

# Clinical Roundtable Monograph

Clinical Advances in Hematology & Oncology

April 2011

## Emerging Treatment Options for Relapsed and Refractory Multiple Myeloma

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A CME Activity  
Approved for 1.0  
AMA PRA  
Category 1 Credit(s)<sup>TM</sup>

**Release Date:** April 2011

**Expiration Date:** April 30, 2012

**Estimated time to complete activity:** 1 hour

**Project ID:** 7895

**Abstract:** Multiple myeloma is a major hematologic malignancy, with an incidence of over 20,000 new diagnoses in the United States each year. Historically, a lack of effective therapies led to a poor patient prognosis. However, the introduction of new agents over the past decade has improved the treatment landscape for these patients, resulting in improved responses and prolonged progression-free and overall survival. Unfortunately, though, nearly all multiple myeloma patients go on to experience relapsed disease. The definition of this progression has also evolved with a growing understanding of the biology of multiple myeloma as well how the disease responds to these newer agents. While refractory multiple myeloma is considered to be a disease that does not respond to a particular therapy, the new definition of relapsed and refractory multiple myeloma includes patients who show disease progression within 60 days of discontinuing therapy. These new definitions are an important consideration when interpreting both previously reported and ongoing clinical trial data. Another major issue in the management of relapsed and refractory multiple myeloma is how to treat patients after they no longer respond to thalidomide, lenalidomide, and bortezomib. Regarding this issue, a number of novel agents are now in clinical trial development; many of them show indications of significant activity, even in heavily pretreated patients. Thus, the introduction of these newer agents has the potential to again make a major impact on multiple myeloma patient outcomes.

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Supported through an educational grant from Onyx Pharmaceuticals



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## Target Audience

This activity has been designed to meet the educational needs of oncologists and other health care professionals who treat patients with multiple myeloma.

## Statement of Need/Program Overview

Multiple myeloma remains the second most common hematologic malignancy in the United States, after non-Hodgkin lymphoma. Historically, multiple myeloma has been a difficult and frustrating disease for patients and their health care providers. Despite the availability of numerous therapeutic options, multiple myeloma remains essentially incurable. Nearly all patients relapse and eventually become refractory to existing treatments. It has recently been suggested that survival time could double with newer therapies. Clinical trials in relapsed/refractory multiple myeloma are currently testing many different combination regimens with novel agents, such as bortezomib, lenalidomide, thalidomide, and carfilzomib. Patients with comorbidities, including renal failure, extramedullary disease, hyposecretory myeloma, and advanced bone disease, require specialized care.

## Educational Objectives

After completing this activity, the participant should be better able to:

- Describe the current state of treatment of patients with relapsed/refractory multiple myeloma
- Analyze new clinical trial data examining combination regimens with novel therapies in relapsed/refractory multiple myeloma
- Identify the best treatment approaches for patients with relapsed/refractory multiple myeloma
- Develop appropriate treatment strategies for relapsed/refractory multiple myeloma patients with comorbidities

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# Introduction

David S. Siegel, MD, PhD

**A**mong the many issues in the management of patients with multiple myeloma (MM), the treatment of patients with relapsed and refractory disease is key. For patients with newly diagnosed MM, several fairly comprehensive and successful treatment options have become available over the past decade. For example, peripheral blood stem cell transplants are now associated with remissions that can be measured in decades. Maintenance therapies in the context of newly diagnosed MM can also achieve prolonged remissions. However, the majority of patients treated for newly diagnosed MM ultimately go on to experience disease relapse. Those treatment options used at the point of treatment for relapsed and refractory MM are highly variable among treatment centers and physicians, and they are also associated with low expectations. The vast majority of the therapeutic strategies used for the treatment of newly diagnosed MM are also effective (to various degrees) in relapsed and refractory patients when implemented appropriately.

Before discussing the optimal and emerging treatment strategies for patients with relapsed and refractory MM, it is useful to define what this disease is, as our understanding, particularly of refractory MM, has changed in recent years. Although refractory MM alone does not respond to a particular therapy, the new definition of relapsed and refractory disease includes patients

who show disease progression within 60 days of discontinuing therapy. Thus, even in the case of a patient whose MM disease is responding extremely well to therapy, if that treatment is discontinued and disease progression becomes evident within 60 days, the patient is defined as having relapsed and refractory MM. This new definition of relapsed and refractory MM has now become widely accepted; it is recognized by regulatory bodies, such as the US Food and Drug Administration (FDA). However, the emergence of this definition makes the interpretation of data on relapsed and refractory MM difficult. It should no longer be assumed that if a patient is relapsed and refractory to a particular treatment then that treatment is no longer effective. Instead, if a patient is responsive to a particular treatment and that treatment is discontinued, and the patient shows signs of disease progression within 60 days, there is an expectation that the patient would respond once again to that particular therapy. Thus, when a therapy is deemed to be effective in a clinical trial of patients defined as having relapsed and refractory MM, this new definition should be considered when interpreting the data.

