Elucidating an Uncommon Disease: Inflammatory Breast Cancer

By Kristine Crane

Valerie Fraser knew something was wrong when she woke up on New Year’s Day in 2007. She felt a swelling in her left breast, but she thought she’d laid on it wrong. Over the next several days, the swelling increased. She’d always had dense breasts, but this was different: The density was not concentrated in one spot but rather was spread over her whole breast, like rubber.

Fraser went to a gynecologist and a radiologist, both of whom thought she had an infection. They thought the masses on the ultrasound were abscesses. But Fraser knew it was something else. She called the local...
breast clinic in her hometown of Royal Oak, Mich., for an appointment, but they couldn’t see her for another 2 months. So she asked the receptionist whether the clinic’s director would take a look at the ultrasound results, and if the director felt she could wait another 2 months, she would wait. Fraser received a call back with an appointment the next day. That resulted in a biopsy a week later. Three weeks after her first symptom, Fraser was diagnosed with stage IIIb inflammatory breast cancer (IBC) and ductal carcinoma grade 2.

Fraser’s story is like that of many women diagnosed with IBC. Women are often misdiagnosed with mastitis, an inflammation of the breast. Unlike most breast cancers, which are first detected as a lump, IBC usually starts out looking like a mosquito bite. It can then morph into a rash resembling an orange peel.

Fraser said her diagnosis “threw me into a tailspin.” She combed the Internet and found out that IBC is the rarest form of breast cancer, as well as the deadliest: IBC represents 2.5% of all breast cancer patients, and only 40% of patients are alive after 5 years, according to the National Breast Cancer Foundation. Fraser also discovered that IBC was typically treated like primary breast cancer, even though it looked like a very different disease.

Defining IBC’s Difference
Massimo Cristofanilli, M.D., chair of medical oncology at Fox Chase Cancer Center in Philadelphia, confirmed that difference. Cristofanilli started studying IBC in the mid-1990s as a fellow at the University of Texas M. D. Anderson Cancer Center in Houston. His retrospective studies of two decades of breast cancer clinical trials revealed that IBC did not respond well to standard chemotherapy of fluorouracil, doxorubicin, and cyclophosphamide.

Cristofanilli spent the next decade trying to give these women other treatment options. At the San Antonio Breast Cancer Conference in 2006, he presented positive findings of a phase II trial with lapatinib (Tykerb) for IBC patients, which showed that 85% had tumor shrinkage of more than 50%. That same year, Cristofanilli became the founding codirector of the country’s first research program and clinic for IBC patients, the Morgan Welch Inflammatory Breast Cancer Research Program and Clinic at M.D. Anderson, named in memory of Morgan Welch, a 24-year-old patient of Cristofanilli’s. Welch had been misdiagnosed, and when Cristofanilli finally saw her, the cancer had already spread to her bones.

When Fraser was looking for information on IBC, Cristofanilli’s lapatinib trial caught her attention. Within 2 weeks of finding his name, she had an appointment. He ordered a PET/CT scan, as well as a test to measure her circulating tumor cells. He put her on trastuzumab (Herceptin), a drug for patients whose tumors overexpress HER2 (true for most IBC tumors), along with the combination chemotherapy docetaxel (Taxotere) and carboplatin. “It was very clear the way they were treating me was a personalized approach,” Fraser said.

After one cycle of the drug combination, Fraser’s tumor mass had shrunk 8 cm. By the end of her third cycle, she was clinically disease free and remains so 4 years later. She is also still taking trastuzumab.

Although Cristofanilli says that Fraser is something of a miracle patient, she is emblematic of his multidisciplinary approach to treating IBC. Now he is the founding director of the IBC Research Program and Clinic at Fox Chase, where typically, he has patients see a diagnostic imaging technician, a pathologist, a radiation oncologist, and a surgeon. He treats them with neoadjuvant therapy before doing surgery, usually a mastectomy. Doctors unfamiliar with IBC may reverse this process, treating IBC as a locally advanced disease. Performing surgery first can cause the tumors to spread even more.

According to Cristofanilli, many oncologists are unfamiliar with the disease because it is so rare. “If you see one to two cases in your practice, you don’t know what it is. You’re afraid,” said Cristofanilli.

Even though treatment options remain limited for IBC patients, both trastuzumab and lapatinib show ongoing promise. According to a review by Cristofanilli and Holly Dushkin, M.D., also of Fox Chase, published in the February 2, 2011 edition of the *Journal of the National Comprehensive Cancer Network*, a phase III prospective randomized trial of trastuzumab in combination with anthracycline- and taxane-based chemotherapy gave encouraging results. Three-year event-free survival was 70% for patients taking trastuzumab, compared with 53% in the chemotherapy-alone group.

Lapatinib is also “potentially effective treatment for relapsed or refractory HER2-positive IBC,” according to a study in the June 2009 edition of *Lancet Oncology*. Although no patients had complete response, 39% had partial response. Cristofanilli expects to present results by the end of the year from a phase II randomized clinical trial for lapatinib with pazopanib (Votrient), an antiangiogenic agent. Although IBC tumors are highly vascular, expressing angiogenic factors such as VEGF (vascular endothelial growth factor), he explained, the antiangiogenic drug bevacizumab (Avastin) has not been as promising as researchers had hoped.

Current IBC research also focuses on moving IBC treatments beyond traditional breast cancer therapies. Cristofanilli and Fredika Robertson, M.D., a professor in the department of experimental therapeutics at M.D. Anderson, received a $7.5 million PROMISE grant from the Komen Foundation in 2008 to identify biomarkers for IBC and find potential therapies. They found that the protein E-cadherin, which is normally lost in regular breast cancer during the epithelial–mesenchymal transition that is believed to have a role in metastases, is retained in IBC tumors. E-cadherin appears to help IBC tumor cells aggregate, which is one of their distinguishing characteristics.

