Researchers Exploring Implications of Minimal Residual Cancer

Klaus Pantel, M.D., Ph.D., director of the Institute of Tumor Biology at the University of Hamburg in Germany, and colleagues started studying minimal residual cancer more than a decade ago when they began seeking an early marker of cancer’s systemic spread. Because bone marrow was routinely tested for micrometastases in leukemia and lymphoma patients, Pantel and his colleagues reasoned that the same approach might work for breast cancer.

Late this summer, their pooled analysis of more than 4,500 breast cancer patients, which was published in the August 25 New England Journal of Medicine, concluded that “the presence of micrometastasis in the bone marrow at the time of diagnosis of breast cancer is associated with a poor prognosis.”

“The old view is that metastases are a late development in cancer,” Pantel said in an interview during the September Symposium on Minimal Residual Cancer in San Francisco, of which he was a co-chair. “But our work and the gene expression analyses that have been done in breast and other cancers indicate that even small tumors can spread. And those that have a tendency to spread may do so very early—most likely before detection.”

Explained Massimo Cristofanilli, M.D., associate professor of breast medical oncology at the University of Texas M. D. Anderson Cancer Center and symposium co-chair: “Most large studies show that for patients at high risk—4+ lymph nodes—we are not improving survival very much, even with the most aggressive chemotherapy such as taxotere. The European data show that bone marrow may contain dormant tumor cells that are not attacked by chemotherapy in common use. New therapeutic strategies are necessary to specifically address this microscopic disease.”

Pantel said that his group has found tumor cells in the blood months after a primary breast tumor has been removed. They believe these cells must originate from a metastatic process because cells from the primary tumor would have a half-life of only about one day.

This finding tallies with a report published last year in Clinical Cancer Research by Jonathan W. Uhr, Ph.D., from the Cancer Immunobiology Center of the University of Texas Southwestern Medical Center in Dallas, and colleagues that showed that 7–22 years after mastectomy, 13 of 36 patients with no evidence of clinical disease had cells in their blood that had all the characteristics of cancer cells, commonly called circulating tumor cells. The half-life of the cells was very short, indicating that they were replenished every few hours by other, replicating tumor cells somewhere in the body. Bone marrow would be a likely depot for such cells, although this supposition has not been proven.

“The [Uhr] report changed the way I think about cancer,” said Daniel F. Hayes, M.D., professor of internal medicine and clinical director of the breast oncology program at the University of Michigan Comprehensive Cancer Center. “These data suggest that women who have had breast cancer previously and are now perfectly fine are walking around with cells that are half loaded, waiting for the next hit.”

So far, only a few U.S. centers (including M. D. Anderson, Cristofanilli said) perform bone marrow aspiration for patients with solid tumors, and then only in the context of a clinical trial. One major reason for this, explains Hayes, is that it’s not yet clear whether or what kind of treatment would change the outlook for patients with micrometastases in the bone marrow. And no surgical–medical groups in the United States have done any relevant clinical trials.

**Tumor Cells in Peripheral Blood**

In 2004, Cristofanilli, Hayes, and their colleagues reported that the circulating tumor cell level in patients with metastatic breast cancer about to start a new treatment is an independent predictor of progression-free and overall survival (see News, Vol. 96, No. 14, p. 1055, “Trial Results Boost Circulating Tumor Cell Field”).

“Measurement of [circulating tumor cells] in blood is not just another measure of tumor load but more prognostic than just measuring single metastatic sites or a tumor marker,” Cristofanilli said. “It tells you more about the biology of the disease, and it leads you to consider more personalized treatment.” He added that the persistence of circulating tumor cells 3–4 weeks after initiation of therapy predicted the clinical effect of treatment before standard imaging modalities, suggesting that measuring circulating tumor cells could be valuable in halting futile therapy sooner rather than later.

An international study testing the clinical significance of circulating tumor cells in blood in patients with metastatic breast cancer is under consideration. Different uses of current therapies, such as use of bisphosphonates, may also be tested.

**Tumor Cell Dormancy?**

The role of the immune system in holding circulating tumor cells and bone marrow tumor cells in check remains unclear. Since some women with breast cancer appear to have dormant tumor cells that later become active, therapy to
stimulate the immune system may be worth investigating.

“Dormancy seems to be a fundamental biologic process but poorly investigated,” Pantel said. “What regulates it?” Some see cancer stem cells, or progenitor or founder cells, that have self-renewal capabilities and permanent survival abilities as key players. Such cells may remain when the rest of the tumor—composed of terminally differentiated cells—shrinks as a result of treatment, Hayes suggested. On the other hand, Uhr sees the situation as a steady state between apoptotic circulating tumor cells and replenishment of them. “We need to find the mechanism that keeps this population from expanding,” he said. “It could lead to new therapies.”

**Rare Event Technologies**

Underlying and helping to ensure the validity of these concepts are advances in technology. Searching for circulating tumor cells in blood and for tumor cells in bone marrow, for example, has been aided by different methods of enrichment, or decreasing the number of irrelevant cells so as to have fewer cells to examine. “How and where you look at such cells can yield very different sensitivities,” said John W. Park, M.D., director of novel therapeutics in breast oncology at the University of California at San Francisco Comprehensive Cancer Center and symposium co-chair, adding that these are rare events in any case.

New imaging devices, such as CellSearch and ACIS, can detect very small numbers of circulating tumor cells in the blood. The tests have helped advance the field, although such techniques have not yet been validated for locating tumor cells in bone marrow.

“This field is at the intersection of a lot of other fields,” Park said in an interview. “For breast cancer in particular, a series of new technology-driven approaches have hit the arena. We’re trying to determine which tumors are more dangerous so that we can tailor treatments appropriately—not overtreat patients who will be cured anyway yet potentially add more treatments for difficult cases. Fortunately, we have a number of different treatments for breast cancer,” Park said. “Certainly, bone marrow testing tells you which tumors are worse than others, but molecular profiling of primary tumors with expression array analysis or RT-PCR–based tests are also in use.”

Such concepts are beginning to be applied to other solid tumors. At the Seminar for Minimal Residual Cancer, for example, Wolfgang Lilleby, M.D., Ph.D., of the Norwegian Radium Hospital, reported finding probable prostate cancer cells in patients’ bone marrow at the time of diagnosis. In a limited study, he and colleagues showed that detection of such cells after “curatively intended radiotherapy is associated with a poor outcome” and may be more sensitive than assessment of prostate-specific antigen levels.

—Gail McBride

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