Therapeutic Advances in Relapsed or Refractory Multiple Myeloma

Presented by Kenneth C. Anderson, MD

Abstract

The past decade has been a time of rapid progress in multiple myeloma, but the future therapeutic landscape may be even more promising, as new agents are better tolerated and novel pathways are exploited. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) now include the proteasome inhibitor carfilzomib and immunomodulatory drug pomalidomide, which are more potent than previous generations of these drugs have been. These agents are extending progression free and overall survival of patients with relapsed refractory myeloma, as is maintenance therapy with lenalidomide after initial therapy of patients with newly diagnosed disease. At the NCCN 18th Annual Conference, Dr. Kenneth C. Anderson from Dana-Farber Cancer Institute reviewed the data leading to the approval of these exciting agents, discussed the efficacy of current regimens, and described the future landscape and the exciting potential of new agents to further improve and extend the lives of patients with myeloma. (*JNCCN* 2013;11:676–679)

I believe not only that multiple myeloma will be a chronic illness, but also that we will see sustained complete responses in a significant fraction of patients,” predicted Kenneth C. Anderson, MD, as he described the emerging landscape in multiple myeloma at the NCCN 18th Annual Conference. Dr. Anderson is the Kraft Family Professor of Medicine at Harvard Medical School and Director of the Lebow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center at Dana-Farber Cancer Institute.

Presented by Kenneth C. Anderson, MD, Kraft Family Professor of Medicine, Harvard Medical School; Director, LeBow Institute for Myeloma Therapeutics; and Director, Jerome Lipper Multiple Myeloma Center, at Dana-Farber Cancer Institute and Brigham and Women's Cancer Center, Boston, Massachusetts.

Dr. Anderson has disclosed that he has served as a consultant for Celgene Corporation; Onyx Pharmaceuticals, Inc.; Gilead Sciences; and sanofi-aventis U.S. and is Scientific Founder: Acetylon, Oncoprep.

Correspondence: Kenneth C. Anderson, MD, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215-5450. E-mail: kenneth_anderson@dfci.harvard.edu

Eight regimens have been approved in the past decade, 2 in the past 7 months, Dr. Anderson noted. By targeting myeloma cells in the bone marrow microenvironment, these drugs have increased overall survival (OS) 3-fold, with additional gains expected from maintenance therapy. “But new approaches are still needed to treat and ultimately prevent relapse. Fortunately, there are exciting novel targeted agents on the horizon,” he said.

First-Line Combinations

After the second-generation proteasome inhibitor carfilzomib was approved for relapsed refractory myeloma, it was then combined with lenalidomide and dexamethasone (CRd) and evaluated as therapy for newly diagnosed disease. Due to a high overall and extent of response, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for multiple myeloma regarding transplant candidates were updated to include this triplet as an initial treatment option under “other regimens.” This joins a growing list of triplets that greatly increase response rates (Figure 1). The combination of lenalidomide/bortezomib/dexamethasone (RVD) has “markedly changed the treatment paradigm,” he said, noting that three-quarters of patients experience at least a very good partial response and half experience a complete or near complete response (CR/nCR). High overall response rates (ORR) are also observed with (cyclophosphamide/bortezomib/dexamethasone (CVD, CyBorD).

Combinations of novel agents used for consolidation after transplant greatly increase the depth and duration of response. Increasingly, molecular CRs are being achieved, that is, patients are negative for minimal residual disease as assessed by polymerase chain reaction or multicolor flow cytometry. This was demonstrated in the GIMEMA study of bortezomib/thalidomide/dexamethasone (VTD) induction before autologous transplant and consolida-

Relapsed or Refractory Multiple Myeloma

Figure 1 Combinations in the first-line treatment of multiple myeloma. Reprinted from Stewart AK, Richardson PG, San-Miguel JF. How I treat multiple myeloma in younger patients. *Blood* 2009;114:5436–5443; with permission. Abbreviations: CR/nCR, complete or near complete response; ORR, overall response rate; VGPR, very good partial remission.

tion after transplant.¹ Molecular CR was previously achieved only with allogeneic transplant.