## **Acknowledgment**

*Dr. Siegel has received honorarium from Celgene Corporation and Millennium Pharmaceuticals, Inc.*

# Overview of Relapsed and Refractory Multiple Myeloma

Ravi Vij, MD

## Prevalence

In 2010, an estimated 20,180 Americans were diagnosed with MM. This disease is the second most common hematologic neoplasm in the United States, comprising 10–15% of hematopoietic neoplasms.<sup>1,2</sup> Further, an estimated 11,000 individuals died from the disease. MM occurs more often among African Americans, who have approximately twice the incidence compared with the white population (14.3 vs 6.7 cases per 100,000 men and 10.0 vs 4.1 cases per 100,000 women).<sup>3</sup>

The management of MM has significantly changed, especially over the past decade, with the introduction of 3 agents: the immunomodulatory agents thalidomide and lenalidomide, and the first-in-class proteasome inhibitor bortezomib. These treatments have markedly improved patient outcomes. As the therapeutic options for patients with newly diagnosed MM have improved, the prevalence of the disease has increased as more and more patients live longer. The 5-year rate of survival improved from 25% to 34% from 1975 to 2003.<sup>3</sup> This increase is based on the ability to achieve more profound and prolonged remissions with the newly available agents, resulting in improved intervals of both progression-free survival (PFS) as well as overall survival (OS). An analysis by Kumar and colleagues demonstrated this fact.<sup>4</sup> Among 2,981 newly diagnosed MM patients, those who were diagnosed within the past decade enjoyed a twofold improvement in OS compared to those patients diagnosed at an earlier time point (44.8 vs 29.9 months;  $P < .001$ ), presumably due to the implementation of newer therapies and treatment strategies. Specifically among relapsing patients, patients treated with 1 or more newer agents (either thalidomide, lenalidomide, or bortezomib) achieved significantly prolonged OS compared with those patients not receiving these agents (30.9 vs 14.8 months;  $P < .001$ ). For those patients who relapsed after stem cell transplantation, individuals whose disease relapsed after the year 2000 had a significantly improved OS compared with patients whose disease relapsed prior to 2000 (23.9 vs 11.8 months;  $P < .001$ ). However, in another study by Kumar and associates, patients with MM who relapsed or were refractory to bortezomib and immunomodulatory drugs had a median OS of 8 months (95% confidence

interval [CI], 6–10) and an event-free survival rate of 5 months (95% CI, 4–5 months).<sup>5</sup>

Nearly all MM patients eventually go on to experience relapsed disease. As Dr. Siegel described, specific definitions for recurring MM have become widespread in the community, with *relapsed* MM defining any patient who experienced disease progression after an initial response to a prior therapy, and *relapsed and refractory* MM applied specifically to patients who have progressed within 60 days of discontinuing treatment.

## Prognosis

Certain molecular markers have traditionally been relied upon for patient prognosis. One of these is the  $\beta_2$ -microglobulin level, which is considered indicative of the tumor mass and a standard measure of the tumor burden.<sup>6</sup>  $\beta_2$ -microglobulin levels are incorporated into the International Staging System (ISS).<sup>7</sup> According to the ISS, patients with  $\beta_2$ -microglobulin levels below 3.5 mg/L and serum albumin levels at or greater than 3.5 g/dL are considered to have stage I MM. Conversely, patients with  $\beta_2$ -microglobulin levels at or greater than 5.5 mg/L have stage III. The remaining patients are described as having “neither stage I nor III” disease; these patients have either a serum albumin level below 3.5 g/dL or a  $\beta_2$ -microglobulin level between 3.5–5.5 mg/L (irrespective of serum albumin level).

Other prognostic biomarkers may also be used in MM. For example, high levels of lactate dehydrogenase (LDH) are associated with advanced disease and lower survival times. Recently, LDH levels were found to remain prognostic even in the era of newer MM agents.<sup>8</sup> In a group of 996 consecutive symptomatic MM patients from 1995–2008, those patients with elevated LDH levels had a significantly lower median OS compared with patients who had normal LDH levels (15 vs 44 months;  $P < .001$ ). This same trend was noted among the subset of patients who had received either thalidomide, lenalidomide, or bortezomib (21 vs 51 months;  $P < .001$ ). Importantly, elevated LDH levels were associated with a poor survival prognosis regardless of ISS stage: the median OS for high versus normal LDH levels was 22 versus 76 months ( $P < .01$ ) for ISS stage I, 11 versus 40 months ( $P < .001$ )

for ISS stage II, and 17 versus 27 months ( $P < .01$ ) for ISS stage III. Additional negative prognostic factors include increased C-reactive protein, chromosomal abnormalities, immunoglobulin isotype, increased plasma cell labeling index levels, and increased bone marrow plasmacytosis.<sup>9-12</sup> A high plasma cell labeling index, evidence of plasmablastic morphology on bone marrow biopsy, and the presence of circulating plasma cells have also been demonstrated to be associated with a poor MM patient prognosis.<sup>13-15</sup>

As we have entered an era of molecular assay development, data from cytogenetic studies using conventional karyotyping and fluorescence in situ hybridization (FISH) in plasma cells obtained from bone marrow aspiration have become a key factor in determining patient prognosis. In addition, gene expression profiling for prognostic purposes, pioneered by Shaughnessy and colleagues,<sup>16</sup> has recently been commercialized.

