Multiple Myeloma: New Uses for Available Agents, Excitement for the Future

Presented by Kenneth C. Anderson, MD

Abstract

With the availability of a new proteasome inhibitor, carfilzomib, and a new immunomodulatory drug, pomalidomide, the treatment of multiple myeloma has become more effective. The updated NCCN Clinical Practice Guidelines in Oncology for Multiple Myeloma provide new recommendations for use of carfilzomib and pomalidomide. As new classes of drugs such as monoclonal antibodies become available, the treatment landscape will be rendered even brighter. (J Natl Compr Canc Netw 2015;13:694–696)

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Multiple Myeloma contain 2 important updates that should translate into more effective treatment with available agents. However, what is particularly exciting to Kenneth C. Anderson, MD, Chair of the NCCN Guidelines Panel, are the novel classes of drugs that will someday enter the armamentarium.

"Immunotherapies and other novel approaches will soon be coming to the clinic," predicted Dr. Anderson, the Kraft Family Professor of Medicine at Harvard Medical School and the Director of the Lebow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center at Dana-Farber Cancer Institute.

Presented by Kenneth B. Anderson, MD, Kraft Family Professor of Medicine at Harvard Medical School and the Director of the Lebow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center at Dana-Farber Cancer Institute, Boston, Massachusetts.

Dr. Anderson has disclosed that he has served as a paid scientific advisor to Acetylon Pharmaceuticals, Inc., Celgene Corporation, Gilead, Multiple Myeloma Research Foundation, OncoPep, Onyx Pharmaceuticals, Inc., and sanofi-aventis U.S., and received other financial benefit from Acetylon Pharmaceuticals, Inc. and OncoPep.

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Key Update to the NCCN Guidelines

Meanwhile, there are new ways to use current agents, according to recommendations in the 2015 NCCN Guidelines:

- Panobinostat/bortezomib/dexamethasone as a category 1 option for relapsed myeloma in patients who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent (IMID);
- Carfilzomib/lenalidomide/dexamethasone as a category 1 option for relapsed myeloma;
- Carfilzomib/lenalidomide/dexamethasone as a category 2A option as primary therapy for transplant candidates; and
- Lenalidomide plus low-dose dexamethasone (recommended last year as primary therapy for non-transplant patients as a result of the FIRST trial[1]) to be given continuously until progression.

Which Patients to Treat? Spectrum is Changing

The definition of multiple myeloma has recently changed, and therefore impacts which patients to treat. The International Myeloma Working Group recently listed the following requirements for the diagnosis of active disease[2]:

- Bone marrow plasmacytosis 60% or greater;
- Abnormal free light chain ratio 100 (involved kappa) or greater or less than 0.01 (involved lambda); and
- Focal bone marrow lesions detected by functional imaging, including PET/CT and/or MRI.

"For the diagnosis of active myeloma in the asymptomatic patient, this is a major change," Dr. Anderson stated. "The spectrum of disease we are now treating is changing." The new definition will help redefine the subset of patients with "smoldering myeloma" who have a 50% risk of progression within 18 months.

Research is defining tumor and host factors that correlate with progression to active disease, and which trials

of novel agents and immune therapies are attempting to delay or prevent this progression. At Dana-Farber Cancer Institute, Dr. Anderson has been leading a study of vaccines that target multiple myeloma antigen-specific peptides to achieve this goal.

For risk assessment in patients with newly diagnosed disease, conventional genomics are still the standard modality, but the efficacy of proteasome inhibitors has largely overcome the adverse prognosis conferred by the t(4:14) translocation. The emerging immune therapies will no doubt alter this even further, he predicted.

Latest Regimens Generate Robust Responses

Patients with newly diagnosed disease are best served with a triplet combination of an IMID, a proteasome inhibitor, and dexamethasone, according to Dr. Anderson. Lenalidomide/bortezomib/dexamethasone (RVD) and cyclophosphamide/bortezomib/dexamethasone (CyBorD) generate responses in more than 90% of patients, including complete responses (CRs) in more than 60%. Most patients then receive high-dose therapy, autologous transplant, and maintenance until progression.

The incorporation of a proteasome inhibitor assures that patients at high risk can have equally good outcomes as those at standard risk. The approval of carfilzomib has enhanced outcomes seen with bortezomib, and the oral proteasome inhibitor ixazomib may be even more beneficial. Ixazomib is now being tested with lenalidomide/dexamethasone in the upfront and relapsed settings, and could be approved in 2015.

Is Transplant Still Needed?

The excellent upfront response to novel therapies has raised the question of whether early transplant is still warranted. The jury is still out on this question, Dr. Anderson said. Retrospective studies have suggested that outcomes after early transplant are not significantly better than those achieved with contemporary induction regimens.[3–5] A recent prospective trial showed only a small advantage for transplant, but the induction regimen was suboptimal.[6]

"We still don't know whether transplant early or late is valuable, but we do know that new strategies can achieve an extent of response that we have not seen before," Dr. Anderson observed.

