Autologous Stem Cell Transplantation and High-Dose Chemotherapy May Improve Survival

A study of 11 patients with lymphoma (five with Hodgkin’s disease; six with non-Hodgkin’s disease) suggests autologous progenitor cell transplantation may be feasible for relapsed AIDS-related lymphoma. Therapy included etoposide, methylprednisolone, cisplatin, and cytarabine (ESHAP) (n = 9) and granulocyte colony stimulating factor (n = 10), followed by acquisition of peripheral blood progenitor cells. Conditioning prior to transplantation consisted of carmustine, etoposide, cytarabine, and melphalan for five patients; the other six patients had this regimen plus total body irradiation. Ten of the patients received highly active antiretroviral therapy. Good engraftment occurred in all patients. The median times to granulocyte and platelet recovery were 12 and 11 days, respectively. Complete remission occurred in seven patients (64%). No major opportunistic infections occurred. This study indicates the need for additional research to identify toxicity and efficacy of autologous stem cell transplantation in these patients.

Stanford V Regimen May Increase Survival for Patients With Newly Diagnosed Hodgkin’s Disease

Data from a European trial (France and Italy) of the Stanford V regimen (doxorubicin, vincristine, mechlorethamine, vinblastine, bleomycin, etoposide, and prednisone) involving 46 patients with AIDS who also had newly diagnosed Hodgkin’s disease demonstrated 78% (n = 39) complete remission, with 68% of the group remaining disease-free at two years. All patients received G-CSF 5 mcg/kg per day on days 3–13 and 17–26 of each cycle. Triple-drug antiretroviral therapy, including a protease inhibitor and prophylaxis against Pneumocystis carinii and candida, also were administered. Although these data suggest that the Stanford V regimen may be more efficacious than ABVD (adriamycin, bleomycin, vincristine, and dacarbazine), in prior trials with ABVD for Hodgkin’s disease, patients with AIDS did not receive highly active antiretroviral therapy. The Stanford V regimen is currently under evaluation as part of the AIDS Malignancy Consortium.

Rituximab Plus Cyclophosphamide, Doxorubicin, and Etoposide May Increase Survival

Rituximab (Rituxan®, Genentech, South San Francisco, CA) is a monoclonal antibody directed against the CD20 protein on the surface of normal and malignant B lymphocytes. An international trial examined 29 patients receiving combination therapies with cyclophosphamide, doxorubicin, and etoposide (CDE) for the treatment of AIDS-related non-Hodgkin’s lymphoma. CDE was administered as a continuous 96-hour infusion, and rituximab 375 mg/m² was given either a) prior to each cycle of CDE, or b) on day eight and day one prior to cycle 1, just prior to cycles 3 and 5, and then on days 28 and 35 after the last cycle. The overall response rate was 86% (83% complete response). Toxicities included grade 3 or 4 neutropenia (79%), anemia (45%), thrombocytopenia (34%), and bacterial infections (34%). The overall survival and progression-free survival at two years were 80% and 79%, respectively.

With Advanced Leukemia

Overexpression of Bcl-2, a protein that inhibits programmed cell death (apoptosis), contributes to drug resistance in patients with acute leukemia. GenasenseTM (Genta, Inc., Berkley Heights, NJ), an antisense Bc-2 able to reduce (downregulate) expression of Bcl-2 protein, was tested in a phase I trial as a possible strategy for overcoming drug resistance. Researchers at Ohio State University and Genta, Inc. conducted the study. Twenty patients with refractory or relapsing acute leukemia were treated with Genasense plus fludarabine, ARA-C, and G-CSF. Of the 20 patients, 9 (45%) had disease response and 7 of the responders had complete remission. Clinical doses of Genasense ranged from 4–7 mg/kg per day. Pharmacokinetic analysis showed that Genasense plasma levels were at the biologically relevant target level (1 mg/ml) after 24-hour infusion. Toxic effects of the combination chemotherapy included central nervous system bleeding (one patient), fever, nausea, emesis, hypocalcemia, hypophosphatemia, and fluid retention. None were dose-limiting, and the side effects were not necessarily attributable to Genasense. The maximum tolerable dose was not reached. This study supports the safety of Genasense and suggests that future trials at 7 mg/kg per day are warranted.

American Association for Cancer Research–National Cancer Institute–European Organization for Research and Treatment of Cancer. (Mention of specific products and opinions related to those products do not indicate or imply endorsement by the Oncology Nursing Forum or ONS.)

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Cetuximab Plus Gemcitabine Increases Survival for Patients With Advanced Pancreatic Cancer

Cetuximab is a monoclonal antibody that targets the epidermal growth factor receptor (EGFR). Potential clinical usefulness of the drug was suggested by previous studies in combination with gemcitabine in a mouse xenograft pancreatic tumor model. Researchers at the University of Texas M.D. Anderson Cancer Center in Houston, Greenwich Hospital (Greenwich, CT), University of Alabama at Birmingham, Trident Medical Center (Charleston, SC), and ImClone Systems (Somerville, NJ) conducted a phase II study. Forty-one patients with measurable advanced pancreatic cancer and EGFR tumor expression by immunohistochemistry were treated with cetuximab and gemcitabine. A loading dose of cetuximab of 400 mg/m² was followed by a weekly maintenance dose of 250 mg/m². Gemcitabine was given at a weekly dose of 1000 mg/m² for up to seven weeks, followed by one week of rest. Subsequent courses of gemcitabine were given weeks one through three and weeks five through seven. After two courses of therapy, 5 patients (12%) had partial responses and 21 (53%) had stable disease or minor responses. The one year overall survival was 32.5%. Adverse effects were skin toxicities (acne-form rash, 38%), folliculitis (16%), fatigue (41%), and grade 1 and 2 fever (38%). This study indicates that cetuximab is well tolerated. Phase III trials are planned.

Acne-Like Rash Predicts Response to Cetuximab in Irinotecan-Refractory Colon Cancer

A phase II trial of cetuximab plus irinotecan (CPT-11) in CPT-11-refractory colon cancer (CRC) showed major objective responses in patients whose tumors were epidermal growth factor receptor (EGFR) positive. Cetuximab is a monoclonal antibody that targets the EGFR. Memorial Sloan-Kettering Cancer Center (New York, NY), Florida Cancer Specialists (Bonita Springs), New York University Medical Center (New York, NY), Pacific Shores Medical Group (Long Beach, CA), ImClone Systems (Somerville, NJ), and University of Alabama at Birmingham carried out the trial. One hundred twenty patients with EGFR-positive tumors were treated with a 400 mg/m² loading dose of cetuximab and then 250 mg/m² weekly, plus irinotecan at the same dose and schedule given previously. Cetuximab-related toxicities were allergic reactions (2% grade 3 and 1% grade 4, all responsive to treatment) and an acne-like skin rash (folliculitis) (63% grades 1–2 and 12% grade 3). Twenty-seven patients (22.5%) achieved a partial response with a median duration of 186 days. Response to therapy correlated with the presence of the acne-form rash, with 30% of those with a rash responding, compared to only 5% of those without a rash (p = 0.001).

Iressa Shows Tumor Regression and Disease Stabilization in Phase II Trial Patients With NSCLC

A phase II, multicenter international trial demonstrated antitumor activity and meaningful symptom relief in patients with non-small cell lung cancer treated with iressa. Iressa is a selective epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI). The primary objectives of this randomized, double-blind, parallel group study were to evaluate the objective tumor response rate and characterize the safety profile of iressa. A secondary objective was to estimate the disease-related symptom improvement rates, using the seven-item lung cancer subscale from the FACT-L questionnaire. Two hundred ten patients were randomized into one of two iressa dosage groups, 250 mg per day or 500 mg per day. EGFR status was not a criterion for eligibility. The overall response rate was 18.7%, and the overall disease control rate (response plus stable disease) was 52.9%. The median progression-free survival was 84 days with 34% of the patients progression-free after four months. The overall disease-related symptom improvement was 38.7% and the median time to improvement was eight days. No difference in efficacy was found for either dosage group; however, fewer patients experienced grade 3 or 4 adverse effects (diarrhea and rash) in the 250-mg per day group.

