blood® How I Treat

How I treat the young patient with multiple myeloma

Sara Gandolfi,[1] Claudia Paba Prada,[2] and Paul G. Richardson[1]

[1]Dana Farber Cancer Institute, Harvard Medical School, Jerome Lipper Multiple Myeloma Center, Boston, MA; and [2]Miami Cancer Institute, Miami, FL

The treatment landscape for multiple myeloma has been transformed by the introduction of novel agents, including immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies. These have been shown to be more effective and generally better tolerated than conventional chemotherapy, with their introduction into clinical practice leading to improved survival. Furthermore, a better understanding of disease biology, improved diagnostic criteria, and the development of sensitive and specific tools for disease prognostication have contributed to better outcome. Treatment in the younger patient can now be individualized based on host and disease features with enhanced monitoring of response and use of high-sensitivity techniques for evaluating residual disease. The current standard of care has been significantly enhanced by novel agents with a paradigm shift toward optional or delayed autologous stem cell transplant as a reasonable choice in selected patients. Conversely, extended treatment with induction of remission followed by maintenance strategies is now a standard of care, conferring prolonged disease control with more manageable toxicities in both the short and long term, as well as improved quality of life. (*Blood*. 2018;132(11):1114-1124)

Introduction

Multiple myeloma (MM) is a plasma cell disorder characterized by clonal proliferation of malignant plasma cells in the bone marrow with monoclonal protein in the serum and/or urine and associated organ dysfunction.[1,2] Therapeutic advances in MM have evolved at an unprecedented pace in the last 15 years, with more than 22 US Food and Drug Administration (FDA) approvals during this period. The median age at diagnosis is 70 years, with 37% of patients younger than 65 years; MM is rare in those younger than 30 years.[2,3] Thus, a considerable proportion of patients are "younger patients," and the issue of optimal treatment strategies is especially germane, with the goal of improving long-term outcome while minimizing the impact of treatment-related toxicity. MM remains incurable, with a natural history characterized by remission and relapse; although overall survival (OS) has increased dramatically with the advent of novel agents, it is important to consider acute and delayed toxicities, the choice of active agents, and quality of life. Indeed, with the widespread use of novel agents, including proteasome inhibitors (PIs), such as bortezomib, ixazomib, and carfilzomib, and the immunomodulatory drugs (IMIDs) thalidomide, lenalidomide, and pomalidomide, OS has improved from 3 years[4] to 7-10 years and beyond.[5] The development of monoclonal antibodies has significantly expanded the therapeutic armamentarium, with the depth and duration of remission improving yet further.[6]

The purpose of this review is to provide a practical approach to the management of newly diagnosed younger MM patients, with a focus on novel treatment approaches. Because there is no established age cutoff to define "young patients," we will consider as such all patients below the age of 65 years, which is also typically used for transplant eligibility.

When to start treatment: new diagnostic criteria

The definition of active MM relies on clinicopathological criteria that require evidence of end-organ damage attributable to the underlying clonal plasma cell disorder.[7,8] However, given the improved tolerability of newer agents, it has become important to identify a subset of patients with smoldering MM (SMM) and an increased chance of progressing to symptomatic disease.

The International Myeloma Working Group (IMWG) revised the disease definition of MM for early diagnosis before end-organ damage occurred.[9] The diagnostic criteria update was prompted by the identification of specific biomarkers that accurately distinguished patients with SMM who have ≥80% probability of progression within 2 years and provided the opportunity for early intervention in those patients with highest risk.[10] Furthermore, the availability of advanced imaging techniques has allowed detection of bone disease at an earlier stage compared with older techniques, such as skeletal survey.[11]

The revised diagnostic criteria are listed in Table 1; the diagnosis of MM now requires the presence of ≥1 myeloma-defining event, which include established CRAB features, as well as 3 specific biomarkers: clonal bone marrow plasma cells ≥60%,[12-14] serum free light chain (FLC) ratio ≥100 (provided the involved FLC level is ≥100 mg/L),[13-16] and ≥1 focal lesion on magnetic resonance imaging (MRI),[17,18] provided it is ≥5 mm.[9] Each of these biomarkers is associated with an 80% risk for progression to symptomatic end-organ damage in independent studies.

Table 1. International Myeloma Working Group diagnostic criteria for MM and related disorders

Disorder	Definition
Non-IgM MGUS	All 3 criteria must be met Serum monoclonal protein (non-IgM type) <3 g/dL Clonal bone marrow plasma cells <10%* Absence of end-organ damage, such as hypercalcemia, renal insufficiency, anemia, and bone lesions that can be attributed to the plasma cell proliferative disorder
SMM	Both criteria must be met: Serum monoclonal protein (IgG or IgA) 3 g/dL, or urinary monoclonal protein 500 mg/24 h, and/or clonal bone marrow plasma cells 10% to 60% Absence of myeloma-defining events or amyloidosis
MM	Both criteria must be met: Clonal bone marrow plasma cells 10% or biopsy-proven bony or extramedullary plasmacytoma Any 1 or more of the following myeloma-defining events: Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically: Hypercalcemia: serum calcium >25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >275 mmol/L (>11 mg/dL) Renal insufficiency: creatinine clearance <40 mL/min or serum creatinine >177 μmol/L (>2 mg/dL) Anemia: hemoglobin value >2 g/dL below the lower limit of normal or a hemoglobin value <10 g/dL Bone lesions: ≥1 osteolytic lesion on skeletal radiography, CT, or PET/CT Clonal bone marrow plasma cell percentage 60% Involved/uninvolved serum FLC ratio 100 (involved FLC level must be 100 mg/L) >1 focal lesion on MRI studies (≥5 mm in size)

Adapted from Rajkumar et al[9] with permission.

*Bone marrow transplantation can be deferred in patients with low-risk MGUS (IgG type, M protein 15 g/L, normal FLC ratio) in whom there are no clinical features concerning for myeloma.

CT, computed tomography; MGUS, monoclonal gammopathy of undetermined significance; PET, positron emission tomography.

Despite this refinement, SMM still represents a clinical dilemma, and there are no unequivocally validated molecular factors to differentiate patients with higher risk for progression. Further research is required to identify markers of progression in these patients, with ongoing clinical trials investigating early treatment in SMM to evaluate this important area.

When we treat

We treat patients with active MM per 2014 IMWG criteria, and we counsel younger patients with SMM who are eligible for early intervention to consider participation in clinical trials as part of their overall treatment strategy, together with careful observation and the use of bisphosphonates for bone loss.

Risk stratification

Recent advances in molecular biology and genetic studies have improved our understanding of the underlying etiology and progression of MM characterized by diverse intraclonal heterogeneity, which affects disease progression and treatment resistance through clonal evolution.[19,20] In addition, the interaction between clonal plasma cells and the bone marrow microenvironment has substantial impact.[19,21]

Given the heterogeneity of this disease, risk stratification represents a challenge. Several studies have validated multiple biological factors influencing risk and prognosis in MM.[22-25]

The Durie-Salmon staging system relies on clinical parameters predicting tumor burden.[26] The International Staging System (ISS) is a simple tool that includes β2-microglobulin and serum albumin and informs on tumor burden and disease impact on the host.[27] The IMWG recently adopted the Revised ISS (R-ISS),[28] which combines the ISS and cytogenetic abnormalities detected by interphase fluorescent in situ hybridization (FISH),[24] as well as lactate dehydrogenase (LDH),[29] to effectively stratify patients with newly diagnosed MM (NDMM) into 3 risk groups (Table 2). In a study of 4445 patients with NDMM from 11 international trials, the 5-year survival rate of patients with stage I, II, or III R-ISS was 82%, 62%, and 40%, respectively,[28] with results showing an improvement in OS using novel therapies across prognostic subgroups compared with the original ISS study, in which patients had minimal exposure to more current treatment.