Overall, MM patients with a hyperdiploid karyotype, with gains affecting mainly the odd-numbered chromosomes (3, 5, 6, 9, 11, 15, 19, and 21), in general have a relatively good prognosis.<sup>17</sup> Conversely, patients with the del(13q) chromosomal deletion tend to have a poor prognosis.<sup>10</sup> Another cytogenetic abnormality associated with a poor prognosis is the t(4;14) chromosomal translocation, which juxtaposes 2 putative oncogenes—*FGFR3* and *MMSET*—in close proximity to the immunoglobulin heavy chain gene promoter on chromosome 14.<sup>18,19</sup> Translocation involving the *Maf* genes, including *b-Maf* located on chromosome 16 (which is altered with a t[14;16] chromosomal translocation) and *c-Maf* located on chromosome 20 (altered with a t[14;20] chromosomal translocation), are both thought to confer a poor prognosis.<sup>20</sup> Patients with deletions of the *p53* gene are among those with the worst prognosis; these patients often present with extramedullary disease.<sup>21,22</sup> A recent case report suggested that the deletion of the *p53* gene could actually have a role in the poor treatment response characteristically displayed by patients with extramedullary MM.<sup>23</sup> In terms of good prognosis, patients with the t(11;14) chromosomal translocation have been found to have superior outcomes and longer survival times compared even with patients who have normal cytogenetics.<sup>10,24</sup>

Ultimately, treatment of MM patients may need to be individualized according to the overall risk profile of the patient. However, according to guidelines from the National Comprehensive Cancer Network (NCCN), the data regarding cytogenetic prognostic abnormalities are too limited to be used to direct patient management.<sup>6</sup> Current treatment options do not lead to sustained remissions in patients with t(14;16), as well as those with deletions within the *p53* tumor suppressor gene, and these patients in particular are in need of novel and improved therapeutic options. Treatment with bortezomib

appears to be associated with comparable rates of remission and PFS among patients with high-risk cytogenetic features, including del(13) chromosomal deletion and t(4;14) chromosomal translocation.<sup>5</sup> However, a recent French analysis demonstrated that the t(14;16) chromosomal translocation may not confer as poor a prognosis as once believed.<sup>25</sup>

### Some Challenging Scenarios

A number of relapsed and refractory patients may require specialized care, especially in the context of their particular co-existing morbidities.<sup>26</sup> For example, up to one-third of patients present with renal insufficiency at the time of their diagnosis.<sup>6</sup> According to a recent consensus statement on behalf of the International Myeloma Working Group, the recommended method to assess renal function in MM patients with stabilized creatinine levels is to measure the estimated glomerular filtration rate using the Modification of Diet in Renal Disease formula.<sup>27</sup> Renal insufficiency itself may confer a poor prognosis with shortened survival times. Reversal of this insufficiency and improvement of renal function, especially within the first few months of initiating treatment, is imperative and can help to improve the overall outcomes of these patients. Thus, the use of more aggressive regimens that can be tolerated by patients with renal insufficiency is an important issue. A study presented at the 2009 American Society of Hematology (ASH) Annual Meeting and Exposition showed that bortezomib-based regimens were associated with rapid improvements in renal function, especially as compared with conventional chemotherapy and immunomodulatory drugs.<sup>28</sup> A bortezomib-based regimen is preferred for MM patients with renal insufficiency.<sup>27</sup> In a recent prospective study of 18 patients with newly diagnosed MM with renal impairment, 38.9% of patients achieved reversal of renal impairment following treatment with bortezomib plus high-dose dexamethasone (median time to reversal: 16 days).<sup>29</sup> Further, 33.3% of patients achieved a renal response, defined by a 50% decrease in serum creatinine levels. Patients in this study also achieved a high rate of overall MM response to the treatment (83.3%), with a median PFS of 12.6 months. The best reversal of renal insufficiency in response to bortezomib therapy is found in patients with light chain–only myeloma and previously untreated myeloma.<sup>30</sup> Even full doses of bortezomib may be used in patients on kidney dialysis; however, it is recommended that bortezomib be administered after the completion of the dialysis if both are scheduled for the same day. Patients with renal insufficiency require dose reductions of immunomodulatory agents, particularly lenalidomide, due to increased hematologic toxicity.<sup>27</sup> However, the importance of

lenalidomide in this setting should not be overlooked, as it may also reverse renal insufficiency in a number of patients.<sup>31</sup>

Another challenging issue is the management of the increasing proportion of patients who present with extramedullary disease. This issue is especially relevant in the setting of patients with relapsed and refractory MM.<sup>32</sup> As the natural history of the disease in these patients is prolonged, more and more patients begin to exhibit signs of extramedullary disease.<sup>33</sup> This increasing incidence may be attributed both to an improved ability to detect extramedullary disease with the increased usage of computed tomography and positron emission tomography scans in the work-up and follow-up of these patients, as well as prolonged survival in the era of improved therapies. A recent analysis of 1,003 MM patients demonstrated a significant increase in extramedullary disease both at initial diagnosis ( $P=.02$ ) and during subsequent follow-up ( $P=.03$ ) during the 2000–2007 time period compared with earlier years.<sup>34</sup> Unfortunately, MM patients with extramedullary disease have a poorer prognosis compared with patients whose disease is confined to the bone marrow. Extramedullary disease is associated with both a decreased OS (hazard ratio [HR], 3.26;  $P<.0001$ ) and a shortened PFS (HR, 1.46;  $P=.04$ ).<sup>34</sup>

Additionally, many patients who experience multiple relapses of their disease may develop hyposecretory or nonsecretory MM. Traditionally, nonsecretory MM has been thought to comprise approximately 3% of all MM patients.<sup>13</sup> However, even late in the disease course, many patients who initially had measurable paraprotein in their serum or urine go on to become nonsecretors. These patients may experience progressive disease with no change in their paraprotein levels. Thus, merely observing paraprotein levels during follow-up may confer a false sense of security.

