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Symposium Report

Management of Multiple Myeloma: Using Emerging Therapies with ASCT

Activity Chairs

Kenneth C. Anderson, MD
Kraft Family Professor of Medicine, Harvard Medical School
Director, Jerome Lipper Multiple Myeloma Center and LeBow Institute for Myeloma Therapeutics
Dana-Farber Cancer Institute
Boston, MA

Joseph R. Mikhael, MD, MEd, FRCPC, FACP
Professor of Medicine, Mayo College of Medicine
Associate Dean, Mayo School of Graduate Medical Education
Deputy Director - Education, Mayo Clinic Cancer Center
Associate Medical Director, Department of Development
Mayo Clinic in Arizona
Scottsdale, AZ

Program Overview

Multiple myeloma (MM) management has undergone profound changes in the past few decades, this is largely due to advances in understanding the disease biology and the development of new therapeutic options. However, this progress has also led to an increasingly complex treatment environment. Numerous questions remain, particularly in the transplant setting, such as the role of high-dose chemotherapy, the use of continuous/maintenance therapy, and the best treatment sequence for a patient with multiple myeloma.

In this CME activity, leading experts in multiple myeloma will review changes in the treatment paradigm, optimal patient selection for transplant, and data from recent clinical trials. They will also provide insight into new strategies for individualized management, the role of early versus late transplant, and how to incorporate novel therapies into clinical practice.

Learning Objectives

Upon successful completion of this educational activity, participants should be better able to:

1. Review the eligibility criteria for stem cell transplant in patients with MM in both the frontline and relapse/refractory settings.
2. Apply clinical evidence for optimal induction, conditioning, and consolidation strategies in patients with MM undergoing stem cell transplant.
3. Utilize effective maintenance therapy in patients with MM who have completed stem cell transplant.

Target Audience

The intended audience for this activity is hematologists, oncologists, bone marrow transplant specialists, and other health care professionals who provide care for patients with MM.

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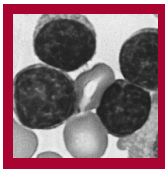

ASBMT™
American Society for Blood and Marrow Transplantation

Executive Office
American Society for Blood and Marrow Transplantation
85 West Algonquin Road, Suite 550
Arlington Heights, IL 60005-4425
(847) 427-0224; fax (847) 427-9656
e-mail: mail@asbmt.org

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Changing Treatment Algorithms in the Management of Multiple Myeloma: In with the New, But Not Out with the Old

Maxim Norkin, MD and John R. Wingard, MD, University of Florida College of Medicine, Gainesville, FL

The introduction of novel treatments over the last decade has significantly improved clinical outcomes in patients with multiple myeloma (MM). Unprecedentedly high rates of durable responses to new chemotherapy regimens have translated to significant improvements in overall survival (OS) , which is now often exceeds 10 years. However, due to high volume of new research data and great variety of available therapeutic approaches it is often difficult for a practicing physician to incorporate new drugs into practice and to select the optimal state-of-the-art approach for each MM patient. Recent advances in initial management and treatment of relapsed disease were the topic in a satellite symposium held in February 2016 at the Tandem BMT meetings in Honolulu, Hawaii.

Initial management of patients with MM with an emphasis on pivotal trials of emergent therapies and the role of autologous stem cell transplant (ASCT) was discussed by Dr. Ken Anderson. He focused on newly diagnosed ASCT-eligible patients with MM. He reviewed recent studies addressing the role of ASCT in patients receiving novel multidrug therapies. Use of high-dose melphalan with ASCT in conjunction with novel anti-myeloma drugs has been associated with clinically significant progression free survival (PFS) benefits across all reviewed studies, and OS improvement in some studies. Triplet induction regimens have generally been found to be more effective than doublet regimens, but may also be associated with greater toxicity. Post-transplant consolidation and maintenance approaches have been associated with higher rates of minimal residual disease negativity and improvement of PFS, but these have not always translated into better OS. Although early ASCT (within 12 months after diagnosis) is currently regarded as standard of care in transplant-eligible patients, the possibility of delayed ASCT (>12 months after diagnosis) is now being investigated to define the most optimal timing for ASCT. Novel drugs such as ixazomib, daratumumab, elatumumab or panobinostat were recently approved in relapsed disease settings and further studies are needed to study their role in newly diagnosed MM. He notes that promising classes of drugs such as checkpoint inhibitors and myeloma cell vaccines are in the pipeline. Taken together, these various studies suggest that the old (ASCT) remains part of the standard of care in transplant-eligible patients with newly diagnosed MM and the new (novel therapies before and after ASCT) are playing growing roles in enhancing long-term benefits.

Dr. Joseph Mikhael discussed current management of patients with relapsed MM. With four new drugs approved (panobinostat, daratumumab, elotuzumab, ixazomib) for relapsed MM in 2015, there are more treatment options available for these patients. Dr. Mikhael discussed the results of the pivotal trials that led to their approval. He noted there remains roles for older therapies including alkylating agents and second ASCT for subsets of patients. He suggested a risk-adjusted approach, such as the Mayo Clinic stratification algorithm for risk-adapted therapy for MM patients, might be useful in selecting treatments for the relapsed patient.

For both initial management and for treatment of the patient with relapsed disease, novel therapies are improving the prospects for patients with MM. Yet there remain important roles for therapies that have been around for some time. Taken together, combining the new with the old provides patients with multiple options for disease control.

Management of Multiple Myeloma: Using Emerging Therapies with ASCT

Kenneth C. Anderson, MD and Joseph R. Mikhael, MD, MEd, FRCPC, FACP, Activity Chairs

High-dose chemotherapy plus autologous stem cell transplant (ASCT) continues to be the standard of care in newly diagnosed transplant-eligible patients with multiple myeloma; however, considerable progress has been made in recent years. Despite impressive advancements, multiple myeloma remains an incurable disease, characterized by multiple relapses and development of resistance to previous therapies. The emergence of novel therapies has not resulted in defining a single regimen that can provide superior outcomes, particularly in the setting of diverse patient populations and disease stages.

The addition of new therapies to the multiple myeloma management armamentarium occurred following the marked progress in understanding the pathogenesis of the disease. Although molecular and genomic prognostic tools have increasing importance in research protocols, the usefulness of possible surrogate outcomes, such as minimal residual disease, is being actively explored.

These new treatment options have increased the complexity of multiple myeloma management, and raised a question about the continuing role of ASCT for managing new multiple myeloma cases. Their potential role in relapsed/refractory multiple myeloma is continuously expanded, as new clinical trial data are reported.

The volume of clinical trial data requires clinicians to be constantly attentive to new developments and guidance for selecting the optimal management approaches for their patients. To assist with the decision process, Vindico Medical Education provided a venue for sharing the latest data on strategies for incorporating novel therapies into the transplant paradigm, as well as their role in managing relapsed and refractory patients with multiple myeloma. Readers can expect to improve their understanding of the evidence supporting the use of these agents from initial treatment through disease relapse, highlighting considerations for risk-based patient subgroups.

Incorporating Novel Therapies into the Transplant Paradigm

Kenneth C. Anderson, MD

High-dose melphalan plus autologous stem cell transplant (ASCT) is the standard management approach in newly diagnosed patients with multiple myeloma (MM) who are eligible for transplant. The era of novel therapies for treating multiple myeloma has enhanced treatment options and modified the role of ASCT. Four major points are supported: 1) triplet novel combination induction therapy increases ASCT response; 2) novel therapies used as induction and as consolidation/maintenance post-transplant have achieved high minimal residual disease (MRD) negativity and improved progression-free survival (PFS); 3) trials of early versus late transplantation with maintenance until progression are ongoing; and 4) novel agents including monoclonal antibodies (mAbs), histone deacetylase (HDAC) inhibitors, and programmed cell death protein 1 (PD-1)/PDL-1 are being integrated into the transplant paradigm.

The benefit of transplantation was established in the 1980s and 1990s. Most randomized trials showed a response and event-free survival (EFS) benefit (Table 1).[1-7] Improvements in overall survival (OS) were not commonly observed.

Table 1. Outcomes of Seminal Randomized Trials of ASCT Versus Conventional Chemotherapy

Author	Patients (N)	Age	ASCT Benefit Shown For		
			CR / VGPR Rate	EFS	OS
Attal M, et al. 19961	200	≤65	YES	YES	YES
Fermand JP, et al. 19986	202	<55	YES	YES	NO
Child JA, et al. 20034	401	≤65	YES	YES	YES
Palumbo A, et al. 20047	194	<70	YES	YES	YES
Fermand JP, et al. 20055	190	55-65	YES	YES	NO
Bladé J, et al. 20053	164	<65	YES	YES	NO
Barlogie B, et al. 20062	516	≤70	NO	NO	NO

Key: ASCT – autologous stem cell transplant, CR – complete response, EFS – event free survival, OS – overall survival, VGPR – very good partial response

Source: References 1-7.