However, the R-ISS study has some limitations, including selection bias, because only younger patients treated in the context of experimental clinical trials were included. Information regarding chromosome abnormalities was not uniform, which limits conclusions to be drawn about their significance, as there was no standardization of FISH analysis, and heterogeneous cutoff levels for LDH were used. Furthermore, the lack of patient-related factors and other features may also influence the prognosis; for example, proliferation index, extramedullary disease, and circulating plasma cells were not included.[30]

In summary, R-ISS represents a reliable algorithm with improved prognostic power compared with the former ISS. We recommend both the ISS and R-ISS prognostic scores. In addition, host-related factors, such as age, performance status, comorbidities, and frailty, should be considered when choosing treatment strategy.[23,24,31,32]

Case 1

A 42-year-old woman was found to be anemic on routine laboratory work. She was also noted to have an elevated serum total protein of 11.3 g/dL and globulin of 7.7 g/dL. Her previous chemistry profile had been normal. She reported progressive fatigue and malaise. She was referred in July 2010, and serum protein electrophoresis showed an immunoglobulin G (IgG) λ paraprotein of 5.22 g/dL, with suppression of uninvolved immunoglobulins. Her hemoglobin was 8.3 g/dL, with normal renal

Table 2. Revised International Staging System for MM

R-ISS stage	Criteria
I	All of the following: Serum albumin ≥3.5 g/dL Serum β2-microglobulin <3.5 mg/L No high-risk CA* Normal serum LDH level
II	Not R-ISS stage I or III
III	Both of the following: Serum β2-microglobulin ≥5.5 mg/L High-risk CA by iFISH or high LDH

Adapted from Palumbo et al with permission.[28]

CA, chromosomal abnormalities; iFISH, interphase FISH.

*High-risk CA: presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16).

function and calcium; her albumin was 3.6 g/dL and β2-microglobulin was 3 mg/L. Skeletal survey revealed osteopenia, but no lytic lesions, and MRI similarly showed no focal lesions but a diffusely abnormal bone marrow signal. Bone marrow biopsy was noteworthy for 80% plasmacytosis, with restriction for λ light chain.

Symptomatic ISS stage I IgGλ myeloma was diagnosed, with a standard risk profile on cytogenetics and FISH. She was enrolled in the IFM/DFCI 2009 clinical trial, a randomized prospective phase 3 study comparing lenalidomide, bortezomib, and dexamethasone (RVD) plus stem cell collection and lenalidomide maintenance (arm A) with RVD followed by an autologous stem cell transplant (ASCT), with RVD consolidation and lenalidomide maintenance (arm B), together with concomitant zoledronic acid. She was randomly assigned to arm B, achieved a partial remission after 2 cycles of RVD and was successfully mobilized after cycle 3, followed by ASCT. Post transplant, very good partial remission (VGPR) was confirmed. She received 2 cycles of RVD consolidation and then lenalidomide as maintenance. After 3 months of maintenance, the patient achieved complete remission (CR). She is currently in her 74th month of continuous lenalidomide treatment, in sustained CR, and has some fatigue and occasional recurrent infections but is otherwise well.

Case 2

A 61-year-old man was referred with a diagnosis of IgGκ gammopathy. He was fatigued but denied other symptoms. Significant anemia was noted, with a hemoglobin of 7.6 g/dL. Renal function and calcium were normal. β2-microglobulin (2.6 mg/L) and albumin (3.3 g/dL) were consistent with ISS stage II disease. Quantitative immunoglobulins were noteworthy for an IgG of 2870 mg/dL, with suppression of uninvolved immunoglobulins, and κ light chains were elevated at 73.7 mg/L with a ratio of 24.2. Skeletal survey showed osteopenia and lytic disease in the spine. Bone marrow biopsy was noteworthy for 60% plasmacytosis, with flow cytometry demonstrating κ light chain–restricted plasma cells. Cytogenetics revealed a normal male karyotype with 46, XY, and FISH analysis was negative.

He was enrolled in the same trial and was randomized to the delayed transplant arm (arm A). He achieved VGPR after 2 cycles of induction with RVD and concurrent zoledronic acid and entered CR after mobilization with high-dose cyclophosphamide and granulocyte-colony stimulating factor. He completed 8 cycles of RVD and tolerated treatment well. He is in a sustained CR at month 64 of continuous lenalidomide maintenance and is asymptomatic.

Choice of initial treatment in the era of novel agents

The incorporation of novel agents in MM treatment has resulted in a major improvement in OS,[33] with induction regimens containing ≥3 drugs, including PIs and IMIDs, appearing to be the best choice for initial therapy (Figure 1).[5,34] The combination of these 2 classes of drugs has shown synergy in preclinical models and clinically, yielding increased response and improved outcome.[34-41] Data from phase I/II trials were recently confirmed in a phase III SWOG study, in which RVD was compared with lenalidomide and dexamethasone alone in NDMM and in a landmark study of RVD with or without early ASCT and lenalidomide maintenance.[42,43] The latter study showed a CR + VGPR rate of 77% and minimal residual disease (MRD) negativity rate of 65%, with a progression-free survival (PFS) of 36 months, in the RVD arm without early ASCT whereas median OS was not reached. These outstanding results, along with ≥63% CR reported with the second-generation PI carfilzomib, in combination with lenalidomide and dexamethasone (KRD),[38] strongly support the use of triplets in NDMM patients. Ixazomib combined with lenalidomide and dexamethasone has shown remarkable overall response rate in 2 single-arm phase II studies in younger transplant-eligible and older patients, with excellent PFS and OS, favorable tolerability, and the added convenience of an all-oral combination.[39,44] Importantly, data from randomized trials using combinations of PIs and IMIDs also show favorable tolerability, with results from the SWOG trial well balanced for adverse events between the 2 groups.[42] Another combination to be considered is cyclophosphamide, bortezomib and dexamethasone (CyBorD), which is highly active in NDMM, although a recent randomized trial found that the triplet regimen containing a PI and an IMID is superior to CyBorD.[45] However, this regimen is particularly useful and part of our practice in patients with acute renal failure suspected to be secondary to light-chain cast nephropathy. Similarly, in patients with underlying neuropathy, we favor KRD, given its minimal neurotoxicity and remarkable efficacy. In younger patients, in whom the risk for vascular toxicity and cardiac complications may be lower, this regimen may be especially valuable.

Our practice

Patients not eligible or choosing not to be included in a clinical trial are treated with RVD for 6-8 cycles as initial treatment or other combinations (eg, KRD, ixazomib/lenalidomide/dexamethasone, or CyBorD), followed by stem cell collection; ASCT is also considered, with maintenance to follow (Figure 1).

Role of stem cell transplant

High-dose chemotherapy followed by ASCT is still considered a standard of care in eligible patients based on a series of randomized trials demonstrating improved PFS and OS.[46-52] Two more recent phase III clinical trials showed a significant PFS benefit and an OS advantage, but induction included doublets

or combinations without PIs.[53,54] The depth and duration of response achieved with the triplet combination of IMID, PI, and dexamethasone and its favorable tolerability is now challenging this paradigm. Given the acute and long-term toxicities of ASCT, including the rare, but life-threatening complication of secondary leukemia, the role of ASCT as part of upfront treatment is an area of active research.[43,53-55] Interestingly, as described above, the French part of the IFM/DFCI 2009 trial has demonstrated a clear PFS advantage but no OS benefit.[43] Competing causes of mortality included acute toxicities of ASCT, as well as rare cases of secondary leukemia, although the follow-up remains short to establish actual rates of long-term toxicity.[43,56] Of note, the IFM study completes lenalidomide maintenance after 1 year, whereas in the ongoing US study, lenalidomide is continued until progression.

The European Myeloma Network/Stichting Hemato-Oncologie voor Volwassenen Nederland (HOVON) recently reported the EMN02/HO95 results.[55] In this phase III trial, patients were treated with CyBorD induction and then randomized to receive ASCT (single or tandem) or bortezomib, melphalan, and prednisone. A second randomization to consolidation therapy vs no consolidation was performed after intensification therapy using RVD, followed by lenalidomide maintenance until progression in both arms. The 3-year estimates of PFS favor the ASCT arm, but again no difference in OS was observed.[55]

None of the above studies addressed the role of ASCT at time of first relapse.[43,53-55] In the trial presented by Palumbo et al, 70% of patients received ASCT as second-line therapy after relapse, whereas Gay et al reported that 43% of patients in the cyclophosphamide-lenalidomide-dexamethasone arm underwent ASCT.[53,54] A pooled analysis of these 2 trials showed that patients receiving conventional chemotherapy, with ASCT as intensification and lenalidomide maintenance after first relapse, had an improvement in OS.[57] However, some caution is warranted with this interpretation, because PFS2 was not a prespecified end point in the original studies, and postrelapse treatment was not homogeneous, with only 10% of patients receiving post-ASCT maintenance.

