MAYO CLINIC

REVIEW

Therapy for Relapsed Multiple Myeloma: Guidelines From the Mayo Stratification for Myeloma and Risk-Adapted Therapy

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Abstract

Life expectancy in patients with multiple myeloma is increasing because of the availability of an increasing number of novel agents with various mechanisms of action against the disease. However, the disease remains incurable in most patients because of the emergence of resistant clones, leading to repeated relapses of the disease. In 2015, 5 novel agents were approved for therapy for relapsed multiple myeloma. This surfeit of novel agents renders management of relapsed multiple myeloma more complex because of the occurrence of multiple relapses, the risk of cumulative and emergent toxicity from previous therapies, as well as evolution of the disease during therapy. A group of physicians at Mayo Clinic with expertise in the care of patients with multiple myeloma regularly evaluates the evolving literature on the biology and therapy for multiple myeloma and issues guidelines on the optimal care of patients with this disease. In this article, the latest recommendations on the diagnostic evaluation of relapsed multiple myeloma and decision trees on how to treat patients at various stages of their relapse (off study) are provided together with the evidence to support them.

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Multiple myeloma, a malignant disorder of clonal plasma cells, remains incurable in most patients despite the development of novel therapies that have improved the depth and duration of responses and prolonged survival for many patients with this disease.[1,2] Advances in our understanding of the biology of the disease aided by novel technologies such as next-generation sequencing show that genetically, the disease is highly heterogeneous,[3-7] although it is possible to stratify patients into different disease risk groups, an approach that can have a meaningful effect on the choice of therapy and clinical outcomes.[8,9] In parallel with this understanding, the field has witnessed a sea change with the development of many novel therapeutic agents, including immunomodulatory drugs (IMiDs) such as lenalidomide[10] and pomalidomide[11,12]; proteasome inhibitors (PIs) including bortezomib, carfilzomib, and ixazomib[13,14]; monoclonal antibodies (MAbs) including daratumumab[15] and elotuzumab[16]; and histone deacetylase inhibitors such as panobinostat[17] that have continued to improve overall survival in patients with this disease. The availability of so many novel agents has led to the development of a multitude of viable treatment options that have also altered the paradigm of therapy. Concomitantly, the

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ARTICLE HIGHLIGHTS

- Major advances have occurred in the therapy of multiple myeloma with several new classes of agents approved in 2015.
- Therapy of relapsed multiple myeloma is becoming more complex due to the development of such novel agents.
- Restaging of myeloma and evaluation for disease evolution is important at the time of relapse.
- Combination therapy that incorporates novel agents such as monoclonal antibodies is recommended.
- Patients should be considered for stem cell transplant at time of relapse.
- The disease can evolve to secondary plasma cell leukemia or extramedullary myeloma at any time.
- Guidelines for therapy of first, second, or third relapse of the disease are provided.

application of tools that reliably assess the "frailty" of patients with myeloma is also helping with decision making, given that many patients with myeloma are elderly and often have significant comorbidities.[18,19]

More than 25 Mayo Clinic physicians with a special interest in the care of patients with multiple myeloma have developed guidelines for therapy for this disease that are based on consensus after a careful review of the current literature. This led to the development of the Mayo Stratification for Myeloma and Risk-Adapted Therapy. The group has published guidelines for newly diagnosed myeloma in 2007, 2009, and 2013.[20-22] These guidelines, which are available online at http://www.msmart.org, are updated regularly as new data become available. Given the recent developments in therapy, Mayo Clinic physicians have updated their consensus opinion on optimal therapy for relapsed multiple myeloma, and these guidelines and their justification are presented. Emphasis is based on the outcomes from randomized controlled trials, but if such data do not exist, the guidelines are based on consensus within the group. We used a standard system for rating the evidence and grading of recommendations as outlined in Table 1. It should be stressed from the outset that it is always preferable to enroll patients in well-designed clinical trials, but if this is not possible, then we follow these guidelines, taking into account the patient's comorbidities[23,24] and wishes after a discussion of various treatment options, the expected toxicity, and potential outcomes.

Given that this article relates only to therapy for relapsed multiple myeloma, we will not discuss the diagnosis and initial management of the disease. The reader is referred to various guidelines that have been published by our group in this regard.[20-22]

DRUGS APPROVED FOR THERAPY FOR MULTIPLE MYELOMA

Currently, there are 6 classes of medications that are used for therapy for relapsed multiple myeloma: (1) IMiDs, (2) PIs, (3) histone deacetylase inhibitors, (4) MAbs, (5) DNA alkylating agents, and (6) glucocorticosteroids. Other agents such as doxorubicin, cisplatin, and etoposide are also often used in combination chemotherapy for multiple myeloma. Although many of these have single agent activity, when used alone the duration of response is limited and the depth of response achieved is often poor. However, when agents from these various classes are used in combination, they are highly active and lead to responses of considerable duration, especially when used in synergistic combinations that also reduce the risk of toxicity. Many of these agents have been used in combination therapy, and we provide a list of randomized studies of therapies for relapsed multiple myeloma in Table 2.

Immunomodulatory Drugs

The prototype IMiD was *thalidomide*,[39,40] although it is not often used in the United States because of the neurotoxicity, fatigue, constipation, and cost. However, it may still be a useful agent, especially in patients with renal insufficiency or cytopenias, in whom it can be safely used and even combined with other agents such as alkylating agents,[41-45] dexamethasone, and PIs with good effect.[29,43,46,47]

Lenalidomide is a second-generation IMiD that is more potent and generally has a better safety profile than does thalidomide. Lenalidomide is approved for initial therapy for myeloma and for relapsed disease. The

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