Maintenance therapy with lenalidomide became a critical part of treatment based on the landmark CAL-GB 100104 study.² Progression-free survival (PFS) was doubled, from 27 months to 46 months ($P < .001$), and despite 80% crossover, an OS advantage was also seen ($P = .028$). “This has been a huge advance,” Dr. Anderson commented. He called concerns about second malignancies arising after lenalidomide maintenance “appropriate,” noting an increase of 2- to 3-fold, but pointed out the influence of other factors, including advanced age, male gender, late stage of disease, and exposure to DNA-damaging alkylating agents before transplantation, which are less commonly used now.

Improving Outcomes With Salvage Therapy With New Agents

The updated 2013 NCCN Guidelines include the addition of the proteasome inhibitor carfilzomib and the immunomodulatory agent (IMiD) pomalidomide plus low-dose dexamethasone as preferred salvage therapy options for relapsed/refractory disease. “Other regimens” now also include bortezomib/vori-

nostat and lenalidomide/bendamustine/dexamethasone. Although established salvage regimens achieve response rates of 40% to 60% and prolong PFS to approximately 1 year and OS to nearly 3 years, these new agents help fill an unmet medical need when disease is no longer sensitive to available therapies (Figure 2), he said.

Pomalidomide

Pomalidomide, a more potent IMiD than lenalidomide, was approved in combination with low-dose dexamethasone (pom/dex) based on the randomized phase II MM-002 trial, which evaluated pom/dex in heavily pretreated patients with relapsed or refractory disease.³ The ORR was 34% with the combination versus 15% with pomalidomide alone; the disease control rate was 81%; and the duration of response was 8.3 months. The major side effects were hematologic, though the regimen was generally well tolerated with dose reductions.

Phase II trials from the Mayo Clinic supported these findings and identified factors that predict for better outcomes.⁴ European investigators also confirmed PFS and OS advantages for pom/dex versus high-dose dexamethasone in heavily pretreated patients with relapsed or refractory disease, yielding a median PFS of 3.6 months ($P < .001$) and an OS that was not yet reached ($P < .001$).⁵ “Pom/dex works when lenalidomide and bortezomib do not in about a third of patients,” Dr. Anderson noted.

	Frontline Treatment	Relapsed	Unmet Need Relapsed or Intolerant
Expected survival (mo)	20–50	14–16	6–10
Sensitivity to therapy	Sensitive	Less sensitive/resistant	Resistant
Treatment limitations, comorbidities	Peripheral neuropathy (~15% at diagnosis)	>80% incidence of peripheral neuropathy; compromised marrow reserve; cytopenia	Intolerant to or ineligible for available therapy
Elderly population (↑ risk for heart, lung, renal, liver dysfunction, diabetes)			

Figure 2 The unmet need in myeloma for better treatment for relapse and refractory disease. Durie BGM. Concise Review of the Disease and Treatment Options; Multiple Myeloma, Cancer of the Bone Marrow. 2011/2012 ed. International Myeloma Foundation; North Hollywood, CA. Available at http://myeloma.org/pdfs/CR2011-Eng_b1.pdf. Accessed May 6, 2013.

Anderson

Studies are underway to support full approval of pomalidomide in patients who have received 1 to 3 prior therapies (the current indication is for relapsed and refractory disease). These studies are based on the phase I MM-005 trial in which pomalidomide/bortezomib/dexamethasone showed responses in 73% of patients, with at least very good partial response in 27%.⁶ “We are quite excited about the concept of combining an IMiD with a proteasome inhibitor, which has now been proven again with this trial,” he said.

Carfilzomib

Carfilzomib is a novel proteasome (chymotryptic) inhibitor with highly selective and irreversible proteasome binding, which yields durable responses in relapsed and refractory disease, without neuropathy. Carfilzomib was approved based on an open-label phase II study involving patients with heavy pretreatment. In this study, the ORR was 23.7%, median duration of response was 7.8 months, median OS was 15.6 months, and adverse events were manageable without cumulative toxicities. Only 12.4% of patients experienced peripheral neuropathy, which was primarily low-grade.⁷

Researchers have shown great interest in using CRd. Response rates of almost 80% and at least very good partial response rates of 41% have been seen in patients with relapsed myeloma.⁸ The phase III ASPIRE trial comparing CRd to Rd is expected to be positive. “Already, this regimen has moved into the upfront setting in myeloma based on the universally high response rates,” he said.