One randomized trial including ASCT as a preplanned option at first relapse was published, prior to the advent of novel agents. No differences in OS were reported, despite a significant advantage in terms of PFS with upfront ASCT.[47] Given the impact of novel agents and other immunotherapeutic strategies on MM outcome, research on the role and timing of ASCT, as well as identification of those subsets of patients in whom the benefit of ASCT outweighs the risk of toxicities, is critical. Participation in prospective trials is encouraged as the treatment paradigm continues to evolve and important unanswered questions remain.[5] Specifically, a key issue is the identification of patient- and disease-specific markers, with the goal of exposing only those who benefit from early ASCT to the procedure.

Our practice

Although ASCT remains a standard of care in MM, this paradigm has evolved with the advent of newer and less toxic therapies, such that a rigid approach to ASCT upfront use outside of clinical studies is difficult to justify.[58] We recommend participation in clinical trials, but for those who are ineligible or decide not to participate, ASCT as an option remains appropriate (Figure 1). For patients preferring to delay ASCT after induction/remission therapy, they should be encouraged to harvest stem cells as soon as a sustained best response is reached (eg, VGPR or better).

Tandem stem cell transplant

The use of planned sequential ASCT has been investigated in several randomized clinical trials,[22,59,60] and meta-analyses have shown superior response rates with tandem ASCT but no difference in OS. However, heterogeneity limits this analysis.[61,62] Recently, the German-Speaking Myeloma Multicenter Group presented long-term follow-up of the HD2 study, which reported no differences in EFS or OS between single and tandem ASCT. Furthermore, preliminary data from the BMT CTN 0702 trial, which randomized patients to receive single ASCT with lenalidomide maintenance vs single ASCT with RVD consolidation and lenalidomide maintenance vs tandem ASCT with lenalidomide maintenance, demonstrated comparable PFS and OS across all 3 treatment arms.[63] Given these results and the concerns of cumulative long-term marrow toxicity from double high-dose alkylation, we do not recommend routine tandem ASCT outside of a clinical trial.

Allogeneic transplant

Myeloablative allogeneic stem cell transplant (allo-SCT) is associated with a transplant-related mortality rate of 40-60%, which has proven prohibitive to the widespread use of this modality in younger patients. As a result, reduced-intensity approaches have been recently investigated.[64] Given that the results of several trials comparing ASCT and allo-SCT in the upfront setting have failed to show any consistent benefit to allo-SCT, and nonrelapse mortality rate has been significantly higher with allo-SCT, it is not recommended as a first-line approach. A reduced-intensity approach allo-SCT can be considered in the salvage setting for younger patients with good performance status and high-risk cytogenetic features, preferably in the context of a clinical trial.

Consolidation

Consolidation following ASCT consists of a short course of multiagent therapy aiming at improving the depth of the response with the goal of prolonging clinical benefit. Four randomized trials have evaluated different post-ASCT approaches, and all have shown an improvement in depth of responses but did not provide OS benefit.[36,65-68] A prespecified analysis of a phase III study presented by Gruppo Italiano Malattie EMatologiche dell'Adulto showed that bortezomib-thalidomide-dexamethasone (VTD) as a consolidation therapy improved PFS, but there was no benefit in terms of OS.[65] A trial conducted by the Nordic Myeloma Study Group compared consolidation with bortezomib after ASCT with no consolidation; the study showed an improvement in response after randomization and significant PFS advantage, but there was no OS benefit.[66] The German group presented a prespecified analysis on combined data from 2 randomized phase III studies of bortezomib consolidation, which confirmed its role in delaying disease progression and improving the quality of responses in NDMM patients following ASCT.[67] Results from the EMN02/HO95 trial[55] also confirmed a PFS advantage in patients receiving consolidation. However, a PFS advantage was observed only in patients

with low-risk cytogenetics.[68] Preliminary results from the BMT-CTN 0702 trial suggested that the addition of RVD consolidation or a second ASCT was not superior to a single ASCT followed by lenalidomide maintenance in the upfront treatment of MM with regard to PFS and OS, although a trend toward PFS benefit was seen in the RVD-treated population and high-risk disease.[63] Follow-up is ongoing and should better help to understand the impact of these results, with all 3 groups achieving excellent outcomes to date, including high-risk disease.

Our practice

Considering that data from the BMT-CTN 0702 trial are still preliminary and that trials have shown a PFS benefit with consolidation treatment, we offer 2-4 cycles of RVD after ASCT in high-risk patients and for those who do not achieve CR after transplant (Figure 1).

Maintenance and continuous therapy

Despite the improvement in PFS and OS with novel approaches and ASCT, relapses are inevitable for the majority of patients, primarily due to incomplete eradication of residual disease. Maintenance is a treatment strategy aimed at prolonging and deepening the response to previous induction, with or without ASCT. As defined, maintenance must be a long-term treatment, typically considered therapy administered for ≥1 year.[69]

Although first attempts at maintenance therapy using conventional chemotherapy, steroids, or interferon-α proved disappointing,[70-75] the advent of novel agents has markedly restored its potential to improve clinical benefit.

Several clinical trials have investigated the role of thalidomide as post-ASCT maintenance.[76-85] These studies were heterogeneous in terms of dosing and schedule, with varied results in terms of outcome.[69,82,86] Thalidomide presents significant dose-limiting toxicity, including peripheral neuropathy and an increased risk for venous thromboembolism, as well as cognitive dysfunction, fatigue, and constipation. Given the better tolerability of lenalidomide, the use of post-ASCT thalidomide is now generally limited to those patients who cannot tolerate the myelosuppressive effects of lenalidomide or other agents.

Three large randomized clinical trials have investigated the role of lenalidomide in the post-ASCT setting.[53,87-89] All of these studies have demonstrated a PFS improvement by ~2.5 years using lenalidomide maintenance, particularly until progression, with varying effects on OS. A recent meta-analysis involving 1209 patients showed significant OS benefit, regardless of the response achieved post-ASCT.[90] Considering these data, the benefits of lenalidomide maintenance after ASCT outweigh the small risk for increased secondary malignancies reported in 2 out of 3 trials,[87,89] and support lenalidomide maintenance post-ASCT being a standard of care.

There are no placebo-control randomized trials investigating bortezomib as maintenance strategy. Two randomized trials have addressed the issue of post-ASCT bortezomib maintenance.[41,91] The phase III HOVON-65/German-Speaking Myeloma Multicenter Group–HD4 trial showed that bortezomib maintenance after bortezomib-containing induction improved the CR rate and was better tolerated than thalidomide. This trial also demonstrated an improvement in PFS and OS, particularly in patients with del17p.[92] Data from the Spanish group showed a PFS advantage in patients treated with post-ASCT bortezomib-thalidomide maintenance compared with thalidomide or α-interferon for up to 3 years, but with no OS advantage. In aggregate, these data suggest a role for bortezomib maintenance in the posttransplant setting, especially for those patients carrying high-risk cytogenetics, such as del(17p). Similar benefit in high-risk patients is also apparent with the long-term use of ixazomib as continuous therapy.

Our practice

Post-ASCT, lenalidomide maintenance is a standard of care and is offered to all patients undergoing ASCT, with dose adjustments and schedule change according to tolerability. High-risk patients, especially those carrying 17p deletion, are offered the addition of bortezomib.[93] Patients who are not willing to participate in clinical trials and who chose to delay ASCT, are offered continuous therapy with both lenalidomide and bortezomib (Figure 1). Ideally, maintenance should be administered until disease progression; however, this approach is not always feasible, and dose adjustment as well as schedule changes and discontinuation may be necessary if toxicity emerges.