“They travel in packs. They actually die if they’re disaggregated,” Robertson said.

Understanding the Emboli
These emboli are particularly resistant to treatment, Robertson explained, adding that breaking them apart could be key to IBC treatment. Kenneth van Golen, Ph.D., a professor at the Center for Translational Cancer Research at the University of Delaware, explained that the tumors are “several cell layers thick. So you might kill off the periphery of cells and the core remains. To get these things individualized makes them easier to target,” he said.
Van Golen thinks IBC cells’ low expression of transforming growth factor β (TGF-β), a protein that controls cell proliferation, may help explain why IBC cells metastasize in emboli. Both in vitro and patient data have shown that non-IBC cells express TGF-β and the cells disseminate as single cells; IBC cells have low TGF-β expression and travel in packs.

Other researchers say that the mutated cten gene may help explain the intransigent nature of emboli. According to Neil Spector, M.D., the director of translational research in oncology at Duke University’s Cancer Institute, IBC cells overexpress cten, a change that essentially disallows a cell’s normal bridging between its basement membrane and cytoskeleton, and directs the cancer cells to the dermal lymphatics, where they rapidly proliferate. Spector wrote a study published in Nature Cell Biology in July 2007 that found the epidermal growth factor receptor (EGFR) upregulates cten and that cten also statistically correlates with HER2 overexpression and metastases to lymph nodes. “It’s very exciting. It’s a nice mechanistic explanation of this mutated form of a structural protein that may help explain why these globs find their way to the lymphatic system,” Spector said. “That says that maybe there’s a target, or therapies that target the regulation of cten.” And lapatinib targets both EGFR and HER2 overexpression, explained Spector, who was one of the authors of the Lancet report showing the drug’s promise.

So understanding cten may be a “foot in the door” to controlling the highly metastatic nature of IBC and potentially other metastatic cancers, Spector said. Some researchers are looking into potential links between IBC and highly aggressive tumors. “A lot of what you see in pancreatic cancer is very similar to IBC,” said van Golen. He has done studies showing that the metastasizing gene Rho GTPase is highly expressed in both pancreatic cancer and IBC. More recently, he is looking at how G proteins that drive Rho-C activation are present in both cancer types. “I think there are common molecular pathways as well,” he said.

Spector agreed, adding that although how IBC metastasizes “really flips the EMT [epithelial–mesenchymal transition] model on its head,” IBC could still provide clues about the metastatic process overall. For one, IBC is easier to study than most metastatic cancers because samples are more obtainable with skin-punch biopsies. However, the real challenge is creating the clinical trials for IBC patients, he said, explaining that regular breast cancer trials often exclude IBC patients because RECIST (Response Evaluation Criteria in Solid Tumors) criteria for measuring tumor response do not recognize IBC.

“[IBC] is really a double whammy for women. The mortality rate hasn’t changed in 30 years, and they are generally excluded from new and exciting treatments,” Spector said. “It’s the worst of all worlds.”

But Spector hopes that other avenues for doing trials might exist. Because IBC affects so few women, it is like childhood leukemia, where you don’t need a trial of 1,000 people for drug approval, he explained. “Assuming you have the right drug and the right target, it might actually be more encouraging for clinical trials.”

Researchers are also pushing for clinical trials on HDAC (histone deacetylase) inhibitors. According to a study by Robertson and Cristofanilli published in the June 1, 2010, issue of Cancer, Merck’s Zolinza (vorinostat), which the U.S. Food and Drug Administration approved in 2006 for cutaneous T-cell lymphoma, inhibits IBC cell growth. Robertson and Cristofanilli are also working on a letter of intent for both phase I and phase II studies with Celgene’s HDAC inhibitor, romidespin (Istodax), for which the FDA granted accelerated approval last January to treat T-cell lymphoma. Their recent preclinical work has shown efficacy against IBC, for which they will submit a late-breaking abstract to the San Antonio Breast Cancer Symposium this December.

**From Patient to Activist**

Meanwhile, IBC experts stress the need to educate both doctors and patients about IBC. Cristofanilli gets e-mails every day from newly diagnosed IBC patients desperate for information and often refers them to one of his patients who have become activists. Fraser is one such patient.

“I wanted to be able to sit alongside doctors, researchers, and be a voice for patients without a voice,” said Fraser. “This cancer has not been studied properly. It has just been part and parcel of other studies. I don’t believe it’s all that rare. Women just don’t get diagnosed.”

Once she was disease free, Fraser wrote a 5-year plan about what she’d like to do as a patient activist. Four years later, Fraser is an advocate with the National Breast Cancer Coalition, vice president of the Michigan Breast Cancer Coalition, and a “Super Advocate” for the National Coalition of Cancer Survivorship. “So many women are delayed in being diagnosed, and they may not receive optimal treatment choices,” Fraser said. “We do women a disservice when we focus only on primary breast cancer and the ‘lump.’ Doctors and breast cancer organizations must educate women on the more aggressive forms of the disease.”

The following websites offer more information on IBC:

- http://www.eraseIBC.com/
- http://www.ibcresearch.org/
- http://www.ibchelp.org/

Dr. Spector reports consultancy relationships with Bessor Pharma, Takeda Pharmaceutical Co. Ltd., and Quintiles. He is also clinical advisor of Syndax Pharmaceuticals Inc. Dr. Cristofanilli is a consultant for Dompé (pharmaceutical) and Alere (diagnostics) for breast cancer research projects.