71] NCT01091831	RD x 4	Tandem ASCT -or- CRD x 6	Each arm randomized to Len alone vs. Len plus prednisone until progression	PFS 3 yr PFS: 60% vs. 38% (p-0.003)
NCT00807599	RD x 4	Single or tandem ASCT -or- RD x 1 year	Len	PFS
IFM/DFCI2009 NCT01191060	RVD x 3	ASCT followed by RVD x 2 -or- RVD x 5	Len until progression for both arms (US) or for one year (French)	PFS
HOVON 95 NCT01208766	VCD x 4	1st randomization: VMP x 4 -or- ASCT (1 or 2) 2nd randomization: RVD x 2 -or- nothing	Len until progression	PFS
Myeloma XI NCT01554852	Intensive arm (for TE patients): CTD, CRD, or CCRD Non intensive arm (for TNE patients): CTD, or CRD. For both arms, based on response, VCD vs. nothing as consolidation	Single ASCT (intensive) -or- nothing (non intensive)	Both arms: Len vs. Len + vorinostat vs. nothing until progression	PFS
Myeloma XI+	Intensive arm (for TE patients): CTD or CRD. Non intensive arm (for TNE patients): CTD, CRD, or CCRD. For both arms, based on response, VCD vs. nothing as consolidation	Single ASCT (intensive) -or- nothing (non intensive)	Both arms: Len vs. nothing until progression	PFS
NCT02315716	CarCyDex	ASCT -or- CarCyDex x 4	Carfilzomib x 18 months	Response rate and PFS
NCT02203643	CarCyDex x 4 CarLenDex x 4 CarLenDex x 4	ASCT followed by CarCyDex x 4 ASCT followed by CarCyDex x 4 CarLenDex x 8	All arms randomized to Len vs. CarLen until progression	Rate of VGPR or better after induction

Abbreviations: CarCyDex: Carfilzomib, Cyclophosphamide, Dexamethasone; CarLen: Carfilzomib, lenalidomide; CarLenDex: Carfilzomib, Lenalidomide, Dexamethasone; CCRD: Carfilzomib, Cyclophosphamide, Lenalidomide, Dexamethasone; CRD: Cyclophosphamide, Lenalidomide, Dexamethasone; CTD: Cyclophosphamide, Thalidomide, Dexamethasone; Len: Lenalidomide; RD: Lenalidomide, Dexamethasone; RVD: Lenalidomide, Bortezomib, Dexamethasone; TE: Transplant Eligible; TNE: Transplant not Eligible; VCD: Bortezomib, Cyclophosphamide, Dexamethasone; VGPR: Very Good Partial Response; VMP: Bortezomib, Melphalan, Prednisone

(SLAM) of cell surface receptors. CS1 is highly expressed in myeloma cells and to a lesser extent NK and CD8+ T-cells [36]. Upon binding of elotuzumab to CS1 on myeloma cells, NK cells are recruited and activated, leading to myeloma cell death. Although elotuzumab lacks single agent activity [37], it has impressive activity when used in combination with lenalidomide [38-40]. As this agent has an acceptable toxicity profile, it is reasonable to hypothesize that it will be well-tolerated in the post-ASCT setting and that it could lead to improved outcomes.

Novel agents

With the exception of ixazomib and elotuzumab, there are currently no ongoing post-ASCT maintenance studies with other novel agents. However, as indicated in Table 4, there are multiple novel agents which are being tested in myeloma and it will only be a matter of time before these agents are tested in the post-ASCT setting. Anti-CD38 antibodies are of particular interest. Daratumumab and isatuximab are two monoclonal antibodies directed against CD38, an antigen highly expressed on myeloma cells. A phase II study of daratumumab has shown single agent activity in very heavily pre-treated patients with an overall response rate of approximately 30% [41]. Activity has been observed in patients who are dual refractory to immunomodulatory agents and proteasome inhibitors, a subgroup of patients who historically have had a dismal prognosis. The side effect profile has thus far been shown to be quite acceptable: the primary toxicity is related to infusion reactions. Notably, the combination of daratumumab with lenalidomide and dexamethasone in relapsed/refractory patients yielded a 75% overall response rate [42]. Isatuximab also has single agent activity and is effective when combined with lenalidomide and dexamethasone in the relapsed/refractory setting [43,44]. Thus it would be hypothesized that an anti-CD38 monoclonal antibody could be safely incorporated into lenalidomide maintenance post-ASCT with improved depth and duration of response. Interestingly, despite the presence of CD38 on activated T-lymphocytes, there have been no reports of immune dysregulation with anti-CD38 antibodies. Of note, the planned HOVON 131 MM/IFM 2015-01 (Table 2) study randomizes patients to VTD induction/consolidation with or without daratumumab and then both arms are

Table 4: Novel agents under investigation for myeloma.