Immunotherapy and monoclonal antibodies

Immune function in MM has recently generated great interest and is an active area of research, with the recent evaluation of checkpoint inhibition in combination with IMIDs, as well as monoclonal antibodies, each of which have shown outstanding activity in advanced disease.[56,94] Impressive quality and durability of response are being seen with CD38-targeting antibodies used in combination and as monotherapy, as well as with anti-SLAMF7 antibody elotuzumab.[95-98] Although elotuzumab as a single agent showed disappointing results, its combination with lenalidomide and bortezomib demonstrated high response rate and improvement in PFS in relapsed and refractory disease, with a manageable toxicity profile.[99-102] Conversely, daratumumab demonstrated powerful activity both as a single agent and in combination, with unprecedented efficacy in relapsed/refractory MM.[103] Two separate phase II studies with daratumumab as a single agent in heavily pretreated patients resulted in a partial response or better in nearly one third of patients. The responses were durable, with the median response exceeding a year, leading to FDA approval.[96,104,105] Two large phase III trials recently reported a remarkable improvement in PFS with the addition of daratumumab to an IMID or PI.[106,107] Daratumumab is generally well tolerated, with the main adverse event being infusion reactions. Both agents are being evaluated in transplant-eligible and transplant-ineligible NDMM patients, with recent results suggesting substantial clinical benefit. These trials will help to address the issue of the integration of such agents in clinical practice, as well as drug sequencing. Another intriguing aspect is their potential role in early vs delayed transplant strategies.

The promising results obtained with therapeutic checkpoint inhibition in multiple cancers has opened the possibility of its application in MM. Despite strong in vitro and in vivo evidence of PD-1/PD-L1 having a role in this disease, results from single-agent nivolumab proved disappointing.[103,108] In contrast, combinations of checkpoint inhibitors with IMIDs have demonstrated

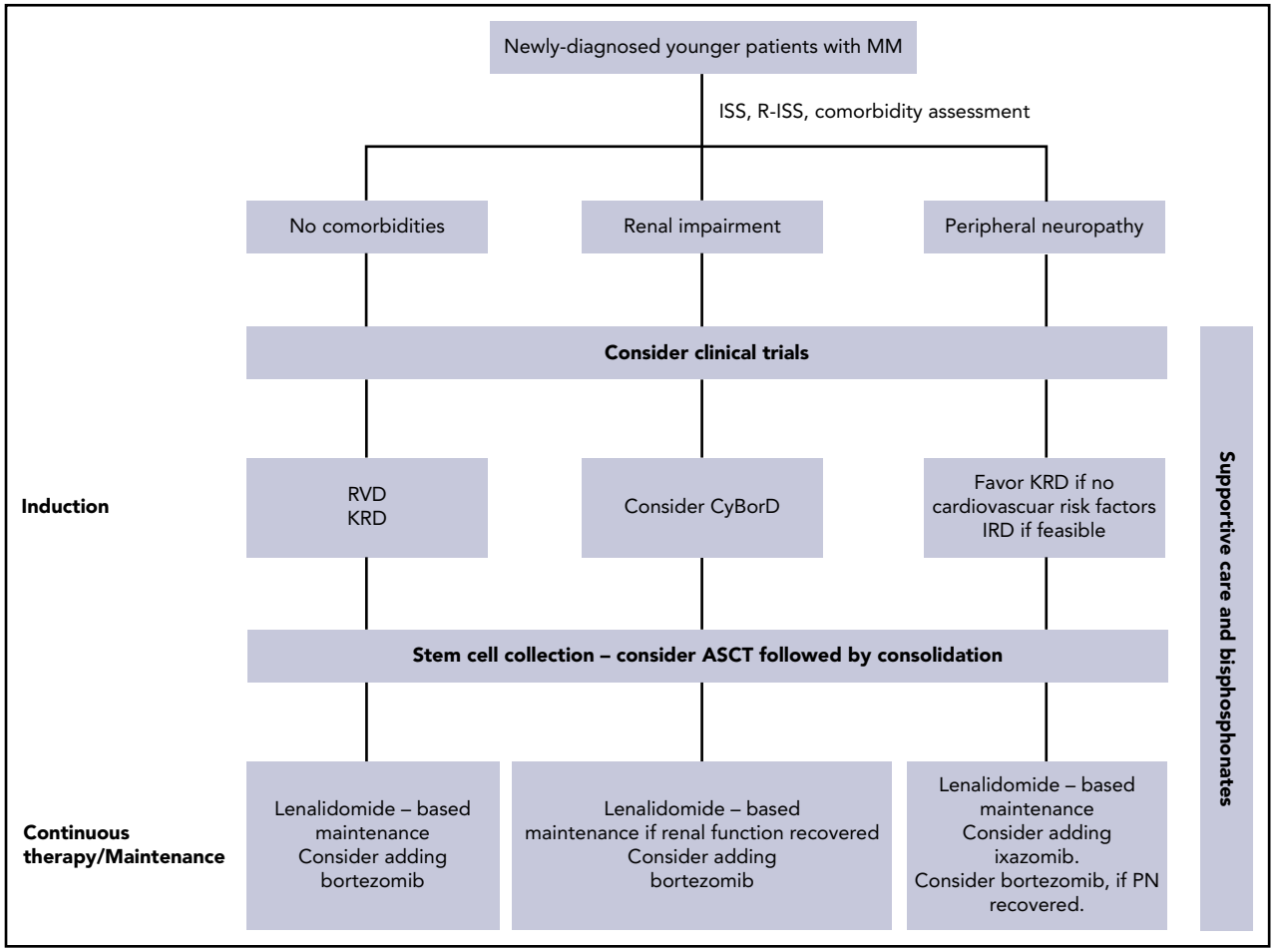

Figure 1. Proposed guidelines for management of younger MM patients. CyBorD, cyclophosphamide, bortezomib, dexamethasone; ISS, International Staging System; KRD, carfilzomib, lenalidomide, dexamethasone; PN, peripheral neuropathy; R-ISS, revised International Staging System; RVD, lenalidomide, bortezomib, dexamethasone; IRD, ixazomib, lenalidomide, dexamethasone.

improved clinical activity, even in patients with double-refractory disease.[109] However, 2 phase III trials evaluating the combination of lenalidomide (NCT02579863) and pomalidomide (NCT02576977) with pembrolizumab in patients with newly diagnosed and relapsed MM, respectively, were closed due to toxicity and inferior survival compared with control upon early analysis. Combinations of checkpoint inhibitors with daratumumab and elotuzumab were also initiated, but the unexpected serious toxicity seen with pembrolizumab led to clinical holds by the FDA with these studies as well (NCT01592370, NCT02252263, NCT02726581). Multiple other targets are now under study, including B-cell maturation antigen. Other exciting strategies include vaccines,[110,111] and especially chimeric antigen receptor–T-cell therapy, which may be paradigm changing for younger patients eligible for this approach.[112,113]

Response assessment and the role of MRD

Response criteria in MM rely on serum and urine measurement of monoclonal proteins and bone marrow assessment, but a serological/morphological CR may still underestimate residual disease. Recently, the IMWG has incorporated multicolor immunofluorescence flow cytometry and gene sequencing with sensitivity of up to 10^{-5} into MM response criteria, as well as the absence of bone disease on positron emission tomography/computed tomography scanning.[114] Two meta-analyses confirmed that MRD-negative status after treatment of NDMM is associated with significant improvement in survival and support the integration of MRD assessment in clinical trials.[115,116] However, the IFM/DFCI trial shows that ~25% of MRD-negative patients still experience relapse at 36 months, despite better PFS and OS curves compared with MRD-positive patients (Figure 2).[43] These data indicate that more sensitive tools are required to detect MRD and question whether current MRD technologies alone are enough to inform patients about prognosis. Newer approaches for measuring MRD, such as single-cell gene sequencing and serum cell-free DNA, may more accurately assess MRD and complement existing methods. Additional data are needed to establish MRD for registration of new agents and to inform clinical practice.[117] Considering the wide array of generally well-tolerated drugs, a reasonable strategy would be to tailor treatment to patient response. In this context, dynamic risk-assessment tools and reliable markers predictive of outcome are warranted, and clinical trials will be pivotal in evaluating these prognostic modalities.

