NEWS BRIEFS

ASCO 2011: Broadening the Horizons of Cancer Research

By Kristine Crane

At the recent American Society of Clinical Oncology (ASCO) meeting—the world’s largest conference dedicated to advancing research on cancer—one session played the devil’s advocate: Why is cancer research failing? Citing the sobering statistic that 900 people in the U.S. die of cancer every day, Lee Ellis, M.D., of the University of Texas MD Anderson Cancer Center in Houston, and colleagues dedicated a panel discussion to understanding how cancer research can be improved.

Part of the problem, Ellis said, starts with faulty mouse models. Because tumors in mice grow much faster than they do in humans, and agents target rapidly dividing cells, results may often end up positive in mice. He added that mice with smaller cell inoculums or the use of genetically engineered mice is needed.

“We need models where tumor growth is slower. We have to conduct animal studies where the cell proliferation rate is not incredibly rapid, giving the tumor time to form its normal microenvironment, with fibroblasts and endothelial cells, at a slower rate,” Ellis said in a follow-up interview.

He also mentioned the importance of injecting tumors in orthotopic, or organ-specific, locations, instead of using subcutaneous mouse models, in which tumors are injected just beneath the skin. Injecting tumors into orthotopic environments would give a much more realistic assessment of how tumors may grow in various organs that are more relevant to growth and metastasis in humans.

Furthermore, genetically engineered mouse models are needed to test different genetic backgrounds, Ellis said. “No two human tumors are built on the same genetic background,” he said. He cited the pancreatic cancer model as one where the KRAS genetic mutation might be prevalent in most human tumors and serves as a good model of human cancer. But because human pancreatic cancer cells carry several disease mutations, other genetic variants should be studied in addition to KRAS-driven tumors.

With the increase in combination therapies, studying combinations in mice before doing so in humans will be important, Ellis said. At his ASCO presentation, he cited...
three studies of combined therapies for colon cancer that had failed in clinical studies. None of the combinations had been previously tested in mouse models, something Ellis found “mind-boggling.”

“Every time you perturb a system, the body is going to react. Sometimes these cytokines released at such levels theoretically increase tumor growth. Sometimes when we add these incredible amounts of drugs, more may not always be better—and may be worse. We are not treating HIV: Cocktails are not always better.”

Ellis emphasized that “we are not studying agents, but regimens,” pointing to promising early-phase studies (first tested in mouse models) in metastatic melanoma patients that combined a BRAF inhibitor and a MEK inhibitor. “In this new era, I hope we are smart enough to study drug combinations in vitro and in mice in vivo before we test them in humans,” he said.

But conducting good experiments depends in part on creating the right research environment. The fierce competition among young scientists is now in part on creating the right research environment. The fierce competition among young scientists is now

Cancer Stem Cells Take Center Stage

Although some scientists have long maintained that stem cells are the seeds of cancer, clues about how to kill stem cells are just beginning to emerge. In the ASCO plenary session, Robert Weinberg, M.D., of MIT, talked about how epithelial–mesenchymal transition (EMT) is at the heart of why cancer stem cells proliferate. “EMT factors can orchestrate dissemination factors in the metastatic cascade,” Weinberg said, explaining that epithelial cells that have undergone EMT can acquire stem cell properties, which allows them to seed new tumors. Weinberg cited in vitro studies of epithelial cells shown to morph into stem cells. That is why therapies need to target both stem cells and non-stem cells, Weinberg said. “We will not succeed if we are only targeting the stem cells.”

Ideally, targeted therapies for breast cancer stem cells would be combined with a debulking agent in the form of standard chemotherapy or an antiangiogenic agent for the other cancerous epithelial cells, according to Max Wicha, M.D., of the University of Michigan, who spoke at an ASCO panel on stem cell research. “Relapse after adjuvant therapy is a phenomenon of cancer stem cells,” he said. At the same time, adjuvant trastuzumab (Herceptin) can reduce breast cancer recurrence by more than 50% in both HER2-positive and HER2-negative patients, Wicha explained. Those pivotal findings, which came out of the NSABP B-31 trial and were published in the New England Journal of Medicine in 2008, revealed that the drug thought to work only on HER2-positive patients also worked on HER2-negative patients. That finding suggests that trastuzumab was targeting stem cells in the HER2-negative patients—because cancer stem cells do express HER2.