Higher doses of carfilzomib (20/56 mg/m²) may be even more effective than the indicated dose of 20/27 mg/m² plus dexamethasone 4 mg. However, Dr. Anderson urged caution in escalating doses of carfilzomib or combining novel IMiDs and proteasome inhibitors to increase response, based on some studies suggesting that toxicity is increased.⁹ “We have wonderful new agents, at least a log more potent, than prior-generation drugs, but because they are more potent, the therapeutic index may be very narrow,” he explained.

Novel Agents: Even More Active

Many agents are in the pipeline in myeloma, including some with new mechanisms of action. “These are the ones I think have the greatest potential,” he said.

“We are excited to finally have monoclonal antibodies in myeloma,” he said (Figure 3). Elotuzumab is a humanized monoclonal immunoglobulin G1 antibody targeting CS1, which is expressed on myeloma cells. In a recent phase II trial in relapsed myeloma, elotuzumab 10 mg/kg combined with lenalidomide/dexamethasone yielded an ORR of 92% and median PFS of 20.8 months.¹⁰ Dr. Anderson said updated results show median PFS is now 24 months “and going strong,” suggesting that the addition of this antibody markedly augments the efficacy of lenalidomide/dexamethasone.

Daratumumab targets CD38 and has broad-spectrum killing activity. In a phase I-II study in advanced myeloma, two-thirds of patients showed at least a minor response with the single agent, and future studies will combine it with lenalidomide/dexamethasone.¹¹

An intriguing class of drugs includes molecules targeting the ubiquitin proteasome system (UPS). The UPS includes the proteasome, which rids cells of unwanted proteins. The deubiquitylating agents (DUBs) target the UPS upstream of the proteasome and may overcome resistance to proteasome inhibitors.¹² Promising studies in animal models are providing the rationale for clinical trials of DUBs in the future. A next-generation oral proteasome inhibitor, MLN9708 (ixazomib), is highly active against

Figure 3 MAB-based therapeutic targeting of myeloma. Reprinted from Tai YT, Anderson KC. Antibody-based therapies in multiple myeloma. *Bone Marrow Res* 2011;924058; with permission.

Relapsed or Refractory Multiple Myeloma

myeloma cell lines and patient cells in preclinical studies, including those resistant to bortezomib, Dr. Anderson reported. In a phase I-II trial of 46 patients with relapsed or refractory disease, 35 patients experienced clinical benefit.¹³ Combinations of MLN 9708 with lenalidomide/dexamethasone achieve high response rates in relapsed and newly diagnosed disease, suggesting the potential of an all oral treatment regimen.

Also exciting is the potential for new targets in myeloma, Dr. Anderson said. Bruton tyrosine kinase inhibitors are proving to be dynamic new agents in other hematologic malignancies and may be active in myeloma as well, since the Bruton tyrosine kinase is implicated in the maturation and function of osteoclasts. “The major activity of this drug is in the microenvironment of the bone, and it has some impact on the tumor cell as well. Clinical trials are ongoing in myeloma,” he reported.

The second new target is the acetyl-lysine recognition domain (bromodomain) 4, which regulates the expression of the c-Myc oncoprotein. Bromodomain 4 blocking completely abrogates c-Myc expression and function and triggers anti-myeloma activity.¹⁴

Rationally based combination therapies—in particular, proteasome inhibitors plus inhibitors of histone deacetylase to inhibit proteasomal and aggresomal degradation of protein, respectively—also achieve synergistic myeloma cytotoxicity in preclinical studies. In the Vantage 088 trial of relapsed and refractory myeloma,¹⁵ vorinostat combined with bortezomib appeared promising, but toxicity led to many discontinuations of the regimen. Clinical trials of more selective oral histone deacetylase-6 inhibitors (ACY1215) with bortezomib¹⁶ are now underway, he said.