Supportive care

General supportive measures include adequate hydration, low-impact exercise, weight control,[118] avoidance of nephrotoxic

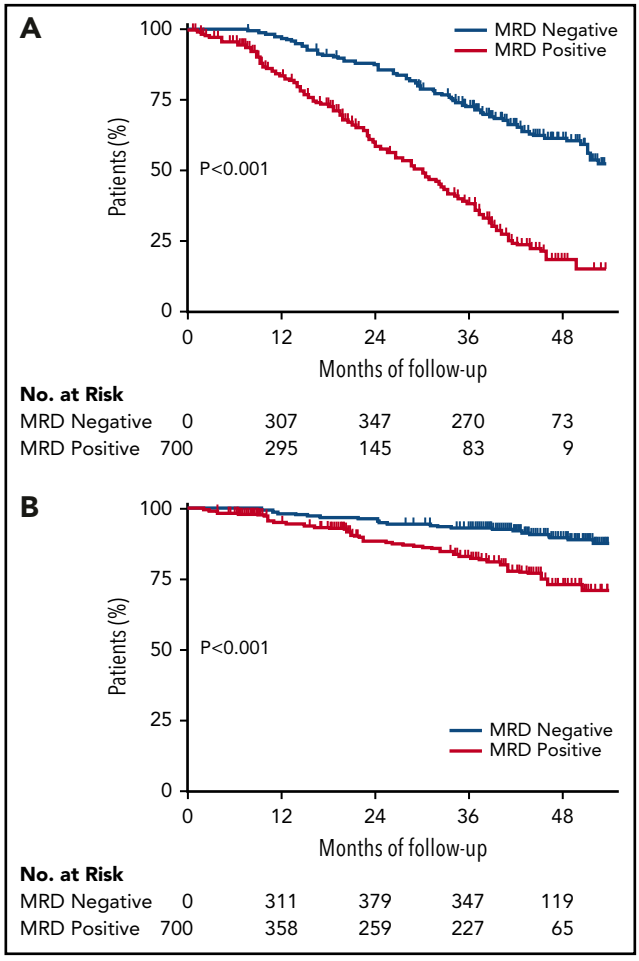

Figure 2. Kaplan-Meier curves for PFS (A) and OS (B), according to MRD, in the IFM trial. Despite PFS and OS being prolonged in MRD-negative patients vs those who were MRD positive (adjusted hazard ratio [aHR], 0.30; 95% confidence interval [CI], 0.23-0.37; $P < .001$ and aHR, 0.34; 95% CI, 0.22-0.51; $P < .001$ respectively), progression occurred in ~25% of MRD-negative patients at a median of 36 months follow-up, which, in turn, impaired OS.[43]

drugs, prevention of neuropathy, and pain management. Attention regarding infection is critical, and antiviral prophylaxis is recommended in patients receiving PIs to minimize the development of herpes zoster reactivation.[119,120]

Thromboprophylaxis is indicated when IMIDs are used. Patients at low risk for thrombosis and receiving IMIDs with daily aspirin (81 or 325 mg) show a low rate of deep vein thrombosis, but this still can affect up to ~5-10% of patients. For patients at higher risk for deep vein thrombosis resulting from other factors, such as prior history, immobility, obesity, cardiovascular disease, and smoking, therapeutic anticoagulation using low molecular weight heparin or warfarin is recommended.[121] Factor Xa inhibitors (direct oral anticoagulants, so-called DOACs) are currently under study in this setting, but appear to be a feasible new approach.

The use of intravenous bisphosphonates, such as zoledronic acid and pamidronate, is recommended, regardless of whether bone lesions have been detected. These interventions have been associated with a reduction in skeletal events and may also have direct antitumor activity.[122] Despite a recent phase II trial comparing the standard-of-care 24-month bisphosphonate treatment with a 4-year treatment not showing OS benefit, a clear reduction in skeletal events was demonstrated.[123] Overall, the benefits of bisphosphonate therapy should be weighed with their toxicities, and preventive strategies must be instituted to avoid renal toxicity or osteonecrosis of the jaw.[25] The RANKL inhibitor denosumab is a promising agent, especially in patients with renal impairment. A post hoc analysis of a phase III clinical trial was not conclusive due to imbalances in the baseline and on-study variables and unequal early withdrawal with censoring in the MM subset. An adequately sized confirmatory phase 3 trial of denosumab and zoledronic acid in MM patients is now complete with positive results reported (NCT01345019).[124]

Other measures include evaluation and management of neuropathy, cytopenias, and diarrhea common to PI and IMID use, with neuropathy an area of particular importance.[125]

Practical considerations

In countries with more limited resources and in which multiple novel agents have not yet been approved for upfront treatment, we suggest the use of best-available induction regimens, favoring triplets such as a PI and/or an IMID with steroids and chemotherapy. Ideally, regimens should include both, such as bortezomib, thalidomide, and dexamethasone (VTD) or cyclophosphamide, thalidomide, bortezomib, and dexamethasone, or CyBorD for 4-6 cycles, followed by ASCT, especially if maintenance strategies are not yet approved. Nevertheless, if after the first initial 3 or 4 cycles the patient has achieved less than a partial response, the use of salvage therapy based on available drugs (eg, RVD, KRD, or regimens including monoclonal antibodies) before transplantation is recommended, as well as consideration of inclusion of other chemotherapeutics, such as anthracyclines. Finally, maintenance with best-available strategies, such as bisphosphonate, thalidomide, and /or bortezomib, should also be considered, with other novel agents held in reserve for relapse, according to respective approvals and availability.

Conclusions and future directions

In conclusion, we recommend that, in younger patients with NDMM, active treatment should be initiated as early as possible, and broadly in accordance with IMWG criteria. Induction treatment should contain an IMID, PI, and steroids, because triplets are associated with increased depth and quality of response as well as clinical benefit. Given the rapidly changing treatment paradigm and the efficacy of novel agent combinations, ASCT can reasonably be kept in reserve for patients who do not wish to initially pursue high-dose therapy, with postinduction continuous therapy using lenalidomide recommended and PIs added as clinically appropriate. In patients undergoing ASCT, consolidation therapy after ASCT is favored, followed by maintenance with lenalidomide. The addition of bortezomib to maintenance therapy should be considered in patients with high-risk cytogenetics, with other PIs also considered as clinically indicated. Typically, the prognostic risk profile of a patient should be determined using clinical and genetic features. In all patients, careful attention to supportive care plays a critical role, not least because it allows the avoidance of early complications that may compromise subsequent therapeutic outcome.[25,118-124] Several other factors should be considered while planning treatment strategy, such as logistics,

out-of-pocket cost, drug availability, social considerations, comorbidities, and patient preference. The current wide availability of options allows a tailored approach, with improved efficacy. New directions include monoclonal antibodies, vaccines, cellular therapy, and small molecules, such as histone deacetylase inhibitors and other targeted therapies, as well as bone-targeting agents, including denosumab.[124,126] Participation in large phase III trials investigating the best approach in newly diagnosed younger patients is strongly recommended and should be considered for all eligible patients.

Acknowledgments

The authors gratefully acknowledge the editorial assistance of Michelle Maglio, Rashana Lord, and Jack Sparacino in the preparation of this manuscript.

This work was supported in part by the R.J. Corman Multiple Myeloma Research Fund.

Authorship

Contribution: S.G. developed the first draft and edited and wrote the manuscript, and C.P.P. and P.G.R. edited and wrote the manuscript.

Conflict-of-interest disclosure: P.G.R. is a member of advisory committees for Celgene, Takeda, Janssen, Oncopeptides, and Amgem and has received research funding from BMS, Takeda, and Celgene. The remaining authors declare no competing financial interests.

ORCID profile: S.G., 0000-0001-6207-4433.

Correspondence: Paul G. Richardson, Dana-Farber Cancer Institute, 450 Brookline Ave, Mayer 228, Boston, MA 02215; e-mail: paul_richardson@dfci.harvard.edu.