After the earlier approval of conventional chemotherapy agents, such as melphalan and steroids such as dexamethasone, novel agents including protease inhibitors and immunomodulatory with different mechanisms of action have received US Food and Drug Administration (FDA) approval for treatment of multiple myeloma in the last 10 years (Table 2) (Figure 1).[8-10] These agents have been incorporated into the transplant paradigm for induction, consolidation, and maintenance therapy of newly diagnosed patients, and have allowed a 3- to 4-fold increase in median patient survival.

Several FDA approvals were achieved in 2015, including the histone deacetylase (HDAC) inhibitor panobinostat in February, followed in November by the approval of 2 monoclonal antibodies (daratumumab and elotuzumab) and ixazomib, the first FDA-approved oral proteasome inhibitor (PI). Many of these agents have indications that restrict their use to at least second-line therapy, and there are often other conditions to be fulfilled, including use in combination with other drugs. In March 2016, the FDA approved a reformulated propylene glyco-free version of melphalan that uses a proprietary sulfobutyl ether solubilizer to improve drug safety and efficacy.[11,12] New approaches to treat and ultimately prevent relapse continue to be explored.

Recent ASCT Efficacy Trials

The benefits of high-dose chemotherapy plus ASCT are well known; however, safer and more effective treatments are continually being sought. The availability of these new therapies prompted studies exploring whether consolidation without ASCT may be part of an alternative therapeutic approach in patients with newly diagnosed multiply myeloma.

ASCT versus Cyclophosphamide-Lenalidomide-Dexamethasone

A Phase 3 2x2 factorial trial enrolled 389 patients to compare consolidation with melphalan 200 mg/m^2 (MEL200) followed by ASCT or with cyclophosphamide-lenalidomide-dexamethasone (CRD).[13,14] After a second

Table 2. FDA-Approved Multiple Myeloma Drugs: 2006-2015

Immunomodulatory Drugs
Lenalidomide
Thalidomide
Pomalidomide
Proteasome Inhibitors
Bortezomib
Carfilzomib
Ixazomib*
Histone Deacetylase Inhibitor
Panobinostat*
Monoclonal Antibodies
Daratumumab*
Elotuzumab*

* Approved in 2015

Source: Chari A. *Am J Hematol/Oncol.* 2015;11:11-16; FDA. http://www.fda.gov/Drugs/

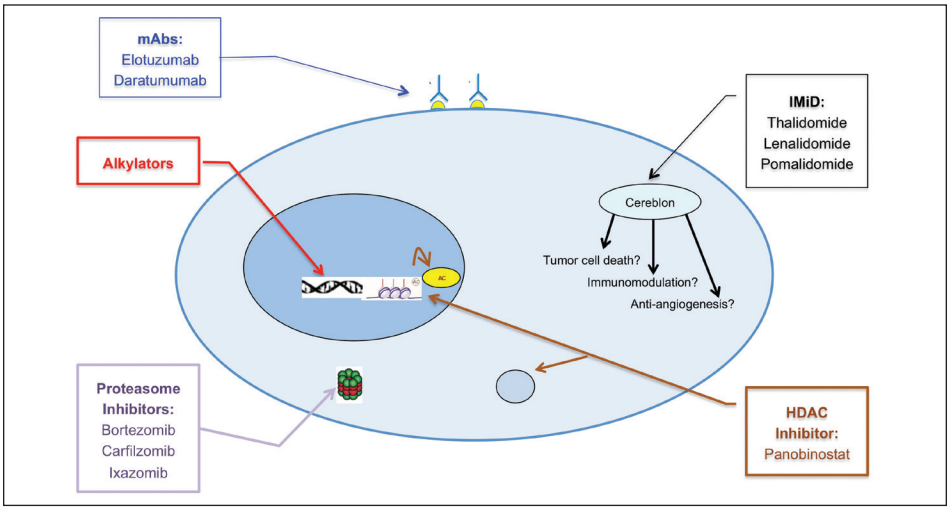

Figure 1. Multiple Myeloma Drug Therapy Classes: Mechanism of Action

Key: HDAC – histone deacetylase, IMiD – immunomodulatory drug, mAb – monoclonal antibody,
Source: Modified from: Ocio EM, et al. *Leukemia.* 2014;28:525-542.

randomization, maintenance therapy was provided by lenalidomide-prednisone (RP) compared with lenalidomide alone (R).

Survival outcomes were significantly improved in the transplant group. During a median follow-up of 54.5 months, patients in the MEL200 group had significantly increased PFS compared with the CRD group (median from start of consolidation: 43.3 vs 28.6 months; *P*<.001) and 4-year overall survival (OS) (86% vs 73%; *P*=.004). Median PFS from the start of maintenance was similar in RP and R groups (37.5 vs 28.5 months; *P*=.34), as was 3-year OS (83% vs 88%; *P*=.21). The authors concluded that consolidation with high-dose melphalan and ASCT remains the preferred option in transplant-eligible patients with newly diagnosed multiple myeloma.[14]

ASCT versus Melphalan-Prednisone-Lenalidomide

Another study also used a 2x2 factorial design to compare consolidation with melphalan-prednisone-lenalidomide (MPR; n=132) or high-dose melphalan and ASCT (MEL200; n=141) in newly diagnosed patients with multiple myeloma.[15,16] All patients received lenalidomide-dexamethasone induction therapy prior to the initial randomization. Post consolidation, qualifying patients from both groups underwent a second randomization (n=251) to lenalidomide maintenance or no maintenance.

After a median follow-up of 51 months, outcomes were more favorable in the MEL200 compared with the MPR group, with longer median PFS (43 vs 22 months; *P*<.001) and greater 4-year OS (82% vs 65%; *P*=.02). In addition, median PFS was significantly longer in lenalidomide maintenance therapy patients compared with those not receiving maintenance therapy (42 vs 22 months; *P*<.001). Three-year OS was numerically but not significantly greater with lenalidomide maintenance therapy (88% vs 79%; *P*=.14). There were no PFS differences between maintenance and no maintenance when comparing MEL200 with MPR (*P* for interaction [P_i]=.99), or between MEL200 and MPR when comparing maintenance to no maintenance (P_i=.93).

ASCT versus Lenalidomide-Bortezomib-Dexamethasone

Intergroupe Francophone Du Myelome/Dana-Farber Cancer Institute (IFM/DFCI) 2009 is a 2-group Phase 3 randomized trial that is comparing ASCT with triplet therapy.[17] One group was given 3 cycles of lenalidomide-bortezomib-dexamethasone (RVD) followed by stem cell mobilization with high-dose cyclophosphamide followed by 5 RVD consolidation cycles and lenalidomide maintenance (RVD arm; n=350). The other received 3 RVD induction cycles followed by stem cell collection and ASCT with MEL200 conditioning, followed by 2 RVD consolidation cycles (transplant arm; n=350). Both arms received lenalidomide maintenance for 1-year. ASCT was planned at the time of relapse in the RVD arm.

At the second interim data analysis after a median follow-up of 39 months, PFS results had reached the pre specified significance level for stopping the study, with PFS 3 years post randomization 61% in the transplant arm compared with 48% in the RVD arm (*P*<.0002), with a consistent benefit across subgroups. Overall survival was 88% in both groups (*P*=.25). The extent and frequency of response increased in favor of the transplant arm, with at least a VGPR in 88% of transplant arm compared with 78% of RVD arm patients (*P*=.001), and a complete response in 58% and 46% (*P*<.01) in each group. These data support continuing ASCT as a standard of care for young patients with newly diagnosed multiple myeloma.

As of September 2015, 48 and 54 deaths had occurred in the RVD and transplant arms.[17] Compared with the RVD arm, the transplant group had more deaths due to toxicity (16% vs 8%) and second primary malignancy (11% vs 2%), which is not surprising in the setting of high-dose melphalan. Myeloma was the cause of 65% and 83% of deaths in the transplant and RVD groups.

Minimal Residual Disease

Minimal residual disease (MRD) may become an important trial endpoint, particularly in younger patients and in a setting where CR rates reach 70% and overall survival rates are increasing.[18] Some studies suggest that the absence of MRD may eventually be used as a surrogate endpoint that can be assessed much earlier than PFS and OS.

In IFM 2009, flow cytometry detected 80% MRD negativity after maintenance in the transplant arm, compared with 65% in the RVD arm ($P<.001$).[17] Next generation sequencing (NGS), another technique for measuring MRD, evaluated MRD in 246 IFM 2009 patients, with results classified as negative ($<10^{-6}$), low-positive (10^{-4}-10^{-6}), and positive ($>10^{-4}$).[19] In this patient sample, NGS was a more sensitive technique for predicting PFS. Patients who were MRD negative and positive prior to maintenance therapy had 4-year PFS of 83% and 33%.

Early or Delayed ASCT in the Era of Novel Agents

The possibility that ASCT may be delayed with the advent of novel therapeutic agents is an important research interest. A retrospective study of 290 patients with multiple myeloma who received immunomodulatory-based initial therapy included patients who received thalidomide-dexamethasone (TD) (n=123) or lenalidomide-dexamethasone (LD; n=167) induction before early (≤12 months after diagnosis; n=173) or late (>12 months after diagnosis; n=112) ASCT.[20] Four-year OS from diagnosis was 73% in both early and delayed groups. Patients who received TD had similar 4-year survivals with early (68%) and late (64%) ASCT, as did patients who received LD with early (82%) or late (86%) ASCT. Time to progression (TTP) was 19.7 months for the early and 18 months for the late ASCT group ($P=.4$), whether induction was with TD or LD.