The recently started NSABP B-47 trial will follow up these results by testing trastuzumab in the adjuvant setting for HER2-negative women. The trial is controversial among oncologists because it fundamentally changes the original application of HER2. But Wicha is confident that the trial may boost support for the stem cell model, which rests, he said, on targeting “a minor population of cells, but they are the key ones.”

Fight Against Cancer Goes Global

As cancer deaths around the world continue to climb—outpacing deaths from malaria, tuberculosis, and HIV/AIDS combined—international organizations are putting cancer on their agendas. With the upcoming United Nations Summit on Non-Communicable Diseases featuring cancer on September 11, “we hope to change the history of cancer,” Edouardo L. Cazap, M.D., president of the International Union on Cancer Control (UICC), told reporters at an ASCO press briefing. “It is extremely important to put cancer on the political agenda.”

Cazap said that 90% of the world’s population cannot access new cancer treatments. Initiatives such as the Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries are working to address these disparities. Taking cervical cancer as an example, Cary Adams, UICC CEO, said that cervical cancer was once the number-one killer of women in the U.S., whereas today it kills fewer than one in 100,000 women. In the developing world, however, it remains a leading cause of death in women.

ASCO also has a training course for medical oncologists, and it will send 10–15 volunteers to Ethiopia and Vietnam. According to Allen Lichter, ASCO CEO, Ethiopia until recently had only one medical oncologist for a population of roughly 80 million people.

Old Drug, New Gold Standard

It wasn’t the biggest story to come out of ASCO, but the data from a phase III trial showed that patients with gastrointestinal stromal tumors (GIST) cut their risk of recurrence in half after 3 years of adjuvant imatinib (Gleevec), and it had people talking.

“This is the kind of data that will change guidelines,” said Mark Kris, M.D., of Memorial Sloan–Kettering Cancer Center in New York, at an ASCO press briefing. The Europe-based study, called SSGXVIII/AIO, included 397 patients with resected GIST in Finland, Germany, Norway, and Sweden, who took adjuvant imatinib for either 12 or 36 months. The 3-year treatment group had a 54% reduction in recurrence, a statistically significant result, according to Heikki Joensuu, M.D., the
study’s lead author and a professor of oncology at the University of Helsinki. “A few years ago, 50% of patients would have died, and 90% [of patients in this trial] survived,” said Joensuu, citing the 92% overall survival rates for patients in the 3-year treatment group and 82% for those in the 1-year treatment group. (Overall survival was the study’s secondary endpoint.) “I can’t think of any other tumor type where the pace of progress has been as rapid.”

Although Joensuu thinks 3 years of imatinib will be standard adjuvant therapy, he said it can also be used in the recurrent, metastatic setting: a follow-up study of patients in the trial at 54 months showed that those whose recurrences were detected early by imaging responded to restarting imatinib. “One needs to follow up with patients when adjuvant imatinib has been stopped. Many recurrences can be detected through imaging,” said Joensuu.

Imatinib, which is taken as a pill, also had mild side effects in patients: The most common were anemia, fatigue, nausea, and muscle cramps, said Joensuu. The U.S. Food and Drug Administration has now approved the drug to treat 10 different types of cancer. It was first granted approval in 2001 for Philadelphia chromosome-positive chronic myelogenous leukemia.

According to Kris, “It’s one of the amazing cancer stories that... patients who had a 50% death likelihood at 5 years, by taking four pills [of imatinib] a day, are alive at 5 years, and the vast majority alive are cancer free.”

At the plenary session, Charles Blanke, M.D., of the University of British Columbia, said, “Three-year therapy with imatinib is now the new gold standard for patients with resected GIST.”

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