CLINICAL INVESTIGATION

The evolving field of post-transplant therapy in multiple myeloma

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Multiple myeloma is characterized by monoclonal protein production, immune dysregulation, renal dysfunction and lytic bone disease. The backbone of therapy for patients eligible for high-dose therapy has been induction therapy followed by consolidation with autologous stem cell transplant. The introduction of immunomodulatory drugs and proteasome inhibitors has led to a dramatic improvement in responses to induction therapy, translating to improved survival following transplant. Despite these successes, nearly all patients will eventually relapse. The role of maintenance therapy following transplant to delay recurrence and improve survival continues to be defined. This review focuses on the most recent clinical trials for maintenance therapy, minimal residual disease detection, the risk of second primary malignancies, as well as future directions in this field.

Keywords: autologous stem cell transplant • immunomodulatory drugs (IMiDs) • maintenance • minimal residual disease assessment • proteasome inhibitor • second primary malignancy

Maintenance therapy in the pre-immunomodulatory drug era

Prior to the introduction of immunomodulatory drugs (IMiDs) to the myeloma armamentarium, post-transplant maintenance strategies primarily involved IFN-α. IFN-α is a cytokine and was first noted to have clinical benefit in a myeloma patient in a case report in 1979 [1]. That same year, four additional patients were reported to have benefited from IFN therapy [2]. It was subsequently studied as single-agent therapy, in combination with chemotherapy, and as maintenance therapy [3]. Attal *et al.* demonstrated the feasibility of IFN-α maintenance following autologous stem cell transplant [4,5]. A later analysis of French transplant data revealed that the inclusion of IFN maintenance therapy did not appear to alter remission duration or overall survival (OS) [6]. A Spanish transplant registry reported that IFN therapy was associated with improved progression-free survival (PFS) and OS [7]. A European registry study comparing 473 patients who had received IFN maintenance with 419 patients who had not reported significantly improved OS (78 vs 47 months) and PFS (29 vs 20 months) with IFN [8]. A randomized study conducted by Powles *et al.* demonstrated that IFN maintenance after transplant improved the median PFS from 27 months in the control group to 46 months with a 52-month follow-up period [9]. However, the benefit was seen only in patients who had achieved a complete response from transplant. Long-term follow-up (5.8 years) of this study revealed that differences in PFS and OS were no longer significant as the majority of patients had subsequently died of their disease [10]. A randomized study performed by the Czech myeloma group that compared maintenance with IFN alone to IFN alternating with dexamethasone failed to show a difference between the two arms [11]. The two meta-analyses that have been performed demonstrate that the benefit in OS achieved through IFN maintenance is small, in the 3–4-month range [3,12]. Not

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surprisingly, given the side-effect profile of IFN, a quality-of-life analysis revealed that patients reported poor quality of life [13]. While routine use of IFN has now ceased, it is interesting to note that a retrospective study, which evaluated the association of polymorphisms in inflammatory genes with response showed that patients who are homozygous for the wild-type ins-allele of *NFKB1*-94ins/delATTG polymorphism had a longer OS with IFN therapy [14]. This result is hypothesis-generating and merits further attention.

Maintenance therapy in the IMiD era

Thalidomide

Thalidomide has had a very intriguing history as a pharmaceutical agent. First introduced in the 1950s as a sedative and anti-emetic, it was then banned in the early 1960s because of its association with severe congenital abnormalities. Thalidomide found its next therapeutic niche in leprosy. In 1998 thalidomide was approved in the US for treatment of erythema nodosum leprosum.

In 1999, Singhal *et al.* published a seminal report of 84 patients with relapsed/refractory myeloma who had been treated with thalidomide [15]. A total response rate of 32% was noted. Thalidomide was subsequently intensely studied in the relapsed/refractory setting as well as for newly diagnosed myeloma patients and became the standard of care. Because of its ease of administration (oral) and lack of associated cytopenias, thalidomide has also been evaluated in the context of maintenance therapy following transplant. To date, there have been eight randomized studies investigating thalidomide following transplant [16–23]. These studies differed with respect to dose of thalidomide and whether or not thalidomide was used in combination with corticosteroids. The results of these studies have recently been reviewed [24]. Some of the trials demonstrated an improvement in OS with thalidomide while others did not. There is some evidence that thalidomide maintenance does not improve outcomes for patients with adverse cytogenetics [25]. Multiple studies have demonstrated that compliance and feasibility of prolonged thalidomide therapy is low because of toxicity, particularly peripheral neuropathy, limiting the median duration of maintenance therapy to approximately 1 year [16,17,23]. Given the more favorable side-effect profile of lenalidomide compared with thalidomide, particularly with respect to neurotoxic effects, the use of thalidomide in the post-transplant setting has diminished in the USA. However, it remains an option, especially when combined with glucocorticoids, for patients who cannot tolerate the myelosuppression of lenalidomide and as a more cost-effective option [26] in countries with limited access to lenalidomide or bortezomib.