Class	Drug	Target
Monoclonal antibodies	Elotuzumab	CS1
	Daratumumab	CD38
	Isatuximab	CD38
	IPH2101	KIR
	1-7F9	KIR
	Nivolumab	PD-1
	Pembrolizumab	PD-1
	Pidilizumab	PD-1
	REGN2810	PD-1
	MPDL3280A	PD-L1
Histone deacetylase inhibitors	Panobinostat	
	Vorinostat	
CXC4	Olaptesed pegol	CXCL12
Apoptosis	ABT199	Bcl-2 inhibitor
DNA repair	Veliparib	PARP 1/2
Nuclear export	KPT330	Exportin-1 inhibitor
Bromodomain	CPI-0610	
Cell cycle inhibitors	Seleciclib	CDK 4/6
	MLN8237	Aurora kinase A
	ARRY-520	KSP
	Dinaciclib	CDK 1, 2, 5, 9
Kinase/Growth Factor inhibitors	Masitinib	FGFR3/PDGFR/c-Kit
	Dasatinib	cKIT/PDGFR
	Enzastaurin	PKC
	GSK2110183	Akt
	Selumetinib	MEK
mTORC	MLN0128	
	INK128	
	Everolimus	
	Temsirolimus	

randomized to daratumumab vs. nothing as maintenance therapy.

Immune checkpoint blockade represents another intriguing therapeutic strategy. Programmed death ligand 1 (PD-L1) is expressed on malignant plasma cells [45]. Additionally, both PD-L1 and its cell surface receptor programmed cell death protein 1 (PD-1) are widely expressed in the myeloma microenvironment, highly suggestive that immune evasion of myeloma cells via the PD-1/PD-L1 pathway plays a role in the persistence of malignant cells[46]. Blockade of this signaling axis has been shown to enhance host antitumor immunity [47]. In a murine model of myeloma with high PD-L1 expression, blockade of PD-L1 improved survival in response to immunotherapy [48]. There is an ongoing phase 2 multi-center study (NCT02331368) evaluating the use of anti-PD1 during the lymphopenic state after high dose chemotherapy and autologous stem cell transplant for multiple myeloma. Another clinical trial is looking at blockade of PD-1 in conjunction with the dendritic cell/myeloma vaccines following stem cell transplantation (NCT01067287).

Chimeric antigen receptor T cell (CAR-T) therapy has been shown to be successful in the treatment of various hematologic malignancies. Recent studies have identified potential target antigens for adoptive transfer of CAR-T cells for multiple myeloma, including CS1, BCMA and NY-ESO-1 [49-52]. BCMA is a protein that is selectively expressed on malignant plasma cells as well as B-lineage cells but not found on normal human tissues [53,54]. Carpenter et al. designed anti-BCMA CARs by transducing T cells with lentiviral vectors and demonstrated that these cells could specifically recognize and kill myeloma cells [51]. NY-ESO-1 is an antigen which has been found to be expressed on some myeloma cells [52,55]. A phase I/II trial evaluating the safety and activity of autologous T cells engineered to express T cell receptors which recognize NY-ESO-1 was conducted in 20 patients with multiple myeloma [56]. Patients were infused with the CAR-T cells 2 days after undergoing ASCT. The engineered T cells were observed to undergo expansion, proliferation, and trafficking to the marrow with activity against antigen-positive malignant plasma cells. Clinical responses were observed in 16 out of 20 (80%) of the patients and were associated with a median progression free survival of 19.1 months. The infusions were well tolerated without significant cytokine-release syndrome. Ongoing clinical trials include a phase I clinical trial (NCT02215967) studying T cells targeting BCMA for previously treated multiple myeloma, a phase I clinical trial (NCT02203825) evaluating the safety of CAR-T cells targeting NKG2D ligands, and a phase I/II study (NCT01886976) of chimeric CD138 antigen receptor modified T cells in relapsed/refractory multiple myeloma.

Myeloma cells have been shown to be able to hijack the bone marrow microenvironment to promote their own proliferation and growth. Hence, agents that are able to target the bone marrow microenvironment represent potential therapies for myeloma. *Myc* is an oncogene that is found in multiple myeloma. *In vitro* and *in vivo* studies with murine models have shown that inhibiting BET bromodomain 4 leads to down-regulation of *Myc* transcription resulting in the hindrance of myeloma cell growth [57]. In addition, *in vitro* studies have demonstrated synergy between the bromodomain inhibitor CPI-203 and bortezomib [58]. A phase I trial (NCT 02157636) evaluating the bromodomain inhibitor CPI-0610 in relapsed/refractory myeloma is currently ongoing.

Another potential target is CXCL12, which is a ligand to CXCR4. Malignant plasma cells have high levels of CXCR4 receptors. CXCL12 and CXCR4 play important roles in the trafficking and homing of myeloma cells to the bone marrow microenvironment [59]. Olaptesed Pegol (NOX-A12) is an inhibitor of CXCL12, and thereby prevents CXCR4 from interacting with CXCL12. Pre-clinical studies have demonstrated synergistic activity with CXCL12-targeting agents and bortezomib [60]. A phase II trial that evaluated the combination of olaptesed with bortezomib and dexamethasone in relapsed/refractory multiple myeloma showed a PFS of 6.5 months and a 73% ORR [61]. Further trials, including a phase III trial are ongoing.

