Achieving Optimal Care for the Relapsed/Refractory Multiple Myeloma Patient

Needs Statement

Multiple myeloma (MM) is the second most common hematologic malignancy in the Unites States[1,2]. Recent therapeutic advances have led to improved survival in MM patients[3]. However, in spite of these advances, MM eventually relapses and remains incurable. Given that MM patients are predominantly elderly and present with comorbidities, relapsed/refractory MM remains especially challenging to treat[4]. A number of factors play a role in therapy selection for refractory/relapsed MM[5]. The optimal choice of treatment depends on the previous lines of therapy, the duration of response, the observed regimen-related toxicities and the presence of high-risk cytogenetic features, among others. Oncologists need to be aware of such factors to be able to devise an optimal care plan for the MM patient. In addition, use of standardized definitions of relapsed/recurring MM are important for the successful interpretation of data from clinical trials and for the identification of specific benefits for a given therapy. Many new therapies for relapsed/refractory MM are currently under investigation, and will potentially provide health care practitioners with more treatment choices. Knowledge of existing and investigational agents will guide clinicians in selecting the best strategy for the treatment of relapsed/refractory MM patients.

Introduction

Multiple myeloma is a neoplastic plasma-cell disorder. It is characterized by uncontrolled differentiation of malignant plasma cells derived from B-cells in the bone marrow and occasionally in other parts of the body. MM accounts for about 13% of all hematologic cancers[6] and is the most common hematologic malignancy among African Americans, and the second most common hematologic malignancy in the Unites States[1,2]. In 2011 there will be about 20,520 new cases of MM with about 10,610 deaths occurring as a result of the disease[7].

Recent years have seen significant advances in the treatment of MM. The development of novel therapeutic agents, such as thalidomide, lenalidomide and bortezomib, has provided higher objective response rates, and an increase in the median overall survival from 3 to about 7 years, especially in the younger patient population[3,8]. However, despite therapeutic advances, all MM patients eventually experience a relapse and MM remains an incurable disease.

Relapsed/refractory MM is especially challenging to treat. The median survival of patients with relapsed/refractory MM is extremely short, 6 to 9 months[4]. Most MM patients are elderly, with a median age of 69[9], and present with comorbidities that require special consideration. The main challenge for the treatment of such patients is to select an optimal therapeutic regimen that successfully balances efficacy and toxicity. Factors guiding treatment decisions are both disease- and patient-related, and will be discussed in more detail below[10]. The complexity of the treatment decisions requires clinicians to be aware of factors playing a role in the choice of therapy. Physicians must

be well educated on the constantly evolving MM therapeutic landscape. They must have a clear understanding of the benefits and treatment-related side effects of current and emerging treatment options.

Definition of relapsed/refractory multiple myeloma

The use of standard definitions for the MM patient population is crucial in order to ensure uniform reporting of clinical trial results and to allow the direct comparison of trial outcomes[11]. The International Myeloma Workshop Consensus Panel 1 (IMWCP1) recently released new definitions of relapsed/refractory MM. These definitions are an important consideration for healthcare professionals when interpreting data from clinical trials[11].

IMWCP1 recommends the classification of patients with relapsed and/or refractory MM into the following main groups – patients with refractory myeloma (includes primary refractory and relapsed and refractory myeloma) and patients with relapsed myeloma[11].

Relapsed Myeloma

Relapsed myeloma patients have disease that previously responded to therapy but has progressed and requires the initiation of salvage therapy[11]. The time to relapse may vary significantly among patients – from weeks to months. Generally, patients must show symptomatic relapse before the initiation of salvage therapy.

Refractory Myeloma

Refractory MM patients are nonresponsive (lack of minimal response, or development of progressive disease) to primary or salvage therapy, or the disease progresses within 60 days of the latest round of therapy. The refractory MM group is further subdivided into relapsed and refractory, and primary refractory myeloma.

Primary refractory

Primary refractory MM patients are patients that have never achieved a response to treatment with any therapy. A small subset of these patients, about 10%, have stable disease – they have never achieved minimal response to treatment, but have no significant change in M protein levels and no evidence of clinical progression. Such patients are called nonresponding-nonprogressive[11] and have a survival prognosis as good as the one for responding patients[12,13]. The treatment of the other 90% primary refractory MM patients (progressive primary refractory[11]) is more challenging and such patients have poor prognosis.