Lenalidomide

Lenalidomide, the second-generation IMiD, was first reported to have activity in myeloma patients with relapsed/refractory disease in a Phase I study in 2002 [27]. Since then it has found widespread use for patients with newly diagnosed, as well as relapsed/refractory disease. Palumbo *et al.* first reported on the use of lenalidomide as both consolidation and maintenance therapy post-transplant [28]. In this Phase II study, patients received induction therapy with bortezomib, doxorubicin and dexamethasone followed by tandem transplant with melphalan (100 mg/m^2). Consolidation therapy consisted of four cycles of lenalidomide plus prednisone followed by maintenance lenalidomide (10 mg/day on days 1–21) until relapse. Subsequently, three randomized trials incorporating lenalidomide maintenance have been reported (Table 1).

The CALGB 100104 trial included 460 patients who were randomized to receive lenalidomide versus placebo as maintenance therapy post-transplant [29]. Treatment was begun at day 100 and consisted of 10 mg/day continuous therapy. This dose was escalated to 15 mg/day after 3 months if tolerated. The study was unblinded early because the primary end point of time to progression was met (46 vs 27 months; hazard ratio [HR]: 0.48; $p < 0.001$) at which point 86/128 patients in the placebo group crossed over to receive lenalidomide. Notably, a significant improvement in OS was observed: at 34 months the OS was 85% in the lenalidomide arm compared with 77% in the placebo arm ($p = 0.03$). In a subset analysis there was PFS benefit for those achieving and not achieving complete response (CR). These results have subsequently been updated at the 2013 International Myeloma Working Group meeting [30]. At a median follow-up of 48 months, the OS was 80% for the lenalidomide arm and 70% for the placebo group ($p = 0.008$) and there was a continued PFS advantage for the lenalidomide arm.

The IFM 2005–02 trial included 614 patients who received two cycles of consolidation therapy with lenalidomide (25 mg/day for days 1–21) prior to starting maintenance therapy (lenalidomide vs placebo) [31]. The initial dose of lenalidomide was 10 mg/day and was escalated to 15 mg/day, if tolerated, after 3 months. The study was also unblinded early due to meeting the primary end point of PFS (median PFS of 41 vs 23 months; HR: 0.5; $p < 0.001$). However, crossover to lenalidomide was not permitted. Unlike the CALGB study, an improvement in OS was not noted: the 3-year OS in the lenalidomide was 80 versus 84% in the placebo arm (HR: 1.25; $p = 0.29$). After longer follow-up (60 months from randomization), the improvement in PFS with lenalidomide maintenance was still evident (42 vs 18%; $p < 0.0001$); however, no difference in OS

Table 1. Lenalidomide maintenance following autologous transplant.

Study	Induction therapy	Dosing schedule	Duration of maintenance	EFS or PFS (maintenance vs no)	OS (maintenance vs no)	Ref.
McCarthy *et al.*	≤2 regimens; 94% received a regimen containing thalidomide, lenalidomide and/or bortezomib	10 mg continuous, increase up to 15 mg	Until progression	EFS: 43 vs 27 months ($p < 0.001$) 3-year PFS: 66 (95% CI: 59–73) vs 39% (95% CI: 33–48)	Median follow-up 34 months: 85 vs 77% ($p = 0.028$) 3-year OS: 88 (95% CI: 84–93) vs 80% (95% CI: 74–86)	[29]
Attal *et al.*	46% received vincristine, doxorubicin and dexamethasone; 46% received bortezomib and dexamethasone; 21% received tandem transplant	All patients received two cycles of consolidation (25 mg/day, 21 out of 28 days); maintenance: 10 mg continuous, increase up to 15 mg	Median of 2 years	EFS: 40 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%	[31]
Palumbo *et al.*	Four cycles lenalidomide/ dexamethasone followed by either tandem transplant or melphalan/ lenalidomide/ prednisone	10 mg (3 weeks on, 1 week off)	Until progression	Median PFS†: 42 vs 22 months ($p < 0.001$)	3-year OS†: 88 vs 79% ($p = 0.14$)	[34]

†Combining tandem transplant and melphalan/lenalidomide/prednisone groups.
EFS: Event-free survival; PFS: Progression-free survival; OS: Overall survival.

at 5 years was seen (68 vs 67%) [32]. Interestingly, this analysis revealed that the median second PFS (time from progression in first line to the second progression or death) was worse in the lenalidomide arm than in the placebo arm (10 vs 18 months; $p < 0.0001$).