Natural killer cells have been shown to have cytotoxic activity against malignant plasma cells. However, myeloma cells have been able to evade host antitumor responses by expressing HLA class I molecules that are ligands to KIRs, which are NK cell inhibitory killer immunoglobulin-like receptors [62,63]. IPH2101 is an anti-

KIR antibody which has been shown to enhance NK-cell killing of myeloma cell lines [64]. A phase I trial of IPH2101 in combination with lenalidomide in relapsed/refractory myeloma showed that IPH2101 was able to occupy all KIR receptors at all dosing cohorts [65]. A currently completed trial, the final results of which are yet to be reported, evaluated the safety and tolerability of another anti-KIR monoclonal antibody, 1-7F9, in patients with myeloma (NCT 00552396).

Finally, although not yet tested clinically in myeloma, there are pre-clinical studies which support the further study of bispecific T-cell engagers (BiTEs). BiTEs are composed of 2 single-chain variable fragments with the ability to bind to a T cell–specific antigen as well as a cancer-specific antigen thus bringing into proximity the effector cells with the malignant cell. Bispecific T cells have been engineered with the ability to target both CD3 and CD138 [66]. In addition, T cells have been made that are targeted against BCMA (BiFab-BCMA) [67]. BiFab-BCMA were found to be effective in activating T cells and to be potently cytotoxic against BCMA-positive cells lines, mediating rapid tumor regression in a xenograft model of myeloma [67].

Minimal residual disease

A major unanswered question is whether there are subsets of patients for whom maintenance therapy is either unnecessary or for whom therapy can be discontinued once a certain end-point has been achieved. Integral to this discussion is the concept of minimal residual disease (MRD). While studies have shown that achievement of CR following ASCT correlates with prolonged survival [68], the ability to measure CR continues to evolve. With the development of sensitive techniques such as multiparametric flow cytometry (MFC), allele-specific oligonucleotide PCR (ASO PCR) and high-throughput sequencing (HTS), smaller and smaller numbers of malignant plasma cells can be detected. In the post-ASCT context, achievement of MRD-negativity appears to correlate with improved outcomes. Pavia et al. used MFC to measure MRD status at day 100 post-ASCT in 295 patients treated on the GEM2000 protocol and found that both PFS and OS were prolonged in patients who were MRD negative [69]. In an analysis of the MRC Myeloma IX trial, MRD positivity at day 100 was associated with inferior PFS and OS [70]. Notably, thalidomide maintenance was associated with an improvement in PFS in the MRD-positive patients but not in the MRD-negative patients. While these results are hypothesis generating, at this time there are insufficient data to support the practice of with-holding maintenance therapy for MRD-negative patients. Recent studies such as the BMT CTN 0702 and IFM/DFCI2009 are performing MRD analysis and these studies will provide additional information regarding the significance of MRD status. However, future studies are needed to prospectively determine 1) whether patients who are MRD-negative at day 100 post-ASCT can be safely monitored without initiating maintenance therapy and 2) whether patients who achieve MRD-negativity while on maintenance therapy can be taken off of maintenance therapy without compromising their long-term outcomes. Of note, the Spanish Myeloma Group is conducting a trial (NCT02406144) in which patients are randomized to lenalidomide/dexamethasone with or without ixazomib for two years in the post-ASCT setting. After completions of the 2 years of therapy, patients who are MRD-negative discontinue maintenance treatment while those who are MRD-positive goes on to receive an additional three years of therapy with lenalidomide/dexamethasone.

Financial cost considerations

Current and future post-ASCT maintenance strategies have the important goals of improved PFS and OS. However, the financial burden of these therapies is a factor which needs to be considered. Maintenance therapy with agents such as lenalidomide is already expensive and costs will further escalate if additional agents such as monoclonal antibodies or other oral chemotherapeutic drugs are added to lenalidomide. The extent to which insurance covers the costs of the medications can vary and, unfortunately for many patients, the out-of-pocket expenses can represent a significant financial burden. Even if insurance does cover costs for patients, it is not clear that our healthcare system can withstand these escalating medication costs.

Conclusion

While outcomes have markedly improved for myeloma patients, this malignancy is currently considered incurable. Thus it is important that both physicians and patients consider the relative benefits and risks of post-ASCT therapy. CALGB 100104 has established that lenalidomide continued until progression significantly improves both PFS and OS, but there is a signal for increased SPMs. Whether other maintenance therapies should be continued until time of progression is uncertain. While it is exciting to speculate that the incorporation of novel agents such as monoclonal antibodies into post-ASCT therapy will further improve outcomes, the impact of these prolonged therapies on quality of life, as well as the financial feasibility of such an approach needs to be determined. Prospective studies are needed to determine whether a more individualized approach to post-ASCT therapy can be developed based on factors such as MRD status, gene expression profiling, and cytogenetics.

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