Essereman said that her Athena Breast Health Network, which sees more than 50,000 women at the University of California medical centers, now includes a routine risk assessment in its screening process.

“People in the top 5%–10% [for breast cancer risk] are identified, contacted by breast health specialists, and counseled about their options,” she said.

To the extent that cost is a disincentive, the Affordable Care Act will, starting next year, require new health insurance plans to cover chemoprevention with no copayment or deductible in high-risk women. That typically means a 5-year breast cancer risk of 1.67% or higher, which includes nearly all American women older than 55 years.

Meanwhile, European researchers are investigating reduced doses of tamoxifen to alleviate some side effects.

Per Hall, M.D., Ph.D., of the Karolinska Institute in Stockholm, was among the researchers who showed that a change in breast density might be a useful surrogate for therapeutic effect. Now his group is about to launch another trial to learn whether women who take lower doses of tamoxifen can achieve the same benefit with fewer side effects. The group plans to randomize 1,000 Swedish women to receive placebo or one of four daily doses of tamoxifen: 20, 10, 5, or 2.5 mg.

“We want to look at density decrease and compliance,” Hall said. “Are women taking the drug, and do they experience side effects? If 5 mg decreases density to the same extent as 20 mg, do the side effects decrease?”

In a later study, the group will test whether a lower dose also reduces breast cancer risk.

“In the 1980s we changed the daily dose from 40 to 20 mg, which is now the standard adjuvant dose,” said Hall. “No one ever tested whether lower doses were effective.”

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Treating Multiple Myeloma: The Cause for Optimism

By Marilyn P. Fenichel

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cancer diagnosis came at a tipping point in understanding and treating this complex disease. Although still considered incurable, multiple myeloma can now be treated with new drugs, resulting in a median life expectancy of 5–7 years and a higher quality of life for many patients.

Multiple myeloma is a disease of plasma cells, a kind of white blood cell. Found in the bone marrow, plasma cells produce antibodies. With multiple myeloma, however, genetic changes in plasma cells cause oncogenes, such as cyclin D, FGFR3, or MAF, to become linked to the plasma cell program, causing cell proliferation. Other genetic changes, such as BRAF, KRAS, or NRAS mutations, can occur independently and promote cell growth. As the disease progresses, it can result in high levels of calcium, renal failure, anemia, and bone lesions—a constellation of problems referred to as CRAB. Moreover, this cancer almost always comes back, often fiercely, and intervals between relapses tend to get shorter.

Information from the genomic sequencing of 200 patients, published in the January 2014 Cancer Cell, reveals multiple myeloma’s complexity.

“Every cancer cell within each patient looks different,” said Jens Lohr, M.D., Ph.D., instructor in medicine at the Dana–Farber Cancer Institute and first author of the study. “This makes therapy difficult because part of the myeloma may respond, while another part may not. It is increasingly clear that we are treating more than one disease in each patient.”

Nonetheless, many researchers and clinicians are optimistic about the prognosis of patients with multiple myeloma. Better up-front treatments combining immunomodulators, such as thalidomide and lenalidomide, and proteasome inhibitors, such as bortezomib, as well as steroids, are available. Most patients respond to these treatments, keeping the disease at bay longer.

Changes in the Field

Many factors are involved in the improved outcomes of multiple myeloma patients. Diagnostic techniques and disease awareness have improved, so patients are diagnosed earlier. A growing trend in the field is to treat these patients before major organ dysfunctions develop. A study in Spain and published in the New England Journal of Medicine found that for some patients, early treatment yielded a survival advantage at 3 years of follow-up. Further studies are needed to determine whether early treatment reduces genetic evolution and the heterogeneity of the involved tumors.

In the 1990s, before the new drugs became available, stem cell transplant was introduced for younger, fitter patients. An effective way to consolidate responses, the procedure involves harvesting the patient’s own stem cells and killing off disease-ridden marrow with chemotherapy. The healthy cells are then put back into the patient’s bone marrow. Although stem cell transplant does not cure multiple myeloma, remissions after transplant can last 10 years in 20%–25% of patients.

Combining immunomodulators and proteasome inhibitors has also proven to be a formidable weapon against the disease.
Immunomodulators work by stimulating NK and T-cell activation, reducing myeloma growth factor secretion in the bone marrow. They also induce apoptosis, or cell death, of multiple myeloma cells by reducing expression of the myeloma survival factor IRF-4. Proteasome inhibitors interfere with degradation of misfolded proteins and influence cell signaling by blocking the final step of the ubiquitin proteasome pathway. This action, too, kills myeloma cells and affects the bone and marrow in a way that stabilizes bone and reduces myeloma support. To further refine the treatment regimen, many clinical trials are testing other combinations and new compounds.

Another promising development is the growing evidence pointing to the value of using lenalidomide as maintenance therapy after up-front treatment. In 2012, the New England Journal of Medicine reported three randomized controlled trials that compared lenalidomide maintenance with placebo, two after transplant and one in transplant-ineligible patients. All studies reported improved progression-free survival with lenalidomide. The median survival time for the lenalidomide maintenance group was 41 months, compared with 23 months for the placebo group. The transplant study that used lenalidomide until disease progression found an 8% survival advantage, even though crossover was allowed after an interim analysis.

A more recent study that randomized young transplant-eligible patients to transplant or no transplant and then to either lenalidomide maintenance or placebo found a survival advantage with lenalidomide but not with transplant as of the last interim analysis presented at the 2013 American Society of Hematology annual meeting. Indefinite lenalidomide and dexamethasone use also showed a survival advantage compared with an 18-month treatment consisting of melphalan, thalidomide, and prednisone, a standard regimen in Europe at the time this study began. Frederic Reu, M.D., associate staff physician at the Cleveland Clinic, noted that “in the current age of novel drugs, it is not clear whether stem cell transplant still prolongs life, although it remains one effective way to extend disease control. For patients who are started on lenalidomide, continued treatment at lower maintenance doses until disease progression appears to yield an improvement in life expectancy, however.”

“The problem is that we may identify a mutation, but we may not have a treatment for it. Even if we did genetic studies of every patient, we may not know what to do with the information.”

Possibility of Targeted Therapies

The big question emerging from the latest sequencing work is whether targeted therapies are now within sight. Researchers are hopeful, but the heterogeneous pattern of the disease has given them pause. “The problem is that we may identify a mutation, but we may not have a treatment for it,” Lohr said. “Even if we did genetic studies of every patient, we may not know what to do with the information.”

But German researchers reported good news about the potential of targeted therapy. After finding a BRAF mutation in one patient, they tried a BRAF inhibitor developed for another cancer. As hoped, the treatment succeeded. This finding points to the need for more studies, as well as more drugs targeted at specific mutations.

Despite the ups and downs in the field, most researchers believe that the future for myeloma patients is brighter. “There is real excitement about the delivery on the promise of immune-based treatments,” said Kenneth C. Anderson, M.D., director of the Jerome Lipper Multiple Myeloma Center and LeBow Institute for Myeloma Therapeutics at the Dana–Farber Cancer Institute. “And we have seen rapid movement from bench to bedside. This is a new day for multiple myeloma, with more positive news and more improvement of outcomes.”

PDQ (Physician Data Query) is the National Cancer Institute’s source of comprehensive cancer information. It contains peer-reviewed, evidence-based cancer information summaries on treatment, supportive care, screening, prevention, genetics, and complementary and alternative medicine. The summaries are regularly updated by six editorial boards. The following PDQ summaries were recently updated:
