Circulating Tumor Cells in Early-Stage Breast Cancer

By Gunjan Sinha

Circulating tumor cells (CTCs), a measure indicating poor prognosis in women with metastatic breast cancer, bode badly for women with early-stage disease as well. Two studies are the first to show that CTCs in peripheral blood are prognostic in non-metastatic disease.

One study, in the July 2012 *Lancet Oncology*, showed that breast cancer patients with CTCs had a fourfold-higher risk of recurrence and death than breast cancer patients with no CTCs.

The study, led by Anthony Lucci Jr., M.D., professor of surgical oncology at the University of Texas M. D. Anderson Cancer Center in Houston, included 302 women with stage I–III operable breast cancer. About 25% of the study group tested positive for CTCs. Of these, 15% relapsed and 10% died during a 5-year follow-up period, compared with 3% and 2%, respectively, of patients with no detectable CTCs. Moreover, the more CTCs per milliliter of blood detected, the higher the likelihood of relapsing or dying. CTCs were measured before chemotherapy.

Lucci’s study accords with interim data from the SUCCESS A trial—the largest ongoing clinical trial aimed to investigate the prognostic significance of CTCs in early breast cancer. The trial includes more than 3,700 women across 250 German study sites. The researchers detected CTCs in 21.5% of 2,026 patients. Furthermore, cancer patients with at least five CTCs detected directly after surgery but before chemotherapy had a fourfold-greater risk of recurrence and a threefold-greater risk of death than patients without CTCs, according to Bernadette Jäger, M.D., at the University of Ulm Women’s Clinic in Ulm, Germany. Jäger presented the interim data at the Eighth European Breast Cancer Conference in Vienna.

But although evidence is mounting that CTCs in blood are associated with poorer outcomes, the question of what to do with that information is wide open, said Justin Stebbing, M.D. Ph.D., professor of medical oncology at Imperial College in London. “Even though it’s increasingly clear that CTCs have a prognostic role, no one knows how to alter treatment to change outcomes.”

**Applying the Knowledge**

Further complicating the question is the little-understood biology of CTCs. Processing the cells kills them, so researchers don’t know whether the cells are living. They may be cells from a primary cancer and they may be able to form secondary metastases. However, the cells may be dead to begin with, merely debris from dead cancer cells, representing a by-product of another process, said Stebbing. “There are a lot of assumptions about these cells.”

As a result, in the U.S. neither the American Society of Clinical Oncology nor the National Comprehensive Cancer Network recommends testing CTCs routinely in breast cancer care. Nevertheless, because the test is noninvasive, some cancer physicians use CTCs to aid prognoses in metastatic breast, colon, and prostate cancers. The cells are also sometimes used as a liquid biopsy—a blood test in real time—to obtain information on the patient’s status without having to perform scans.

The guidelines will probably change, however, as more data from large-scale trials are published. Jäger expects researchers to publish final results from the SUCCESS A trial in 2013. For that trial, the researchers are also evaluating patients’ CTC counts directly after chemotherapy and at 2 and 5 years later, which will yield much-needed information on whether chemotherapy affects CTC levels and whether this effect is associated with disease progression or survival.

**Ramping Up Trials**

Jäger also helped launch a new trial, DETECT III, which will investigate adding lapatinib to standard treatment in patients with HER2-negative metastatic breast cancer and HER2-positive CTCs. The rationale for the study comes from the knowledge that HER2 status can change as cancer advances, and this may be one reason why standard chemotherapy may fail in this group. By adding a HER2 targeted therapy in women who test positive for CTCs expressing HER2, the researchers will evaluate whether the additional therapy prolongs progression-free survival.

Lucci and colleagues continue to accrue patients into their study to increase its power and perform subset analyses, he said. The researchers are particularly interested in studying women with estrogen receptor–positive cancers with no lymph node involvement. This group is traditionally thought to have a lower risk of relapse,
although a substantial number do relapse, said Lucci. “If we can determine whether CTCs are an important predictor of relapse in that group, then we could potentially use the information to help to make chemotherapy decisions,” he said.

Jäger agrees: “If CTCs can be used to direct treatment, it will be one more step toward enabling us to tailor treatment to individual patients.”

Myeloproliferative Cancers: Treatment Prospects for Rare Diseases

By Vicki Brower

Myelofibrosis (MF), a rare myeloproliferative disease originating in bone marrow stem cells, has until recently left patients with few treatment options. But the emergence of JAK2 inhibitors and the resurgence of interferon may change that.

Ruxolitinib, the first approved JAK2 inhibitor, substantially improved quality of life in MF patients enrolled in two large phase III trials—COMFORT I and COMFORT II—according to a study published last March in the New England Journal of Medicine. Ruxolitinib reduced spleen enlargement, the primary end-point, in 41.9% of the trials’ 155 treated patients, compared with 0.7% of the 154 patients on placebo. Patients on placebo also experienced reduced abdominal pain, cachexia, and night sweats. Now a study in the June 20 online version of Blood reports survival benefit as well as a reduction in spleen enlargement and other symptoms: 75% of patients taking ruxolitinib were still alive at 30 months, compared with 55% in the control group.

Despite these encouraging results, some experts point out that the drug’s effects are mainly palliative. “Ruxolitinib did not normalize bone marrow [or] stop disease progression, and symptoms returned rapidly when discontinued,” said Ayalew Tefferi, M.D., professor of hematology and oncology at the Mayo Clinic in Rochester, Minn.

The discovery of the JAK2 mutation in myeloproliferative neoplasms (MPNs) in 2006 to some extent put a rare disease that affects roughly 166,000 patients in the U.S. in the spotlight. Two years later, the World Health Organization designated MPNs as cancer. Researchers initially hoped that targeting the JAK2 mutation might be curative, like targeting the abnormal Philadelphia chromosome in chronic myelogenous leukemia with imatinib. But MPNs have proven much more genetically complex than anticipated, explained Ross Levine, M.D., a researcher at Memorial Sloan–Kettering Cancer Center in New York and a JAK2 discoverer.

“We now know that the JAK2 V617→F mutation, which occurs more often in MPNs than any other mutation, is not a driver mutation, and ruxolitinib is not the new imatinib,” Levine said. The JAK2 V617→F mutation occurs in patients with other myeloproliferative diseases: half of patients with MF or essential thrombocythemia (ET), and 90% of those with polycythemia vera (PV), which are characterized by an overproduction of platelets and red blood cells, respectively. ET and PV may progress to MF, and all three MPNs may develop into acute myeloid leukemia.

But doctors can’t tell who will progress and who should be treated.

Ten other JAK2 inhibitor trials are ongoing, according to Srdan Verstovsek, M.D., Ph.D., primary investigator on the ruxolitinib trials, but many believe that they will not treat MPNs’ cause, abnormal stem cells. The only cure is bone marrow transplantation, which has low success rates in MF and is not generally done in ET and PV, explained Verstovsek, of the University of Texas M. D. Anderson Cancer Center in Houston. MF patients may live only a few years after diagnosis, but the course of PV and ET can be relatively indolent.

Interferon Trials

Alongside the development of JAK2 inhibitors for MPNs is a surge of interest in interferon. Twenty-five years of experience in 47 trials has shown that sometimes, long-term treatment produces molecular and hematological remissions, reduces JAK2 burden, and slows disease progression. Experts are divided, with some endorsing interferon as promising and others betting on a combination of JAK2 inhibitors and epigenetic-targeting drugs, telomerase-targeting drugs, or heat shock protein inhibitors. Interferon has been used for years in Europe even in newly diagnosed patients, but it is still