The reason underlying differences in OS outcome between the American and French studies is an area of intense discussion [33]. It has been noted that the induction regimens for the French trial (primarily bortezomib/dexamethasone or vincristine, doxorubicin, dexamethasone [VAD]) did not include an IMiD, while 74% of the patients in the CALGB trial received an IMiD prior to transplant. No consolidation therapy was given in the CALGB trial. There was also a difference in duration of lenalidomide therapy: in the French study lenalidomide was discontinued at a median of 2 years (range: 1–3 years), while lenalidomide was continued until progression in the CALGB trial. Finally, 21% of patients had undergone tandem transplant and 25% of patients received dexamethasone/cyclophosphamide/etoposide/cisplatin pretransplant consolidation in the IFM trial. The results from the longer term follow-up for the CALGB 100104 trial are eagerly awaited. At this time, the use of lenalidomide maintenance post-transplant can be considered a standard of care in the USA.

Finally, the results of the Italian transplant and maintenance study have recently been reported [34]. In this trial, newly diagnosed patients received induction therapy with four cycles of standard lenalidomide/dexamethasone. Patients were then randomized to consolidation with MPR (melphalan, lenalidomide, prednisone; six cycles) versus tandem transplant (melphalan 200 mg/m^2). All patients were again randomized to receive either lenalidomide maintenance (10 mg, days 1–21 of 28 days) or no maintenance. The 5-year OS was 78% for the tandem transplant + lenalidomide maintenance group, 67% for the tandem transplant without maintenance group, 70% for the MPR plus lenalidomide maintenance group and 59% for the MPR without maintenance group. The median PFS (combining the MPR and the tandem-transplant groups) was 42 months for the lenalidomide maintenance group and 21.6 months for the observation group ($p < 0.001$). The 3-year OS, when analyzed from the start of maintenance, did not show a significant difference (88% for the lenalidomide arm and 79% for the observation arm; $p = 0.14$), but did show a significant OS benefit when analyzed on an intent to treat basis from the time of randomization. Lenalidomide maintenance improved the CR rate in both arms. While this study also addresses the

question of transplant versus no transplant, it demonstrates improved PFS with lenalidomide maintenance therapy.

When examining the IFM 2005–02 study, 74% of the lenalidomide arm and 43% of the placebo arm patients had grade 3 or 4 events [31]. For hematologic grade 3 and 4 adverse events, 58% were in the lenalidomide arm and 22% were in the placebo arm. In the lenalidomide group, 27% of the patients discontinued treatment due to adverse events and 15% of the placebo arm patients discontinued treatment. For the CALGB 100104 study, 69% of the lenalidomide arm and 30% of the placebo arm patients developed a grade 3 or 4 adverse event [29]. For hematologic grade 3 and 4 events, 48% were in the lenalidomide arm and 17% were in the placebo arm. In the lenalidomide arm, 10% of patients stopped therapy due to adverse events and 1% of the placebo patients and 6% of the lenalidomide crossover placebo patients stopped lenalidomide maintenance due to adverse events.

The three transplant studies have shown a PFS benefit for lenalidomide maintenance following autologous transplant. Two of the three maintenance studies have shown an OS benefit. Long-term follow-up will be necessary to understand the differences between studies so as to improve patient outcomes.

Bortezomib

Bortezomib was the first proteasome inhibitor to be approved for the treatment of myeloma. It has shown significant activity in both newly diagnosed and relapsed/refractory patients [35–37]. Notably, bortezomib has been shown to improve outcomes for those patients with adverse risk disease associated with t(4;14) and chromosome 13 deletion [38–40]. European and American trials have been conducted to examine the use of bortezomib as consolidation/maintenance. Cavo *et al.* conducted a study in which newly diagnosed patients were randomized to receive thalidomide/dexamethasone with or without bortezomib [40]. Following tandem transplant, patients then received two additional cycles of TD or bortezomib/thalidomide/dexamethasone as consolidation. Higher response rates were noted in the bortezomib-containing arm, and this arm had a significantly higher incidences of adverse events, including peripheral neuropathy. Arkansas's Total Therapy 3 regimen also incorporated bortezomib into the induction (bortezomib/dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide) and maintenance regimens (bortezomib/thalidomide/dexamethasone) [41].

The HOVON-65/GMMG-HD4 trial included 827 newly diagnosed patients who were randomized to VAD or bortezomib, doxorubicin, dexamethasone (PAD) induction therapy followed by transplant and then maintenance therapy consisting of thalidomide on the VAD arm and bortezomib (every other week for 2 years) on the PAD arm [42]. Given the study design, it was difficult to directly compare the maintenance regimens. However, it was noted that bortezomib was better tolerated than thalidomide. Bortezomib maintenance significantly improved the nCR + CR rate and the PFS calculated from the time of transplant was longer in the bortezomib arm. The OS for the PAD arm was superior when adjusted for International Scoring System (HR: 0.80; 95% CI: 0.65–1.00; p = 0.047). It is also important to note that patients who were in renal failure at the time of initial presentation or had del17 abnormalities had improved OS in the bortezomib-containing arm as compared with the thalidomide arm. The patients with other low- and high-risk cytogenetic abnormalities did not have a significant PFS and OS advantage with bortezomib [42–44].

