Intraperitoneal Chemotherapy

Ovarian Cancer *from page 1*

successful surgical cytoreduction (debulking) and who were then given chemotherapy via a combined intravenous-intraperitoneal approach as opposed to the standard intravenous-only approach.

The most recent of these trials showed a 16-month improvement in median overall survival in 205 women who received combined intravenous-intraperitoneal chemotherapy. According to the NCI, the study was strong and free of the complexities of earlier studies.

The NCI issued the announcement "based on these combined results" and because intraperitoneal (IP) chemotherapy "has not been adopted into standard practice" despite the published evidence of efficacy, according to NCI statements and a "Q&A" posted on the Internet (http://ctep.cancer.gov/highlights/ovarian.html).

The "best data sources" suggest that less than 1% of women with ovarian cancer receive IP chemotherapy, NCI said. The treatment was first proposed several decades ago because residual ovarian cancer after surgery and initial recurrences are primarily confined to the abdomen.

Many women, moreover, are not undergoing optimal surgical debulking to minimal or no gross residual disease, which is the first step to improved survival and an important prerequisite for chemotherapy, according to the NCI.

Dr. Edward L. Trimble of the NCI said in a recently published editorial that the rate of optimal surgical debulking varies dramatically between centers from 20% to 80% (Gynecol. Oncol. 2006;100:3-4). And in its announcement, the NCI said that women undergoing surgery for presumed ovarian cancer "should undergo surgery by a gynecologic oncologist or a surgical team with expertise in the staging and cytoreduction of ovarian cancer."

Participants in the recently published trial (patients with stage III ovarian cancer or primary peritoneal carcinoma) were required to have no residual tumors greater than 1 cm in diameter. The patients were randomized to receive intravenous (IV) paclitaxel over a 24-hour period followed by either IV cisplatin on day 2 (the IV group) or IP cisplatin on day 2 and IP paclitaxel on day 8 (the IP group). The regimen was administered every 3 weeks for a total of six cycles.

Only 42% of the 205 patients in the IP group completed all six planned cycles of IP therapy—and 48% received three or fewer cycles—due to its toxic effects and catheter complications.

Still, there was a significant increase in median progression-free survival and median overall survival in these patients (approximately 6 months and 16 months), compared with patients who received only IV therapy, reported Dr. Deborah K. Armstrong of Johns Hopkins Kimmel Cancer Center in Baltimore and her coinvestigators in the Gynecologic Oncology Group (N. Engl. J. Med. 2006;354:34-43).

Dr. Stephen A. Cannistra, who commented on the study in an editorial, said the increase in survival is "one of the largest benefits ever observed for a new therapy in gynecologic oncology." The IP route, he noted, has a "considerable" pharmacologic advantage, allowing higher doses of certain drugs to be administered (N. Engl. J. Med. 2006;354:77-9).

Practice will change, he and others say, but the change will be more complex than it was following the NCI's announcement in 1999, which encouraged a combination of chemotherapy and radiation, rather than radiation alone, for cervical cancer.

For one thing, IP chemotherapy requires familiarity with catheter placement, peritoneal administration, and management of catheter-related complications. Also, the optimal IP regimen is unknown, and physicians will undoubtedly attempt to reduce the higher toxicity of IP therapy by adjusting doses and dosing schedules and by substituting drugs.

The NCI emphasizes that the additional toxicity of IP therapy is "generally transient" and manageable. Still, the institute is encouraging further trials, particularly to address the issue of toxicity, and is planning a "broad-based dissemination and educational plan."

The NCI considers making clinical announcements when trials have "identified an intervention" that is available to the general public and that "substantially improves with reasonable certainty the survival outcome for a significant number of people."

In 2005, an estimated 22,220 in the United States were diagnosed with ovarian cancer and an estimated 16,210 died from the disease. More than half of women with ovarian cancer present with advanced-stage disease, and only 45% of women survive 5 years after diagnosis, according to the NCI. ■

Atypical Lobular Hyperplasia Has Higher Breast Ca Risk Than Ductal

BY BRUCE JANCIN
Denver Bureau

San Antonio — All women with atypical hyperplasia in a benign breast biopsy are at significantly increased risk of developing breast cancer, but the magnitude of risk is greater when the pathology involves atypical lobular hyperplasia than it is with atypical ductal hyperplasia, according to data from the Nurses' Health Study.

The adjusted odds ratio for developing breast cancer was 5.24 for those with atypical lobular hyperplasia.

DR. COLLINS

Only about 60% of the breast cancers that develop in women with either atypical lobular hyperplasia or atypical ductal hyperplasia occur in the ipsilateral breast. For this reason, both types of atypical hyperplasia are best regarded for purposes of clinical management as markers of a generalized bilateral increase in breast cancer risk, Dr. Laura C. Collins said at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

She reported on 2,016 participants in the Nurses' Health Study who had a benign breast biopsy; 395 of them subsequently developed breast cancer. The 1,621 controls were matched to the cancer patients by age and year of their benign breast biopsy.

