Myeloma Researchers Gain Genome, New Targets, and New Concerns

By Vicki Brower

Multiple myeloma captured the headlines twice in one week this spring: first with the death of former vice presidential candidate Geraldine Ferraro after battling the disease for 12 years and then with the first large-scale genome sequencing of myeloma. By sequencing the genomes of 38 myeloma patients, researchers uncovered mutations and pathways that might not have showed up had they sequenced only one patient’s genome.

They were surprised at some of their findings. “We learned an enormous amount of totally new information from our study, starting with entirely new genes and processes that were not on anybody’s radar and which had never been connected to cancer before,” said author Todd Golub, M.D., director of the cancer institute at the Broad Institute in Cambridge, Mass. The team, which includes scientists from TGen in Scottsdale, Ariz., is working now on sequencing more than 200 other patient samples.

Published in Nature in April, the study demonstrated that myeloma is a great deal more complicated and unstable than had been thought. Co-author A. Keith Stewart, M.D., dean for research at the Mayo Clinic in Scottsdale, Ariz., said it confirmed the importance of the NF-κB pathway and revealed mutations of genes involved in protein translation and blood coagulation, as well as in epigenetic mechanisms. The discovery of mutations in BRAF genes could have an immediate effect, making it possible to test existing drugs that target BRAF mutations.

Beginning With Thalidomide

The sequenced genome exemplifies the “explosion of knowledge” about myeloma in the past decade that began with the drug thalidomide in 1999, said Heather Landau, M.D., oncologist at Memorial Sloan-Kettering Cancer Center in New York. “Before 1999, our armamentarium was very slim,” she said. With only 20,000 new cases per year in the U.S., research in myeloma lagged behind that of other cancers. And patients faced a bleak diagnosis, living a median of 3–5 years; those with high-risk disease survived 1–2 years. With the introduction of thalidomide, an immunomodulatory drug (IMiD) in 1999 and then the proteasome inhibitor bortezomib in 2006, survival rates began to rise.

Yet many questions remain: How aggressively should patients be treated upfront? Which drugs are best for newly diagnosed and relapsed patients? What drugs should be used for maintenance therapy and for how long? The challenges are formidable: From a molecular standpoint, myeloma is an unusually heterogeneous and genetically unstable disease. There are still no drugs that can successfully treat most high-risk individuals, who account for 15% of all patients, and the prognosis for these and older patients remains bleak, said Constantine Mitsiades, M.D., Ph.D., medical oncologist at Dana-Farber Cancer Institute in Boston. Moreover, after successive treatments,
formerly low-risk patients often develop high-risk disease, and even triple and quadruple drug combinations fail.

Finally, three troubling reports suggest that patients taking lenalidomide, a second-generation IMiD, showed a higher incidence of secondary cancers. At the recent American Society of Clinical Oncology meeting, a group led by Antonio Palumbo, M.D., of the University of Torino in Italy, reported on a trial in which patients received melphalan–prednisone, melphalan–prednisone–lenalidomide, or that triple therapy followed by lenalidomide as maintenance therapy. In these three arms, secondary cancers occurred in 2.6%, 5.9%, and 8% of patients, respectively.

A second group, led by A.C. Rossi at Weill Cornell Medical College in New York, studied 72 patients taking clarithromycin, lenalidomide, and dexamethasone and then continuous lenalidomide for 6 years. They found 11 new diagnoses after an average of 31 lenalidomide cycles: six skin cancers; two colon cancers; and one each of prostate cancer, pancreatic cancer, and melanoma. In a third trial, 29 of 231 patients taking lenalidomide developed new cancers, compared to just four in the placebo arm.

In April, the U.S. Food and Drug Administration said that it was watching for reports of secondary cancers in patients taking lenalidomide for myeloma or myelodysplastic syndromes.

**Combinations**

But for now, lenalidomide and bortezomib constitute the backbone of myeloma treatment, having largely replaced or supplemented other chemotherapies. Researchers continue to test them as maintenance therapies. Most recently, for instance, a phase III trial with bortezomib in 370 patients after autologous stem cell transplant, discussed at May’s 13th International Myeloma Workshop in Paris, showed statistically significant improvement in progression-free survival times for patients in the bortezomib arm (27 months) compared with patients in the control arm (20 months), who had no treatment after transplant. Moreover, 45% of the bortezomib group had a complete response, compared with 35% of control subjects, a statistically significant difference. The estimated overall survival was 87% in both groups after a median follow-up of 27 months.

Many investigators believe that the most promise lies in combining the two drugs with other therapies. Last year, Dana-Farber’s Paul Richardson, M.D., reported in Blood that combining lenalidomide with bortezomib and dexamethasone resulted in a 100% response rate in newly diagnosed patients, with 74% having a 90% reduction in tumor burden and 57% entering complete remission with four to eight cycles. Similar results had been seen only with relatively toxic regimens of repeated chemotherapy, melphalan, and stem cell transplant, he noted. Other trials are looking at the effect of a two- versus a three- versus a four-drug regimen.