### Acknowledgment

*Dr. Vij has performed contracted research for Celgene Corporation and Onyx Pharmaceuticals, Inc. He has received consulting fees from Celgene Corporation, Millennium Pharmaceuticals, Inc., and Onyx Pharmaceuticals, Inc. He is on the speakers' bureau of Celgene Corporation and Millennium Pharmaceuticals, Inc.*

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# Current Treatment Approaches for Relapsed or Refractory Multiple Myeloma

David S. Siegel, MD, PhD

The history of MM treatment has unfortunately suffered from a lack of what could be considered “traditional” or standard therapies. Those agents that have been demonstrated to have the greatest efficacy against MM have only been introduced over the past decade. Before this, there were no proven long-standing therapies that could be relied upon for these patients.

## Conventional Chemotherapy

Certain combination chemotherapy regimens have been found to have an important role in the treatment of relapsed and refractory MM. The combination of dexamethasone, cyclophosphamide, etoposide, and platinum (DCEP) was to be an effective combination regimen for the treatment of relapsed MM following high-dose chemotherapy and autologous stem cell transplantation.<sup>1</sup> DCEP is associated with the decrease in size or disappearance of bone marrow lesions on magnetic resonance imaging (MRI); patients with a complete response to DCEP on MRI have superior rates of event-free survival and OS compared with patients who continue to have the persistent appearance of lesions.<sup>2</sup> Another study showed that DCEP was effective as a third-line salvage therapy in relapsed or refractory MM patients; it was associated with an overall response of 58.3%, with 2 of 12 patients achieving a complete response and 5 of 12 patients achieving a partial response.<sup>3</sup> The median duration of response in these patients was 9 months (range, 4–36). DCEP is also an important therapeutic option for peripheral stem

cell mobilization in MM. The use of DCEP as mobilizing therapy was examined in a study of 55 patients. Mobilization was successful in 87% of patients, with 75% of patients able to have more than  $4 \times 10^6$ /kg CD34-positive cells collected.<sup>4</sup> This regimen was also associated with improved tolerability and higher efficacy compared with high-dose cyclophosphamide in a study of 116 patients.<sup>5</sup> More recently, the addition of vincristine, adriamycin, and dexamethasone (VAD) prior to DCEP was investigated as a mobilizing therapy in patients with previously untreated MM.<sup>6</sup> The VAD-DCEP sequence was associated with a 76.4% rate of successful stem cell mobilization, but with far less toxicity than traditionally observed with VAD plus high-dose cyclophosphamide. Further, VAD-DCEP treatment led to a 73% overall response rate among this patient population. A shorter schedule of DCEP accommodating outpatient administration may be just as effective in MM, producing similar stem cell mobilization rates as the traditional DCEP schedule.<sup>7</sup>

Another important combination chemotherapy regimen established in MM is the combination of cisplatin, doxorubicin, cyclophosphamide, and etoposide (PACE). Most studies involving this regimen in MM have focused on its combination with either dexamethasone and thalidomide (DT-PACE) or bortezomib, dexamethasone, and thalidomide (VDT-PACE). For example, a phase I trial of VDT-PACE as first-line induction and stem cell mobilization therapy in newly diagnosed MM patients reported a predictable incidence of hematologic toxicity.<sup>8</sup> After 2 cycles of this therapy, 10 of 12 patients achieved a

partial response or better. Following autologous stem cell transplantation, 9 patients achieved a complete response, and the remaining 3 patients achieved a partial response. Early results of the Total Therapy 3 trial also showed that VTD-PACE induction and consolidation therapy were able to achieve high rates of stem cell mobilization and initial response.<sup>9</sup> Treatment of relapsed MM with DT-PACE resulted in a 32% rate of partial response and a 16% rate of complete remission in another study.<sup>10</sup> Interestingly, some poor-prognosis patients, including those with elevated LDH levels, achieved better responses compared to those patients with normal LDH levels ( $\geq$  partial response: 43% vs 27%;  $P=.01$ ; complete response or near complete response: 25% vs 11%;  $P=.01$ ). Patients with a del(13) chromosomal deletion responded equally as well to DT-PACE as did patients without this cytogenetic abnormality. Blastoid variant MM (frequently observed in patients with extramedullary disease) has a particularly poor prognosis. This variant was shown to be responsive to DT-PACE in a study of 26 patients with relapsed and/or refractory MM.<sup>11</sup> A 59% rate of overall response was demonstrated in this study, but despite this initial good response, patients still had relatively short durations of PFS and OS.

### Autologous Stem Cell Transplantation

Autologous stem cell transplantation is a very controversial subject for MM patients. It is associated with high response rates, increased OS, and prolonged event-free survival,<sup>12</sup> and it has become a standard of care for eligible newly diagnosed patients following induction therapy.<sup>13</sup> Among these patients, autologous stem cell transplantation has become a mainstay of treatment. Results from a clinical trial suggested that high-dose therapy is more beneficial than standard-dose therapy with autologous stem cell transplantation, resulting in higher median OS (54 vs 42 months).<sup>14</sup> However, these data have been disputed by another study, which showed no difference in either PFS or OS after a median follow-up of 76 months.<sup>15</sup> This discrepancy may be explained, at least in part, by the use of different chemotherapy regimens between studies.

