Multiple Myeloma: Advances Reported in 2013 Are Useful in the Clinic

Presented by Kenneth Anderson, MD

Abstract

Studies on multiple myeloma reported in 2013 offer support for maintenance after induction and consolidation in newly diagnosed patients eligible for transplantation and for continued lenalidomide in patients not eligible for transplantation. The newest available agents, carfilzomib and pomalidomide, are approved to treat relapsed/refractory myeloma, and in combination they produce impressive response rates and durability. On the horizon, new classes of agents promise even more impressive gains in remission and survival. (*J Natl Compr Canc Netw* 2014;12:808–811)

Studies reported in 2013 can help clinicians better manage multiple myeloma, while anticipating even better treatments and outcomes after drugs currently in the pipeline become available, according to Kenneth Anderson, MD, Kraft Family Professor of Medicine, Harvard Medical School, Director, LeBow Institute for Myeloma Therapeutics, Dana-Farber/Brigham and Women's Cancer Center, Boston. Dr. Anderson chairs the NCCN Guidelines Panel for Multiple Myeloma, and he described the latest treatment advances and what's on the horizon at the NCCN 19th Annual Conference.

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Dr. Anderson has disclosed that he has served as a scientific advisor for Celgene Corporation, Gilead, OncoPep, Onyx, and sanofi-aventis, and has received other financial benefit from OncoPep and Acetylon.

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Based on data published or presented in 2013, Dr. Anderson gave the following recommendations for the current treatment of newly diagnosed patients:

- In newly diagnosed transplant candidates, 3-drug regimens incorporating immunomodulatory drugs and proteasome inhibitors before and after transplant can prolong progression-free and overall survivals.
- Lenalidomide/dexamethasone until progression is the standard of care for patients with newly diagnosed myeloma not eligible for transplant.
- Lenalidomide maintenance until progression prolongs progression-free and overall survivals; the slightly increased risk of secondary cancers appear to be limited to patients who received melphalan/prednisone or high-dose therapy and autologous stem cell transplant.

From the American Society of Hematology 2013 Meeting

Transplant-Eligible Patients

In transplant-eligible patients, the same novel agents used in induction are increasingly being used for consolidation after transplant to increase the depth and duration of response.

In a study from The Netherlands, carfilzomib plus thalidomide and dexamethasone was given for 4 cycles before transplantation, and then as consolidation.[1] Almost all patients showed response (96%), including those with high-risk features (90%). "This was very impressive, so the use of a proteasome inhibitor before, and as consolidation after, transplant is becoming more of a practice," he observed.

Consolidation is now followed by maintenance therapy, largely based on the impressive outcomes seen in CALGB 100104, where lenalidomide almost doubled the median progression-free survival, offering an overall survival benefit as well.[2] A meta-analysis presented at the American Society of Hematology (ASH) annual conference confirmed the benefit of lenalidomide maintenance, finding a 51% reduction in the risk of recurrence with maintenance.[3]

"What seems to be unfolding is that there is a slight risk of secondary malignancies, but the benefit far outweighs the risk," Dr. Anderson suggested. The risk seems confined to patients who have received melphalan/prednisone or high-dose melphalan before autotransplantation.

What about bortezomib for maintenance? At ASH, Sonneveld et al[4] reported that bortezomib-based maintenance consistently improved progression-free survival and that median overall survival had not been reached; long-term outcomes were also improved in patients presenting with renal failure.

Nontransplant Candidates

At the ASH plenary session, results from the pivotal FIRST trial lent support to the concept of continuous treatment in newly diagnosed patients who are *not* transplant candidates.[5] In this trial, patients were randomized to receive continuous lenalidomide plus low-dose dexamethasone until progression, lenalidomide for 72 weeks, or melphalan/prednisone/thalidomide for 72 weeks. Continuous lenalidomide/dexamethasone was associated with a highly significant 28% reduced risk of progression, establishing continuous lenalidomide as a new standard of care.

"As soon as either of the fixed regimen arms were stopped, there was an immediate separation of the curves," Dr. Anderson noted. The continuous [lenalidomide/dexamethasone] arm also had a very impressive duration of response (35 vs 22 months), and prolonged time to second antimyeloma therapy. Lenalidomide plus low-dose dexamethasone was superior across all subgroups for progression-free survival, with an acceptable safety profile.