The Nordic Myeloma Study Group reported the results of a trial in which 370 patients were randomized to receive bortezomib consolidation (days 1, 4, 8, 11 out of a 3-week cycle for two cycles then once weekly days 1, 8, 15 in a 4-week cycle for four cycles) versus no consolidation after transplant [45]. The PFS was 27 months in the bortezomib arm compared with 20 months in the control arm (p = 0.05) and no difference in OS was observed. The Spanish Myeloma Group have reported preliminary results of a trial in which patients were randomized to different induction regimens and following transplants were randomized to three arms: thalidomide plus bortezomib versus thalidomide versus IFN [46]. The PFS was better in the thalidomide–bortezomib arm but there were no OS differences and bortezomib did not overcome the poor prognosis associated with high-risk cytogenetics. In the absence of a clinical trial, bortezomib maintenance is commonly given in the every-other-week dosing schedule in an effort to reduce the risk of peripheral neuropathy and for 2 years based on the HOVON-65/GMMG-HD4 study.

Lenalidomide–bortezomib–dexamethasone maintenance

Despite maintenance strategies, patients with high-risk disease continue to have inferior outcomes compared with those with standard-risk disease. Nooka *et al.* recently reported a study in which patients with high-risk disease (as defined by deletion of p53, deletion of 1p, t(4;14), t(14;16) or plasma cell leukemia) who had undergone autologous stem cell transplant received up to 3 years of lenalidomide, bortezomib and dexamethasone (RVD) combination therapy followed by single-agent lenalidomide [47]. Although a small study,

the results were promising with a 3-year OS of 93%. Notably Arkansas's 2006–66 study, the successor to Total Therapy 3, also included 3 years of RVD post-transplant [48]. When compared with Total Therapy 3, which used thalidomide in place of lenalidomide, there were no differences in outcomes and patients with high-risk disease as defined by their gene expression profiling testing continued to have inferior outcomes. More studies are needed to determine whether RVD maintenance should be routinely used for patients with high-risk disease.

Determining minimal residual disease

As response rates continue to improve with the introduction of novel agents, so too have our capabilities of detecting residual disease improved. Initially a complete response was determined via immunofixation and plasma cell numbers on bone marrow biopsy. With the advent of free light chain testing, as well as more rudimentary methodologies to determine clonality (immunohistochemistry or immunofluorescence), came the definition of a stringent complete response (Table 2) [49]. Recently, multiparametric flow cytometric (MFC) and allele-specific oligonucleotide (ASO) PCR techniques have yielded definitions of immunophenotypic and molecular (respectively) complete responses [50].

MFC involves the use of immunofluorescence and antibodies directed against markers of plasma cells and can differentiate between normal and malignant plasma cells. The sensitivity of this technique has reached 10^{-4} [51]. Different groups have used different panels and experts are now meeting to create consensus guidelines for the use of MFC. ASO PCR requires the preparation of patient-specific primers for the rearranged region of the immunoglobulin heavy chain genes which involves extraction of RNA from myeloma cells and reverse transcription. The sensitivity of using ASO PCR with primers complementary to the variable region of the immunoglobulin heavy chain has reached 10^{-5} [52]. The use of fluorescent-PCR has also been investigated with a reported sensitivity of up to 10^{-3} [53].

A recent study by Puig *et al.* compared ASO real-time quantitative PCR with MFC. A total of 170 patients were assessed [54]. However, in only 42% of the cases could PCR be used because of difficulties with sequencing, failure to amplify or primer design. Of the evaluable patients, persistent disease was identified in 54% using PCR and in 46% of the cases using MFC. Although the PCR technique appeared slightly more sensitive, the low applicability rate coupled with the higher expense led the authors to recommend that MFC be considered the method of choice for determining minimal residual disease (MRD).

The ability to detect MRD is only important if it correlates with outcome and can be used to guide treatment strategies. In Puig's study, patients with $<10^{-4}$ residual myeloma cells, as determined by either MFC or ASO, had a significantly improved PFS [54]. Paiva *et al.* assessed MRD by MFC at day 100 post-transplant in 295 newly diagnosed patients treated on the GEM2000 protocol [55]. Both PFS and OS were significantly longer in patients who were MRD-negative. MRD status by MFC was noted to be the most important prognostic factor for both PFS and OS as determined by multivariate analysis. In a study by Rawstron, MRD was assessed by MFC in patients treated on the MRC Myeloma IX trial [56]. These authors found that the presence of MRD post-transplant (day 100) was associated with inferior PFS and OS. The use of thalidomide maintenance increased the PFS in the MRD-positive group, but not the MRD-negative group. A subset of patients was also assessed approximately 7 months after the day 100 assessment. In this group, 28% of MRD-positive patients receiving thalidomide became MRD-negative as compared with 3% of patients who did not receive thalidomide. These results suggest that the role of thalidomide maintenance therapy might be restricted to those patients who do not achieve MRD-negative status. Prospective trials involving randomization of MRD-negative patients to maintenance vs monitoring are needed to further explore this hypothesis.

