

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Emerging Options for Combination Therapy in Multiple Myeloma



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H&O How has the diagnosis of multiple myeloma evolved?

AR Previously, the definition of active disease required the presence of myeloma cells, an M spike, and end organ damage, meaning the patient had to meet the CRAB criteria: Calcium, Renal disease, Anemia, and/or Bone involvement. In recent years, a subgroup known as ultra-high-risk smoldering myeloma was added to the definition of myeloma. These patients have marrow involvement exceeding 60%, a light chain ratio over 100, or more than 1 focal lesion as identified by magnetic resonance imaging. These 3 factors are considered myeloma-defining events or biomarkers of disease. In these patients, the risk of progressing to active disease within 2 years is approximately 90%. Patients with these characteristics should receive treatment.

H&O What are the goals of treatment?

AR It is now possible to consider the specifics of not only the disease but also the patient, including any comorbidities, to form an overall picture. I believe in personalizing the treatment goal, as well as the management strategy, to each patient. Ideally, the goal for every newly diagnosed fit patient is to achieve a deep complete remission, currently defined as the absence of minimal residual disease. In a patient who is elderly or frail, however, this goal may do more harm than good, and improving quality of life should be a major consideration.

H&O What types of therapy are currently in use?

AR The armamentarium has grown lately. The backbone remains immunomodulatory therapy, and 3 agents are now approved: lenalidomide (Revlimid, Celgene), pomalidomide (Pomalyst, Celgene), and thalidomide. Proteasome inhibitors are another important component; the available ones are bortezomib (Velcade, Takeda), carfilzomib (Kyprolis, Amgen), and ixazomib (Ninlaro, Takeda). Unfortunately, corticosteroids remain a part of

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every treatment regimen, as well. The newest and most exciting class of drugs is the monoclonal antibodies. Daratumumab (Darzalex, Janssen) and elotuzumab (Empliciti, Bristol-Myers Squibb) were approved in 2015. There is also one histone deacetylase inhibitor, panobinostat (Farydak, Novartis). Alkylating agents are also used, alone or in combination with novel agents. Mixing and matching agents from these classes of therapies has translated into improvements in outcome and survival for our patients.

H&O What is the first-line treatment approach?

AR The approach is personalized to the patient. The most reasonable first-line therapy is a triplet regimen, unless there is a compelling reason not to use one. Based on data presented at the 2016 American Society of Hematology meeting and published in *Blood* by Moreau and colleagues, the most powerful triplet consists of an immunomodulatory drug (IMiD), a proteasome inhibitor, and a corticosteroid. We now see overall response rates of more than 90%, and even up to 100% in certain data sets.

H&O How do you determine when to move to another line of therapy?

AR The guidelines state that a new treatment should be initiated at the time of progression or relapse. Relapse is defined as a complete remission followed by a resurgence of the disease. There are 2 different ways of thinking about progression. Previously, progression was defined as any manifestation of end-organ damage; this is now known as a clinical relapse. With the recent ability to monitor patients so closely, identification of a biochemical relapse is now another way to define progression. The International Myeloma Working Group provides specific definitions of progression based on criteria for levels of protein in the serum and urine, as well as the ratio of light chains. Another time to change therapy is when a patient becomes intolerant to the current regimen.

H&O When is combination therapy considered?

AR The short answer is “always.” There needs to be a compelling reason not to use combination therapy. In general, the goal of treatment is to induce remission. Whether used as induction therapy in newly diagnosed disease or for treatment in relapse, triplets are the most effective tools to achieve remission. A single drug used as continuous therapy can be used to prolong remissions as maintenance therapy.

H&O What types of agents are used together?

AR The most common combination remains an IMiD, a proteasome inhibitor, and a corticosteroid. The monoclonal antibody daratumumab now has an indication for use in combination with a proteasome inhibitor or an IMiD. Elotuzumab is partnered with an IMiD, but data also support use with a proteasome inhibitor. Several combinations consist of an IMiD with an alkylator, particularly cyclophosphamide. Cyclophosphamide has also been used with the proteasome inhibitors bortezomib and carfilzomib.

H&O What is known about how to sequence agents in the relapsed setting?

AR There is no standard sequence regimen in the relapsed/refractory setting, and use varies among different treatment centers. It can be helpful to review the eligibility criteria of certain clinical trials, noting the previous treatments that patients received before starting the study drug. Most high-volume myeloma centers establish a protocol based on clinical experience or trial data. In general, this area requires more attention. The field is moving quickly, and clear guidelines will likely not be available for some time. Approaches to sequencing can be based on factors such as the patient’s history, comorbidities, and tolerability of prior therapies. Increasing data suggest that mechanisms of resistance might be overcome by using the synergy associated with different combinations, and this knowledge may help inform a more logical decision-making process. Studies with response-adapted therapies are not available, but would be helpful.