Researchers are also working on improved versions of the current drugs. One side effect of the proteasome inhibitors is neuropathy, and a second-generation IMiD called carfilzomib, which may produce less neuropathy than bortezomib. Carfilzomib has been safely combined with lenalidomide and dexamethasone, Stewart said, and a phase III trial is now comparing the three-drug combination to lenalidomide and dexamethasone alone.

A third-generation IMiD, pomalidomide, alone and in combination with other drugs, is also under development in patients resistant to lenalidomide and bortezomib, according to Kenneth Anderson, M.D., a professor at Harvard Medical School in Boston and director of the Dana-Farber Cancer Institute’s multiple myeloma center.

**Targets Galore**

Meanwhile, myeloma researchers are working on a variety of new targets. The Nature study confirmed strong links between the NF-κB and Ras–RAF signaling pathways in myeloma. Half of the patients had NRAS or KRAS mutations, and 11 mutated genes turned up in the NF-κB pathway.

The researchers also found that 4% of patients have BRAF-activating mutations. The Roche/Plexxikon BRAF inhibitor PLX-4032, or vemurafenib, developed for melanoma, can now be tested in patients with the V600E activating mutation, Golub said.

Even before the genome was sequenced, myeloma researchers were interested in the histone proteins, which play a role in gene regulation and epigenetic changes. Currently, two histone deacetylase inhibitors, vorinostat and panobinostat, are in phase III testing, and others are in earlier-stage trials. But the sequenced genome uncovered mutations in three genes that regulate histone proteins, one of which corresponds to a chromosomal translocation that occurs in high-risk patients. The Multiple Myeloma Research Foundation now is launching a 3-year collaboration to validate several of these histone-modifying enzymes.

Other targets under development include those related to microRNAs (miRNAs). Bart Barlogie, M.D., director of the Myeloma Institute for Research and Therapy at the University of Arkansas in Little Rock, showed that miRNAs play an important role in high-risk disease in an April 2010 study in Proceedings of the National Academy of Sciences. He found high levels of miRNAs in high-risk patients and discovered that one gene, EIF2C2, or Argonaute 2, controls miRNA maturation, which could underlie the overexpression of miRNAs in myeloma. Targeting either Argonaute 2 or the miRNAs themselves could lead to new treatments, Barlogie said.

Another new target, this one identified by Anderson, is CS1, a cell surface glycoprotein, which is highly expressed on...
myeloma cells and only minimally on normal cells. Elotuzumab, a humanized monoclonal antibody against CS1, has been tested in preclinical studies with lenalidomide, providing a rationale for a combination trial, Anderson said. Results from a randomized phase II trial in relapsed patients with elotuzumab, reported at this year’s annual meeting of the American Society of Clinical Oncology, established that the response rate was better with the lower dose and in those who had received only one prior therapy. On the basis of this finding, trying this combination earlier in the disease makes sense, said investigator Philippe Moreau, M.D., from the University Hospital in Nantes, France.

Anderson has also elucidated the underlying immunodeficiency in myeloma, which includes an increase of the interleukin 17 cytokine. He said that an antibody to interleukin 17 is now in preclinical studies.

Yet another potential target is heat shock protein 90 (HSP90). Synta Pharmaceuticals is testing ganetespib, a second-generation HSP90 inhibitor, in a phase I study alone and with bortezomib. Many proteins associated with myeloma are known “client proteins” of HSP90, said principal investigator Sagar Lonial, M.D., of Emory University in Atlanta. After treatment with bortezomib, HSP90-related proteins increase as a mechanism of resistance.

Another new drug is IMGN901, or lorvorotuzumab, an antibody to CD56—a cell surface protein on the myeloma cells in about 70% of patients. A study of relapsed or refractory patients with lenalidomide and dexamethasone conducted by Jesus Berdeha, M.D., from the Sarah Cannon Research Institute in
Nashville, Tenn., showed the antibody to be active. He said that of 12 patients enrolled, two achieved a “very good” partial response and four had partial responses.

The plethora of information on potential targets coming from genome sequencing and other studies has injected increasing complexity as well as new hope into this field. Although researchers believe that the genomic discoveries will eventually lead to better treatments, most agree that personalized treatments are still years away.

“Not only are new treatments needed, but the biggest challenge is to determine who needs what treatment,” Landau said.

Dr. Anderson has reported a consultant or advisory role with Bristol-Myers Squibb, Celgene, Merck, Millennium, Novartis, and Onyx. Dr. Stewart has reported a consultant or advisory role with Millennium and receiving honoraria from Celgene. Dr. Richardson has reported a consultant or advisory role with Bristol-Myers Squibb, Celgene, Johnson & Johnson, Millennium, and Novartis.

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