The value of transplant may be determined by the ongoing IFM/DFCI 2009 study involving 1000 patients with newly diagnosed multiple myeloma. All patients receive RVD and are then randomized to standard treatment with high-dose therapy and autologous stem cell transplantation followed by lenalidomide maintenance versus additional RVD followed by lenalidomide maintenance, with transplant on relapse. The only variable is early versus delayed transplant. The trial will also rigorously assess minimal residual disease with multicolor flow cytometry, sequencing, and new imaging modalities, as well as determine whether maintenance can be discontinued in patients without minimal residual disease.

Current Agents in Relapsed Disease

By end of 2015, Dr. Anderson expects that several new strategies will be approved for use in multiple myeloma. Some of these new strategies could involve experimental agents that are currently showing great promise in trials of relapsed disease.

Pomalidomide plus low-dose dexamethasone produced responses in about one-third of patients with disease refractory to lenalidomide, bortezomib, or both in the phase III STRATUS study.[7] Another 2014 study combined pomalidomide with bortezomib/dexamethasone in lenalidomide-refractory disease and showed an 84% to 86% response rate and median progression-free survival (PFS) of 16 months in patients with standard-risk disease versus 9.5 months in those with high- or intermediate-risk disease.[8]

Carfilzomib/lenalidomide/dexamethasone also made news last year by reducing progression by 34% in the ASPIRE trial, without adding cardiac toxicity.[9] Even more impressive was the combination of carfilzomib/pomalidomide/dexamethasone, which produced a 70% response rate and median duration of response of 18 months.[10] These results suggest that a second-generation IMID plus a second-generation proteasome inhibitor has additive benefit.

"We will see these and more and more such triplets in relapsed disease because of their higher overall and extent of response," Dr. Anderson said.

Novel Approaches to Relapsed Disease

Promising new classes of drugs include monoclonal antibodies (Figure 1). Elotuzumab, daratumumab, and

SAR650984 exert effects through antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and/or apoptosis or growth arrest via intracellular signaling pathways. When these monoclonal antibodies are used in combination with lenalidomide/dexamethasone, response rates of up to 90% and durations of response up to 3 years are seen, even in high-risk disease. Dr. Anderson predicted that elotuzumab and daratumumab are likely to be approved in 2015.

In current studies, he noted, "The numbers are small but the concept is special…. In subsets refractory to all FDA-approved myeloma drugs, antibodies are working."

The immunotoxin indatuximab ravtansine (BT062) links the CD138 monoclonal antibody targeting syndecan on myeloma cells to a maytansanoid toxin, and is another potent approach that has been combined with lenalidomide/dexamethasone. In relapsed/refractory multiple myeloma, it has demonstrated an 83% response rate in a small 2014 study.[11]

Protein degradation via histone deacetylase (HDAC) inhibition is another novel strategy. Panobinostat was approved in 2014 as a result of a PFS benefit shown in PANORAMA-1,[12] but tolerability was a concern. Toxicity is expected to be less with selective HDAC6 inhibitors, in particular, the oral drug ricolinostat (ACY-1215). In combination with lenalidomide/dexamethasone, ricolinostat produced responses even in patients with lenalidomide-refractory disease.[13]

Additional drugs in early development include novel agents targeting Bruton tyrosine kinase (BTK), kinesin spindle protein (KSP), cyclin dependent kinases (CDKs), bromodomain 4, and nuclear transport. Additionally, researchers are able to target uncommon mutations, such as *BRAF*, and treat patients earlier in the disease course to impede clonal evolution. The PD1 inhibitors may also prove valuable when used in combination with immunomodulatory drugs, monoclonal antibodies, and vaccines. Finally, inhibitors of serine threonine kinase 4 may be able to restore tumor suppressor function in myeloma.

Concluding, Dr. Anderson suggested that the future is bright for new treatment avenues in this disease. "Myeloma has become a chronic illness in many patients," he noted. "As we have more classes of novel agents, especially immunotherapies, it will become a chronic illness in the majority of patients, with curative potential."

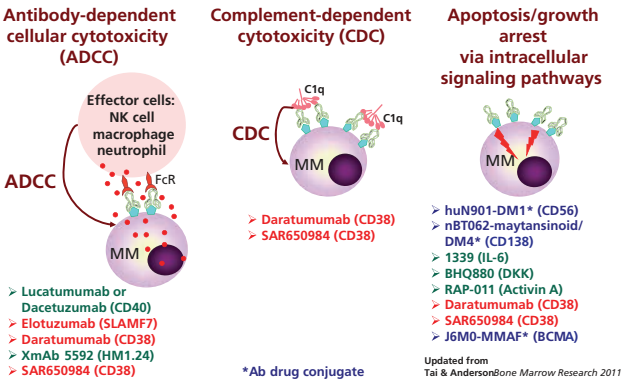

Figure 1 Monoclonal antibody–based therapeutic targeting of multiple myeloma.
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