Basic Research

Iressa Enhances Radiation Response and Reduces Angiogenesis

Researchers at the University of Wisconsin (Madison) evaluated the effectiveness of iressa in combination with radiation for the treatment of human squamous cell carcinoma (SCC) of the head and neck. Treatment of human SCCs grown in culture showed a dose-dependent antiproliferative response to iressa. A mouse xenograft model was used to examine treatment with iressa (25 mg/kg per day for two weeks) and radiation (7 x 3 Gy, twice a week for four weeks) or radiation alone. Treatments with iressa or radiation alone resulted in partial or transient tumor regression. However, the combination of iressa plus radiation produced profound tumor regression or regrowth delays. A mouse xenograft model of angiogenesis was used to show that iressa reduced tumor size and the number or caliber of associated capillaries. It also reduced the establishment of new blood vessels near the tumor. These results suggest that iressa may enhance the effectiveness of radiation by inhibiting angiogenesis.

New Compound May Overcome Resistance to Gleevec™ for Patients With CML

The FDA recently approved Gleevec™ (imatinib mesylate, Novartis Pharmaceuticals, East Hanover, NJ) for treatment of chronic myeloid leukemia (CML). It inhibits Bcr-abl, a tyrosine kinase, involved in signaling proliferation of cancer cells. Researchers at the Medical College of Virginia in Richmond and St. Elizabeth’s Medical Center in Boston showed, contrary to expectations, treatment of Bcr-abl-positive leukemic cells with Gleevec results in a delayed activation of another kinase, mitogen-activated protein kinase (MAPK), as a cytoprotective response. They found also that MEK1/2 inhibitors would overcome this response. Together, Gleevec and MEK1/2 inhibitors acted synergistically to induce programmed cell death (apoptosis) in Bcr-abl-positive cell cultures. This work suggests that combinations of Gleevec and MEK1/2 inhibitors may be an effective strategy for patients with CML.

Faslodex™ Reduces Estrogen-Receptor Expression in Tamoxifen-Resistant Breast Cancer Cells

Tamoxifen, an antiestrogen, is effective in treating estrogen-receptor (ER)-positive breast tumors; however, after prolonged exposure to tamoxifen, tumors can become resistant to the antihormone. When resistance develops, tumor proliferation is associated with intracellular signaling via the epidermal growth factor receptor (EGFR)/mitogen-activated protein kinase (MAPK) pathway. Researchers at the Tennon Center for Cancer Research (Cardiff, UK) studied the activity of Faslodex™ (fulvestrant, AstraZeneca Pharmaceuticals, LP, Wilmington, DE), an antihormone that decreases the number of estrogen receptors (downregulates) in tamoxifen-resistant breast cancer cells. A seven-day treatment of Faslodex decreased ER expression by 80% in control and tamoxifen-resistant cells. Faslodex also inhibited proliferation of control cells by 90% and tamoxifen-resistant cells by 60%. In the tamoxifen-resistant cells, Faslodex inhibited the activity of EGFR and MAPK, but this effect was not observed in the control cells. Expression of transforming growth factor alpha, known to mediate EGFR activation, also was reduced in tamoxifen-resistant cells. In summary, this work suggests that ER may play a role in stimulating EGFR/MAPK signaling, leading to cell proliferation in tamoxifen-resistant breast cancer cells. Downregulation of ER by Faslodex may contribute to its antitumor effects.