**RESEARCH HIGHLIGHTS**

**Clinical Research**

**Idiotype Vaccine for Non-Hodgkin Lymphoma Shows Promise**

Researchers from Freiburg University Medical Center in Germany developed a novel production strategy for individual idiotype vaccines using anchored reverse transcriptase polymerase chain reaction cloning of variable segments of the idiotype genes for antibody transcripts from lymphoma biopsies. Recombinant idiotype Fab fragments were expressed in E. coli and purified. Vaccine production was successful in 89% of attempted cases via this strategy. Eighty patients with B cell non-Hodgkin lymphoma who had relapsed after chemotherapy received repeated intradermal vaccinations with 0.5–1.65 mg Fab fragment mixed with a lipid-based adjuvant over two to four weeks. Injections of 150 micrograms of granulocyte macrophage–colony-stimulating factor (GM-CSF) were given subcutaneously at the vaccination site immediately after each immunization. Mild fever and fatigue were common and attributed to the GM-CSF. Ten of 17 evaluable patients had progression-free survival of at least 4 months, and 4 had ongoing progression-free survival at 10 months. Anti-Fab antibodies developed in 5 of 17 patients, and anti-Fab T cell responses were found in 6 of 15 patients. The researchers concluded that the results demonstrate the feasibility, tolerability, and immunogenicity of the vaccine in these patients with non-Hodgkin lymphoma. They recommended further trials of this strategy for idiotype vaccination for patients with non-secreting B cell non-Hodgkin lymphoma.

**R115777 Induces Responses in Patients With Myeloid Leukemia**

Zanestratm™ (R115777, Johnson and Johnson, New Brunswick, NJ) is a selective oral farnesyltransferase inhibitor that disrupts oncogenic transformation and tumor growth caused by factors such as ras, Rho B, and p53. Researchers presented the results of a multicenter phase II trial of Zanestrat as a single agent in the treatment of acute myelogenous leukemia (AML). A total of 252 adults with refractory (N = 135) or relapsed (N = 117) AML were treated with 600 mg twice a day for 21 days every four weeks. The median survival was 3.1 and 2.1 months for the relapsed and refractory groups, respectively. For those who achieved a partial or complete response (11 of 169 evaluated [6%], 95% confidence interval 3%–11%), the median survival was 12.2 months. The non-hematologic toxicities associated with Zanestrat were fatigue (6%) and hypokalemia (5%). The researchers concluded that Zanestrat as a single agent is able to induce responses in heavily pretreated patients with AML and is well tolerated. A study is under way to examine the effectiveness of Zanestrat for newly diagnosed older adult patients.

**Gemtuzumab Ozogamicin Induces Responses in Patients With CD33-Positive Acute Myeloid Leukemia**

The Mylotarg Study Group presented the results of a phase II study of gemtuzumab ozogamicin (Mylotarg®, Wyeth, Madison, NJ) for the treatment of patients with acute myeloid leukemia (AML). Gemtuzumab ozogamicin is an antibody therapy that targets CD33-positive leukemic cells. In this study, 157 patients aged 60 years or older were in their first relapse were treated with 9 mg/m² via IV on days 1 and 15. All patients received the first dose, 117 received the second dose, and 4 received a third dose. In this study, a remission was characterized as 5% or fewer leukemic blast cells in the bone marrow, 9 g/dl or less hemoglobin, 1,500/microliter or fewer absolute neutrophil count, and independence from red cell or platelet transfusions. Thirty-eight patients (24%, 95% confidence interval = 18, 32) achieved remission, with 35% lasting 12 months or longer. The median relapse-free survival was 6.8 months. The most common toxicities were fever (13%), sepsis (15%), chills (11%), pneumonia (8%), and mucositis (3%). The infection rate was 29%, and hematologic toxicities occurred with elevated aspartate aminotransferase (16%), alanine aminotransferase (8%), and bilirubin (29%). Two patients (1%) developed fatal hepatic veno-occlusive disease. The researchers concluded that gemtuzumab ozogamicin as a single agent for older patients with CD33-positive AML has a potential benefit with an acceptable toxicity profile.

**Molecular Mechanisms**

**Mouse Model for Human EVI1 Myelodysplasia Aids in Understanding**

EVII is an aggressive oncogene that is inappropriately expressed in patients with acute myeloid leukemia, myelodysplastic syndrome, or chronic myeloid leukemia. The expression of EVI1 disrupts normal differentiation of granulocytes and erythrocytes and favors differentiation of megakaryocytes. Clinical features include cytopenia and dysplasia of one or more hematopoietic cell lineages. Researchers at the University of Illinois at Chicago and the University of Chicago developed a murine model for myelodysplastic syndrome with a very poor prognosis by transplanting murine bone marrow infected with an EVI1-expressing retrovirus into syngeneic recipients. After 10 months, the mice developed pancytopenia and other morphologic features consistent with
myelodysplastic syndrome. The defects in the mice were found to result from, at least in part, the dysregulation of specific target genes that are needed for hematopoiesis.

Ki67 May Be a Predictor of Relapse-Free Survival for Patients With Breast Cancer

Researchers from the Royal Marsden Hospital in London, England, reported the results of a study investigating whether tissue levels of the proliferation marker Ki67 could predict long-term outcomes for patients treated with nonadjuvant therapy in the Arimidex® (anastrozole, AstraZeneca, Wilmington, DE) (A) and Tamoxifen (T), Alone or in Combination (C) trial. Patients with estrogen receptor (ER)-positive, invasive, operable breast tumors (2 cm or larger) were randomized to receive a 12-week treatment of A, T, or C prior to surgery. Core biopsies were repeated after two weeks of treatment, and samples were taken from the surgical specimen or another core biopsy was done at 12 weeks. Tumor size was measured with calipers to determine the objective response. Ki67 and ER levels were measured in all tissue samples. A total of 330 patients with a mean age of 72 were enrolled in the study (A, n = 113; T, n = 108; and C, n = 109). The data analysis showed that Ki67 levels were significantly reduced in all three groups at 2 and 12 weeks, although very little change occurred from 2–12 weeks. The decrease in Ki67 was greater for patients treated with A compared to T or C (p = 0.01) at both time points. The researchers concluded that Ki67 might be used as an outcome marker for patients with breast cancer treated with nonadjuvant therapy.

