RESEARCH HIGHLIGHTS

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Women With Node-Positive Breast Cancer Obtain Benefits From Adjuvant Chemotherapy

Researchers from the University of Vermont in Burlington presented results from the analysis of data from the Cancer and Leukemia Group B trials for the effects of adjuvant chemotherapy in younger and older women. The purpose of the study was to determine the benefits and toxicities of adjuvant chemotherapy for women with node-positive breast cancer. Data from 6,489 patients were analyzed for all four trials by age group. Sixty-one percent of the biopsies were estrogen-receptor positive and 56% were progesterone-receptor positive. Fifty-seven percent of the women received tamoxifen therapy in addition to chemotherapy regimens. Women older than 65 had more positive lymph nodes ($p < 0.05$). Multivariate analysis demonstrated that small tumor size, a low number of positive lymph nodes, higher doses of chemotherapy agents, and the use of tamoxifen all were associated with longer relapse-free survival. No correlation with age existed. The researchers concluded that older women had similar dose-related benefits from adjuvant chemotherapy as younger women in reducing breast cancer-related relapse and mortality. They also noted that older women had a higher mortality rate because of more deaths related to causes other than breast cancer. In addition, women older than 65 were greatly underrepresented in clinical trials.

Older Patients Are Underrepresented in Cancer Clinical Trials

Investigators from the U.S. Food and Drug Administration's Center for Drug Evaluation and Research analyzed data from clinical trials for cancer drugs involving 29,350 patients, comparing cancer statistics and percentages of patients involved in clinical trials by age group. Older patients were defined as those older than 65. The percentage of patients older than 65 who were diagnosed with specific types of cancer were 49% for breast cancer, 67% for lung cancer, 70% for colorectal cancer, 71% for pancreatic cancer, 44% for ovarian cancer, and 54% for leukemias. However, the percentages of patients older than 65 who were enrolled in clinical trials were 45% for breast cancer, 35% for lung cancer, 41% for colorectal cancer, 33% for pancreatic cancer, 31% for ovarian cancer, and 24% for leukemias. The disparity increased with increasing age. The researchers concluded that underrepresentation of older patients in clinical trials hampers efforts to assess the risks and benefits of therapies for older patients. They recommended developing strategies to increase the enrollment of older patients in cancer clinical trials and designing prospective trials specifically for older adults.

Paclitaxel Plus Standard Therapy May Improve Outcomes for Patients With Head and Neck Cancer

The results of a multicenter, phase III trial comparing standard cisplatin and 5-fluorouracil with cisplatin, 5-fluorouracil, and paclitaxel for the treatment of locally advanced head and neck cancer were presented by researchers from Hospital 12 de Octubre in Madrid, Spain. The trial involved 384 patients randomly assigned to one of the two treatment arms. Pretreatment patient characteristics were well balanced between the two treatment groups. Patients who received paclitaxel had no signs of tumor progression at a median of 23 months compared to 18 months for those who received standard therapy. For patients who received paclitaxel, tumor growth was halted in 33% compared to 14% of those who received standard therapy. The organs involved in speaking and swallowing (larynx, pharynx, and tongue) were preserved in 88% of the patients who received paclitaxel compared to 75% of those who did not receive paclitaxel. Side effects were similar in the two groups, although those who received standard therapy were more likely to experience severe mucositis. Follow-up is continuing; those who received paclitaxel are surviving significantly longer than the median 38 months associated with the standard chemotherapy regimen.

Antiangiogenesis Drug May Benefit Patients With Metastatic Colorectal Cancer

Bevacizumab (Avastin™, Genentech Inc., South San Francisco, CA) inhibits vascular endothelial growth factor (VEGF), a protein that enhances blood vessel growth (angiogenesis) necessary for tumor survival. Researchers from Duke University Medical Center in Durham, NC, presented the results of a phase III trial of standard chemotherapy (irinotecan, 5-fluorouracil, and leucovorin) compared to standard therapy plus bevacizumab. In this study, 800 patients were randomized to one of the two treatment arms. Tumors were shown to shrink by half in 45% of the patients who received bevacizumab and 35% of the patients who received the standard therapy. Furthermore, patients who received bevacizumab survived a median of 20.3 months compared to 15.6 months for those who did not receive it. Cancer progression was delayed for a median of 10.6 months for patients who received bevacizumab and 6.2 months for those who did not. Phase II trials of bevacizumab suggested that bleeding, thrombosis, proteinuria, and hypertension were possible safety issues. However, in this phase III trial, only hypertension was identified as a potential problem and it was readily treatable with oral medications. The researchers also noted that the risk of gastrointestinal perforation, although rare, may be increased with the addition of bevacizumab to standard therapy.

Adjuvant Oxaliplatin May Reduce Risk of Disease Recurrence in Patients With Colorectal Cancer

Researchers from Hospital Saint Antoine in Paris, France, presented the results from an international phase III trial of oxaliplatin for the treatment of locally advanced colorectal cancer. The study involved 2,248 postsurgical patients diagnosed with stage II or III colon cancer who were assigned randomly to

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receive standard chemotherapy (5-fluorouracil and leucovorin) or standard chemotherapy plus oxaliplatin (FOLFOX). The FOLFOX regimen was well tolerated; however, neutropenia and peripheral neurotoxicity occurred at a higher rate in patients who received oxaliplatin compared to those who did not. The investigators found that 78% of patients who received FOLFOX had no signs of cancer three years after beginning treatment. This is compared to 73% of those who received standard chemotherapy.