Interestingly, several trials have identified patients who are MRD-negative but immunofixation electrophoresis-positive [55,56]. However, the outcomes of these patients differed among the trials. Whether the MRD-negative/immunofixation electrophoresis-

Table 2. Complete response criteria.

Response type	Response criteria
Complete	Negative serum and urine immunofixation electrophoresis + no soft tissue plasmacytoma + <5% plasma cells on bone marrow aspirate/biopsy
Stringent complete	Complete response + normal free light chain ratio + no clonal cells by bone marrow immunohistochemistry or immunofluorescence
Immunophenotypic complete	Stringent complete response + no detectable phenotypically aberrant clonal plasma cells by >4 color multiparametric flow cytometry on an analysis of at least one million total bone marrow cells
Molecular complete	Stringent complete response + no identifiable allele-specific oligonucleotides on PCR with a sensitivity of 10^{-5}

positive patients are a consequence of the long half-life of some intact immunoglobulins or represents residual extra-medullary disease remains to be determined. One limitation of both ASO-PCR and MFC methodologies is that they only detect disease in the bone marrow.

Finally, a recent study utilized high-throughput sequencing as a methodology to detect MRD following induction therapy in myeloma patients and compared the results to those that were achieved with MFC and ASO-PCR [57]. High-throughput sequencing involves amplification and sequencing of immunoglobulin gene segments using locus-specific primer sets and has a sensitivity of 10^{-6} [58]. The deep sequencing technique could be applied in 91% of the patients and had a concordance of 83 and 85% with MFC and ASO-PCR, respectively. Further studies are needed to determine which methodology for MRD detection will become the gold standard.

Imaging to assess post-transplant response

In the newly diagnosed setting, PET/computed tomography (CT) has been demonstrated to have high sensitivity (85%) and specificity (92%) in detecting myelomatous lesions [59]. Normalization of fluorodeoxyglucose-PET uptake following induction therapy prior to autologous stem cell transplant has been correlated with improved OS [60]. However, the role of PET/CT in evaluating response after transplant is less clear. In a study assessing the use of PET/CT in myeloma patients following autologous or allogeneic stem cell transplant, a sensitivity of 54.6%, a specificity of 82.1% and an overall accuracy of 65.5% were reported. These authors noted that while PET/CT could be used to detect disease, the sensitivity in the post-transplant setting was significantly lower than in the pretreatment setting [61]. In addition, the sensitivity was related to the response based on the Uniform Response Criteria: a lower sensitivity (34.1%) was noted for patients who had achieved a very good partial response as opposed to patients who had recurrent or progressive disease (80%). Zamagni *et al.* reported on a series of patients who underwent PET/CT at time of diagnosis, following thalidomide/dexamethasone induction therapy, and following double autologous stem cell transplantation [62]. They noted improved PFS and OS for patients who were PET/CT-negative 3 months post-transplant as compared with those who remained PET/CT-positive. A subsequent study evaluated the performance of PET/CT versus whole-body MRI in determining the remission status following transplant [63]. The sensitivity, specificity and overall accuracy for PET/CT and MRI were 50/80, 85.7/38.1 and 74.2/51.6%, respectively. Notably, there was very little concordance in identified lesions between the two imaging studies (11.5%). The use of MRI in this setting may be limited because of its inability to differentiate between viable and nonviable lesions. At this time, neither the National Comprehensive Cancer Network nor the International Myeloma Working Group recommends routine use of PET/CT or MRI following transplant. Further studies are needed to identify the subsets of patients for whom the use of these imaging modalities would be beneficial.

Progression on maintenance therapy

It is not unusual for the first signs of relapse on maintenance therapy to be biochemical changes such as derangement in the free light chain ratio or reappearance of a monoclonal protein on immunofixation electrophoresis. In the absence of evidence of active disease, it is unclear whether the patient should be continued on their current dose of lenalidomide, whether the dose should be escalated, or whether therapy should be switched all together. Several ongoing clinical trials are addressing this common clinical scenario. One approach for patients with biochemical progression on maintenance lenalidomide involves dose escalation of lenalidomide and the addition of dexamethasone (NCT01463670) (Table 3). A more unusual approach involves the addition of thalidomide to lenalidomide (NCT01927718). This is based on prior clinical studies showing the feasibility of combining the two IMiD agents together, along with dexamethasone, in the relapsed/refractory setting [64,65].