Switching From Adjuvant Tamoxifen to Anastrozole May Decrease Risk of Death for Patients With Breast Cancer

Tamoxifen is a common therapy for patients with estrogen receptor (ER)-positive breast cancer. Because researchers have had some concern regarding the potential carcinogenic and cardiovascular effects of tamoxifen, the safety and efficacy of switching to nonsteroidal aromatase inhibitors was investigated. Researchers from the Italian Tamoxifen Ari-midex® (anastrozole, AstraZeneca, Wilmington, DE) Trial and the University of Genoa compared outcomes for postmenopausal women with ER-positive breast cancer who had received adjuvant therapy with tamoxifen for at least two years (20 mg per day). A total of 426 patients were assigned randomly to continue tamoxifen or switched to anastrozole (1 mg per day). Groups were balanced in terms of age, tumor size, tumor grade, treatment of primary tumors, and median time on tamoxifen before randomization. Women were followed until they had received tamoxifen or tamoxifen followed by anastrozole for a total of five years or until they reached a major trial endpoint (disease recurrence, second primary tumor, or death). Data analysis showed that 26 events occurred in the tamoxifen group (19 recurrences, five second primary tumors, and two deaths in the absence of progression). Ten events occurred in the anastrozole group (eight recurrences and two second primary tumors). Serious events were more common for the women who continued on tamoxifen. The researchers concluded that switching patients to anastrozole may reduce their risk of relapse and death.

Magnetic Resonance Imaging May Predict Response to Tamoxifen for Breast Cancer Prevention

Magnetic resonance imaging (MRI) is a highly sensitive technology for identifying occult malignant breast changes. Researchers from the University of Colorado Health Sciences Center in Denver investigated whether MRI could be used as an intermediate marker for tamoxifen response by comparing proliferative changes in breast tissue before and after tamoxifen treatment. In their study, 24 women who had pretreatment MRI scans within four weeks of beginning tamoxifen treatment and after six months of treatment. Women who previously had received systemic chemotherapy or radiation treatment were excluded from the study. MRI images were examined for enhancement and changes in enhancement. Nine sets of images (53%) showed decreased enhancement on the post-treatment imaging; two had pretreatment enhancement that was suspicious for malignancy and was completely eliminated on the post-treatment MRI. Eight sets of images (47%) showed pretreatment enhancement that was unchanged on the post-treatment MRI. The investigators concluded that MRI may be useful as an intermediate marker for tamoxifen response.

Additional Research Highlights

New Breast Test May Be Useful for Detecting Early Cellular Changes

Duke University Medical Center in Durham, NC, announced the development of a new test that surveys cells from the entire breast. This new technology is the result of collaboration between the University of Kansas Medical Center in Kansas City and Duke Comprehensive Cancer Center in Durham, NC. A slender needle is used to sample breast tissue for signs of atypia and silencing of genes that code for proteins such as RAR beta. Silencing the RAR beta gene may increase the risk of breast cancer because it is important in a regulatory signaling pathway. The new test will undergo clinical trials at three centers nationwide: University of Kansas Medical Center, Duke Comprehensive Cancer Center, and the Arthur G. James Cancer Hospital and Richard J. Solove Research Institute at the Ohio State University in Columbus. Researchers hope that the test will be especially useful for detecting changes in dense breast tissue that are difficult to image by mammography. Identification of early changes in breast tissue will permit the initiation of preventive measures such as tamoxifen, cyclooxygenase-2 inhibitors, beta carotene, or flaxseed oil to eradicate abnormal cells and potentially prevent breast cancer.

Patients With Early-Stage Breast Cancer Are at Risk for Reduced Relative Chemotherapy Dose Intensity

Researchers from the University of Rochester Medical Center in New York, University of Washington in Seattle, and Duke University in Durham, NC, reported the results of a nationwide study of predictors of low-dose intensity in adjuvant breast cancer chemotherapy (Journal of Clinical Oncology, Vol. 21, pp. 4524–4531). In their study, a retrospective survey of 1,243 community oncology practices was done to extract data from 20,799 patient records. Data included demographic and clinical characteristics, chemotherapy dose modifications, incidence of febrile neutropenia, and patterns of use of colony-stimulating factor (CSF). The researchers found that despite the fact that clinical trials support sustaining full dose intensity for early-stage breast cancer and the good evidence for a threshold of relative dose intensity (RDI) below which little clinical benefit exists, many patients do not receive RDI chemotherapy. In fact, they found that nearly two-thirds of the patients surveyed received less than 85% of the RDI when adjusted for differences in regimen dose intensity. Using multivariate analysis, the researchers found that several factors may be predictors for reduced RDI: increased age; chemotherapy with cyclophosphamide, methotrexate and fluorouracil, or cyclophosphamide, doxorubicin, and fluorouracil; a 28-day schedule; body-surface area greater than 2 m²; and no primary CSF prophylaxis. The researchers concluded that patients with early-stage breast cancer are at significant risk for reduced RDI when treated with chemotherapy. The risk factors should enable nurses to establish supportive measures to maximize the delivery of full dose intensity chemotherapy.