Personalized, Targeted Treatment Options Offer Hope of Multiple Myeloma as a Chronic Disease

Author: Anna Azvolinsky, PhD

Keith Stewart, MB, ChB

Researchers are working hard to turn multiple myeloma (MM), a cancer of the plasma cells in the bone marrow, into a chronic disease. “There has been dramatic progress over the past decade and survival has almost doubled,” said Keith Stewart, MB, ChB, dean of Research at the Mayo Clinic in Scottsdale, Arizona. “There is an increasing belief that some patients can be cured of their disease. This has happened because of bortezomib and lenalidomide.”

Twenty to thirty years ago, the average patient with MM could be expected to live approximately two years after diagnosis; over the past decade, survival times have increased to four to seven years.[1] Despite these improvements, however, new approaches are still needed. Patients with relapsed or refractory disease show limited responses and eventually progress, making the development of less toxic and more effective therapies crucial.

New targeted agents—next-generation proteasome inhibitors (PIs) and immunomodulatory agents, histone deacetylase (HDAC) inhibitors, a targeted antibody, and AKT/PI3K inhibitors, among others—are actively being developed, with many in late-stage trials for relapsed or refractory disease as add-ons to approved therapies (Table). Trials of combination therapy for newly diagnosed MM are also under way.

Current Multiple Myeloma Treatment Options

The treatment paradigm for MM is complex. The immunomodulators lenalidomide and thalidomide, as well as the PI bortezomib have emerged as the backbones of therapy. Two- or three-drug combinations with these agents have become the standard of care for both newly diagnosed and relapsed/refractory patients, including the combination of bortezomib with lenalidomide. The three-drug regimen of lenalidomide, bortezomib, and dexamethasone has shown a 100% response rate in patients who are newly diagnosed.[2]

“Both bortezomib and lenalidomide originally showed efficacy in relapsed and refractory myeloma,” said

Kenneth C. Anderson, MD

Kenneth C. Anderson, MD, professor of Medicine at Harvard Medical School, director of the Jerome Lipper Multiple Myeloma Center and LeBow Institute for Myeloma Therapeutics, and the vice chair of the Joint Program in Transfusion Medicine at Dana-Farber Cancer Institute in Boston, Massachusetts.

Both lenalidomide and thalidomide are oral immunomodulatory agents given in combination with dexamethasone, a steroidal anti-inflammatory and immunosuppressant. Although the full mechanism of action of these agents is not clear, they have been shown to have direct antitumor and tumor microenvironment effects, inducing tumor cell death.

Lenalidomide has demonstrated improvement in both progression-free survival (PFS) and overall survival (OS) as a maintenance therapy in three phase III clinical trials. However, prolonged use of the drug can result in development of other primary cancers in 2% to 8% of patients. Whether lenalidomide maintenance therapy should be the standard of care is questionable. “Personally I think there is enough evidence to use lenalidomide as maintenance, but it is controversial partly because of a lack of survival benefit in some studies,” said Stewart. Despite the worrisome secondary cancer incidence, Stewart believes that the overall benefits of lenalidomide outweigh the risks.

The other established MM therapy, bortezomib, is a selective, reversible PI. The function of the proteasome is to break down extra and damaged proteins in the cell. Because cancer cells are thought to have more damaged protein buildup, bortezomib is thought to cause death of these cells more readily than normal cells.

“Most patients receive bortezomib initially,” said Stewart. “Lenalidomide is used by some as initial therapy but also employed in maintenance and at first relapse.”

Next-Generation Immunomodulator

Pomalidomide is the newest immunomodulator to show efficacy, currently under review by the FDA for relapsed or refractory disease. “Pomalidomide can achieve responses in 30% to 40% of patients whose myeloma is refractory to bortezomib and lenalidomide,” said Anderson.

A next-generation immunomodulator, pomalidomide is an analogue of thalidomide that exhibits greater immunotherapeutic potency. The drug is being tested as both a monotherapy and in combination with dexamethasone in phase III trials, as well as with bortezomib in earlier-phase trials. Initially, pomalidomide will be used in those who failed or cannot tolerate lenalidomide. “It’s a very effective drug and quite well

tolerated, and so there may be some uptake earlier in the disease course," said Stewart.

Next-Generation Proteasome Inhibitors

Carfilzomib is an irreversible PI with a different structure and mechanism from bortezomib. The FDA recently granted carfilzomib accelerated approval based on a 266-patient phase II trial. The accelerated indication is for patients who have received at least two prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of the last therapy.

"The drug achieves responses of 20% [that last] for 8 months. Survival is [approximately] 15 months in patients whose myeloma is refractory to bortezomib," said Anderson.

Phase III trials are now testing the PI as a monotherapy, in comparison with bortezomib, and in combination with lenalidomide and dexamethasone, all in patients who have been previously treated. Earlier-stage trials in treatment-naïve patients are also ongoing. Pending positive results of these trials, the FDA will grant carfilzomib standard approval.

According to Stewart, carfilzomib is about as effective as bortezomib, but comes with much less neurotoxicity. "Like all drugs, it has its challenges, but it is a very welcome addition to our tool kit and offers more hope for patients," he added.

Another agent, ixazomib (MLN9708), is the first oral PI in development. "MLN9708 has already shown activity and tolerability in myeloma, and is now under evaluation in a phase III clinical trial [in combination with lenalidomide and dexamethasone]," Anderson said. "The prospect of all-oral therapy for myeloma appears very promising."

Targeted Antibodies

Elotuzumab is a monoclonal antibody directed against a specific cell surface glycoprotein, CS1, that is highly expressed on MM cells but only minimally found on normal plasma cells. In a phase II trial in combination with lenalidomide, the antibody showed promising response rates in previously treated patients. Two phase III trials with this combination in both newly diagnosed and previously treated patients are ongoing.