Footnote

Submitted 5 May 2017; accepted 1 June 2018. Prepublished online as *Blood* First Edition paper, 2 July 2018; DOI 10.1182/blood-2017-05-693606.

REFERENCES

1. Kyle RA, Rajkumar SV. Multiple myeloma. *N Engl J Med*. 2004;351(18):1860-1873.
2. Palumbo A, Anderson K. Multiple myeloma. *N Engl J Med*. 2011;364(11):1046-1060.
3. Kazandjian D. Multiple myeloma epidemiology and survival: a unique malignancy. *Semin Oncol*. 2016;43(6):676-681.
4. Rajkumar SV, Fonseca R, Dispenzieri A, et al. Thalidomide in the treatment of relapsed multiple myeloma. *Mayo Clin Proc*. 2000; 75(9):897-901.
5. Richardson PG, Laubach JP, Munshi NC, Anderson KC. Early or delayed transplantation for multiple myeloma in the era of novel therapy: does one size fit all? *Hematology Am Soc Hematol Educ Program*. 2014;2014:255-261.
6. Touzeau C, Moreau P, Dumontet C. Monoclonal antibody therapy in multiple myeloma. *Leukemia*. 2017;31(5):1039-1047.
7. Rajkumar SV. Treatment of multiple myeloma. *Nat Rev Clin Oncol*. 2011;8(8): 479-491.
8. Rajkumar SV, Gahrton G, Bergsagel PL. Approach to the treatment of multiple myeloma: a clash of philosophies. *Blood*. 2011; 118(12):3205-3211.
9. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15(12): e538-e548.
10. Rajkumar SV, Merlini G, San Miguel JF. Haematological cancer: redefining myeloma. *Nat Rev Clin Oncol*. 2012;9(9):494-496.
11. Zamagni E, Nanni C, Patriarca F, et al. A prospective comparison of 18F-fluorodeoxyglucose positron emission tomography-computed tomography, magnetic resonance imaging and whole-body planar radiographs in the assessment of bone disease in newly diagnosed multiple myeloma. *Haematologica*. 2007;92(1):50-55.
12. Rajkumar SV, Larson D, Kyle RA. Diagnosis of smoldering multiple myeloma. *N Engl J Med*. 2011;365(5):474-475.
13. Kastritis E, Terpos E, Moulopoulos L, et al. Extensive bone marrow infiltration and abnormal free light chain ratio identifies patients with asymptomatic myeloma at high risk for progression to symptomatic disease. *Leukemia*. 2013;27(4):947-953.
14. Waxman AJ, Mick R, Garfall AL, et al. *Modeling the risk of progression in smoldering multiple myeloma* [abstract]. J Clin Oncol. 2014;32(15 suppl). Abstract 8607.
15. Dispenzieri A, Kyle RA, Katzmann JA, et al. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. *Blood*. 2008;111(2):785-789.
16. Larsen JT, Kumar SK, Dispenzieri A, Kyle RA, Katzmann JA, Rajkumar SV. Serum free light chain ratio as a biomarker for high-risk smoldering multiple myeloma. *Leukemia*. 2013;27(4):941-946.
17. Hillengass J, Fechtner K, Weber MA, et al. Prognostic significance of focal lesions in whole-body magnetic resonance imaging in patients with asymptomatic multiple myeloma. *J Clin Oncol*. 2010;28(9):1606-1610.
18. Kastritis E, Moulopoulos LA, Terpos E, Koutoulidis V, Dimopoulos MA. The prognostic importance of the presence of more than one focal lesion in spine MRI of patients with asymptomatic (smoldering) multiple myeloma. *Leukemia*. 2014;28(12): 2402-2403.
19. Morgan GJ, Walker BA, Davies FE. The genetic architecture of multiple myeloma. *Nat Rev Cancer*. 2012;12(5):335-348.
20. Bahlis NJ. Darwinian evolution and tiding clones in multiple myeloma. *Blood*. 2012; 120(5):927-928.
21. Mitsiades CS, Mitsiades NS, Munshi NC, Richardson PG, Anderson KC. The role of the bone microenvironment in the pathophysiology and therapeutic management of multiple myeloma: interplay of growth factors, their receptors and stromal interactions. *Eur J Cancer*. 2006;42(11):1564-1573.
22. Attal M, Harousseau JL, Facon T, et al; InterGroupe Francophone du Myélome. Single versus double autologous stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2003;349(26):2495-2502.
23. Palumbo A, Bringhen S, Mateos MV, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. *Blood*. 2015;125(13):2068-2074.
24. Fonseca R, Bergsagel PL, Drach J, et al; International Myeloma Working Group. International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. *Leukemia*. 2009;23(12): 2210-2221.
25. Terpos E, Morgan G, Dimopoulos MA, et al. International Myeloma Working Group recommendations for the treatment of multiple myeloma-related bone disease. *J Clin Oncol*. 2013;31(18):2347-2357.
26. Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer*. 1975;36(3):842-854.
27. Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma [published correction appears in *J Clin Oncol*. 2005;23(25):6281]. *J Clin Oncol*. 2005;23(15):3412-3420.
28. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for multiple myeloma: a report from International Myeloma Working Group. *J Clin Oncol*. 2015;33(26):2863-2869.
29. Terpos E, Katodritou E, Roussou M, et al; Greek Myeloma Study Group, Greece. High serum lactate dehydrogenase adds prognostic value to the international myeloma staging system even in the era of novel agents. *Eur J Haematol*. 2010;85(2):114-119.
30. Dispenzieri A. Myeloma: management of the newly diagnosed high-risk patient. *Hematology Am Soc Hematol Educ Program*. 2016;2016:485-494.
31. Munshi NC, Anderson KC, Bergsagel PL, et al; International Myeloma Workshop

Consensus Panel 2. Consensus recommendations for risk stratification in multiple myeloma: report of the International Myeloma Workshop Consensus Panel 2. *Blood*. 2011; 117(18):4696-4700.

32. Avet-Loiseau H, Attal M, Moreau P, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myélome. *Blood*. 2007;109(8):3489-3495.

33. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia*. 2014; 28(5):1122-1128.

34. Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. *Blood*. 2010;116(5):679-686.

35. Palumbo A, Bringhen S, Rossi D, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. *J Clin Oncol*. 2010; 28(34):5101-5109.

36. Cavo M, Tacchetti P, Patriarca F, et al; GIMEMA Italian Myeloma Network. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *Lancet*. 2010;376(9758): 2075-2085.

37. Roussel M, Lauwers-Cances V, Robillard N, 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 Myélome. *J Clin Oncol*. 2014;32(25):2712-2717.

38. Jakubowiak AJ, Dytfeld D, Griffith KA, et al. A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. *Blood*. 2012;120(9): 1801-1809.

39. Kumar SK, Berdeja JG, Niesvizky R, et al. Safety and tolerability of ixazomib, an oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma: an open-label phase 1/2 study. *Lancet Oncol*. 2014;15(13):1503-1512.

40. Moreau P, Avet-Loiseau H, Facon T, et al. Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide plus dexamethasone as induction treatment before autologous stem cell transplantation in newly diagnosed multiple myeloma. *Blood*. 2011;118(22):5752-5758, quiz 5982.

41. Rosiñol L, Oriol A, Teruel AI, et al; Programa para el Estudio y la Terapéutica de las Hemopatías Malignas/Grupo Español de Mieloma (PETHEMA/GEM) group. 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):1589-1596.

42. Durie BG, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet*. 2017;389(10068): 519-527.

43. Attal M, Lauwers-Cances V, Hulin C, et al; IFM 2009 Study. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. *N Engl J Med*. 2017;376(14): 1311-1320.

44. Moreau P, Masszi T, Grzasko N, et al; TOURMALINE-MM1 Study Group. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016; 374(17):1621-1634.

45. Moreau P, Hulin C, Macro M, et al. VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial. *Blood*. 2016;127(21): 2569-2574.

46. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Français du Myélome. *N Engl J Med*. 1996; 335(2):91-97.

47. Fermand JP, Ravaud P, Chevret S, et al. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial. *Blood*. 1998;92(9): 3131-3136.