Secondary malignancies

Initial reports of three randomized studies involving lenalidomide maintenance raised the concern of an increased rate in second primary malignancies (SPM). In the two trials involving maintenance therapy after transplant, Attal *et al.* [66] reported a SPM incidence of 2.6% in the lenalidomide group versus 0.04% in the placebo group, while McCarthy *et al.* [67] reported incidences of 2.6 versus 1.7%, respectively. The nontransplant trial conducted by Palumbo *et al.* [68] reported an incidence of 8% in the arm which contained lenalidomide in both induction and maintenance as compared with 6% in the arm, which contained lenalidomide in the induction phase only and 3% in the arm which did not contain lenalidomide. Upon further follow-up, the CALGB 100104 study reported that the cumulative incidence risk of SPM was greater in the lenalidomide arm than in the placebo arm ($p < 0.008$) and that the cumulative incidence risk of progression and death was higher in the placebo arm when compared with the lenalidomide arm [29]. In total, there were eight (3.5%) hematological malignancies and ten (4.3%)

Table 3. Ongoing post-transplant maintenance trials.

ClinicalTrials.gov identifier	Setting	Duration of maintenance therapy
NCT00729118	Lenalidomide + vorinostat maintenance	Until progression
NCT01816971	Lenalidomide/carfilzomib/dexamethasone induction, transplant, lenalidomide/carfilzomib/dexamethasone consolidation and maintenance	Four cycles of consolidation, ten cycles of maintenance
NCT01264315	Lenalidomide maintenance after tandem auto-allo transplant	Until progression or molecular remission
NCT01718743	Lenalidomide + ixazomib maintenance	Until progression
NCT00445692	Lenalidomide + clarithromycin + dexamethasone maintenance	Clarithromycin/dexamethasone for 1 year, lenalidomide until progression
NCT01927718	Addition of thalidomide to patients on lenalidomide maintenance with biochemical progression	Until progression
NCT01463670	Intensification of lenalidomide dose and addition of dexamethasone for patients with biochemical progression on maintenance lenalidomide	Until progression
NCT01245673	Transplant, MAGE-A3 vaccine plus activated T cells, then lenalidomide maintenance	Until progression
NCT01793051	3 months of minocycline/placebo with lenalidomide maintenance	Until progression
NCT00084747	Bortezomib maintenance	8 months
NCT00839956	Bortezomib + vorinostat maintenance	12 months
NCT01745588	For relapsed/refractory patients: claritromycin/pomalidomide/dexamethasone × 4 cycles, transplant, pomalidomide maintenance vs clarithromycin/pomalidomide/dexamethasone × 9 cycles, pomalidomide maintenance	Until progression

solid tumors in the lenalidomide arm compared with 1 (0.4%) and 5 (2.1%) in the placebo arm. The IFM 05–02 study subsequently reported 13 (4.2%) hematological malignancies and ten (3.3%) solid tumors in the lenalidomide arm versus five (1.6%) and four (1.3%), respectively, in the placebo arm [31]. Neither study showed significant differences in the incidence of non-melanoma skin cancers.

A variety of studies have subsequently been reported which attempt to determine the extent to which the IMiD versus non-IMiD therapy, the transplant, or the underlying disease contribute to the SPM risk. The Arkansas group analyzed their data from their TT2 and TT3 trials and found no difference in the incidence of SPM despite the TT2 protocol lacking lenalidomide [69]. Palumbo *et al.* performed a pooled analysis of 2459 newly diagnosed MM patients from nine European Myeloma network trials. The cumulative incidence of SPM at 3 years was 2.0% for patients who had received lenalidomide and alkylator therapy as compared with 1.1% for those who did not receive lenalidomide [70]. Overall, the SPM incidence rate was lower than expected in all treatment groups. Notably, the cumulative incidence of death from myeloma was lower in the group which received lenalidomide (13.8 vs 26.1%), highlighting a benefit–risk ratio in favor of lenalidomide. In a retrospective pooled analysis of 11 clinical trials of lenalidomide-based therapies for relapsed/refractory myeloma patients, the overall incidence rate of SPM was 3.62, but dropped to 2.08 when noninvasive skin cancers were excluded [71]. This rate was noted to be comparable to the expected rate for older adults based on Surveillance, Epidemiology, and End Results (SEER) data and did not vary by duration of lenalidomide therapy. When 703 patients from the MM-009 and MM-010 Phase III trials were analyzed, the incidence rate in the lenalidomide/dexamethasone arms was found to be 3.98 as compared with a rate

of 1.38 in the placebo/dexamethasone arms. However, this observed difference was attributed to an increased rate of non-melanoma skin cancers in the lenalidomide arm (2.40 vs 0.91).

Fouquet *et al.* performed a retrospective study of patients who were treated with lenalidomide/dexamethasone for at least 2 years (median duration of 3 years). The annual incidence rate of SPM was 1.96% [72]. In an analysis of patients who had received long-term lenalidomide therapy in the context of the BiRd regimen (clarithromycin, lenalidomide, dexamethasone), the development of SPM was not associated with age, undergoing autologous stem cell transplant, or number of cycles of lenalidomide therapy [73]. It was noted that the incidence of SPM in their cohort was not statistically different from expected based on SEER data (2.85 vs 2.1 per 100 person-years).