In another retrospective study, patients underwent early (n=136) or delayed (n=86) ASCT.[21] The delayed ASCT group received planned maintenance therapy after stem cell harvest, with the intent to proceed with ASCT at first relapse. After a median follow-up of 32 months, the 5-year overall survival from diagnosis in the early and delayed ASCT patients was 68% and 88% ($P=.106$).

Clinical Trials of Novel Therapies with ASCT

Residual disease is responsible for relapse and a less than optimal duration of disease-free survival after high-dose chemotherapy with ASCT. Accordingly, investigating the potential of novel therapies to improve treatment response and survival outcomes has comprised a major research effort in recent years, with strategies including triplet induction regimens, systematic consolidation, and maintenance therapy.

The availability of new agents increases the number of 3-drug induction combinations that can be tested for their ability to improve patient outcomes. Many, but not all, of these combinations have been associated with superior overall response.[18]

Bortezomib Single Agent Consolidation Therapy: Nordic Myeloma Study Group

A Nordic Myeloma Study Group trial randomized 270 patients with newly diagnosed multiple myeloma to consolidation therapy with 20 doses of bortezomib during 21 weeks starting 3 months after ASCT or to no consolidation.[22] Progression-free survival was 27 and 20 months for bortezomib and control patients ($P=.05$), and OS was similar between groups. A near CR (nCR) or better was achieved by 45% of bortezomib compared with 35% of control group patients ($P=.055$). Response improvements after randomization were observed in 57% of bortezomib compared with 36% of control patients ($P=.007$). Quality of life (QOL) was similar between groups. This study demonstrated that single agent bortezomib consolidation therapy after ASCT in bortezomib-naïve patients improved PFS without compromising QOL.

Bortezomib-thalidomide-dexamethasone Induction and Consolidation: Total Therapy 3

Three Total Therapy (TT) clinical trials were performed that investigated active treatment regimens starting with induction.[23] Protocols varied considerably among the 3 studies; however, all used melphalan-based tandem transplants. Phase 2 TT1 (n=231) included 3 VAD (vincristine-doxorubicin-dexamethasone) induction cycles, Phase 3 TT2 (n=668) included an experimental arm with thalidomide (TT2+Thal) added from induction through consolidation and maintenance, and Phase 2 TT3 (n=303) included 2 cycles of bortezomib-thalidomide-dexamethasone (VTD)-PACE (cisplatin-doxorubicin-cyclophosphamide-etoposide) for induction and consolidation, with VTD for first year maintenance and TD in years 2 and 3.

Data compiled after a median follow-up of 17.1, 8.7, and 5.5 years for TT1, TT2, and TT3 provided estimates of 35%, 52%, 59%, and 79% 5-year CR in TT1, TT2-Thal, TT2+Thal, and TT3. Most comparisons of OS, PFS, CR duration, and TTP were consistent with improvements in patient outcomes with successive TT protocols that introduced more intensive induction therapy before tandem transplantation, with consolidation chemotherapy after transplantation. These data demonstrate that incorporating these drugs into transplant protocols has had considerable impact on patient outcomes.

Bortezomib-thalidomide-dexamethasone Induction and Consolidation Therapy: GIMEMA Italian Myeloma Network

A Phase 3 randomized GIMEMA network trial enrolled patients with newly diagnosed myeloma to compare bortezomib-thalidomide-dexamethasone (VTD) with TD as induction therapy before double ASCT, and as consolidation therapy after, given as two 35-day cycles.[24] In the per protocol analysis (VTD, n = 160; TD, n = 161), CR/nCR rates before starting consolidation were not significantly different in the VTD and TD groups (63.1% vs. 54.7%). Post consolidation data from patients who completed the allocated treatment revealed significantly higher rates of CR (60.6% vs 46.6%; $P=.012$), CR/nCR (73.1% vs 60.9%; $P=.020$), and upgrade to CR post-consolidation (30.5% vs 16.7%; $P=.03$) for VTD compared with TD patients. Landmark analysis after a median follow-up of 30 months from the start of consolidation revealed 3-year PFS in VTD and TD patients of 60% and 46% ($P=.042$), with a 3-year probability of relapse or progression of 39% and 52 % ($P=.040$). Superior PFS was observed with VTD compared with TD consolidation across poor prognosis subgroups including t(4;14) and/or del(17q), del(13q), beta-2 macroglobulin (β_2-M) >3.5 mg/L, LDH >190 U/L, and international staging system (ISS) stages II or III. The results of this study established incorporating bortezomib into consolidation therapy after ASCT, despite re-administration after inclusion in induction therapy before ASCT.

Bortezomib-doxorubicin-dexamethasone Induction and Bortezomib Maintenance: HOVON-65

The Phase 3 randomized HOVON-65 trial was another classic study that investigated the survival benefit of adding bortezomib during induction and then during maintenance given every 2 weeks for 2 years in newly diagnosed multiple myeloma.[25] Vincristine-doxorubicin-dexamethasone followed by tandem transplant and thalidomide maintenance was compared with bortezomib-doxorubicin-dexamethasone followed by double transplant and bortezomib maintenance in 824 patients with Stage II or

III multiple myeloma. CR/nCR was superior after induction that included bortezomib compared with vincristine (31% vs 15%; *P*<.001) and bortezomib compared with thalidomide maintenance (49% vs 34%; *P*<.001). After a median follow-up of 41 months, PFS was superior in the group receiving bortezomib during induction and maintenance (35 vs 28 months; *P*=.002).

In the subgroup of high-risk patients with creatinine >2 mg/dL at baseline, the bortezomib group had superior median PFS (30 months vs 13 months; *P*=.004) and OS (54 vs 21 months; *P*<.001).[25] High-risk patients with 17p deletion in the bortezomib group also had superior PFS (26 vs 12 months; *P*=.024) and 3-year OS (69% vs 17%; *P*=.028).[26]

Lenalidomide Single Agent Maintenance

Several trials have studied outcomes with lenalidomide maintenance after ASCT. An IFM network study compared lenalidomide maintenance therapy with placebo, given until relapse in 614 patients.[27] After a median follow-up of 45 months from randomization, the 4-year PFS was 60% vs 33%, with OS similar between groups (73% vs 75%).

A CALGB study randomized 460 patients with stable disease or a marginal, partial, or complete response 100 days after ASCT to lenalidomide or placebo until disease progression.[28] The median time to progression (TTP) was significantly longer in the lenalidomide group compared with the placebo group (46 vs 27 months; *P*<.001).

Maintenance Therapy in Patients Who Achieve CR after ASCT or Conventional Chemotherapy

Data from 4 Phase 3 trials of 1964 patients with newly diagnosed multiple myeloma were retrospectively analyzed to explore the impact of continuous maintenance therapy in patients who achieved a complete response.[29] Data were pooled from 5 trials of ASCT-eligible patients and 2 of elderly ASCT-ineligible patients, which revealed a PFS benefit with maintenance in patients receiving either ASCT (62 vs 41 months; HR 0.45, *P*=.02) or conventional chemotherapy (53 vs 21 months; HR 0.45, *P*<.001). The PFS was longer in transplant compared with no transplant patients (59 vs 42 months; *P*=.01). Multivariate analysis revealed independent effects of both maintenance therapy and ASCT on PFS and OS in patients achieving CR.

Table 3. Patient Response After Adding an Additional Drug to RVD

Response	RVD N=66	RVDD N=70	VDCR N=41
CR + nCR	39% (51%)*	33%	32%
≥VGPR	67% (75%)*	59%	59%
≥PR	100%	97%	93%

*Phase 2 cohort

Key: CR – complete response; nCR – near CR; PR – partial response, RVD – lenalidomide-bortezomib-dexamethasone, RVDD – RVD with pegylated liposomal doxorubicin, VDCR - RVD plus cyclophosphamide VGPR – very good PR

Source: Richardson PG, et al. *Blood.* 2010;116:679-686; Jakubowiak AJ, et al. *Blood.* 2011;118:535-543; Kumar S, et al. *Blood.* 2009:114 Abstract 127; Kumar S, et al. *Leukemia.* 2010;24:1350-1356; Kumar S, et al. *Blood.* 2012;119:4375-4382.

Lenalidomide-Bortezomib-Dexamethasone Regimen

Lenalidomide-dexamethasone (RD) is a standard of care for patients with previously untreated multiple myeloma without an intent for immediate ASCT. The RD was compared with lenalidomide-bortezomib-dexamethasone (RVD) induction in SWOG Phase 3 trial S0777.[30] After induction, patients were maintained on RD until progressive disease (PD), toxicity, or withdrawal. After a median 385 days on maintenance, CR, VGPR, and ORR (PR or better) were achieved by more RVD compared with RD patients. The RVD compared with RD group had clinically meaningful improvement in median PFS (43 vs 30 months; HR 0.712; *P*=.0037) and longer OS (75 months v. 64 months; HR 0.709; *P*=.0250). Neuropathy grade ≥3 was observed more frequently in RVD compared with RD patients (24% vs 5%; *P*<.0001). The RVD had an acceptable safety and tolerability profile despite this adverse event (AE).