H&O Is it known whether certain treatments will work better in certain types of patients?

AR This is another area under study. Multiple myeloma is still considered a single disease. Subtyping is more precise in many other malignancies, such as lymphoma and leukemia. Anecdotally, it is recognized that there are several different types of myeloma. Physicians can identify patients who are particularly sensitive or resistant to certain types of therapy. There are patients who maintain a remission for years, and others who do not make it to 6 months. The disease has different clinical manifestations, but it is not yet known how to identify them up-front. Certain therapies are toxic or have overlapping toxicities. For example, it is necessary to avoid a drug associated with neuropathy in a patient who has diabetes or who developed neuropathy from prior chemotherapy.

H&O What is known about the genetic components of multiple myeloma?

AR We are learning more about the “personality” of myelomas. Translocations are an important component of the disease. The t(4;14) translocation was previously considered an adverse finding, but the negative effects can be overcome with proteasome inhibitors. Similarly, pomalidomide overcomes the negative effects of the 17p deletion. New drugs such as venetoclax (Venclexta, AbbVie/Genentech) seem particularly beneficial for patients with a t(11;14) translocation. Novel technologies will help define the disease. For example, next-generation sequencing can identify targetable mutations via

molecular profiling. Classification of multiple myeloma might follow that of some solid tumors, which are categorized based on a targetable driving mutation rather than the anatomic site or cell of origin.

H&O Are there any other promising areas of research?

AR An exciting development in hematology is the chimeric antigen receptor T-cell therapies. Signaling lymphocytic activation molecule family member 7 (SLAMF7) and the B-cell maturation antigen (BCMA) are targets in multiple myeloma. BCMA is being targeted with antibodies or bispecific T-cell engagers, as well.

At the 2017 ASH meeting, Dr Adam Cohen presented early data for a study of BCMA-specific CAR T cells. The report provided data for 21 treated patients with multiple myeloma. Three regimens were evaluated: 5×10^8 CAR T cells alone (cohort 1), cyclophosphamide at 1.5 g/m^2 plus 5×10^7 CAR T cells (cohort 2), and cyclophosphamide at 1.5 g/m^2 plus 5×10^8 CAR T cells (cohort 3). In cohort 1, 6 of 9 patients responded, with 1 ongoing stringent complete response at 21 months, and other responses lasting 1.5 months to 5 months. In cohort 2, responses were seen in 2 of 5 patients, but each patient developed progressive disease (at 2 months and 4 months). In cohort 3, at a median follow-up of 1 month, 5 of 6 patients responded, and 1 was not yet evaluable.

We are also learning more about the microenvironment, allowing for therapeutic targeting beyond the malignant cells. For example, evidence suggests that T cells may be a potential target.

H&O Do you have any other suggestions on the management of patients with multiple myeloma?

AR It is important to realize that we are not just treating myeloma, but the whole patient. It is necessary to consider a patient's preferences and maximize the use of

supportive care. For example, bone strengthening with bisphosphonates prevents skeletal-related events and can also improve survival. It is important to control pain, and to focus on renal health. A goal should be to maintain the patient's quality of life.

Disclosure

Dr Rossi is an advisor for Celgene, Amgen, Janssen, and Thrasos.

Suggested Readings

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

Chng WJ, Dispenzieri A, Chim CS, et al; International Myeloma Working Group. IMWG consensus on risk stratification in multiple myeloma. *Leukemia*. 2014;28(2):269-277.

Cohen AD, Garfall AL, Stadtmauer EA, et al. Safety and efficacy of B-cell maturation antigen (BCMA)-specific chimeric antigen receptor T cells (CART-BCMA) with cyclophosphamide conditioning for refractory multiple myeloma (MM) [ASH abstract 505]. *Blood*. 2017;130(suppl 1).

Ely S, Forsberg P, Ouansafi I, et al. Cellular proliferation by multiplex immunohistochemistry identifies high-risk multiple myeloma in newly diagnosed, treatment-naive patients. *Clin Lymphoma Myeloma Leuk*. 2017;17(12):825-833.

Mark TM, Guarneri D, Forsberg P, et al. A phase I trial of high-dose lenalidomide and melphalan as conditioning for autologous stem cell transplantation in relapsed or refractory multiple myeloma. *Biol Blood Marrow Transplant*. 2017;23(6):930-937.

Mikhael JR, Dingli D, Roy V, et al; Mayo Clinic. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines 2013. *Mayo Clin Proc*. 2013;88(4):360-376.

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

Palumbo A, Avez-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: a report from International Myeloma Working Group. *J Clin Oncol*. 2015;33(26):2863-2869.

Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15(12):e538-e548.

Reeder CB, Reece DE, Kukreti V, et al. Long-term survival with cyclophosphamide, bortezomib and dexamethasone induction therapy in patients with newly diagnosed multiple myeloma. *Br J Haematol*. 2014;167(4):563-565.