Chemotherapy Culture Differences Persist, but Molecular Insights Foster Change

By Steve Benowitz

When Michael Gnant, M.D., reported long-term results of an Austrian Breast and Colorectal Cancer Study Group (ABCxiety Group) trial in December at the San Antonio Breast Cancer Symposium, he expected skeptics. The study showed dramatically fewer recurrences and lower risks of death in young women with early-stage breast cancer who added the bone metastasis drug zoledronic acid to adjuvant endocrine therapy compared with hormone treatment alone.

In the four-arm, phase III trial, Gnant and his co-workers randomly assigned 1,803 premenopausal women with early-stage, estrogen receptor–positive breast cancer to receive either tamoxifen or the aromatase inhibitor anastrozole, or each treatment with zoledronic acid, for 3 years. The women had a low to moderate risk of relapse and had not received adjuvant chemotherapy after surgery. After a median follow-up of 84 months, the researchers showed that, compared with hormone therapy alone, the risk for recurrence dropped by 28%, and risk of death decreased by 36%.

The initial trial results had already been reported at the American Society of Clinical Oncology annual meeting in 2008, and later in the New England Journal of Medicine. A discussant in San Antonio noted that because the results met the trial endpoints, physicians could justifiably use the results in clinical practice.

Still, Gnant, professor of surgery at the Medical University of Vienna, wondered whether oncologists would be ready to follow the regimen he used: avoiding chemotherapy, in younger, premenopausal women with early-stage breast cancer, which for many physicians goes against traditional clinical practice. Many would and already had based some of their treatment regimens on the results of genomic testing. Yet, said Gnant, “Most of the practice guidelines I know tend to recommend cytotoxic chemotherapy in younger, premenopausal women out of principle.”

Chemo Cultural Divide: U.S. and Europe

To Gnant, a larger issue exists: an “overreliance on chemotherapy” in the U.S., and sometimes a chemotherapy cultural divide between the U.S. and Europe.

“I don’t think women should be treated with adjuvant chemotherapy just because they are young and could possibly have more aggressive disease,” he said. “We need to counsel patients about endocrine responsiveness and the expected benefits of treatments. Further evidence will make the endocrine approach more popular. It should not be overlooked that a sizable portion of breast cancer patients have low-risk disease and are endocrine responsive.”

Gnant called his findings a “change in treatment strategy and a paradigm shift, but more so in the U.S.” This isn’t about perception; it’s about data,” said Gnant. “There’s a clear difference in chemotherapy treatment culture. We know that in U.S. institutions, for many years, nearly every breast cancer patient under 50 had adjuvant chemotherapy. Now, we have a tendency to counsel our patients...
on the basis of the biological status of their disease. I don't think this is an observation uniquely connected to breast cancer. I would assume it applies to other cancers as well.”

According to oncologist Gilberto de Lima Lopes Jr., M.D., senior consultant in medical oncology and assistant director for clinical research at the Johns Hopkins Singapore International Medical Centre, “Culture can play an important role in what oncologists prescribe and the way they practice.”

Lopes said that with the advent of genomic testing, fewer differences in chemotherapy usage will occur across countries; however, “there is still an impression among European oncologists that U.S. oncologists are more aggressive in terms of using chemotherapy in the adjuvant setting in breast cancer.” Lopes noted that earlier versions of the St. Gallen guidelines—which many consider the standard clinical practice guidelines for breast cancer in Europe—recommended chemotherapy only for patients with larger tumors (usually 2 cm and larger). Most U.S. oncologists would start considering chemotherapy with tumors larger than 1 cm, thanks to findings more than a decade ago from a National Surgical Adjuvant Breast and Bowel Project study, which found that everyone with a 1-cm tumor benefited from chemotherapy.

But more broadly, attitudes on cancer care may differ between the U.S. and Europe, according to Brazilian-born Jonas de Souza, M.D., an instructor in the department of medicine at the University of Chicago. “The mindset in the U.S. war on cancer is that oncologists and patients often want the newest, the best, and to cure the cancer, often prolonging life at all costs, regardless of the quality of life,” he said. “Physicians have their patients’ best interests in mind, but it’s our culture here to always want more, even though sometimes more may be harmful. Some patients may be reluctant about palliative care because they associate it with hospice and see it as giving up. They want the next therapy.”

De Souza said that in the U.S., patients and physicians tend to strive for any extra benefit, even if it is only a few months. He pointed to regorafenib, a multikinase inhibitor recently shown to prolong life by 1.4 months as a third-line therapy compared with placebo in 700 patients with metastatic colorectal cancer. But the drug had substantial side effects. “It’s seen and marketed as a success, but in reality it’s adding more fatigue, diarrhea, and other possible side effects. The focus here is too often on prolonging life rather than quality of life. I’m not sure a drug such as regorafenib can be uniformly called a success just yet,” he said.