Importantly, the majority of studies that established the benefit of autologous stem cell transplantation in MM patients were conducted prior to the widespread availability of the newer MM agents: thalidomide, lenalidomide, and bortezomib. The Intergroupe Francophone du Myélome (IFM) 2005/01 study was designed to evaluate autologous stem cell transplantation in the era of these newer agents.<sup>16</sup> Symptomatic MM patients in this study who were treated with bortezomib plus dexamethasone induction therapy achieved significantly higher complete response/near complete response rates following autologous stem cell transplantation compared with patients

who received VAD induction therapy (40% vs 22%;  $P=.0001$ ). Additionally, fewer patients in the bortezomib plus dexamethasone arm required a second autologous stem cell transplantation compared with patients in the VAD arm (34% vs 47%). After a median follow-up of 32.2 months, the respective median PFS in each group was 36.0 and 29.7 months, respectively. Another study has also been conducted to evaluate autologous stem cell transplantation following induction therapy with newer agents.<sup>17</sup> In this study of 450 MM patients, the combination of bortezomib, dexamethasone, and thalidomide resulted in markedly higher response rates following autologous stem cell transplantation than the combination of thalidomide plus dexamethasone (complete response or near complete response: 55% vs 29%; very good partial response: 76% vs 53%). Overall, the results of both of these trials suggest that autologous stem cell transplantation remains an excellent therapeutic strategy in the era of the newer MM agents.

Autologous stem cell transplantation is an important therapeutic option for patients with relapsed and refractory MM. A retrospective case series of 25 consecutive patients concluded that patients who undergo a second autologous stem cell transplantation are likely to experience more nephrotoxicity, and the treatment-related mortality rate was reported to be 8%.<sup>18</sup> In a separate study of 26 patients who underwent a second autologous stem cell transplantation (median time from first autologous stem cell transplantation, 20.4 months), a partial response or better was achieved in 69% of patients.<sup>19</sup> The median OS in this study was reported to be 65.4 months, and no treatment-related deaths occurred after the second transplantation. Similarly, a pilot European study of 32 relapsed and progressing MM patients also showed that a second autologous stem cell transplantation was safe and effective, with 7 patients achieving a better response compared to their first transplant.<sup>20</sup> Most recently, a single center review of 41 patients with relapsed MM who received a salvage autologous stem cell transplantation reported a median time between transplants of 37 months (range, 3–91 months).<sup>21</sup> The overall response rate in these patients was 55%, with a treatment-related mortality of 7%. After a median follow-up of 15 months, the median OS and median PFS were determined to be 20.7 months and 8.5 months, respectively. Importantly, this study also included a multivariate analysis to identify prognostic factors, which included at least 5 prior lines of therapy and a time to progression after initial transplantation of 12 months or less. Available guidelines lack recommendations, but the general consensus is that salvage autologous stem cell transplantation should be offered only with the goal of inducing long-term remission in patients who had achieved a durable response for 18–24 months following the first transplantation.<sup>22</sup>



## Response Rates

Response rates in relapsed or refractory MM vary according to the patient population. Obviously, patients who have had induction therapy and an autologous stem cell transplant, but who then relapsed 4 years later, are much different than patients who were treated with lenalidomide and dexamethasone, maintained on that therapy for 2–3 years, relapsed on therapy, and then went on to receive bortezomib as a third line of therapy. There are too many potential scenarios to use for defining each of these patient sets. Thus, the best information to rely upon for response rates is the clinical trials that were performed to establish the newer agents thalidomide, lenalidomide, and bortezomib. However, it is important to remember that the patient populations studied in these trials to a large extent no longer exist. There is extensive experience with the combination of lenalidomide, bortezomib, and dexamethasone in any number of settings, and fortunately the response rate for those combinations is well over 50%, again depending on the population evaluated.

## Areas for Needed Improvements

The majority of improvements that are needed in MM surround the area of developing new agents. There are certainly potential refinements based on the agents that are currently available in terms of their doses, their schedules, and the order in which they are administered. However, these advancements would amount to relatively minor contributions compared to the larger step forward of getting new drugs approved and incorporated into the treatment strategies for relapsed and refractory disease. We are fortunate in that there are many investigational agents in clinical trials right now that seem to have significant efficacy; many of them are expected to meet the standards for approval at some point in the relatively near future. It is hoped that we will soon see the impact of these agents, including carfilzomib, pomalidomide, and elotuzumab. But again, although there might be incremental improvements with the tools that we currently have, there will likely not be dramatic differences in the expectations that we have for relapsed and refractory patients without the introduction of new therapies.

## Acknowledgment

Dr. Siegel has received honorarium from Celgene Corporation and Millennium Pharmaceuticals, Inc.

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# New Treatment Options in Relapsed and Refractory Multiple Myeloma

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## Newer MM Agents in the Relapsed and Refractory Setting

The treatment of MM was revolutionized with the introduction of the immunomodulatory agents thalidomide and lenalidomide, as well as the first-in-class proteasome inhibitor bortezomib. Although thalidomide, as the first of the newer MM agents, made a tremendous impact in the treatment of MM, no major randomized pivotal study established its efficacy in this setting. A study of 84 patients with relapsed and refractory MM was published, in which patients were treated with single-agent thalidomide.<sup>1</sup> In this study, thalidomide was associated with significant clinical activity, inducing decreases in serum or urine levels of paraprotein in 32% of patients. Subsequently, other major studies were conducted that established bortezomib and lenalidomide as approved agents in relapsed and refractory MM.