Secondary cancers were not observed in the FIRST trial for patients who had not received an alkylator or melphalan. "Lenalidomide in and of itself is not conferring risk," Dr. Anderson explained.

"Based on the FIRST trial, [lenalidomide/dexamethasone] is likely to trump melphalan/prednisone–containing regimens because response rates and duration are higher, and there is not a secondary cancer risk," he concluded.

In a similar population, Italian investigators showed that 3 bortezomib-containing regimens, followed by bortezomib maintenance, were also effective, suggesting that regimens be selected based on the patient's tolerability of full versus reduced-dose therapy.[6]

The new proteasome inhibitor carfilzomib is also being incorporated into induction and maintenance schemas in non–transplant-eligible patients, producing "quite impressive frequency and extent of response," Dr. Anderson noted.

In the study by Bringhen et al,[7] carfilzomib/cyclophosphamide/dexamethasone was given as induction followed by carfilzomib maintenance; 77% of patients had a very good partial response or better, 2-year progression-free survival was 76%, and 2-year overall survival was 87%.

"As in the transplant setting, carfilzomib has moved upfront in newly diagnosed, non–transplant-eligible patients," he observed.

According to Dr. Anderson, the most exciting development for newly diagnosed patients is the oral proteasome inhibitor MLN9708, or ixazomib. In combination with lenalidomide/dexamethasone, ixazomib achieved a 94% response rate in a phase I study by Richardson et al.[8] Among the 11 evaluable patients who showed a stringent complete response or complete response, 9 (82%) were negative for minimal residual disease. Furthermore, a 100% decrease over baseline in M-protein or serum-free light chain was seen in 61% of patients. Some patients have now been stable on ixazomib maintenance for 4 years.

"We are now building on the [lenalidomide/dexamethasone] platform, not by adding bortezomib or carfilzomib but rather adding ixazomib, and the results are very impressive, indeed," Dr. Anderson noted. "This is exciting because it is an all-oral regimen without much neuropathy."

Relapsed/Refractory Disease

"We have very exciting initial therapy, we have consolidation treatments, and we have established the

principles of maintenance, but, unfortunately, patients with myeloma tragically relapse," Dr. Anderson acknowledged.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Multiple Myeloma for relapsed/refractory disease include bortezomib, bortezomib plus liposomal doxorubicin, and lenalidomide/dexamethasone as category 1 recommendations. Among the other "preferred regimens" are now carfilzomib as a single agent and pomalidomide/dexamethasone, for patients who have received at least 2 prior therapies and experienced progression within 60 days of the last one. Dr. Anderson described the most recent, highly positive data for these 2 agents.

At ASH 2013, the MM-003 study showed that weekly pomalidomide plus low-dose dexamethasone was superior to high-dose dexamethasone alone for progression-free and overall survival in heavily pretreated patients. [9] In a further analysis, the fall in M-protein correlated with outcome.[10] A phase I dose-escalation trial of pomalidomide/dexamethasone plus bortezomib was also presented at ASH, showing good tolerability, a 67% response rate, and a 33% rate of stable disease.[11] The drug is effective even in patients with 17p deletion, and a registration trial of pomalidomide/dexamethasone is in progress.

Carfilzomib is also being evaluated in combination with lenalidomide/dexamethasone versus lenalidomide/dexamethasone in patients with relapsed myeloma in a registration trial, ASPIRE. The 3-drug regimen has also been tested in newly diagnosed patients, where a "remarkable extent and frequency of response" (94%) was observed, including 80% complete or near complete responses after 12 cycles.[12]

Perhaps the greatest effect will be seen when carfilzomib and pomalidomide are used together, Dr. Anderson predicted.

In a study by Shah et al[13] in patients who had a median of 5 prior lines of therapy, half with high-risk cytogenetics, the overall response rate was 70%, clinical benefit rate was 83%, median duration of response was nearly 18 months, and overall survival exceeded 18 months. "These are exciting data," he commented. "This means we get months-to-years of benefit with novel therapies, even in the context of relapsed myeloma and adverse cytogenetics."

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