48. Child JA, Morgan GJ, Davies FE, et al; Medical Research Council Adult Leukaemia Working Party. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med*. 2003; 348(19):1875-1883.

49. Fermand JP, Katsahian S, Divine M, et al; Group Myelome-Autogreffe. High-dose therapy and autologous blood stem-cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long-term results of a randomized control trial from the Group Myelome-Autogreffe. *J Clin Oncol*. 2005;23(36): 9227-9233.

50. Gertz MA, Ansell SM, Dingli D, et al. Autologous stem cell transplant in 716 patients with multiple myeloma: low treatment-related mortality, feasibility of outpatient transplant, and effect of a multidisciplinary quality initiative. *Mayo Clin Proc*. 2008; 83(10):1131-1138.

51. Bladé J, Rosiñol L, Sureda A, et al; Programa para el Estudio de la Terapéutica en Hemopatía Maligna (PETHEMA). High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: long-term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. *Blood*. 2005;106(12):3755-3759.

52. Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321 [published correction appears in *J Clin Oncol*. 2006;24(17):2687]. *J Clin Oncol*. 2006;24(6):929-936.

53. Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. *N Engl J Med*. 2014;371(10):895-905.

54. Gay F, Oliva S, Petrucci MT, et al. Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: a randomised, multicentre, phase 3 trial. *Lancet Oncol*. 2015;16(16): 1617-1629.

55. Cavo M, et al. Intensification therapy with bortezomib-melphalan-prednisone versus autologous stem cell transplantation for newly diagnosed multiple myeloma: an intergroup, multicenter, phase III study of the European Myeloma Network (EMN02/HO95 MM Trial) [abstract]. *Blood*. 2016; 128(22). Abstract 673.

56. Richardson PG. Point/counterpoint: routine use of autologous stem cell transplantation in multiple myeloma. One size does not fit all. *Oncology (Williston Park)*. 2016;30(8): 747-749.

57. Gay F, Oliva S, Petrucci MT, et al. Autologous transplant vs oral chemotherapy and lenalidomide in newly diagnosed young myeloma patients: a pooled analysis. *Leukemia*. 2017;31(8):1727-1734.

58. Rosiñol L, Kumar S, Moreau P, Cavo M. Initial treatment of transplant-eligible patients in multiple myeloma. *Expert Rev Hematol*. 2014;7(1):43-53.

59. Cavo M, Tosi P, Zamagni E, et al. Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 Clinical Study. *J Clin Oncol*. 2007; 25(17):2434-2441.

60. Mai EK, Benner A, Bertsch U, et al. Single versus tandem high-dose melphalan followed by autologous blood stem cell transplantation in multiple myeloma: long-term results from the phase III GMMG-HD2 trial. *Br J Haematol*. 2016;173(5):731-741.

61. Kumar A, Kharfan-Dabaja MA, Glasmacher A, Djulbegovic B. Tandem versus single autologous hematopoietic cell transplantation for the treatment of multiple myeloma: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2009;101(2): 100-106.

62. Naumann-Winter F, Greb A, Borchmann P, Bohlius J, Engert A, Schnell R. First-line tandem high-dose chemotherapy and autologous stem cell transplantation versus single high-dose chemotherapy and autologous stem cell transplantation in multiple myeloma, a systematic review of controlled studies. *Cochrane Database Syst Rev*. 2012; 10:CD004626.

63. Stadtmauer EA, Pasquini MC, Blackwell B, et al. Comparison of autologous hematopoietic cell transplant (autoHCT),

bortezomib, lenalidomide (Len) and dexamethasone (RVD) consolidation with Len maintenance (ACM), tandem autoHCT with Len maintenance (TAM) and autoHCT with Len maintenance (AM) for up-front treatment of patients with multiple myeloma (MM): primary results from the randomized phase III trial of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0702 – StaMINA Trial) [abstract]. *Blood* 2016; 128(22). Abstract LBA-1.

64. Dhakal B, Vesole DH, Hari PN. Allogeneic stem cell transplantation for multiple myeloma: is there a future? *Bone Marrow Transplant*. 2016;51(4):492-500.

65. Cavo M, Pantani L, Petrucci MT, et al; GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto) Italian Myeloma Network. 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.

66. Mellqvist UH, Gimsing P, Hjertner O, et al; Nordic Myeloma Study Group. Bortezomib consolidation after autologous stem cell transplantation in multiple myeloma: a Nordic Myeloma Study Group randomized phase 3 trial. *Blood*. 2013;121(23): 4647-4654.

67. Einsele H, Knop S, Vogel M, et al. Response-adapted consolidation with bortezomib after ASCT improves progression-free survival in newly diagnosed multiple myeloma. *Leukemia*. 2017;31(6):1463-1466.

68. Sonneveld P, Beksac M, van der Holt B, et al. Consolidation followed by maintenance therapy versus maintenance alone in newly diagnosed, transplant eligible patients with multiple myeloma (mm): a randomized phase 3 study of the European Myeloma Network (EMN02/HO95 MM Trial) [abstract]. *Blood*. 2016;128(22). Abstract 242.

69. Sengsayadeth S, Malard F, Savani BN, Garderet L, Mohty M. Posttransplant maintenance therapy in multiple myeloma: the changing landscape. *Blood Cancer J*. 2017; 7(3):e545.

70. Fritz E, Ludwig H. Interferon-alpha treatment in multiple myeloma: meta-analysis of 30 randomised trials among 3948 patients. *Ann Oncol*. 2000;11(11):1427-1436.

71. 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):1020-1034.

72. Alexanian R, Weber D, Dimopoulos M, Delasalle K, Smith TL. Randomized trial of alpha-interferon or dexamethasone as maintenance treatment for multiple myeloma. *Am J Hematol*. 2000;65(3):204-209.

73. Belch A, Shelley W, Bergsagel 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):94-99.

74. Berenson JR, Crowley JJ, Grogan TM, et al. Maintenance therapy with alternate-day prednisone improves survival in multiple myeloma patients. *Blood*. 2002;99(9): 3163-3168.

75. Shustik C, Belch A, Robinson S, et al. A randomised comparison of melphalan with prednisone or dexamethasone as induction therapy and dexamethasone or observation as maintenance therapy in multiple myeloma: NCIC CTG MY.7. *Br J Haematol*. 2007; 136(2):203-211.

76. Attal M, Harousseau JL, Leyvraz S, et al; Inter-Groupe Francophone du Myélome (IFM). Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood*. 2006;108(10):3289-3294.

77. Barlogie B, Tricot G, Anaissie E, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *N Engl J Med*. 2006;354(10):1021-1030.

78. Spencer A, Prince HM, Roberts AW, et al. Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. *J Clin Oncol*. 2009;27(11):1788-1793.

79. Lokhorst HM, van der Holt B, Zweegman S, et al; Dutch-Belgian Hemato-Oncology Group (HOVON). 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):1113-1120.

80. Krishnan A, Pasquini MC, Logan B, et al; Blood Marrow Transplant Clinical Trials Network (BMT CTN). Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial. *Lancet Oncol*. 2011;12(13):1195-1203.

81. Morgan GJ, Gregory WM, Davies FE, et al; National Cancer Research Institute Haematological Oncology Clinical Studies Group. The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis. *Blood*. 2012; 119(1):7-15.

82. Morgan GJ, Davies FE, Gregory WM, et al. Long-term follow-up of MRC Myeloma IX trial: Survival outcomes with bisphosphonate and thalidomide treatment. *Clin Cancer Res*. 2013;19(21):6030-6038.

83. Maiolino A, Hungria VT, Garnica M, et al; Brazilian Multiple Myeloma Study Group (BMMSG/GEMOH). 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):948-952.

84. Kagoya Y, Nannya Y, Kurokawa M. Thalidomide maintenance therapy for patients with multiple myeloma: meta-analysis. *Leuk Res*. 2012;36(8):1016-1021.

85. Stewart AK, Trudel S, Bahlis NJ, 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):1517-1523.

86. McCarthy PL, Palumbo A. Maintenance therapy for multiple myeloma. *Hematol Oncol Clin North Am*. 2014;28(5):839-859.

87. Attal M, Lauwers-Cances V, Marit G, et al; IFM Investigators. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012; 366(19):1782-1791.