The use of bortezomib in the relapsed and refractory setting is largely based on the results of the phase III APEX trial.<sup>2</sup> In fact, this was the first study in the era of the newer agents to demonstrate in a randomized fashion that the newer agent could have a greater positive effect in the relapsed setting than the prior-used chemotherapy regimens. The APEX study randomized 669 relapsed MM patients to treatment with either bortezomib or high-dose dexamethasone, both administered as a single agent. Crossover from dexamethasone to bortezomib was allowed in the event of disease progression. Bortezomib, compared with high-dose dexamethasone, induced significantly higher rates of overall response (38% vs 18%;  $P < .001$ ), as well as complete response (6% vs <1%;  $P < .001$ ). Further, patients in the bortezomib group had twice the median time to progression compared with the high-dose dexamethasone group (6.22 vs 3.49 months;  $P < .001$ ). These positive responses also translated into an improved rate of 1-year OS (80% vs 66%;  $P = .003$ ; HR 0.57;  $P = .001$ ). The results of an updated efficacy analysis with an extended follow-up were reported (median follow-up: 22 months).<sup>3</sup> This analysis demonstrated an even higher overall response (43%) and complete response rate (9%) with bortezomib treatment. Approximately half of the responding patients (56%) achieved an improved

response with longer therapy. Importantly, despite the fact that many patients crossed-over from the high-dose dexamethasone arm, the median OS was significantly prolonged in the bortezomib group (29.8 vs 23.7 months). Interestingly, the del(13) chromosomal deletion had no impact on survival in the bortezomib-treated arm.

Two major phase III studies led to the widespread recommended use of lenalidomide plus dexamethasone in relapsed and refractory MM. Both were large randomized studies, one conducted in North America (MM-009) and one in Europe (MM-010), with a primary efficacy endpoint of time to progression.<sup>4,5</sup> Both demonstrated with very similar results that the lenalidomide plus dexamethasone combination achieved superior response rates, PFS, and OS. Together, the 2 studies enrolled 692 MM patients who had received at least 1 prior therapy; many of the patients were heavily pretreated prior to study enrollment (failed  $\geq 3$  chemotherapy lines). Patients were randomized to treatment with either dexamethasone alone or lenalidomide plus dexamethasone. In MM-009, the overall response rates were 19.9% versus 61.0%, respectively ( $P < .001$ ), with complete responses occurring in 14.1% and 0.6%, respectively ( $P < .001$ ). The median time to progression was significantly prolonged in the combination group compared with dexamethasone alone (11.1 vs 4.7 months;  $P < .001$ ), as was the median OS (29.6 vs 20.2 months;  $P < .001$ ). In MM-010, patients in the dexamethasone alone and lenalidomide plus dexamethasone arms achieved overall response rates of 24.0% and 60.2%, respectively ( $P < .001$ ), with complete responses occurring in 3.4% and 15.9% of patients, respectively ( $P < .001$ ). The median time to progression was again significantly prolonged in the lenalidomide plus dexamethasone arm versus the dexamethasone alone arm (11.3 vs 4.7 months;  $P < .001$ ). Further, patients in the lenalidomide arm achieved a significantly improved OS (HR, 0.66;  $P = .03$ ).

## Combination Therapy With Novel Agents

Perhaps even more important to the utility of these newer agents in relapsed and refractory MM were the early studies that were performed demonstrating their benefit when combined with other agents, includ-

ing corticosteroids and anthracyclines. For example, a phase III international clinical trial randomized 646 patients with relapsed and refractory MM to treatment with either single-agent bortezomib or bortezomib plus pegylated liposomal doxorubicin.<sup>6</sup> The median time to progression was significantly increased among patients treated with the bortezomib combination compared with bortezomib monotherapy (9.3 vs 6.5 months;  $P=.000004$ ; HR 1.82, 95% CI, 1.41–2.35). Similarly, the proportion of patients alive at 15 months was also significantly increased in the combination arm (76% vs 65%;  $P=.03$ ). A similar proportion of patients treated with bortezomib plus pegylated liposomal doxorubicin versus single-agent bortezomib achieved an overall response (44% vs 41%), but the median duration of response was increased significantly between the 2 arms (10.2 vs 7.0 months;  $P=.0008$ ). This important study led to the approval of the bortezomib plus pegylated liposomal doxorubicin in the setting of relapsed and refractory MM.

Based on promising data in the preclinical setting, subsequent clinical evaluations have now demonstrated that the combination of these agents (thalidomide, lenalidomide, or bortezomib) either together or with other drugs may potentiate their cytotoxicity. For example, the combination of lenalidomide, bortezomib, and dexamethasone (RVD) was found to achieve responses in nearly 60% of patients with relapsed and refractory MM.<sup>7</sup> The phase II study that showed this outcome was conducted based on preclinical data showing an additive effect between lenalidomide and bortezomib in a model of bortezomib-refractory MM cells. The bortezomib plus lenalidomide combination was further successfully evaluated in heavily-pretreated relapsed and refractory patients.<sup>8,9</sup> Importantly, it has also been shown that RVD is one of the most active regimens in patients with newly diagnosed MM.