A single-arm Phase 2 study of RVD enrolled 31 previously untreated patients who received 3 RVD induction cycles followed by stem cell harvest and ASCT using melphalan 200 mg/m^2 conditioning.[31] Nonprogressive patients received 2 RVD consolidation cycles following the same induction schedule using the last tolerated dose. Maintenance lenalidomide was given for 1 year. The depth of response improved at each Phase, and MRD negativity increased from 16% after induction to 54% after ASCT, 58% after consolidation, and 68% after maintenance.

Using a combination of RVD has been associated with up to 100% of newly diagnosed patients achieving at least a PR. Adding doxorubicin or cyclophosphamide to the RVD base in efforts to improve proportions of patients with at least a VGPR have not been successful (Table 3), although treatments were active in patients with adverse cytogenetics.[32-36]

Tolerability of Combination Treatments

Toxicity was increased in the combination treatments. Hematologic toxicity was more severe with the addition of chemotherapy, and treatment-related mortality was observed with VDCR. In the RVD combination, the addition of bortezomib to lenalidomide-dexamethasone did not appear to increase the risk of DVT. The risk of peripheral neuropathy was moderately increased over bortezomib alone.

De Novo Strategies to Improve CR: 2nd Generation Proteasome Inhibitor

A Phase 2 study investigated combined carfilzomib-thalidomide-dexamethasone (KTd) as induction/consolidation therapy for previously untreated patients with multiple myeloma eligible for transplant (n=91).[37] Patients were divided among 4 carfilzomib dose levels, given on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. Four cycles of consolidation therapy were provided after ASCT. After a median follow-up from registration of 23.2 months, data available from 3 groups indicate an overall CR of 63% (58% to 67% among dose groups), with at least a PR achieved by 94% to 100% of patients in the 3 groups. There was no difference in response between standard and high-risk subgroups based on cytogenetics and ISS Stage 3 disease.

A Phase 1/2 study of carfilzomib-lenalidomide-dexamethasone (CRd) as a frontline treatment for multiple myeloma was performed in 53 newly diagnosed patients using 3 carfilzomib doses (20, 27, or 36 mg/m^2).[38] After cycle 4, stem cell collection was performed for transplant eligible patients. The 36 mg/m^2 dose was expanded in Phase 2 (n=36). Best responses in the entire cohort included 98% ≥PR, 81% ≥VGPR, 62% ≥nCR, and 42% sCR. Comparing response outcomes in dose groups at equivalent time points, response rates were fairly similar across the 3 doses.

However, sCR showed a dose-response relationship, with 0%, 25%, and 43% sCR after 8 cycles among the 20, 27, and 36 mg/m^2 doses, although interpretation is limited due to the small numbers in each group. The ISS and cytogenetics were not associated with rate or depth of response; however, patient numbers were small.

Newly Approved Drugs Agents for Multiple Myeloma

Improved Formulation: Proplyene Glycol-free Melphalan

A propylene glycol-free formulation of melphalan (PGF-Mel) designed to improve drug solubility and stability was approved in March 2016.[11,39] PGF-Mel is indicated for: 1) use as a high-dose conditioning treatment prior to stem cell transplantation in patients with multiple myeloma; and 2) the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

The new formulation uses a proprietary β-cyclodextrin sulfobutyl ether that is also used in other FDA-approved parenteral drugs. The new formulation allows longer administration duration and slower infusion rates, and there is less risk of renal and cardiac toxicities.

Bioequivalence was supported by a Phase 2a cross-over study.[40,41] Transplant candidate patients (n=24) were randomized to receive PGF-Mel or standard melphalan on day -3 and the alternative formulation on day -2 prior to ASCT. Pharmacokinetic studies of blood samples obtained at 10 post-dose time points up to 8 hours after dosing revealed bioequivalence of PGF-Mel with the standard formulation, with maximum plasma concentration and area under the plasma concentration-time curve approximately 10% greater after PGF-Mel administration compared with the standard formulation (Figure 2).

A Phase 2b study in patients undergoing ASCT confirmed the safety and efficacy of the new formulation.[39] Patients (n=61: 5 with relapsed disease; 56 newly diagnosed) were administered the new formulation in 100 mg/m^2 doses on days -3 and -2 prior to transplantation. At day 100, all patients had a response, with stringent CR (sCR), CR, and VGPR observed in 13%, 8%, and 61% of patients.

The most common non-hematologic AEs of all grades were diarrhea (93%), nausea (90%), fatigue (77%), hypokalemia (74%), and vomiting (64%). Most grade 3/4 AEs were hematologic (neutropenia, leukopenia, lymphopenia, thrombocytopenia in 98% to 100% of patients; anemia in 66% of patients).

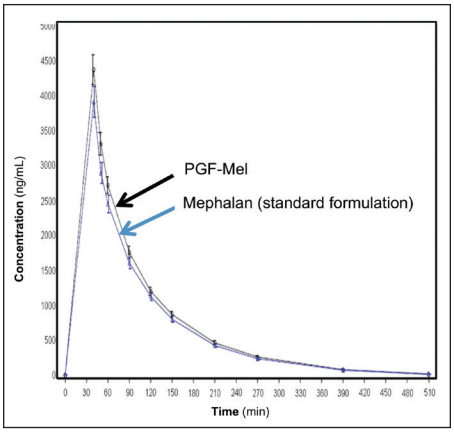

Figure 2. Propylene Glycol-free Melphalan (PGF-Mel) Bioequivalence with Melphalan

Source: Aljitawi OS, et al. *Bone Marrow Transplant.* 2014;49:1042-1045.

Oral Proteasome Inhibitor: Ixazomib

Ixazomib, the first FDA-approved oral PI, is indicated in combination with lenalidomide and dexamethasone for patients who have received at least one prior therapy.[42] Ixazomib was also studied as therapy for newly diagnosed myeloma as a weekly formulation in an all-oral combination therapy with the 2 additional drugs.[43] A Phase 1 dose escalation study was followed by a Phase 2 study using the dose recommended from Phase 1. Patients received up to 12 induction cycles of the combination. Stem cell collection was allowed after 3 cycles, and ASCT was deferred until after 6 cycles. Patients who completed 12 induction cycles were allowed to continue on ixazomib maintenance, given at the last tolerated induction dose, until progression or unacceptable toxicity occurred. With a median follow-up of 14.3 months, ORR (≥PR) was noted in 92% of patients, with response deepening as the number of cycles increased. Depth of response improved for 5 of 25 patients (20%) while on ixazomib maintenance therapy.

After a median treatment duration of 26.6 months in Phase 2 study subjects, the 21 patients who received maintenance therapy had responded to induction therapy, of whom 52% had CR/sCR (Table 4).[44] Treatment response was rapid, with a median 0.99 months (range from 0.92 to 5.78) to first response (≥PR). Median time to best response was 7.46 months (range from 1.02 to 24.74). Ten (48%) of the patients improved their response during maintenance.

Table 4. Response on Ixazomib Maintenance (n=21)

	PR	≥VGPR	≥nCR	≥CR	sCR
Proportion with outcome	29	71	62	52	19

Key: CR – complete response, nCR – near CR, PR – partial response, sCR – stringent CR, VGPR – very good PR

Source: Kumar S, et al. Presented at: ASH 2014; San Francisco; Abstract 82.

HDAC Inhibitor: Panobinostat

Panobinostat was approved by the FDA in February 2015 with an indication for relapsed and refractory myeloma in combination with bortezomib-dexamethasone.[45] Panobinostat was also studied in combination with lenalidomide-bortezomib-dexamethasone in a Phase 2 trial of newly diagnosed myeloma.[46] Of 39 patients who completed 4 cycles and were evaluable for efficacy, the ORR was 94%, with a CR/nCR in 46% of patients. There was no effect of panobinostat on stem cell collection/mobilization or on the quality of the graft. These results suggest that a randomized trial is warranted.

