RESEARCH HIGHLIGHTS

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Clinical Research

Imatinib Is Superior to Interferon Alpha Plus Cytarabine for Patients With Chronic Myeloid Leukemia

Researchers from the University of Chicago presented a summary of the International Randomized Interferon Versus STI571 Study comparing the efficacy of imatinib (STI571, Gleevec™, Novartis Pharmaceuticals, East Hanover, NJ) monotherapy and interferon plus AraC (cytarabine) for chronic myeloid leukemia. Imatinib inhibits the Bcr-Abl tyrosine kinase that is important in cell proliferation in Philadelphia-chromosome-positive chronic myeloid leukemia. A total of 1,106 patients aged 18–70 were randomized into groups receiving imatinib 400 mg per day (n = 553) or interferon (target 5 µg/m² per day subcutaneously) plus AraC (target 20 mg/m² SC for 10 days every month) (n = 553). The study arms were balanced in terms of risk. Median follow-up was 14 months. Criteria allowed crossover based on intolerance or treatment failure. Statistically significant differences (p = 0.001) were found between the two arms (imatinib and interferon plus AraC) as follows: Complete hematologic response was 94.4% and 54.6%, respectively; major cytogenetic response was 82.6% and 20.3%, respectively; complete cytogenetic response was 67.8% and 7.4%, respectively; and 12-month progression-free survival was 97.2% and 80.3%, respectively. The researchers concluded that for patients with newly diagnosed, chronic-phase, chronic myeloid leukemia, imatinib is superior to interferon plus AraC in terms of all the endpoints examined.

Imatinib Offers Quality-of-Life Advantages Compared to Interferon Alpha Plus Cytarabine

Although interferon alpha has been shown to induce relatively high hematologic response rates for patients with chronic myeloid leukemia, the improvement occurs at a cost in quality of life. A significant number of patients withdraw from interferon therapy within six months. Researchers from the International Randomized Interferon Versus STI571 Study Group presented data comparing the effects of imatinib (STI571, Gleevec™, Novartis Pharmaceuticals, East Hanover, NJ) monotherapy and interferon plus AraC (cytarabine) on quality of life for patients with chronic myeloid leukemia. Quality of life was assessed using the Functional Assessment of Cancer Therapy–Biologic Response Modifiers instrument at baseline, monthly for six months, and then every three months. The primary endpoint was the Trial Outcome Index (TOI), a composite of physical, functional, and treatment-specific subscales. Of the 1,067 patients who were eligible, 83% completed at least six of the nine assessments. For the imatinib group, TOI scores remained stable relative to the baseline, whereas the interferon plus AraC group demonstrated a significant decline in scores. The researchers concluded that imatinib offers a clear advantage over interferon in terms of quality of life during therapy.

Proteasome Inhibitor Bortezomib Represents a Novel Treatment for Multiple Myeloma

Cell proliferation requires the activation of intracellular regulatory proteins by proteasomes. Significantly, the proteasome activates NF-κB, a protein important in regulating cancer cell division. The results of a multicenter trial of the selective proteasome inhibitor bortezomib (Velcade™, Millennium Pharmaceuticals, Cambridge, MA) for patients with relapsed or refractory multiple myeloma were presented. Patients received 1.3 mg/m² IV push on days 1, 4, 8, and 11 of a 21-day cycle for up to eight cycles. For some patients, dexamethasone was added after two or four cycles. Patients were enrolled in two cohorts (n = 78 and 124). For cohort one (n = 78), the overall response rate was 32%, and of these, 27% had major responses (4% complete and 23% partial). The mean duration of complete or partial responses had not been reached at 10.2 months. The responders showed evidence of improved hemoglobin, performance status, quality of life, and levels of non-M protein immunoglobulins. Bortezomib may be a novel potential therapy for patients with relapsed or refractory multiple myeloma.

