As Metastasis Yields its Biological Secrets, Researchers Hope To Apply Findings

By Steve Benowitz

When Patricia Steeg, Ph.D., showed last year that women whose breast cancers overexpress the HER2 gene had substantial rates of cancer that spread to the brain, she knew she had found what she called “the perfect storm”: Women with this form of metastatic breast cancer were becoming victims of scientists’ success.

According to Steeg, who is chief of the women’s cancer section at the laboratory of molecular pharmacology at the National Cancer Institute, about a third of women with metastatic HER2-positive breast cancer are developing metastases to the brain. Not long ago, brain metastasis was not a particular concern, she noted, because it occurred in only about 15% of metastatic breast cancers and usually near the time of death. Most women died before the cancer took hold there. But because clinicians are doing a better job of controlling the disease systemically, particularly with the advent of the monoclonal antibody drug trastuzumab, more and more women have kept the disease at bay from the neck down. But the cancer cells weren’t being destroyed and sought refuge elsewhere. “They are getting brain metastasis as a sanctuary site, where most therapeutics can’t reach,” Steeg said. “[Trastuzumab] can’t penetrate the blood–brain barrier when a metastasis forms.”

Steeg’s “perfect storm” scenario illustrates how, as scientists are gaining a greater understanding of the molecular biology underlying cancer metastasis, they are increasingly faced with new challenges. For Steeg, HER2-positive metastatic disease represents “a very different situation from in the past,” adding that “we need to do something about it.” Predicting which patients will experience recurrence is usually nearly impossible.

Steeg turned to GlaxoSmithKline’s lapatinib, a small-molecule kinase inhibitor of both the HER2 receptor and epidermal growth factor receptor. It was approved by the U.S. Food and Drug Administration in 2007 for metastatic HER2-positive breast cancer patients, though she termed the results “not overly promising when it came to disease regression.”

She decided to take the prevention route instead. “It occurred to us that it’s very different to ask the drug to melt a golf ball–sized tumor versus to prevent the outgrowth of a few cells to form that tumor,” she said. She and her colleagues set up a preclinical model to test this potential preventive effect.

In this issue of the Journal, Steeg and her coworkers report their results. The researchers injected metastatic breast cancer cells that either over- or underexpressed HER2 into mouse hearts. They randomized the mice either to a placebo or to two doses of lapatinib. After 24 days, they counted the tiny micrometastases and the larger macrometastases.

They found that lapatinib prevented the formation of large metastases in the brain by about 50% in cells that expressed epidermal growth factor receptor and HER2, reducing HER2 signaling. “I’m hopeful that it will have a lot of activity in the prevention setting,” Steeg said.

Understanding Metastasis Biology

The recent upsurge in breast cancer metastases to the brain is “a harbinger of
what’s to come as we develop better therapies for many cancers that don’t penetrate the brain,” said Eric Winer, M.D., a medical oncologist at the Dana-Farber Cancer Institute in Boston. In ovarian, lung, and colon cancers, for example, brain metastases haven’t been a common problem—yet. He’s optimistic that a new generation of tyrosine kinase inhibitors and small molecules will be developed that will reach the brain but notes that they still have to reach, and act on, the cancer there.

Developing such drugs depends on continuing efforts to improve the understanding of the biology involved. “Translational issues relate not only to the ability to get drugs into the brain but also to the question of whether brain metastases are different,” Winer said. “Are brain metastases different in some ways from their parent cells?” he asked, adding that many unanswered questions remain about the nature of the brain’s microenvironment.

“Metastasis is a very inefficient process,” said Ann Chambers, Ph.D., professor of oncology at the University of Western Ontario in London. Chambers uses imaging to detail the metastatic process. Many tumor cells commonly reach a distant organ and remain there, viable yet dormant, even though few will form metastases, she said. “There can be a whole population of dormant micrometastases.”

Only a few cells reach the bloodstream and lead to disease that can kill, she said. “We’ve shown that these dormant cells can’t be killed by conventional chemotherapy. This leads to the idea that killing cells that are growing but leaving cells behind that the chemotherapy didn’t touch can give rise to late-growing metastasis. “Metastasis as a field has been limited by a lack of models and long-term studies,” she said. “The genes involved don’t seem to be linear the way that genes in earlier tumor progression work. It seems a more plastic process. Why does one cell keep growing, while others that seem exactly the same do not?”