88. Gay F, Cavallo F, Caravita T, et al. Maintenance therapy with lenalidomide significantly improved survival of young newly diagnosed multiple myeloma patients [abstract]. *Blood*. 2013;122(21). Abstract 2089.

89. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366(19):1770-1781.

90. Attal, A, Palumbo A, Holstein SA, et al. Lenalidomide (LEN) maintenance (MNTC) after high-dose melphalan and autologous stem cell transplant (ASCT) in multiple myeloma (MM): a meta-analysis (MA) of overall survival (OS) [abstract]. *J Clin Oncol*. 2016; 34(suppl 15). Abstract 8001.

91. Sonneveld P, Schmidt-Wolf IG, van der Holt B, 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*. 2012;30(24): 2946-2955.

92. Sonneveld P, Salwender H-J, Van Der Holt B, et al. Bortezomib induction and maintenance in patients with newly diagnosed multiple myeloma: long-term follow-up of the HOVON-65/GMMG-HD4 Trial [abstract]. *Blood*. 2015;126(23). Abstract 27.

93. Terpos E, Sezer O, Croucher P, Dimopoulos MA. Myeloma bone disease and proteasome inhibition therapies. *Blood*. 2007;110(4): 1098-1104.

94. Laubach JP, Tai YT, Richardson PG, Anderson KC. Daratumumab granted breakthrough drug status. *Expert Opin Investig Drugs*. 2014;23(4):445-452.

95. Plesner T, Arkenau HT, Gimsing P, et al. Phase 1/2 study of daratumumab, lenalidomide, and dexamethasone for relapsed multiple myeloma. *Blood*. 2016;128(14): 1821-1828.

96. Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. *N Engl J Med*. 2015;373(13):1207-1219.

97. Martin TG, Hsu K, Strickland SA, Glenn MJ, Mikhael J, Charpentier E. A phase I trial of SAR650984, a CD38 monoclonal antibody, in relapsed or refractory multiple myeloma [abstract]. *J Clin Oncol*. 2014; 32(suppl 5). Abstract 8532.

98. Lonial S, Kaufman J, Laubach J, Richardson P. Elotuzumab: a novel anti-CS1 monoclonal antibody for the treatment of multiple myeloma. *Expert Opin Biol Ther*. 2013;13(12): 1731-1740.

99. van Rhee F, Szmania SM, Dillon M, et al. Combinatorial efficacy of anti-CS1

monoclonal antibody elotuzumab (HuLuc63) and bortezomib against multiple myeloma. *Mol Cancer Ther*. 2009;8(9):2616-2624.

100. Jakubowiak AJ, Benson DM, Bensinger W, et al. Phase I trial of anti-CS1 monoclonal antibody elotuzumab in combination with bortezomib in the treatment of relapsed/refractory multiple myeloma. *J Clin Oncol*. 2012;30(16):1960-1965.

101. Lonial S, Vij R, Harousseau JL, et al. Elotuzumab in combination with lenalidomide and low-dose dexamethasone in relapsed or refractory multiple myeloma. *J Clin Oncol*. 2012;30(16):1953-1959.

102. Zonder JA, Mohrbacher AF, Singhal S, et al. A phase 1, multicenter, open-label, dose escalation study of elotuzumab in patients with advanced multiple myeloma. *Blood*. 2012;120(3):552-559.

103. Kumar SK, Anderson KC. Immune therapies in multiple myeloma. *Clin Cancer Res*. 2016; 22(22):5453-5460.

104. Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. *Lancet*. 2016;387(10027):1551-1560.

105. Usmani SZ, Weiss BM, Plesner T, et al. Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma. *Blood*. 2016;128(1):37-44.

106. Palumbo A, Chanan-Khan A, Weisel K, et al; CASTOR Investigators. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;375(8): 754-766.

107. Dimopoulos MA, Oriol A, Nahi H, et al; POLLUX Investigators. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;375(14): 1319-1331.

108. Lesokhin AM, Ansell SM, Armand P, et al. Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a phase Ib study. *J Clin Oncol*. 2016;34(23):2698-2704.

109. Mateos M-V, Orlowski RZ, DiCapua Siegel DS, et al. Pembrolizumab in combination with lenalidomide and low-dose dexamethasone for relapsed/refractory multiple myeloma (RRMM): final efficacy and safety analysis. J Clin Oncol. 2016;34(suppl 15): 8010-8010.

110. Rosenblatt J, Vasir B, Uhl L, et al. Vaccination with dendritic cell/tumor fusion cells results in cellular and humoral antitumor immune responses in patients with multiple myeloma. *Blood*. 2011;117(2):393-402.

111. Rosenblatt J, Avivi I, Vasir B, et al. Vaccination with dendritic cell/tumor fusions following autologous stem cell transplant induces immunologic and clinical responses in multiple myeloma patients. *Clin Cancer Res*. 2013;19(13):3640-3648.

112. Mikkilineni L, Kochenderfer JN. Chimeric antigen receptor T-cell therapies for multiple myeloma. *Blood*. 2017;130(24):2594-2602.

113. Cohen, A., et al., Safety and efficacy of b-cell maturation antigen (BCMA)-specific chimeric antigen receptor T cells (CART-BCMA) with cyclophosphamide conditioning for refractory multiple myeloma (MM) [abstract]. *Blood*. 2017;130(suppl 1). Abstract 505.

114. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol*. 2016;17(8): e328-e346.

115. Munshi NC, Avet-Loiseau H, Rawstron AC, et al. Association of minimal residual disease with superior survival outcomes in patients with multiple myeloma: a meta-analysis. *JAMA Oncol*. 2017;3(1):28-35.

116. Landgren O, Devlin S, Boulad M, Mailankody S. Role of MRD status in relation to clinical outcomes in newly diagnosed multiple myeloma patients: a meta-analysis. *Bone Marrow Transplant*. 2016;51(12):1565-1568.

117. Anderson KC, Auclair D, Kelloff GJ, et al. The role of minimal residual disease testing in myeloma treatment selection and drug development: current value and future applications. *Clin Cancer Res*. 2017;23(15): 3980-3993.

118. Hofmann JN, Liao LM, Pollak MN, et al. A prospective study of circulating adipokine levels and risk of multiple myeloma. *Blood*. 2012;120(22):4418-4420.

119. Chanan-Khan A, Sonneveld P, Schuster MW, et al. Analysis of herpes zoster events among bortezomib-treated patients in the phase III APEX study. *J Clin Oncol*. 2008;26(29): 4784-4790.

120. Vickrey E, Allen S, Mehta J, Singhal S. Acyclovir to prevent reactivation of varicella zoster virus (herpes zoster) in multiple myeloma patients receiving bortezomib therapy. *Cancer*. 2009;115(1):229-232.

121. Palumbo A, Rajkumar SV, Dimopoulos MA, et al; International Myeloma Working Group. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. *Leukemia*. 2008;22(2):414-423.

122. Van Acker HH, Anguille S, Willemen Y, Smits EL, Van Tendeloo VF. Bisphosphonates for cancer treatment: mechanisms of action and lessons from clinical trials. *Pharmacol Ther*. 2016;158:24-40.

123. Avilès A, Nambo MJ, Huerta-Guzmàn J, Cleto S, Neri N. Prolonged use of zoledronic acid (4 years) did not improve outcome in multiple myeloma patients. *Clin Lymphoma Myeloma Leuk*. 2017;17(4):207-210.

124. Raje N, Vadhan-Raj S, Willenbacher W, et al. Evaluating results from the multiple myeloma patient subset treated with denosumab or zoledronic acid in a randomized phase 3 trial. *Blood Cancer J*. 2016;6(1):e378.

125. Richardson PG, Delforge M, Beksac M, et al. Management of treatment-emergent peripheral neuropathy in multiple myeloma. *Leukemia*. 2012;26(4):595-608.

126. Laubach JP, San-Miguel JF, Hungria V, et al. Deacetylase inhibitors: an advance in myeloma therapy? *Expert Rev Hematol*. 2017; 10(3):229-237.