Relapsed and refractory

Relapsed and refractory myeloma is defined as relapse in patients who achieved at least a minimal response. In such patients the disease becomes either non-responsive during salvage therapy or progresses within 60 days of the last treatment[11]. A significant number of factors play a role in the selection of proper therapy for relapsed and refractory myeloma patients. Especially challenging for treatment are patients who have received multiple prior lines of therapy; they have limited treatment options beside participation in clinical trials.

Factors influencing treatment selection for relapsed/refractory multiple myeloma

Many factors are involved in the selection of treatment options for patients with relapsed/refractory MM. Physicians must consider all characteristics associated with the disease for the individual patient in order to devise an optimal treatment plan. Some of the most important factors[5] that influence therapy choice are listed below.

Disease-related factors

A number of chromosomal changes have been associated with poor prognosis for MM patients. Among those are deletions or structural anomalies of chromosome 13 (in about 10-20% of the patients) translocations of the heavy chain gene on chromosome 14 – t(4;14) (in about 15-20% of patients) and t(14;16) (in about 2-10% of patients), and deletion of *p53* on chromosome 17p13 (in 10% of patients)[14]. Patients with any of these high-risk features usually require combination therapies. For example lenalidomide-dexamethasone combinations with or without added bortezomib lead to better outcomes in patients with del 13 or t(4;14) abnormalities, but the prognosis remains poor for patients with 17p13 or chromosome 1 abnormalities[15-17].

Patient-related factors

Most MM patients are elderly and the chance of experiencing complications as a result of treatment increases with age. Such patients may benefit from reduced-dose therapies. For example, in elderly patients, lower dose lenalidomide in combination with lower-dose dexamethasone results in reduced myelosuppression without compromising efficacy[18]. In addition, elderly patients often have comorbidities that complicate therapy. Comorbidities have a substantial effect on overall survival and influence treatment choices for MM patients[19]. For example, one of the most commonly observed comorbidities associated with poor prognosis is renal impairment. For such patients agents like bortezomib can be beneficial[20].

Regimen-related factors

An important aspect in the treatment of patients with relapsed/refractory MM is the thorough evaluation of the prior line of therapy. Analysis of the types of drugs and combinations used in the past will guide decisions on whether to retreat with the same drugs, either alone or in combination. In addition, re-treatment with the agents that have shown little efficacy can be avoided[21]. Additionally, treatment choices depend on the duration of response to the initial therapy. Patients with remissions lasting longer than 6 months may be considered for re-challenging with the initial treatment regimen, or a new agent may be added to the preceding therapy. By contrast, patients with shorter-lasting remissions would require a switch to a new therapeutic agent[22].

The toxicity of the previous treatment regimen must also be considered. One of the most commonly occurring complications in MM patients is peripheral neuropathy (PN). PN can be both disease- and treatment-related. Agents like thalidomide, lenalidomide and bortezomib have all shown PN side effects. However, new drugs in development, such as the second-generation proteasome inhibitor carfilzomib, have not shown neurotoxic side effects and may prove beneficial[23].

Novel therapies approved for the treatment of relapsed/refractory MM

Currently, there is no widely accepted best standard of care for relapsed/refractory MM. Therapy choice depends on a number of factors, as discussed above. Several treatment options have proven particularly useful in the treatment of MM. Those include the

immunomodulatory drugs (IMiDs) thalidomide and lenalidomide, and the proteasome inhibitor bortezomib.

Thalidomide and thalidomide-based combinations

Thalidomide was the first novel agent in the IMiDs class and is now widely used in the treatment of relapsed/refractory MM either alone or in combination with other agents. Thalidomide monotherapy produces complete or partial response rates of about 29.4%, and about a 14-month median overall survival[24]. Toxicities associated with thalidomide include constipation, fatigue, rash and peripheral neuropathy. These toxicities are dependent both on the dose and on treatment duration[25]. A significant risk of venous thrombosis has not been observed for thalidomide alone, but a risk of up to 28% was observed for a combination of thalidomide with anthracyclines or dexamethasone[26-28].

Thalidomide in combination with dexamethasone is indicated for the treatment of newly diagnosed MM. However, thalidomide/dexamethasone, when used in relapsed/refractory MM patients, resulted in a higher response rate compared to thalidomide alone, even in disease that was refractory to dexamethasone[29]. Several other thalidomide combination approaches have been investigated, but are not currently approved for the treatment of MM.