Rituximab Can Overcome BCL2-Associated Drug Resistance

Rituximab is a monoclonal antibody directed against the CD20 protein located on the surface of normal and abnormal B lymphocytes. The drug can be used to treat B-cell lymphomas because the normal cells that may be destroyed by the antibody are replaced by new cells and the abnormal cells are permanently destroyed. Researchers from France presented the results of a study comparing the effectiveness of cyclophosphamide, hydroxydoxorubicin, vincristine, and prednisone (CHOP) versus rituximab plus CHOP (R-CHOP) in the treatment of elderly patients with diffuse large B-cell lymphoma (DLBCL). The objective of this study was to determine whether rituximab would improve outcomes for patients whose tumors expressed BCL2 protein, known to be

Peptide Vaccination Can Induce Remission in Patients With Acute Myelogenous Leukemia

Researchers from the University of Texas M.D. Anderson Cancer Center presented the results of a phase I trial of a novel agent designed to induce a specific immune response against leukemia cells. PR1 peptide is a nine amino acid HLA-A2 restricted peptide derived from proteinase three. T-cell immunity to PR1 correlates with cytogenetic remission in chronic myeloid leukemia patients treated with interferon or bone marrow transplantation. Nine patients with several types of leukemia were enrolled in the study and treated in cohorts of three at three different dose levels: 0.25 mg, 0.5 mg or 1 mg of PR1 in incomplete Freund’s adjuvant subcutaneously. None of the patients developed antibodies to PR1. Adverse events included a cutaneous injection reaction (grade two) in one patient at dose level three that resolved after one week and mild fatigue in four patients. At the time of the report, one patient at dose level two and three patients at dose level three were in complete remission. PR1-specific cytotoxic T lymphocytes were induced in all four patients with complete remission. The researchers concluded that this study is the first direct evidence that peptide vaccination of patients with leukemia can induce specific immunity against leukemia cells and lead to remission.

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an important inhibitor of apoptosis and associated with poor prognosis for patients with DLBCL. Patients were randomized into groups receiving eight cycles of standard CHOP therapy or R-CHOP where rituximab was 375 mg/m². Tissues from 292 patients were examined for BCL2 levels using standard immunohistochemistry techniques. Of these tissues, 193 (66%) were found to be BCL2 positive and 99 (34%) were BCL2 negative. The response rates were significantly different, at 78% for R-CHOP and 61% for CHOP in the BCL2-positive group (p = 0.009); however, no difference existed for the two treatments at 76% versus 73% in the BCL2-negative group (p = 0.7). At two years median follow-up, R-CHOP was associated with significantly improved overall survival in the BCL2-positive group (67% versus 48%, p = 0.004) but not in the BCL2-negative group (72% versus 67%, p = 0.6). The researchers concluded that R-CHOP contributed a significant survival benefit for patients with tumors that are BCL2 positive.

**Double Autotransplant Strategy Is Safe and Effective for Patients With Newly Diagnosed Multiple Myeloma**

The results of a study by Italian researchers, the Bologna 96 Clinical Trial, suggested improved outcomes using double autologous stem cell transplantation for patients with multiple myeloma. This multicenter, prospective, randomized trial of single versus double transplantation of autologous peripheral blood stem cells included only patients who had not been treated previously for multiple myeloma. The results from treatment of 220 patients (n = 110 for each group) were reported. The chemotherapy regimen included vincristine, adriamycin, and dexamethasone for four cycles; melphalan 200 mg/m² prior to the first transplantation; and melphalan 120 mg/m² plus busulfan 12 mg/kg prior to the second transplantation. The group receiving the double transplantation had a significantly longer duration of remission (median 44 versus 27 months; p = 0.005) and an extended event-free survival (median 34 versus 25 months; p = 0.05). The researchers concluded from this preliminary analysis that double autotransplantation is safe and effective for patients with newly diagnosed multiple myeloma and yields an 80% overall response rate. The treatment prolongs the duration of remission compared to single autotransplants.

**Anti-CD80 Monoclonal Antibody May Be Used to Treat Patients With Non-Hodgkin’s Lymphoma**

CD80 is an antigenic site expressed transiently on the surface of activated B lymphocytes and most B-lymphoma cells. IDEC-114 is an antibody directed against CD80 that has been shown in vitro and in vivo to bind to B lymphoma cells and induce cell-mediated cytotoxicity. Preliminary clinical data from a multicenter, phase I and II, dose-escalating trial in the United States for patients with relapsed or refractory follicular non-Hodgkin’s lymphoma were presented. The study objectives were to evaluate the safety, efficacy, and pharmacokinetics of IDEC-114. Patients received the agent once weekly over four weeks in doses of 125, 250, or 275 mg/m² infused over one hour with no dose-limiting toxicities reported. Adverse events were grade one or grade two only. A total of nine patients, three in each group, were enrolled, with a median age of 54 years and a median of two prior lymphoma therapies (range = 1–5). The pharmacokinetic profile was acceptable. The results suggest that IDEC-114 is safe and potentially effective for relapsed or refractory follicular lymphoma. A phase II trial is ongoing.