Finally, a recent meta-analysis of 3254 newly diagnosed patients treated on seven randomized, controlled Phase III trials revealed that the cumulative 5-year incidence of all SPMs at 5 years was 6.9% in patients who received lenalidomide as compared with 4.8% in those who did not ($p = 0.037$) [74]. This elevated risk was a consequence of increased hematological malignancies (3.1 vs 1.4%; $p = 0.029$) and not solid tumors. Furthermore, exposure to lenalidomide and oral melphalan was associated with an increased risk of hematological SPMs, but not lenalidomide and intravenous melphalan. Notably, exposure to lenalidomide and cyclophosphamide or lenalidomide and dexamethasone was not associated with increased SPM risk. It was again noted that the cumulative incidences of death due to myeloma or treatment-related events were higher than those due to SPMs. In aggregate these studies show a small but measurable increased risk of SPM with lenalidomide and a decreased risk of progression and death with lenalidomide.

There are fewer studies which have addressed the impact of bortezomib maintenance on SPM development. In the final analysis of the VISTA trial, which examined bortezomib/melphalan/prednisone versus melphalan/prednisone in transplant ineligible patients, the incidences of hematological malignancies and solid tumors were similar in both treatment arms, providing evidence that bortezomib does not appear to contribute to an increased risk of SPM [75]. In another trial involving nontransplant candidates, bortezomib/melphalan/prednisone/thalidomide followed by bortezomib/thalidomide maintenance was compared with bortezomib/melphalan/prednisone without maintenance [76,77]; however, no SPM rates were reported.

Krishnan *et al.* conducted a retrospective cohort study to assess the risk of SPM after autologous stem cell transplant in MM patients [78]. They found that the overall cumulative incidence was 5.3% at 5 years and 11.2% at 10 years (excluding non-melanoma skin cancers). There was a trend toward increased risk of SPM with thalidomide exposure (odds ratio 3.5; $p = 0.15$).

With respect to the question as to whether myeloma itself predisposes to SPM, there have been multiple studies which have observed an increased risk of hematological malignancies. In a retrospective cohort study in Asian patients, the incidences of SPM in 3970 newly diagnosed myeloma patients and 15,880 patients without myeloma were compared. The overall incidence of SPM in myeloma patients was not statistically significantly different but the incidence of hematological malignancies was 11-fold greater [79]. An analysis of myeloma cases in the SEER database between 1973 and 2008 demonstrated an overall lower risk of breast, prostate and colon cancers but a higher risk of hematological malignancies (particularly acute myeloid leukemia [AML]) [80]. Interestingly, no association was observed between the SPM rate and the introduction of novel therapies. A Swedish cancer registry study demonstrated an 11-fold increase in the incidence of AML/myelodysplastic syndrome in myeloma patients [81]. Notably, there was an eightfold increase in the incidence of AML/myelodysplastic syndrome in monoclonal gammopathy of undetermined significance patients who would not have received chemotherapy. This implies that there is an intrinsic defect in the hematopoietic system in patients with plasma cell disorders which predisposes them to developing leukemia.

Quality of life

Historically, few randomized myeloma trials have included formal health-related quality-of-life (HRQoL) assessments as either primary or secondary end points [82]. Stewart *et al.* reported the National Cancer Institute of Canada Clinical Trials Group Myeloma 10 Trial which randomized patients to thalidomide–prednisone maintenance therapy versus observation following autologous stem cell transplant [19]. The HRQoL assessment revealed that the patients on the thalidomide–prednisone arm experienced worse HRQoL scores for cognitive function and for symptoms of dyspnea, constipation, thirst, leg swelling, numbness, dry mouth and balance problems, consistent with the side-effect profile of thalidomide. In general, lenalidomide is better-tolerated than thalidomide; however, neither the CALGB 100104 [29] nor IFM 05–02 [31] studies included formal quality-of-life assessment as end points. As it is not uncommon for patients to receive maintenance lenalidomide therapy for a number of years, it will be important to determine the impact of this prolonged therapy on quality of life.

The Mayo group recently published the results of a survey that was completed by over 700 myeloma patients [83]. In this survey patients were asked to identify the most worrisome potential toxicity associated with maintenance therapy, whether they would choose maintenance therapy if it offered a PFS benefit, but not an OS benefit, and the impact of mild versus moderate toxicity as well as cost of treatment on decision-making. Responders chose numbness/tingling, low blood counts and blood clots in the legs as the most worrisome potential toxicities. Interestingly, 92% of patients responded that they would choose maintenance therapy if there was a PFS but no OS benefit in the setting of mild toxicity while 77% would choose therapy in the setting of moderate toxicity. 'Mild' and 'moderate' were not explicitly defined in the survey. In the setting of less than 1-year improvement in OS and mild toxicity, the percentages of patients who would choose maintenance therapy decreased (46, 42 and 32%, respectively) as cost of treatment per month increased from US$25 to $250 to $10,000. Clearly, patients, just like physicians, are trying to weigh the relative importance of improved survival, toxicity and cost in their decision-making process.