Elotuzumab is among the most interesting new agents for MM because it is targeted directly against MM cells and because it is the first monoclonal antibody developed for the disease, said Stewart.

Another monoclonal antibody, daratumumab, targets CD38, which is highly expressed on the surface of MM cells. The antibody has exhibited several mechanisms of action against MM, including induction of cell death. Interim phase I/II results presented at the American Society of Clinical Oncology (ASCO) Annual Meeting in June demonstrated that the antibody is well tolerated and has activity in relapsed/refractory patients.

MM is beginning to be stratified into lower- and high-risk disease based on genetic rearrangements and mutations, including a deletion in the p53 gene.[3] "Patients with…a p53 deletion for example, are at high risk, and therefore candidates for novel protocols with agents not dependent on p53," said Anderson. These include the antibodies elotuzumab and daratumumab.

Table. Approved Agents and Selected Therapies in Development for Multiple Myeloma

Agent	Mechanism of Action	Delivery Route	Approval Status	Company
Velcade (bortezomib)	Proteasome inhibitor	IV or subcutaneous	Approved for both 1st- and 2nd-line treatment	Millennium Pharmaceuticals (Takeda Pharmaceuticals)
Revlimid (lenalidomide)	Immunomodulatory, antiangiogenic, antineoplastic properties	Oral	Approved for 2nd-line but also reimbursed for 1st-line and maintenance use	Celgene Corporation
Thalomid (thalidomide)	Immunomodulatory, antiangiogenic, antineoplastic properties	Oral	Approved for 1st-line treatment	Celgene Corporation
Kyprolis (carfilzomib)	Proteasome inhibitor	IV	Accelerated approval July 2012 for relapsed/refractory patients who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent	Onyx Pharmaceuticals
Pomalidomide (CC-4047)	Immunomodulatory, antiangiogenic, antineoplastic properties	Oral	Application submitted to the FDA for treatment of relapsed/refractory patients who have received at least 2 prior therapies	Celgene Corporation
Ixazomib (MNL9708)	Proteasome inhibitor	Oral	Not approved; in phase III trial for relapsed/refractory setting and phase II trials for 1st line treatment	Millennium Pharmaceuticals (Takeda Pharmaceuticals)
Elotuzumab (BMS-901608)	Anti-CS1 monoclonal antibody	IV	Not approved; in phase III trials for both relapsed/refractory and 1st-line settings	Bristol-Myers Squibb
Daratumumab	Anti-CD38 monoclonal antibody	IV	Not approved; in phase I/II trials for refractory/relapsed patients	Genmab/Janssen Biotech
Panobinostat (LBH-589)	HDAC inhibitor	Oral	Not approved; in multiple phase I/II trials in relapsed/refractory patients	Novartis Pharmaceuticals
Perifosine (KRX-0401)	Akt/PI3K inhibitor	Oral	Granted FDA Fast Track Designation; in phase III trials in relapsed/refractory patients	Aeterna Zentaris
Rocilinostat (ACY-1215)	HDAC inhibitor	Oral	Not approved; in phase I trials in relapsed/refractory patients	Acetylon Pharmaceuticals

HDAC indicates histone deacetylase.

Other Oral Targeted Agents

Panobinostat is an oral drug that inhibits the enzyme HDAC, resulting in tumor cell death. Panobinostat is being tested in a phase III trial in combination with bortezomib in relapsed/refractory patients. So far, panobinostat has achieved stable disease in patients with MM when used as a monotherapy. But when combined with bortezomib, "there are remarkably increased responses, even in the bortezomib-refractory setting," said Anderson.

Another HDAC inhibitor, rocilinostat, is in early-phase clinical trials in combination with lenalidomide. Rocilinostat is specific for HDAC6 and is thought to induce fewer side effects compared with nonspecific HDACs.

Another oral agent also in a phase III trial in relapsed/refractory patients in combination with bortezomib is perifosine, an Akt inhibitor. Akt is part of the PI3/AKT pathway.

With the first large-scale genomic sequencing analysis of MM completed in 2011, new mutations and pathways that may lead to new insights and drug therapies are being uncovered.[4] Among the important myeloma pathways identified were NF-κB and the Ras-Raf pathway, providing new druggable targets. Approximately 4% of patients with MM harbor an activating BRAF mutation, including the V600E mutation. A phase II trial testing the BRAF inhibitor vemurafenib in MM is ongoing.

Over the next five to seven years, results from ongoing phase III trials with the targeted agents described here may lead to approval of these agents. Many other targeted agents in early-stage trials await clinical validation.

"It is a most exciting time, as we are developing second-generation novel proteasome inhibitors and immumodulatory drugs, as well as entirely new classes of agents," said Anderson. "Ultimately, we will need to use combinations of novel agents to treat newly diagnosed myeloma, followed by effective maintenance therapies in order to prevent minimal residual disease and its genetic evolution, resulting in relapsed and refractory disease."

"Patients should be optimistic that further advances are on the way," said Stewart.

References

1. Sirohi B, Powles R. Multiple myeloma. *Lancet*. 2004;363(9412):875-887.
2. Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. *Blood*. 2010;116:679-686.
3. Kapoor P, Kumar S, Fonseca R, et al. Impact of risk stratification on outcome among patients with

multiple myeloma receiving initial therapy with lenalidomide and dexamethasone. *Blood*. 2009;114(3):518-521.

4. Chapman MA, Lawrence MS, Keats JJ, et al. Initial genome sequencing and analysis of multiple myeloma. *Nature*. 2011;471(7339):467-472.