Monoclonal Antibodies

Elotuzumab

Elotuzumab is a SLAMF7-directed immunostimulatory antibody that was approved by the FDA in November 2015 for use in combination with lenalidomide and dexamethasone for treating patients with multiple myeloma who have received 1 to 3 prior therapies.[47] Trials of elotuzumab in patients with ASCT are ongoing.[48]

Daratumumab

Daratumumab is a CD38 antibody that was also approved by the FDA in November 2015 for treating patients with multiple myeloma who have received ≥3 prior lines of therapy including a PI and an immunomodulatory agent, or who are double-refractory to those agents.[49] Daratumumab was studied in a Phase 1/2 trial in patients with relapsed myeloma or relapsed myeloma that was refractory to ≥2 lines of therapy.[50] In the dose escalation phase, a maximum tolerated dose (MTD) was not identified at doses up to 24 mg/kg. The median time since diagnosis for

the 72 patients in the dose expansion phase (part 2) was 5.7 years, and they had received a median of 4 prior treatments. Patients received 8 (n=30) or 16 (n=42) mg/kg once weekly for 8 doses, twice monthly for 8 doses, and monthly for up to 24 months. The ORR was 36% in the 16 mg/kg group, including 2 CR and 2 VGPR. The median PFS was 5.6 months. These data supported the FDA approval of daratumumab at a recommended dose of 16 mg/kg.[49]

Ongoing Trials

Cassiopeia

The Phase 3 Cassiopeia study will evaluate the effect of adding daratumumab to bortezomib-thalidomide-dexamethasone (VTD) on sCR rate after consolidation therapy and PFS after daratumumab maintenance therapy in transplant eligible previously untreated patients with multiple myeloma.[51] Four induction cycles with VTD with or without daratumumab will precede ASCT, followed by 2 consolidation cycles with the randomized treatment. Responders will be re-randomized to 2-year maintenance with daratumumab or observation only. MRD negativity post ASCT is a secondary outcome. The study has a targeted enrollment of 1080, and an estimated completion date in 2024.

EMN/HOVON

This Phase 3 trial in patients with previously untreated multiple myeloma is comparing: 1) bortezomib-melphalan-prednisone (VMP) with high dose melphalan followed by ASCT; 2) lenalidomide-bortezomib-dexamethasone (RVD) as consolidation versus no consolidation; and 3) single versus tandem high-dose melphalan (HDM) with ASCT.[52] Four cycles of VCD induction and stem cell apheresis are followed by randomization to either 4 cycles of VMP or 1 or 2 cycles of the high-dose therapy, with a subsequent randomization to RVD or none. All patients will receive lenalidomide maintenance until relapse, and the VMP group will receive HDM/ASCT at relapse. MRD negativity status by the end of consolidation is a secondary outcome. The study has an estimated enrollment of 1500 patients, and a targeted completion date in 2021.

Myeloma Cell Vaccine

Preliminary results from a small patient-specific myeloma vaccine study suggested that a larger study of combining vaccination with maintenance lenalidomide following ASCT was warranted.[53] Accordingly, a Phase 2 trial is planned with a target enrollment of 132 patients who will be randomized among vaccine/granulocyte macrophage colony-stimulating factor (GM-CSF) plus lenalidomide maintenance, lenalidomide alone, or lenalidomide/GM-CSF.[54]

Checkpoint Inhibitors

Recent bone marrow studies showed increased PD-L1 mRNA and surface expression in bone marrow myeloma cells from newly diagnosed and relapsed/refractory multiple myeloma (RRMM) patients compared with plasma cells from healthy donors.[55] The PD-1/PD-L1 blockade abrogated stromal cell-induced multiple myeloma growth, and the effect was enhanced with lenalidomide.

Pembrolizumab, a monoclonal antibody against PD-1, is approved for treating melanoma and NSCLC.[56] A Phase 1 trial of pembrolizumab-lenalidomide and low dose dexamethasone included 50 patients with RRMM who had failed a median of 4 prior therapies, with 72% having previous treatment with ≥3 prior lines of therapy.[57] After a median follow-up of 296 days, the ORR in 17 efficacy analysis patients was 76%, including 5 of 9 (56%) patients who were refractory to lenalidomide. These initial results show promising activity in heavily pretreated patients.

HDAC6 Histone Deacetylase Inhibitor

Ricolinostat, a selective histone deacetylase 6 (HDAC6) inhibitor, is a well-tolerated daily oral medication. Ricolinostat increases Th-1 cytokine production and decreases regulatory T-cells. Ricolinostat also increases central and effector memory for multiple myeloma specific cytotoxic T lymphocyte cytotoxicity, costimulatory molecules, and proliferation. As a single agent, ricolinostat has been shown to stimulate ≥50% autologous myeloma cell lysis. When added to PD-L1 blockade, 90% or greater multiple myeloma cytotoxicity is achieved.

When ricolinostat is combined with bortezomib, lenalidomide, or pomalidomide in patients with RRMM, an approximate 50% response has been observed, including in lenalidomide refractory patients. For example, in a Phase 1b trial of ricolinostat in combination with lenalidomide and dexamethasone, an ORR was observed in 63% of 24 patients with RRMM, with 36% of 11 patients refractory to lenalidomide having ≥PR.[58] Other trials are ongoing.[59]

Summary

Triplet novel combination induction and consolidation therapy increase response to ASCT. Studies of early versus late transplantation with maintenance until progression are ongoing. Novel agents included in induction and consolidation/maintenance therapies post-transplant provide higher MRD negativity and improve PFS. Most regimens include combinations of agents, with several classes represented in approved therapies for multiple myeloma.

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Treating the Relapsed Patient with Multiple Myeloma in the Era of New Therapies

Joseph R. Mikhael, MD, MEd, FRCPC, FACP

Autologous stem cell transplant (ASCT) remains the standard of care for multiple myeloma (MM). However, most patients eventually relapse. A remarkable research effort is addressing the need for improved outcomes, with an unprecedented US Food and Drug Administration (FDA) approval of 3 drugs for treating multiple myeloma in November – December 2015.[1] With these increasing treatment options, clinicians should have an evidence-based strategy for deciding which agents to select for their patients with relapsed myeloma. A practical algorithm developed from both disease and patient-based factors can be useful in this challenging environment.

The standard treatment paradigm begins with dividing patients between transplant-eligible and ineligible status (Figure 1). Prior to consolidation with stem cell transplant or the incorporation of novel agents into consolidation, the initial therapies are very similar between the 2 patient categories.

The three late 2015, FDA approvals, two monoclonal antibodies (mAb) and the first FDA-approved oral proteasome inhibitor (PI), will have an important impact on managing patients with relapsed multiple myeloma. The HDAC inhibitor panobinostat, approved in February 2015, also expands treatment options for this patient population.

Daratumumab: The Phase 2 SIRIUS Trial

CD38 is highly and almost ubiquitously expressed on myeloma cells, and is observed at low levels on normal lymphoid cells, which made it a promising therapeutic target in multiple myeloma.[2-6] Daratumumab is a human monoclonal antibody that binds to CD38-expressing malignant cells, inducing cell death through multiple pathways including complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and direct apoptosis.

The ongoing Phase 2 SIRIUS trial provided the pivotal data supporting the FDA approval of daratumumab for patients who have received at least 3 prior lines of therapy, including a PI and immunomodulatory drug (IMiD), or who are double-refractory to these classes of drugs.[7,8] This 2-stage study randomized 34 patients to daratumumab 8 mg/kg every 4 weeks, or 16 mg/kg every week for 8 weeks, every 2 weeks for 16 weeks, and every 4 weeks thereafter during the first stage. Data from this first stage established the 16 mg/kg dose for the second stage that enrolled an additional 90 patients.

Patients were heavily pretreated, and most were refractory to multiple lines of PI and IMiD treatment (Table 1). Most patients (95%) were double refractory.

In the primary analysis after a median 9.3 month follow-up (range 0.5 to 14.4), a rapid response was observed, with a 1.0 month (range 0.9 to 5.6) median time to first response that deepened with time in approximately one-fourth of patients. The overall response rate (ORR) was 29% in this heavily refractory population, comprised of 17% partial response (PR), 9% very good partial response (VGPR), and 3% stringent complete response (sCR). Responses were observed in prespecified subgroups regardless of prior therapy, ranging from 21% ORR for patients refractory to BORT+LEN+CARF+POM to 30% for patients refractory to PIs and IMiDs. Similarly, responses occurred in subgroups that were not based on prior therapies, including those with high-risk cytogenetics (ORR 20%) and extramedullary disease (ORR 21%).

Median progression free survival (PFS) was 3.7 months (95% confidence interval [CI]: 2.8, 4.6). Approximately two-thirds (65%; 95% CI: 51.2%, 75.5%) of patients were alive after 12 months. At a clinical cutoff 6 months later, median OS was 17.5 months (13.7- not estimable [NE]).