Ongoing studies

There are a number of ongoing studies which are investigating alternative maintenance regimens following autologous transplant (Table 3). Many of these are lenalidomide-based and include strategies such as adding MLN-9708 (an oral proteasome inhibitor), vorinostat (an histone deacetylase inhibitor), clarithromycin/dexamethasone or minocycline. Notably, these regimens contain all oral therapies. There is also interest in the use of immunotherapy in combination with lenalidomide. For example, one trial is evaluating day +2 infusion of co-stimulated T-cells primed with MAGE-A3 and Prevnar followed by lenalidomide maintenance starting on day 100 (NCT01245673). Several bortezomib-based studies are also underway, including bortezomib plus vorinostat. Pomalidomide is currently being studied in the context of maintenance after salvage transplant and it is reasonable to presume that it will one day be investigated as a maintenance strategy following initial transplant.

Conclusion

There is still much to be learned about the use of lenalidomide and bortezomib in the post-transplant setting. Longer-term follow-up and analysis of outcome based on factors such as presence/absence of MRD and cytogenetics/gene expression profiling for already completed trials is eagerly awaited. In one transplant study, bortezomib improved PFS and OS in del17 patients and those in renal failure at presentation. In another study, bortezomib and thalidomide did not improve PFS in high-risk cytogenetic patients and so far has not been shown to improve OS. Lenalidomide has improved PFS and OS in two of three transplant studies and PFS in another. Whether all patients need to be on maintenance therapy or whether we can identify those, perhaps through their MRD status, who do not require maintenance therapy, remains to be deter-

Table 4. Novel agents under investigation for myeloma.

Class	Drug	Target
Monoclonal antibodies	Elotuzumab	CS1
	Daratumumab	CD38
	SAR650984	CD38
	nBT062-DM4	CD138
	Lorvotuzumab	CD56
	Dacetuzumab	CD40
	Lucatumumab	CD40
	Tabalumab	BAFF
	Siltuximab	IL6
	IPH2101	KIR
Histone deacetylase inhibitors	Vorinostat	
	Panobinostat	
	Romidepsin	
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
HSP90	Tanespimycin	
	Ganetsepib	
mTORC	MLN0128	
	INK128	
	Everolimus	
	Temsirolimus	
Apoptosis	ABT199	Bcl-2 inhibitor
DNA repair	Veliparib	PARP 1/2
Nuclear export	KPT330	Exportin-1 inhibitor
Proteasome inhibitors	Marizomib	
	Oprozomib	
	Ixazomib	

mined. Ultimately, the ideal maintenance regimen will be one which, in addition to significantly improving survival, is also characterized by ease of administration, a side-effect profile that allows for chronic treatment with minimal effect on quality of life, the lack of serious long-term consequences and is cost effective.

Future perspective: novel agents

The therapeutic landscape for myeloma within the next 10 years will expand beyond IMiDs and proteasome inhibitors to encompass monoclonal antibodies, kinase inhibitors and signal transduction pathway inhibitors, as well as immune-based therapies [84]. A description of agents which are currently undergoing investigation in myeloma patients is shown in Table 4. While it is expected that these agents will first be tested either alone or in combination with standard therapies in the relapsed/refractory setting, it is tempting to speculate that some may find a role in the post-transplant maintenance setting.

Financial & competing interests disclosure

PL McCarthy has served on advisory boards and received honoraria from Celgene, Millennium, Sanofi, Onyx and Janssen. SA Holstein has served on advisory boards and received honoraria from Celgene and Millennium. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Executive summary

Overview

- The goal of maintenance therapy following autologous stem cell transplant for myeloma patients is to improve both progression-free survival and overall survival without diminishing quality of life.

Immunomodulatory drug-based maintenance therapy

- Randomized studies involving thalidomide as maintenance therapy have not shown a consistent overall survival benefit and prolonged thalidomide maintenance is infrequently used because of its side-effect profile.
- Randomized studies involving lenalidomide have demonstrated marked improvements in progression-free survival. One study has shown a significant improvement in overall survival, a second has shown a trend to overall survival benefit while the third has not shown an overall survival benefit. Currently single-agent lenalidomide is commonly used post-transplant.

Minimal residual disease

- Multiparameter flow cytometry and allele-specific oligonucleotide PCR are two emerging technologies, which can detect very low (10^{-4}–10^{-5}) levels of malignant plasma cells.
- The role of minimal residual disease assessment post-transplant to predict outcome and determine treatment plan is under investigation.

Second primary malignancies

- The underlying plasma cell disorder, autologous stem cell transplant and lenalidomide maintenance all contribute to an increased risk of secondary primary malignancies, particularly hematological malignancies.

Future perspective

- Maintenance therapy will likely evolve to include not only newer generation immunomodulatory drug and proteasome inhibitor agents, but also new classes of drugs which are currently being investigated such as monoclonal antibodies, cell signaling inhibitors, and cell cycle inhibitors.

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