Lenalidomide and lenalidomide-based combinations

Lenalidomide is a newer IMiD agent. It is a more potent, amino-substituted derivative of thalidomide with an improved toxicity profile. A phase II study of lenalidomide monotherapy resulted in a 26% response rate and a 23 month overall survival[30]. Most side effects, including myelosuppression, neutropenia and thrombocytopenia were manageable with dose reduction. Lenalidomide monotherapy did not significantly increase the risk of venous thrombosis[30].

An effective treatment option approved for use in the relapsed/refractory MM setting is the combination of lenalidomide with dexamethasone. Clinical studies have shown an overall response rate of about 60% (compared to 20% for dexamethasone alone) and significantly improved overall survival[31,32]. Most significant adverse events from the treatment with lenalidomide/dexamethasone combination were neutropenia, thrombocytopenia and venous thromboembolism. Various other lenalidomide-based combinations are currently being investigated.

Bortezomib and bortezomib-based combinations

Bortezomib is the first proteasome inhibitor to be approved for the treatment of MM. In the relapsed/refractory setting (the APEX trial), bortezomib was superior to dexamethasone in patients who had received one to three previous lines of therapy[33]. Common side effects included gastrointestinal events, peripheral neuropathy and thrombocytopenia. Bortezomib is especially attractive for use in patients with advanced renal failure[34].

The combination of liposomal doxorubicin with bortezomib was approved in 2007 for the treatment of relapsed/refractory MM. Approval was based on a phase III comparison of the doxorubicin/bortezomib combination to bortezomib monotherapy in bortezomib-naïve patients who had received at least one prior MM therapy. The combination of liposomal doxorubicin and bortezomib showed improved time to progression and response duration[35]. Increased incidence of neutropenia, thrombocytopenia, fatigue, and

gastrointestinal events was observed in the doxorubicin/bortezomib arm of the study. Several ongoing studies are investigating the use of double[36], triple[37] and even quadruple[38] combinations based on bortezomib.

Promising emerging treatments for relapsed/refractory MM

Refractory/relapsed MM patients have, normally, failed several lines of treatment. Such patients are encouraged to enroll in clinical trials of investigational therapeutics or in trials of novel combinations of approved drugs.

Second-generation proteasome inhibitors

Patients relapsing after IMiD and bortezomib treatment have an especially poor prognosis[39]. Promising results in such cases have been observed with the second-generation proteasome inhibitor carfilzomib. Carfilzomib was tested in patients who had received more than two (occasionally five, or more) previous lines of therapy. Results from a large phase II study showed an overall response rate of 24% with median overall survival of 15.5 months[40]. Carfilzomib had a favorable toxicity profile and most importantly, minimal neuropathy, unlike its predecessor bortezomib[23]. Carfilzomib seems to have comparable activity in patients with unfavorable cytogenetic features, including del 13q, t(4;14) and t(14;16)[41]. Carfilzomib has also been investigated in combination with lenalidomide and dexamethasone in heavily pretreated patients with relapsed/refractory MM. The combination led to an overall response rate of 78% without new toxicities[42].

Several other second-generation proteasome inhibitors are currently under investigation, though in earlier stages of clinical development. NPI-0052, ONX 0912 and CEP-18770 are all in phase I development[43].

IMiDs

Pomalidomide is the most promising new IMiD currently under investigation. A multicenter phase I/II study examined the safety and efficacy of pomalidomide alone, or in combination with low-dose dexamethasone in patients with relapsed/refractory MM who had received 2 or more lines of treatment. In addition, patients in the study were resistant to lenalidomide and bortezomib. Clinical activity was observed with or without dexamethasone, with comparable overall survival for both arms of the study. However, the pomalidomide/dexamethasone combination showed a better partial response rate, 34%, compared to 13% in the pomalidomide arm of the study. Major adverse events included neutropenia, thrombocytopenia, anemia, pneumonia and fatigue. Low rates of peripheral neuropathy, deep vein thrombosis, and renal failure were also observed[44]. The combination of pomalidomide with dexamethasone is currently in phase III clinical trials. The triple combination, of pomalidomide, bortezomib and dexamethasone is also being studied.

Targeted therapies

Two new histone deacetylase (HDAC) inhibitors, vorinostat and panobinostat, are showing promising results in clinical trials. Both agents have been tested in combination with bortezomib in bortezomib-refractory MM and showed favorable response rates and tolerability profiles[45,46].