References

1. Terragna C, Zamagni E, Petrucci MT, et al. Molecular remission after bortezomib-thalidomide-dexamethasone compared with thalidomide-dexamethasone as consolidation therapy following double autologous transplantation for multiple myeloma: results of a qualitative and quantitative analysis. *Haematologica* 2011;96(s1):S96. Abstract P224.
2. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med* 2012;366:1770-1781.
3. Jagannath S, Hofmeister CC, Siegel DS, et al. Pomalidomide with low-dose dexamethasone in patients with relapsed and refractory multiple myeloma who have received prior therapy with lenalidomide and bortezomib: updated phase 2 results and age subgroup analysis [abstract]. *Blood* 2012;120: Abstract 450.
4. Lacy MQ, Kumar S, LaPlant B, et al. Pomalidomide plus low-dose dexamethasone in relapsed myeloma: long term follow-up and factors predicting outcome in 345 patients [abstract]. *Blood* 2012;120: Abstract 201.
5. Dimopoulos MA, Lacy MQ, Moreau P, et al. Pomalidomide in combination with low-dose dexamethasone demonstrates a significant progression-free survival and overall survival advantage in relapsed/refractory multiple myeloma: a phase 3, multicenter, randomized, open-label study [abstract]. *Blood* 2012;120: Abstract 6.
6. Richardson PG, Hofmeister CC, Siegel D, et al. MM-005: A phase 1, multicenter, open-label, dose-escalation study to determine the maximum tolerated dose for the combination of pomalidomide, bortezomib, and low-dose dexamethasone in patients with relapsed or relapsed/refractory multiple myeloma [abstract]. *Blood* 2012;120: Abstract 727.
7. Siegel DS, Martin T, Wang M, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. *Blood* 2012;120:2817-2825.
8. Wang W, Bensinger W, Martin T, et al. Interim results from PX-171-006, a phase II multicenter dose-expansion study of carfilzomib, lenalidomide, and low-dose dexamethasone in relapsed and/or refractory multiple myeloma [abstract]. *J Clin Oncol* 2011;29(Suppl 15): Abstract 8025.
9. Papadopoulos KP, Lee P, Singhal S, et al. A phase 1b/2 study of prolonged infusion carfilzomib in patients with relapsed and/or refractory multiple myeloma: updated efficacy and tolerability from the completed 20/56 mg/m² expansion cohort of PX-171-007 [abstract]. *Blood* 2011;118: Abstract 2930.
10. Richardson PG, Jagannath S, Moreau P, et al. A phase 2 study of elotuzumab in combination with lenalidomide and low-dose dexamethasone in patients with relapsed/refractory multiple myeloma: updated results [abstract]. *Blood* 2012;120: Abstract 202.
11. Plesner T, Lokhorst H, Gimsing P, et al. Daratumumab, a CD38 monoclonal antibody in patients with multiple myeloma: data from a dose-escalation phase I/II study [abstract]. *Blood* 2012;120: Abstract 73.
12. Chauhan D, Tian Z, Nicholson B, et al. A small molecule inhibitor of ubiquitin-specific protease-7 induces apoptosis in multiple myeloma cells and overcomes bortezomib resistance. *Cancer Cell* 2012;22:345-358.
13. Richardson PG, Baz R, Wang L, et al. Investigational agent MLN9708, an oral proteasome inhibitor, in patients with relapsed and/or refractory multiple myeloma: results from the expansion cohorts of phase 1 dose-escalation study [abstract]. *Blood* 2011;118: Abstract 301.
14. Delmore JE, Issa GC, Lemieux ME, et al. BET bromodomain inhibition as a therapeutic strategy to target c-Myc. *Cell* 2011;146:904-917.
15. Dimopoulos ME, Jagannath S, Yoon S-S, et al. Vantage 088: vorinostat in combination with bortezomib in patients with relapsed/refractory multiple myeloma: results of a global, randomized phase 3 trial. Presented at the 2011 American Society of Hematology Annual Meeting. Abstract 811.
16. Santo L, Hideshima T, Kung AL, et al. Preclinical activity, pharmacodynamic, and pharmacokinetic properties of a selective HDAC6 inhibitor, ACY-1215, in combination with bortezomib in multiple myeloma. *Blood* 2012;119:2579-2589.