The recommended infusion duration for daratumumab suggest a minimum of 6.5 to 7.6 hours for each administration, with longer time required if an infusion-related reaction (IRR) occurs.[7] In the SIRIUS study, IRRs were common, and were predominantly grade 1/2 (43% of patients), grade 3 in 5%, no grade 4 reactions were observed.[8] Over 90% of the IRRs occurred during the first infusion, with 7% of patients having an IRR at more than 1 infusion. The most common IRR included nasal congestion (12%), throat irritation (7%), and cough, dyspnea, chills,

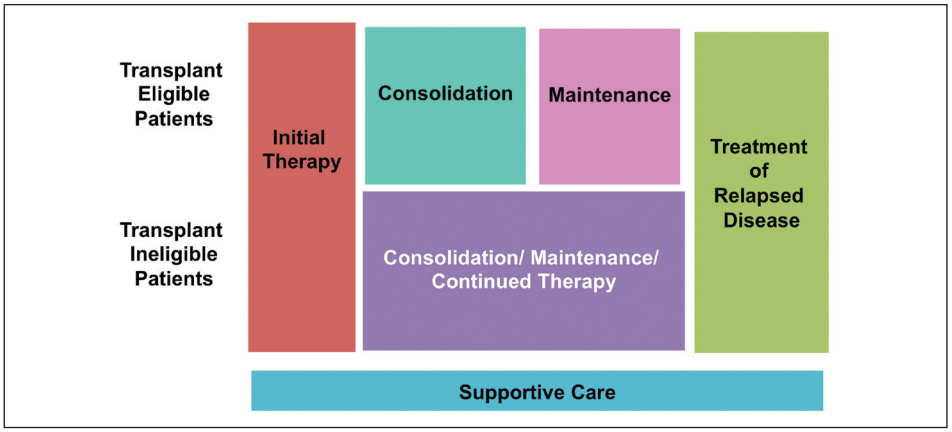

Figure 1. Managing Myeloma: The Components

Source: FDA. Available at: http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm. Accessed March 25, 2016.

Table 1. SIRIUS Trial: Baseline Refractory Status to Prior Therapies

Refractory to:	% (n = 106)
Last prior therapy	97
Proteasome Inhibitor and immunomodulatory drug	95
Bortezomib (BORT)	90
Carfilzomib (CARF)	48
Lenalidomide (LEN)	88
Pomalidomide (POM)	63
Alkylating agent	77
BORT+LEN	82
BORT+LEN+CARF	40
BORT+LEN+POM	54
BORT+LEN+CARF+POM	31
BORT+LEN+CARF+POM+Thalidomide	11

Source: Lonial S, et al. *Lancet.* 2016;http://dx.doi.org/10.1016/S0140-6736(15)01120-4

and vomiting (6% each). No patients discontinued treatment due to an IRR or daratumumab treatment-related adverse events (TRAEs).

Conclusions derived from the SIRIUS study support that this fully human mAb has encouraging efficacy in heavily pretreated and refractory multiple myeloma patients who have exhausted other therapeutic options. Efficacy was consistent across all subgroups. Daratumumab was well-tolerated, with IRRs typically grade 1/2, which were usually observed during the first infusion. Several Phase 1 through 3 studies of daratumumab are ongoing, including investigations of combinations with other therapies.[9] The PI and IMiDs may be logical partners for daratumumab due to lack of overlapping toxicities, and studies are underway exploring those combinations. These results suggest that daratumumab may become part of a new standard of care in this setting.

Elotuzumab: The Phase 3 ELOQUENT-2 Study

Elotuzumab is a humanized IgG1 immunostimulatory monoclonal antibody with a dual mechanism of action.[10-13] Elotuzumab specifically targets signaling lymphocyte activation molecule-F7 (SLAMF7, also known as cell surface marker 1), a glycoprotein highly expressed on myeloma and natural killer cells but not on normal tissues. Binding to SLAMF7 directly activates natural killer cells, but not myeloma cells. Elotuzumab also activates natural killer cells via CD15, enabling selective killing of myeloma cells through antibody-dependent cell-mediated cytotoxicity (ADCC), with minimal effects on normal tissue.

The Phase 3 ELOQUENT-2 study enrolled patients with RRMM who had 1 to 3 prior lines of therapy, with randomization to elotuzumab-lenalidomide-dexamethasone (elotuzumab group; n=321) or to lenalidomide-dexamethasone (control group; n=325).[14] A 1-year PFS of 68% in the elotuzumab compared with 57% in the control group decreased to 41% and 27% at 2 years. A elotuzumab benefit was maintained through 3 years, with PFS of 26% and 18%.[15] Median PFS was 19.4 compared with 14.9 months (hazard ratio [HR] 0.73; 95% CI: 0.60, 0.89; *P*=.0014). Benefits were consistent across key elotuzumab subgroups, including elderly and cytogenetic high-risk patients. Interim OS showed a strong trend for a benefit in the elotuzumab group (43.7 vs 39.6 months; upper limit not reached; *P*=.0257), and ORR was 79% and 66% (*P*=.0002).

Elotuzumab was well-tolerated, with IRR occurring in 10% of elotuzumab group patients. Most were grade 1/2 adverse events (AEs), and primarily included pyrexia, chills, and hypertension, with 1% grade 3. Most IRRs (70%) occurred with the first dose. Infusion was interrupted in 5% of patients for a median of 25 (range, 5 to 70) minutes. Two patients (1%) discontinued due to IRR. The elotuzumab group had a modest increase in AEs compared with the 2-drug regimen. Increased autoimmunity and immune dysregulation were not observed, and infection rates were similar in the 2 groups in comparisons based on drug exposure.

In conclusion, the ELOQUENT-2 study showed a significant and clinically meaningful increase in PFS and ORR when elotuzumab was added to lenalidomide-dexamethasone. The PFS benefit in the elotuzumab group was consistent across key subgroups. The AEs were not substantially increased with elotuzumab compared with treatment with lenalidomide-dexamethasone alone. This study provided the first Phase 3 data supporting a PFS benefit of an mAb in combination with lenalidomide-dexamethasone in patients with RRMM. Several other ongoing elotuzumab studies are exploring a variety of patient populations, drug combinations, and regimens.[16]

Ixazomib: The Phase 3 TOURMALINE-MM1 Study

Protease inhibitors have become part of the backbone of multiple myeloma therapy; however, long-term treatment can be limited by toxicities, development of drug resistance, and the need for frequent clinic attendance.[17] The PI ixazomib, approved by the FDA in November 2015 as a weekly oral formulation, is indicated in combination with lenalidomide and dexamethasone (IRd) for treating patients with multiple myeloma who have received ≥1 prior therapy.[18] This combination provides the first all-oral triplet regimen containing a PI and an IMiD.

Data from the first interim analysis of the Phase 3 TOURMALINE-MM study provided

Table 2. TOURMALINE: Ixazomib Treatment Response

Response rates	IRd (N=360)	Placebo-Rd (N=362)	*P*-value
Confirmed ORR (≥PR), %	78.3	71.5	.035
CR+VGPR, %	48.1	39.0	.014
Response categories			
CR, %	11.7	6.6	.019
PR, %	66.7	64.9	–
VGPR, %	36.4	32.3	–
Median time to response, months	1.1	1.9	–
Median duration of response, months	20.5	15.0	–
Median TTP, months	21.4	15.7	.007

KEY: CR – complete response, IRd – ixazomib-lenalidomide-dexamethasone, ORR – overall response rate, PR – partial response, Rd – lenalidomide-dexamethasone, TTP – time to progression, VGPR – very good PR

SOURCE: Moreau P, et al. *Blood.* 2015;126; Abstract 727.

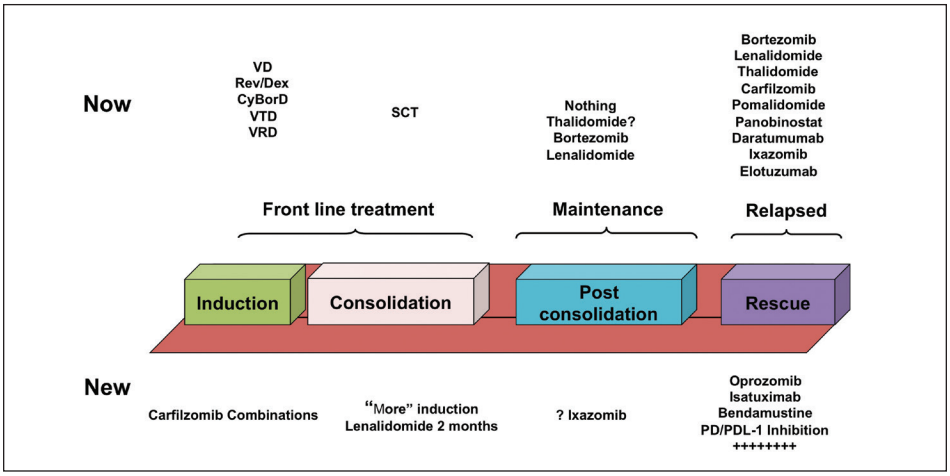

Figure 2. Treatment Sequence in Multiple Myeloma

Key: CyBorD – cyclophosphamide/bortezomib/dexamethasone, Rev/Dex – lenalidomide/dexamethasone, SCT – stem cell transplantation, VD – bortezomib/dexamethasone, VTD – bortezomib/thalidomide/dexamethasone, VRD – bortezomib/lenalidomide/dexamethasone

Source: Ocio EM, et al. *Leukemia.* 2014;28:525-542.