**Strategies Differ; Questions Remain**

Steeg points out that such drugs could be difficult to develop, regardless of whether lapatinib pans out as a metastasis prevention drug for breast cancer. “If an agent thwarts metastases, you’re not likely to see activity in resistant metastatic patients, which is where we would test it in phase I trials,” she said. “We probably would see the best activity while in the adjuvant setting. We need to ask whether an agent will prevent a micrometastasis from growing out, and such adjuvant trials are large and expensive.”

Although drug development has its issues, many researchers debate the best approach to take in dealing with metastasis. “We’ve always thought of intervening in the steps of metastasis,” said Dan Welch, Ph.D., professor of pathology at the University of Alabama at Birmingham and a pioneer, along with Steeg, in metastasis suppressor gene discovery. “But patients already have disseminated cancer cells at diagnosis, and that’s where we need to focus our attention. We have targets now—several metastasis suppressors inhibit growth at the secondary site. So, we’re moving in the direction of a Gleevec [imatinib] for metastasis.”

Dan Theodorescu, M.D., Ph.D., professor of urologic oncology and molecular physiology at the University of Virginia in Charlottesville, agrees on focusing attention at the original site. “If a patient has metastasis, after surgery, chemotherapy, and radiation, you want to try to prevent metastatic colonization, where the small metastasis becomes a large one,” he said.

“Intrinsic in that is that you’ve had to block growth at the metastatic site or attack the microenvironment at the distant organ or a combination of those approaches,” he added. “Treating when there is only microscopic disease should in theory allow you to be able to block tumor growth because you’re not allowing the cancer to acquire a blood supply needed to convert to a clinical metastasis.”

Theodorescu said that “implicit in such therapies is that they are lifelong in individuals who don’t have visible metastasis but are at high risk.” Although adjuvant chemotherapy is common enough in cancer patients at risk for developing metastasis, he said, “using a targeted therapy that way is very different conceptually.

“Chemotherapy is based on the idea that you will kill a certain number of cancer cells. With a targeted therapy, you’re trying to stop the metastatic colonization. You’re unlikely to kill the disease, but instead hold it down,” he said. The duration is different as well. Chemotherapy is given in defined cycles for a limited period; a targeted approach is lifelong, though they are not mutually exclusive. Adjuvant chemotherapy may be followed by tamoxifen for breast cancer, for example. Several trials are testing these targeted approaches.

At Amgen, scientists are testing a humanized monoclonal antibody, denosumab, in several phase III trials to gauge its potential effectiveness in curbing bone destruction and delaying bone fractures in several metastatic cancers, including breast and prostate. The antibody inhibits its RANK ligand, which halts the local production of osteoclasts and bone breakdown. Denosumab “alters the continues on page 1057
microenvironment, making it hostile for the establishment of bone metastasis,” said Roger Dansey, M.D., global development lead for denosumab oncology at Amgen in Thousand Oaks, Calif.

Edith Perez, M.D., director of the breast cancer program at the Mayo Clinic in Jacksonville, Fla., and her colleagues are testing two targeted antimetastasis approaches in an international, multicenter, four-arm study called ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization), which compares trastuzumab and lapatinib in early breast cancer patients. In the trial, patients are given one of four therapies for 1 year: trastuzumab; lapatinib; trastuzumab for 3 months followed by lapatinib for 9 months; or both drugs concurrently. The primary endpoint is progression-free survival, with secondary endpoints such as overall survival and the development of brain metastasis. It will include about 8,000 patients in nearly 50 countries.

Steeg thinks that the ALTTO trial will answer the question of whether lapatinib will prevent the formation breast cancer metastasis “in the setting of where we think the cells have disseminated but haven’t grown out yet.” She predicts that in addition to a group of standard drugs that are available as first-line therapies for primary breast, colon, and other cancers, eventually, “there will be a second, separate slate that is specific to the metastatic setting.

“I’m hoping that we will have a toolbox of drugs to prevent brain metastasis,” she said. “Many companies have not considered whether a drug is brain permeable when they select a lead agent. But because brain metastasis is considered an unmet medical need, it may be a speedier pathway to approval for some. I think that, 5 years from now, we’ll have a toolbox of brain-permeable drugs and then we will be able to do something about brain metastasis.”