The combination of bortezomib or lenalidomide with histone deacetylase (HDAC) inhibitors (such as vorinostat or panobinostat) is another promising avenue of therapy for relapsed and refractory MM patients. Phase I and II clinical trials have demonstrated responses associated with these combinations in bortezomib-refractory MM patients. For example, a phase Ib dose-escalation study of bortezomib plus panobinostat reported a 76% clinical benefit rate and a 70% rate of overall response.<sup>10</sup> Importantly, a majority (60%) of patients who were refractory to bortezomib responded to this combination. There are now ongoing phase III trials of bortezomib plus vorinostat or panobinostat in relapsed and refractory MM.<sup>11,12</sup>

Another potentially exciting combination is the Akt-targeted inhibitor perifosine with bortezomib. Based on

promising preclinical data providing evidence of a synergistic relationship between these 2 agents,<sup>13</sup> a phase I/II study of perifosine, bortezomib, and dexamethasone was conducted that suggested that this 3-drug combination was associated with sustained responses in relapsed and refractory patients.<sup>14</sup> A phase III clinical trial is now comparing this combination with bortezomib monotherapy.<sup>15</sup>

### Promising Data With Investigational Agents

The second-generation proteasome inhibitor carfilzomib was developed based on a unique chemical structure. Carfilzomib represents an important milestone in the development of novel MM agents for several reasons. As a single agent, carfilzomib has demonstrated clinical activity in heavily pretreated relapsed and refractory MM patients. Approximately one-third (34%) of patients have been found to achieve a clinical benefit (defined as minimal response or better) with carfilzomib, an important finding because these patients had heavily pretreated disease not expected to respond to therapy. The overall response (defined as partial response or better) was 24%, and the median OS was 15.5 months.<sup>16</sup> Additionally, many of these responses have occurred in bortezomib-refractory patients (28% rate of clinical benefit, 17% overall response rate), showing that carfilzomib does not exhibit cross-resistance despite the fact that it also acts as a proteasome inhibitor.<sup>16</sup> In bortezomib-naïve, relapsed patients treated with carfilzomib, a majority (55%) achieved a partial response or better.<sup>17</sup> These exciting data suggest that carfilzomib is probably the most active single agent in relapsed MM. Another reason why carfilzomib represents such an important advance in MM is due to its favorable toxicity profile. Unlike bortezomib and thalidomide, which are commonly associated with peripheral neuropathy, patients treated with carfilzomib have shown only limited low-grade peripheral neuropathy.

Carfilzomib has also been investigated in combination with lenalidomide and dexamethasone (CRd). In a dose-escalation study of heavily pretreated patients with relapsed and refractory MM, 78% of patients achieved a clinical benefit, and 59% of patients achieved an overall response to this combination.<sup>18</sup> Deep and rapid responses to CRd have also been observed in newly diagnosed patients, with best response rates of 100% of patients achieving a partial response or better and 55% of patients achieving a complete response or near complete response.<sup>19</sup>

Other novel proteasome inhibitors with potential for use in MM include NPI-0052 and MLN9708. These agents are in early stages of evaluation.<sup>20,21</sup>

The novel thalidomide derivative pomalidomide is another very promising agent in relapsed and refractory

MM, both as a single agent and as part of combination therapy. In relapsed and refractory patients with less pretreated disease, the combination of pomalidomide plus low-dose dexamethasone was associated with a 54% clinical benefit rate (defined as very good partial response, partial response, or minor response) and an 86% rate of 6-month OS.<sup>22</sup> In more heavily pretreated patients, pomalidomide with or without low-dose dexamethasone was demonstrated to be active, with a clinical benefit (defined as partial response or better) in 28% of patients.<sup>23</sup>

Among several antibodies currently under investigation in MM, elotuzumab is one of the most well studied in clinical trials. This antibody is directed against CS1, a cell surface glycoprotein highly expressed on MM cells. In addition to monotherapy, elotuzumab is also under evaluation in combination with bortezomib and with lenalidomide plus dexamethasone, all in the setting of relapsed and refractory MM. Both of these combinations were based on predictions of synergy in preclinical studies.<sup>24</sup> Updated results of a phase I trial of bortezomib combined with elotuzumab reported a 48% overall response rate.<sup>25</sup> This combination was suggested to be able to overcome resistance to bortezomib, as 50% of bortezomib-refractory patients achieved an overall response. Importantly, the time to progression in this study was increased from approximately 6 months for bortezomib monotherapy to approximately 9 months with the elotuzumab plus bortezomib combination. However, this conclusion regarding time to progression must be interpreted cautiously, as this trial was not a comparator study. In a phase I/II trial, Lonial and colleagues examined the use of elotuzumab in combination with lenalidomide and low-dose dexamethasone in 28 patients with relapsed or refractory MM.<sup>26</sup> The overall response rate was 82%, and the regimen had a manageable safety profile. In a phase II trial testing the combination of elotuzumab with lenalidomide and dexamethasone, a very high overall response rate (84.6%) was observed.<sup>27</sup>

## Conclusion

This short review represents only a fraction of the significant development that has occurred in the treatment of relapsed and refractory MM over the past decade, ranging from the introduction of thalidomide, lenalidomide, and bortezomib, to their subsequent second-generation derivatives such as carfilzomib, to newer agents such as perifosine, pomalidomide, and elotuzumab. By taking advantage of novel targets and using unique mechanisms of action, many of the newest agents have shown remarkably high single-agent activity, even among relapsed and refractory patients. Perhaps even more important are the potential benefits these novel agents have when combined

with thalidomide, lenalidomide, and bortezomib. Excitingly, these combinations have achieved unthinkable profound and durable responses even among patients with heavily pretreated disease.