Table 3. mSMART Regiment Abbreviations

Regimen	Constituent Drugs
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
CyBorD	cyclophosphamide, bortezomib, dexamethasone
Dara	daratumumab
ICd	ixazomib, cyclophosphamide, dexamethasone
IRd	ixazomib, lenalidomide, dexamethasone
KPd	carfilzomib, pomalidomide, dexamethasone
KRd	carfilzomib, lenalidomide, dexamethasone
PAD	bortezomib, adriamycin, dexamethasone
Pom-dex	pomalidomide, dexamethasone
PVd	pomalidomide, bortezomib, dexamethasone
RAD	lenalidomide, adriamycin, dexamethasone
Rd-Elo	lenalidomide, dexamethasone, elotuzumab
VDD	bortezomib, doxorubicin, dexamethasone

Source: mSMART. https://http://www.msmart.org/home.html. Accessed March 25, 2016.

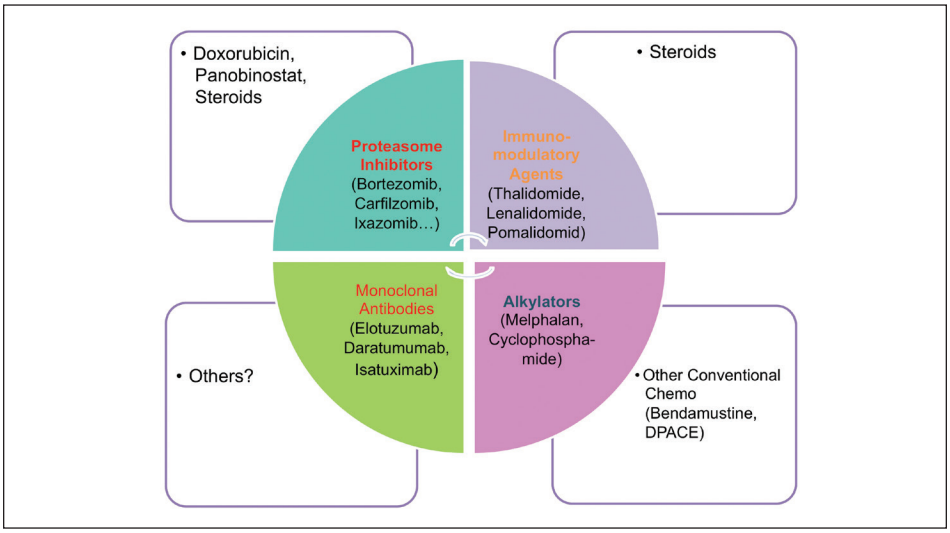

Figure 3. The Four Pillars of Myeloma Therapy

Source: Ocio EM, et al. *Leukemia*. 2014;28:525-542.

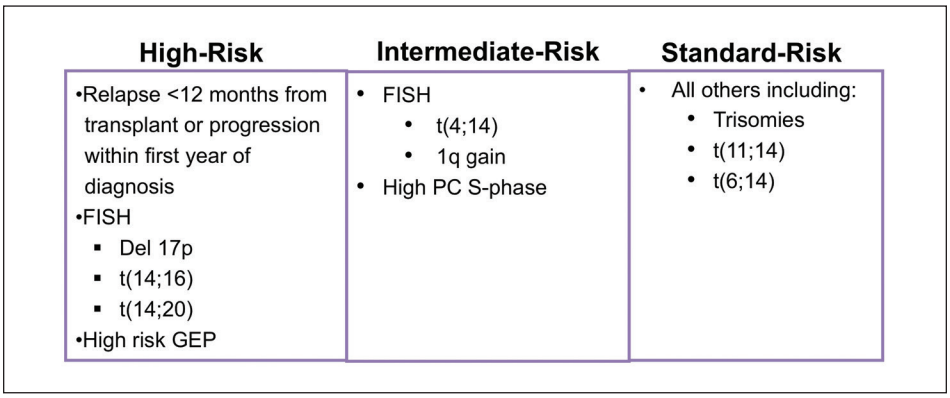

Figure 4. mSMART 2.0: Classification of Relapsed MM

Key: FISH - fluorescence in situ hybridization, GEP – gene expression profile, PC – plasma cells

Source: Dispenzieri et al. *Mayo Clin Proc*. 2007;82:323-341; Kumar et al. *Mayo Clin Proc*. 2009 84:1095-1110; Mikhael et al. *Mayo Clin Proc*. 2013;88:360-376.

the pivotal data supporting the FDA approval of ixazomib.[17,19] Patients (n=722) with RRMM were randomized between IRd and placebo-lenalidomide-dexamethasone, administered in 28-day cycles that were repeated until progression or unacceptable toxicity occurred. In a median follow-up of approximately 15 months, median PFS was significantly longer with IRd compared with the placebo group (20.6 vs 14.7 months; *P*=.012). Consistent benefit was observed across prespecified patient subgroups, including patients with standard versus high-risk cytogenetics. After a median follow-up of 23 months, the median OS had not been reached in either arm.

The superior ORR (≥PR) observed in the IRd group was contributed to by an increased CR rate compared with placebo group patients (11.7% vs 6.6%; *P*=.019) (Table 2). Median time to progression (TTP) was significantly greater in the IRd compared with the placebo group.

Adverse events in the IRd group were consistent with reported safety profiles for the individual drugs and were more common in the IRd group; however, they were primarily low-grade, manageable, and without clinical complications. The higher frequency of grade ≥3 AEs was primarily due to thromobocytopenia. Patient reported quality of life was similar between groups. Peripheral neuropathies were observed at a lesser frequency (27%) than observed with bortezomib (43%).[20]

In conclusion, IRd was associated with a significant and clinically meaningful improvement in PFS compared with Rd in patients with RRMM. Adding ixazomib to Rd was associated with limited additional toxicity, and a favorable lack of neuropathy. The combination may provide a valuable standard of care option, particularly when an all-oral regimen is preferable in older or less fit patients.

Isatuximab: In the Pipeline

Isatuximab is an investigational humanized anti-CD38 antibody that is also being studied in Phase 1 and 2 trials as a single agent and in combined therapy for patients with relapsed/refractory multiple myeloma.[21,22] The infusion time with isatuximab is shorter than that required for daratumumab.[23]

The New Treatment Landscape for Multiple Myeloma

A significant proportion of persons with multiple myeloma never achieve a cure; accordingly, physicians benefit from having multiple options that they can tailor treatment to patient characteristics at each stage of the disease (Figure 2). These options also vary among drug classes as newer agents, such as monoclonal

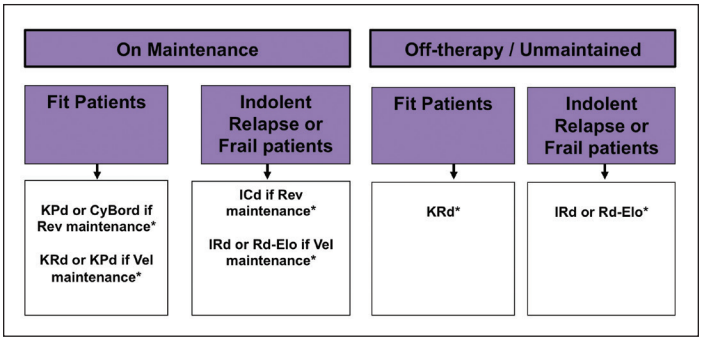

Figure 5. First Relapse Off-Study

*Consider salvage auto SCT in patients eligible for ASCT who have not had transplant before; Consider 2nd auto SCT if eligible and >18 months unmaintained or >36 months maintained response to first auto.

Source: Dispenzieri et al. *Mayo Clin Proc.* 2007;82:323-341; Kumar et al. *Mayo Clin Proc.* 2009 84:1095-1110; Mikhael et al. *Mayo Clin Proc.* 2013;88:360-376.

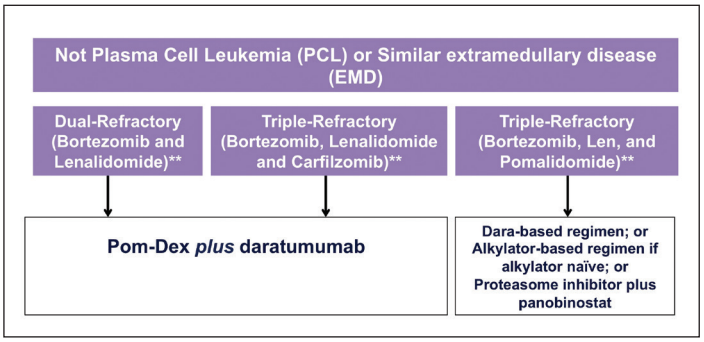

Figure 6. Second or Later Relapse* Off-Study

*If single refractory, refer to First Relapse algorithm.

**Auto transplant is an option, if transplant candidate and feasible.

Source: Dispenzieri et al. *Mayo Clin Proc.* 2007;82:323-341; Kumar et al. *Mayo Clin Proc.* 2009 84:1095-1110; Mikhael et al. *Mayo Clin Proc.* 2013;88:360-376.