Of the women with atypical hyperplasia in a benign breast biopsy, 75 went on to develop breast cancer. That translated into an adjusted 3.93-fold greater risk of developing the malignancy for women with atypical hyperplasia compared with those who had a benign breast biopsy showing only nonproliferative changes, said Dr. Collins, a pathologist at Beth Israel Deaconess Medical Center and Harvard Medical School, Boston.

The adjusted odds ratio for developing breast cancer was 2.76 for women with atypical ductal hyperplasia, 5.24 for those with atypical lobular hyperplasia, and 8.12 for women with both histologic abnormalities.

The risk of developing breast cancer was roughly twice as great 10 years or longer following a benign biopsy featuring atypical ductal hyperplasia as in the first 10 years of follow-up. In contrast, breast cancer risk in women with atypical lobular hyperplasia remained steady over time.

Atypical lobular and atypical ductal hyperplasia also differed in terms of the impact menopausal status at the time of the benign breast biopsy had on subsequent breast cancer risk. Women who were premenopausal at the time of a benign breast biopsy showing atypical lobular hyperplasia had a 6.67-fold increased breast cancer risk. Women who were postmenopausal at the time of biopsy had a 3.41-fold increased risk.

In contrast, patients who were premenopausal when they had a breast biopsy showing atypical ductal hyperplasia had a 2.59-fold increased risk of subsequent breast cancer, whereas those who were postmenopausal at the time of their benign biopsy had a 4.04-fold increased breast cancer risk, Dr. Collins noted.

The Nurses' Health Study is an ongoing prospective study involving U.S. registered nurses aged 25-55 years at entry. At present, more than 237,000 women are enrolled. ■

Letrozole Surpasses Tamoxifen in Head-to-Head Breast Ca Trial

BY MARY ANN MOON
Contributing Writer

The aromatase inhibitor letrozole compares favorably with tamoxifen as an adjuvant treatment for hormone receptor–positive breast cancer in postmenopausal women, reported Dr. Beat Thürlimann and associates in the Breast International Group 1-98 trial.

Interim results of this multinational phase III clinical trial at the 2-year mark "indicate that letrozole is an effective option for standard adjuvant therapy, with a relatively favorable safety profile," compared with tamoxifen. Letrozole was superior to tamoxifen in decreasing the risk of distant metastases, said Dr. Thürlimann of the Swiss Group for Clinical Cancer Research and the Senology Center of Eastern Switzerland, Kantonsspital, St. Gallen, and associates.

Letrozole (Femara) was approved in December for adjuvant treatment of early hormone-sensitive breast cancer in postmenopausal women, based on the results of the BIG 1-98 trial. The trial involved 8,010 postmenopausal women with invasive breast cancer that was positive for estrogen receptors, progesterone receptors, or both. The women were randomly assigned to receive one of three regimens after surgery: monotherapy with either letrozole or tamoxifen for 5 years, letrozole for 2 years followed by tamoxifen for 3 years, or tamoxifen for 2 years followed by letrozole for 3 years.

This planned interim analysis compared outcomes after a median of 26 months for the 4,003 women assigned to letrozole initially with those of the 4,007 assigned to tamoxifen initially (New Engl. J. Med. 2005;353:2747-57).

Disease-free survival was significantly greater in the letrozole group, and the drug was particularly effective in reducing recurrences at distant sites. The 5-year estimates of disease-free survival were 84% in the letrozole group and 81.4% in the tamoxifen group.

Subgroup analysis showed that letrozole was superior to tamoxifen for the subset of patients who received chemotherapy, the subset who did not receive radiotherapy, and the subset with positive axillary nodes.

Letrozole significantly decreased the cumulative incidence of breast cancer relapse, compared with tamoxifen. "This difference became evident 1 year after randomization, and there was an absolute difference of 3.4 percentage points at 5 years," they noted.

More patients in the letrozole group than in the tamoxifen group reported adverse events, but the incidence of life-threatening adverse events was 1.7% for both. Bone fractures were more frequent with letrozole (5.7% vs. 4.0%), and the interval before sustaining a fracture was significantly shorter.

Letrozole was associated with fewer thromboembolic events (1.5% vs. 3.5%), episodes of vaginal bleeding (3.3% vs. 6.6%), endometrial biopsies (2.3% vs. 9.1%), and invasive endometrial cancers (0.1% vs. 0.3%).

The overall incidence of adverse cardiovascular events was similar in the two groups (letrozole, 3.7%; tamoxifen, 4.2%), but more women on letrozole had severe cardiac events (2.1% vs. 1.1%).

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