**Ara-G Analog Has Antitumor Activity With Lymphoblastic Leukemia and Lymphoma**

T lymphocytes and T lymphoblasts are known to be extremely sensitive to deoxycytosine and its analog, ara-G. However, the use of ara-G has been limited because of the difficulties encountered in its synthesis and because it is poorly water soluble. 506U78 is a soluble pro-drug form of ara-G that is demethylated rapidly in the serum to become ara-G. Thus, the drug has promise as a useful form of the active compound. A phase I trial of 506U78 previously had shown that the maximum tolerated dose in adults is 40 mg/kg per day for five days. The dose-limiting toxicity was shown to be neurologic (seizures, obtundation, and ascending paralysis). The results of a multicenter (Cancer and Leukemia Group B and Southwest Oncology Group) study in the United States examining a dosing regimen of 1.5 g/m² per day on an alternate day schedule (days one, three, and five) for patients with relapsed T-cell acute lymphoblastic leukemia or lymphoblastic lymphoma were presented. A total of 40 patients were enrolled, and 38 were evaluable for response. The overall response rate was 32% (95% confidence interval [CI]: 18%–49%). Seizures and confusion occurred in one patient but resolved; another developed hallucinations but was also on narcotics. Bone marrow suppression was the primary toxicity. Grade three or four neutropenia and thrombocytopenia occurred in 43% and 33% of patients. The overall survival for the 40 patients was 4.6 months (95% CI: 3–10 months). The one-year overall survival was 32% (95% CI: 16%–47%) and the one-year disease-free survival was 40% (95% CI: 10%–70%). The researchers concluded that 506U78 is well tolerated and shows significant activity for patients with relapsed or refractory T-cell acute lymphoblastic leukemia or lymphoblastic lymphoma. They suggested that trials for patients with newly diagnosed T-cell malignancies are warranted.

**Clinical Research**

**Lung Tumor Regression May Occur With Intratumoral Injection of INGN 201 and Radiation Therapy**

A report in the January 2003 issue of _Clinical Cancer Research_ (Vol. 9, pp. 93–101) presented the results of a study evaluating the feasibility and mechanisms underlying induction of p53 genes and radiation therapy for patients with non-small cell lung cancer. In a prospective, single-arm, phase II trial, 19 patients who were not eligible for chemoradiation or surgery received radiation therapy (60 Gy over six weeks) and three intratumoral injections of adenoviral p53 (Ad-p53 or INGN 201) on days 1, 18, and 32. The most common adverse effects were grade one or two fevers (79%) and chills (53%). After three months, computerized tomography and bronchoscopic findings showed 1 complete response (5%), 11 partial responses (58%), 3 with stable disease (16%), and 2 with progressive disease (11%); 2 patients were not evaluable (11%). At 24 hours after injection and over the course of treatment, the expression-specific p53-related genes were shown to increase. The authors concluded that intratumoral injection of Ad-p53 (INGN 201) combined with radiation therapy is well tolerated and tumor regression is evident in significant numbers of patients.

**Improved Quality-of-Life Scores Exist for Patients With Cancer Taking Oxandrolone**

Research results presented at the 27th Clinical Congress of the American Society for Parenteral and Enteral Nutrition suggested that oxandrolone, exercise, and nutrition can increase weight and lean tissue and improve quality of life for patients suffering weight loss because of cancer or HIV infection. Oxandrolone is a synthetic testosterone derivative that is thought to contribute to increased protein synthesis and improved nitrogen balance. One hundred twenty-eight patients who were HIV-positive and 139 patients with cancer were enrolled in two open-label, four-month studies. All patients had been actively losing weight. All patients received education in nutrition and exercise and were given oxandrolone (20 mg per day). The majority of the patients who were HIV-positive and 80% of the patients with cancer either gained or maintained weight. In addition, patients in both groups had improved quality of life and activities of daily living scores.