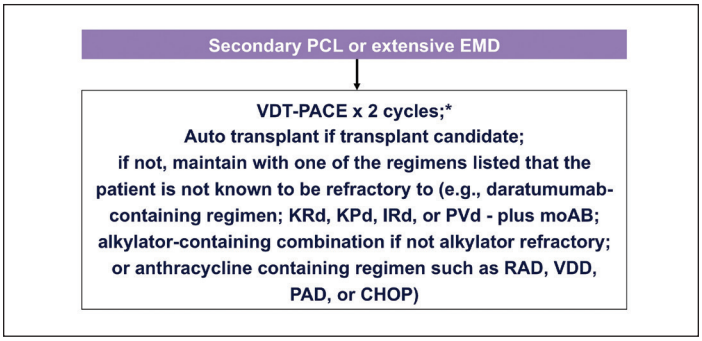

Figure 7. Second or Later Relapse – Off-Study

*CVAD or similar regimen can be used in place of VDT-PACE in older patients or patients with poor functional status.

Source: Dispenzieri et al. *Mayo Clin Proc.* 2007;82:323-341; Kumar et al. *Mayo Clin Proc.* 2009 84:1095-1110; Mikhael et al. *Mayo Clin Proc.* 2013;88:360-376.

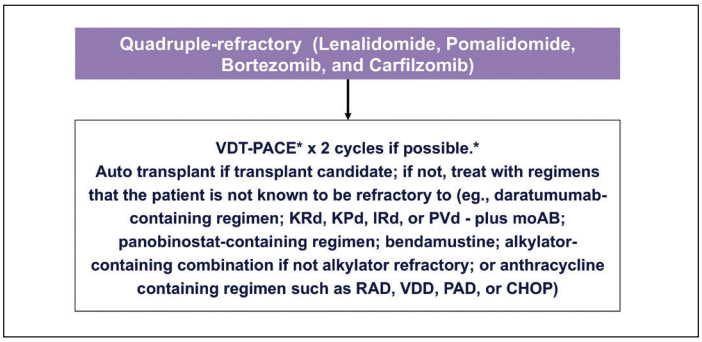

Figure 8. Second or Later Relapse – Off-Study

*CVAD or similar regimen can be used in place of VDT-PACE in older patients or patients with poor functional status.

Source: Dispenzieri et al. *Mayo Clin Proc.* 2007;82:323-341; Kumar et al. *Mayo Clin Proc.* 2009 84:1095-1110; Mikhael et al. *Mayo Clin Proc.* 2013;88:360-376.

antibodies, become available, with more options anticipated as the development and approval of new agents and new combinations continues.[24]

Presently, there are 4 main pillars for myeloma therapy (Figure 3). Alkylators remain an important pillar in the care of patients with myeloma. IMiDs, PIs, and the recent FDA approval of mABs complete the 4 pillars. Other agents, such as steroids, doxorubicin and other conventional chemotherapeutic agents, and the HDAC panobinostat, may be considered as adjunctive, or add-on therapy, that can be used in conjunction with these pillars.

mSMART: Mayo Stratification for Myeloma and Risk-adapted Therapy

A useful algorithm was developed by Mayo Clinic that can help clinicians who do not have clinical trials available to enroll their patients.[25] A dedicated website provides detailed resources to help with decision-making (msmart.org). The mSMART strategy classifies relapsed patients with multiple myeloma into high, intermediate, and standard risk (Figure 4).[26-28] Highest risk patients are those who have relapsed within a year of transplant; patients with del 17p, t(14;16), or t(14;20) on fluorescence in situ hybridization (FISH) molecular assay; or those who have the cardinal features of a high-risk gene expression profile. Intermediate risk patients are primarily those with t(4;14). Patients who do not qualify for high or intermediate risk are considered standard risk. The division of patients among high-, intermediate-, and standard-risk is approximately 20%, 20%, and 60%.

The algorithms list treatment options based on patient and disease characteristics, acknowledging that the best management is enrollment in a clinical trial. Regimens are represented in the algorithms with common abbreviations (Table 3). In addition to relapsing myeloma, treatment guidelines are provided for newly diagnosed myeloma, bisphosphonate use in myeloma, supportive care, vitamin D replacement, Waldenstrom's macroglobulinemia, and amyloid light-chain (AL) amyloidosis.

Most patients are given maintenance therapy; however, a subset of patients do not require maintenance treatment. Patients who relapse while on maintenance who are generally fit are usually given a 3-drug combination such as carfilzomib-lenalidomide-dexamethasone (KRd) or

cyclophosphamide-bortezomib-dexamethasone (CyBorD) (Figure 5). For patients who have been on bortezomib maintenance, carfilzomib-lenalidomide-dexamethasone (KRd) or carfilzomib-pomalidomide-dexamethasone (KPd) treatment is suggested at relapse. For frail patients, ixazomib is recommended either with cyclophosphamide (ICd) or lenalidomide (IRd), depending on their previous maintenance therapy.

For patients off therapy, carfilzomib-lenalidomide-dexamethasone (KRd) has the most robust data, and is an appropriate choice. Consideration can also be given to IRd or elotuzumab-lenalidomide-dexamethasone (Rd-Elo).

Options change as patients progress through dual and triple refractory status. Recommended treatments are divided between patients with and without plasma cell leukemia (PCL) or similar extramedullary disease (EMD) (Figures 6, 7). Treatment for quadruple-refractory patients follows a separate algorithm (Figure 8).

Use of a Second ASCT for Relapsed Myeloma

ASCT remains a standard of care in first-line therapy for myeloma in eligible patients. As many of those patients will experience a deep and durable response to ASCT, a second ASCT can be considered at relapse. Most transplant centers will consider a second ASCT if 3 criteria are met based on experience with the first ASCT: 1) the patient must have had a benefit (ie, deepened response) from the first ASCT; 2) the ASCT must have been well-tolerated; and 3) at least 18 to 24 months of PFS must have been achieved following the first ASCT (although a bare minimum of 12 months is required).[29-31] The second ASCT may be expected to achieve a PFS that is 50% to 70% of what was observed following the first ASCT.

Summary

Therapy for myeloma has undergone remarkable advancement, with radical changes occurring in the last 6 months. Monoclonal antibody therapy has become an important part of the clinician's armamentarium for treating relapsed patients, and is expected to provide benefit across the spectrum of disease stages. Oral proteasome inhibition is now able to deliver the same treatment mechanism with less toxicity and greater convenience. Optimal combinations and sequences are not yet clearly defined, but the ability to individualize therapy is expanding considerably.

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1. **Which of the following statements is true?**
   A. Triplet novel combination induction therapy increases ASCT response.
   B. Novel therapies used as induction and as consolidation/maintenance post-transplant have not achieved improved progression-free survival.
   C. Trials of early versus late transplantation with maintenance until progression have been discontinued due to futility.
   D. Monoclonal antibodies, histone deacetylase inhibitors, and programmed cell death protein 1 are not currently being integrated into the transplant paradigm.

2. **The GIMEMA Italian Myeloma Network showed that after a median followup of 30 months from the start of consolidation 3-year PFS with bortezomib-thalidomide-dexamethasone therapy was:**
   A. 10%
   B. 20%
   C. 30%
   D. 60%

3. **In the subgroup of high-risk patients with creatinine >2 mg/dL at baseline, the Phase 3 HOVON-65 study showed that compared to the vincristine group:**
   A. The bortezomib group had superior median PFS.
   B. The bortezomib group had higher mortality rate than placebo PFS.
   C. High-risk patients with 17p deletion in the bortezomib group had inferior PFS.
   D. High-risk patients with 17p deletion in the bortezomib group had inferior 3-year OS.

4. **What is the mechanism of action of ixazomib?**
   A. SLAMF7-directed immunostimulatory antibody
   B. CD 38 monoclonal antibody
   C. Oral proteasome inhibitor
   D. HDAC inhibitor

5. **What is the mechanism of action of elotuzumab?**
   A. SLAMF7-directed immunostimulatory monoclonal antibody
   B. CD 38 monoclonal antibody
   C. Oral proteasome inhibitor
   D. HDAC inhibitor

6. **Which of the following drugs is a monoclonal antibody against PD-1?**
   A. Ricolinostat
   B. Pembrolizumab
   C. Daratumumab
   D. Panobinostat

7. **Which of the following best describes the results of the Phase 3 ELOQUENT-2 study in patients with relapsing-remitting multiple myeloma?**
   A. A lower 1-year and 2-year PFS in the elotuzumab to the control group
   B. A higher 1-year and lower 2-year PFS in the elotuzumab to the control group
   C. The same 1-year and 2-year PFS in the elotuzumab to the control group
   D. A higher 1-year and 2-year PFS in the elotuzumab to the control group

8. **Which of the following drugs is one of the 4 main pillars for myeloma therapy?**
   A. Dexamethasone
   B. Doxorubicin
   C. Alkylators
   D. Panobinostat

9. **According to the mSMART strategy, which of the following patients would be classified as high risk?**
   A. Patients with t(6;14)
   B. Patients with t(4;14).
   C. Patients with t(11;14)
   D. Relapse within one year of transplant

10. **You are treating a 55-year-old male with FISH t(14:20) who has progressed within 11 months of his diagnosis. Based on the Mayo mSMART strategy, your preferred treatment regimen would be chosen from the:**
    A. High-risk category
    B. Low-risk category
    C. Intermediate-risk category
    D. Standard-risk category

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