Erlotinib Shows Activity in Treating Bronchioloalveolar Cell Carcinoma

Signaling via the epidermal growth factor receptor is implicated in tumor cell proliferation. Erlotinib inhibits the epidermal growth factor receptor tyrosine kinase and previously has shown promise for the treatment of patients with advanced non-small cell lung cancer who had failed initial chemotherapy. The most dramatic results appeared to occur in patients with bronchioloalveolar cell carcinoma (BAC). Researchers from Memorial Sloan-Kettering Cancer Center in New York, NY, and Vanderbilt-Ingram Cancer Center in Nashville, TN, presented the results of a phase II trial of erlotinib for treatment of patients with BAC. Of the 30 patients who completed one month of therapy at the time of the report, 8 achieved a partial response (major objective response rate 27%, 95% confidence interval 13%–44%). Of these patients, five had never smoked, two had smoked less than 10 pack-years, and one was a former heavy smoker. The study is ongoing, and more patients are being enrolled. The researchers concluded that the activity in nonsmokers may suggest that important differences exist between smokers and nonsmokers that affect their responses to chemotherapy.

Oral PKC 412 Shows Activity Against Acute Myeloid Leukemia

One-third of patients with acute myeloid leukemia have a specific genetic mutation resulting in an abnormal version of the protein called FLT3 tryosine kinase that is necessary for normal blood cell maturation. In acute leukemia, immature blood cells (blasts) reproduce rapidly and displace normal red and white blood cells and platelets in the bone marrow. Increased activity of the abnormal FLT3 tyrosine kinase is implicated in these processes. The drug PKC 412 has been developed to target the abnormal FLT3 tyrosine kinase protein. In preclinical studies, PKC 412 demonstrated activity in cell culture and animal models. Researchers from Dana-Farber Cancer Institute in Boston, MA, presented results from a collaborative phase II trial of PKC 412 for treating patients with acute myeloid leukemia who had specific mutations in the gene that codes for FLT3 tyrosine kinase. In this study, 14 patients received oral PKC 412 three times a day. For 12 of these patients, the numbers of circulating blasts decreased by more than 50%. In two patients, the blasts disappeared completely. In five of the patients, the numbers of blasts in the bone marrow were reduced by more than 50%. The drug was well tolerated, with grade I and II nausea being the most common side effect. The researchers concluded that patients' responses to PKC 412 were similar to the initial responses of patients to Gleevec® (imatinib mesylate, Novartis Pharmaceuticals, East Hanover, NJ) for treating chronic myelogenous leukemia and that further studies are warranted.

Cancer Vaccine Trial Suggests Possible Benefit

Researchers from the Lombardi Cancer Center in Washington, DC, and the National Cancer Institute in Bethesda, MD, presented the results of a vaccine trial for patients with carcinoembryonic antigen- (CEA-) positive tumors. The vaccine, TRICOM, targets CEA, a protein found on specific cancers (breast, lung, stomach, colon, and pancreas) but not on normal cells. Fifty-eight patients were enrolled in the study and received fowlpox TRICOM followed by monthly booster injections of the same vaccine, vaccinia TRICOM followed by monthly booster injections of the fowlpox TRICOM, or vaccinia TRICOM followed by monthly booster injections of the fowlpox TRICOM plus the immune system booster granulocyte macrophage–colony-stimulating factor (GM-CSF). Most patients had colon cancer. A complete response occurred in one patient, and five showed decreasing CEA levels. Twenty-five had stable disease. Those who received the vaccinia TRICOM plus fowlpox boosters and GM-CSF had the best CEA-specific T cell responses. Side effects included mild fever, skin reactions, and swelling of the lymph nodes. A phase II trial for patients with colon or pancreatic cancers is planned.

Magnetic Resonance Imaging May Be Beneficial for Breast Cancer Screening for Women at High Risk

Researchers from Erasmus Medical Center in Rotterdam, the Netherlands, presented the results of part of the Dutch Magnetic Resonance Imaging (MRI) Screening Study that evaluated the use of twice yearly clinical breast examination, yearly mammography, and yearly contrast-enhanced MRI for women at high risk for breast cancer resulting from either a mutation in the *BRCA1* or *BRCA2* genes or a strong family history of breast cancer. In this study, 1,905 women were followed for a mean of two years. In that group, 40 breast cancers were found and 46% were smaller than 1 cm. For the women with breast tumors, 77% had lymph nodes free of cancer cells. The sensitivity of clinical breast examination for finding these tumors was 16%, and the sensitivity of mammography was 36%, whereas the sensitivity of MRI was considerably higher at 71%. However, MRI was found to be less specific than the other two modalities, with 88% specificity for MRI compared to 97% for clinical breast examination and 95% for mammography. Therefore, MRI is more likely to lead to additional tests for noncancerous lesions. The researchers concluded that MRI is more sensitive but less specific than mammography. However, the high number of cancers that were found early in this study, at more curable stages, suggests that intensive surveillance of women at high risk for breast cancer may reduce the number of deaths from this disease.

Use of Statin Therapy May Reduce Cancer Risk

Statins inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase that regulates a cell-signaling pathway. These agents are used commonly to control serum cholesterol levels. Preclinical studies indicate that statins can trigger apoptosis in cancer cells. Researchers from the Academic Medical Centre at the University of Amsterdam in the Netherlands investigated the use of cardiovascular medications, including statins, in 3,219 patients with cancer and 16,976 matched controls. The data examined were from pharmacy drug-dispensing records and hospital discharge records in eight Dutch cities. Appropriate controls for confounding variables were performed. The researchers found that the use of statins was associated with a 20% reduction in cancer risk and that statins were especially protective when used for more than four years. Termination of the medication for six months resulted in loss of the protective effect. Lifestyle factors, such as smoking, were not accounted for in this study. The authors concluded that more research is needed on whether statins can reduce cancer risk. ONS