As a result, the management of MM has improved to such a degree that patients are now achieving significant prolongation of life. The 5-year survival in 2003 was estimated at approximately 34%, and the median expected 3-year OS is now approaching 7 to 10 years. Are we satisfied? Definitely not—we are still unable to provide a cure for most MM patients. Some comprehensive and aggressive approaches for treatment of early-stage MM, including initial autologous stem cell transplantation followed by consolidation and long-term maintenance therapy, may provide a cure to select patients, but it is still early to make this conclusion. However, the systematic development of novel agents and new strategies is helping patients, even those with relapsed and refractory disease, to live longer. This is an effort of many academic centers and investigators, cooperative groups and international groups, the pharmaceutical industry, and nonprofit organizations, such as the Multiple Myeloma Research Consortium.

## Acknowledgment

*Dr. Jakubowiak has received consulting fees from Millennium, Celgene, Onyx, Ortho Biotech, Bristol-Myers Squibb, and Exelixis. He has received fees for non-CME services from Millennium, Celgene, and Ortho Biotech.*

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# Slide Library

## Epidemiology of MM

**Prevalence**

- More than 61,000 people in the United States<sup>1</sup>

**Incidence**

- About 20,000 people are diagnosed with MM each year in the United States<sup>1</sup>

**Mortality**

- Nearly 11,000 US MM patients die each year<sup>1</sup>

**Demographics**

- Median age at diagnosis is 70 years<sup>1</sup>
- Incidence is twice as high in African Americans as in whites<sup>1</sup>
- More frequent in men than women<sup>1</sup>

1. Siegel RL, et al. Cancer Statistics, 2011. CA Cancer Clin J. 2011;61:9-26. <http://aapublications.aacrjournals.org>. Accessed November 10, 2011. © American Cancer Society. All rights reserved. This article is intended solely for the personal use of the individual user and is not to be disseminated broadly. See <http://aapublications.aacrjournals.org> for more information. Image copyright American Cancer Society. All rights reserved. November 10, 2011.

## Select Negative Prognostic Factors

Prognostic Factors	Findings
<b>β<sub>2</sub>-microglobulin<sup>1</sup></b>	↓ Levels (marker of tumor burden)
<b>C-reactive protein (CRP)<sup>2</sup></b>	↑ Levels (prognostic marker for imiplus-1)
<b>Chromosomal abnormalities<sup>3</sup></b>	Type and number of abnormalities may affect prognosis
<b>Immunoglobulin heavy chain<sup>4</sup></b>	Immunoglobulin A associated with poorer prognosis
<b>Lactate dehydrogenase (LDH)<sup>5</sup></b>	↑ Levels correlate with aggressive symptoms like presence of disease
<b>Plasma cell labeling index (PCL)<sup>6</sup></b>	↓ Levels (white plasma cell proliferation)
<b>Bone marrow plasmacytosis<sup>7</sup></b>	↑ Level reflects tumor burden
<b>Prognostic myeloma<sup>8</sup></b>	↑ Incidence of adverse events may indicate poorer prognosis

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## Cytogenetic Abnormalities

Chromosomal abnormality (FISH-based)	Incidence (%)	Prognosis
Hyperdiploidy	30%-45%	Favorable
Deletion 13q	-	Intermediate
13q14	7.8%-21%	Intermediate
13q32	1.9%-5%	Poor
13q44	0.5%-15%	Poor
del 17p	11%	Poor
del 17q	-	Poor
+ del 17q	+ 9.6%	Poor
+ del 17q	+ 31.9%	Poor

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## Chemotherapy Regimens in Multiple Myeloma

- Dexamethasone, cyclophosphamide, etoposide, and platinum (DCEP)
- Vincristine, adriamycin, and dexamethasone (VAD) prior to DCEP
- Cisplatin, doxorubicin, cyclophosphamide, and etoposide (PACE)
- PACE plus dexamethasone and thalidomide
- PACE plus bortezomib, dexamethasone, and thalidomide

## ASCT in MM

ASCT has been associated with:

- High response rates
- Increased overall survival
- Prolonged overall time survival

**Results from the IFM study<sup>1</sup>**

- Bortezomib plus thalidomide plus dexamethasone induction therapy achieved significantly higher complete response rate compared to VAD induction therapy
- Transplantation increased in patients who received VAD induction therapy
- Fewer patients in the bortezomib plus dexamethasone arm required a second autologous stem cell transplantation compared with patients in the VAD arm

**Results from the CoMM study<sup>2</sup>**

- The combination of bortezomib, dexamethasone, and thalidomide resulted in markedly higher response rates compared to dexamethasone stem cell transplantation than the combination of bortezomib plus dexamethasone

ASCT: autologous stem cell transplantation; IFM: Intergroup Comparison of Thalidomide, Vincristine, Doxorubicin, and Dexamethasone; CoMM: Comparison of Bortezomib, Dexamethasone, and Thalidomide. 1. Haravesh A, et al. J Clin Oncol. 2007;25:104-114. 2. Haravesh A, et al. J Clin Oncol. 2007;25:104-114.

## Newer MM Agents in the Relapsed and Refractory Setting

- Thalidomide**
  - Significant clinical activity, inducing decreases in serum or urine levels of paraprotein in 32% of patients<sup>1</sup>
- Bortezomib**
  - Overall response of 43%; complete response of 9%<sup>2</sup>
- Lenalidomide plus dexamethasone**
  - Overall response of 61%; complete response of 0.6%<sup>3</sup>
  - Overall response of 60.2%, complete response of 15.9%<sup>4</sup>

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