Suppression of PI3K/Akt signaling has also been investigated in the context of MM treatment. Perifosine inhibits Akt activation, and also affects a number of other important signal transduction pathways. Although not exciting as a monotherapy, perifosine in combination with bortezomib and dexamethasone has shown encouraging activity. The combination was tested in patients that had been heavily pretreated with bortezomib, resulting in a 41% overall response rate and a 25 month median overall survival in a phase I/II trial[47].

Educational Needs

- MM accounts for about 13% of all hematologic cancers and is the most common hematologic malignancy among African Americans in the US.
- In 2011 there will be about 20,520 new cases of MM with about 10,610 deaths occurring as a result of the disease.
- Despite therapeutic advances, all MM patients eventually experience a relapse and, therefore, MM remains an incurable disease.
- The International Myeloma Workshop Consensus Panel 1 has recently released new definitions of relapsed/refractory MM. Standardized definitions for relapsed/refractory MM will allow the effective use and interpretation of clinical trial data.
- Factors influencing treatment decisions for relapsed/refractory MM are disease-, regimen- and patient-related.
- Management of relapsed/refractory MM should be individualized by assessing factors playing role in treatment choice decisions.
- The development of novel therapeutic agents, such as thalidomide, lenalidomide and bortezomib has led to significant advances in the treatment of MM.
- Agents like thalidomide, lenalidomide and bortezomib have shown peripheral neuropathy side effects.
- New drugs in development, such as the second-generation proteasome inhibitor carfilzomib, have not shown neurotoxic side effects and may prove beneficial.
- Disease-related factors, such as unfavorable cytogenetic features, play an important role in treatment selection. Newer therapeutics, like carfilzomib, have comparable activity in patients with unfavorable cytogenetic features.
- Refractory/relapsed MM patients have, normally, failed several lines of treatment. Such patients are encouraged to enroll in clinical trials of investigational therapeutics or in trials of novel combinations of approved drugs.

Gap Analysis

Practice Gap	***Educational Need***	***Desired Clinician Change***	***Learning Objective***
Clinicians are not aware of, or do not understand current definitions related to relapsed/refractory MM patient populations	Standardized definitions for relapsed/refractory MM need to be used to ensure effective use and correct interpretation of clinical trial data	Improved knowledge of definitions of relapsed/refractory MM as per *International Myeloma Workshop Consensus Panel 1* recommendations	Describe relapsed/refractory MM patient populations according to international standards
Clinicians are not familiar with all factors guiding treatment decisions in the relapsed/refractory MM setting	A number of factors need to be considered when making treatment decisions for relapsed/refractory MM patients	Improved understanding of patient-, disease- and regimen-related factors when devising a treatment plan for relapsed/refractory MM patients	Summarize factors influencing the selection of therapy for relapsed/refractory MM
A plethora of available treatment approaches for relapsed/refractory MM complicates optimal treatment selection	Given the wide range of treatment options, clinicians will benefit from education on the efficacy and safety of available agents and drug combinations	Improved understanding of the scope and limitations of existing treatment options	Assess the efficacy and safety data on current therapeutic options for relapsed/refractory MM
Clinicians might not be fully aware of new treatments that are being investigated in late-stage clinical trials	A number of investigational drugs and novel combinations of approved therapeutics are currently in clinical trials; ongoing education will help clinicians to effectively incorporate new treatments into practice	Improved knowledge of investigational therapies and emerging treatment modalities	Analyze data on novel treatments for relapsed/refractory MM

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Proposed Title for Program

Achieving Optimal Care for the Relapsed/Refractory Multiple Myeloma Patient

Learning Objectives

1. Describe relapsed/refractory MM patient populations according to international standards
2. Summarize factors influencing the selection of therapy for relapsed/refractory MM
3. Assess the efficacy and safety data on current therapeutic options for relapsed/refractory MM
4. Analyze data on novel treatments for relapsed/refractory MM

Proposed Agenda

1. Classification of relapsed/refractory MM patient populations according to International Myeloma Workshop Consensus Panel 1 recommendations
2. Patient-, disease- and regimen-related factors influencing treatment plan decisions for relapsed/refractory MM patients
3. Efficacy and safety of current therapeutic options for the treatment of relapsed/refractory MM
4. New and emerging treatment options for relapsed/refractory MM