Quality-of-life concerns can inadvertently get pushed into the background, noted John L. Marshall, M.D., director of the Ruesch Center for the Cure of GI Cancers and chief of hematology and oncology at Georgetown University’s Lombardi Comprehensive Cancer Center in Washington, D.C. He recently hosted a symposium at Georgetown on cancer care that examined the value of cancer treatments and what cancer patients want.

“It comes down to maintaining hope. Patients continuing to take treatment is hopeful; if they run out of treatments, they are waiting to die. Doctors are incentivized to continue to try to help patients with metastatic disease. It’s easier to treat patients rather than tell them we have nothing else to try. That’s part of our culture,” he said.

“U.S.-trained physicians tend to take chemotherapy to later stages,” agreed Lopes. “In Europe and other parts of the world, for a variety of reasons—culture, limited resources—physicians frequently stress less chemotherapy and perhaps more quickly consider palliative care and hospice, options focusing on the quality of life.”

Health Care Systems, Limited Resources Affect Chemo Usage

Differences in patient and physician access to chemotherapy drugs also affect their usage around the world, said Marshall. “The U.S. concept of third-party payers feeds a perception that chemotherapy is free therapy, so patients often want third- and fourth-line therapies even if those therapies are very unlikely to help,” Marshall said. “Many other countries don’t have the same broad access.”

Lopes added that, compared with Europe and elsewhere, U.S. oncologists have always had more opportunity to choose treatments. Physicians treating patients receiving Medicare or who have private insurance, as well as those in the Veterans Administration system, in general can use practically any U.S. Food and Drug Administration–approved drug if it is considered the standard treatment. In Europe, however, many medical systems tend to be more restrictive.

And low-resource settings simply can’t offer chemotherapy to everyone with cancer—it is usually reserved for those who can afford private insurance or can pay out of pocket. In these developing countries, along with countries with nationalized health care systems, such as Europe and Canada, oncologists may not have as much incentive to prescribe chemotherapy as they do in places such as the U.S., where their salaries may depend in part on reimbursement fees for chemotherapy prescriptions, said Mark Clemons, M.D., an English-born breast cancer specialist and associate professor of medicine at the University of Ottawa. “If you have two treatments that have equivalent patient efficacy but markedly different physician reimbursement, there might be a tendency to order one more than the other. This is an issue that is frequently brought up at international cancer conferences.”

Molecular Testing Trumps Other Treatment Considerations

Although studies such as Gnant’s may illuminate and even exacerbate any cultural

Gilberto de Lima Lopes Jr., M.D.
differences in treatment that exist, many experts say that genomic testing and the ability to detail the molecular makeup of tumors—and guide cancer treatment—have already begun to blur such differences. In breast cancer, perhaps more so than in any other type, a growing ability to better predict the benefit of therapy for some patients is an example of how advances in molecular diagnostics have begun to change practice.

Genomic tests such as Oncotype DX have begun to change the chemotherapy landscape and take personalized medicine to a new level. Oncotype can predict the likelihood of benefit from chemotherapy and of disease recurrence in women with early-stage, hormone-sensitive breast cancer.

“Oncotype DX is increasingly being used in North America, as are other gene array tests, to better predict what treatments will help a patient and which will not,” said Clemons. Many reports indicate that Oncotype has markedly reduced use of adjuvant chemotherapy, he continued. “Oncotype has almost given ‘permission’ to physicians not to use chemotherapy. When a patient sees the test results that frequently show almost no advantage of giving chemotherapy over endocrine therapy, most don’t want chemotherapy.

“I think the pendulum is swinging away from chemotherapy in both pre- and post-menopausal women in North America, but in measured amounts,” Clemons continued. “People are beginning to realize that it’s not that you are giving a lesser treatment by giving women with breast cancer endocrine treatment; you are giving her the correct treatment for her disease. The more that research shows the molecular details of individual tumors, the more that patients can be stratified and treatments personalized.”

Treatment guidelines have also begun to reflect these new tests. Lopes said that more recent versions of the St. Gallen guidelines have included predictive factors in treatment decisions, compared with older guidelines that recommended basing therapy solely on tumor size and hormone receptor status. The guidelines also note that chemotherapy should be given to appropriately selected patients.

“Breast cancer is the prototype for the future of what we hope will be doing more specific targeted, individualized therapy for all our patients. We can’t do that in all diseases today,” noted Lopes. “Clearly, our ability to better categorize patients has enabled us to treat them better.”