RESEARCH HIGHLIGHTS

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CLINICAL RESEARCH

Imatinib Mesylate Improves Outcomes for Patients With Chronic Myeloid Leukemia

The results of a phase III, multicenter trial comparing imatinib mesylate (Gleevec™, Novartis Pharmaceuticals, East Hanover, NJ) with standard therapy for patients with newly diagnosed chronic myeloid leukemia were presented by the International Gleevec Study Group. Imatinib mesylate is a tyrosine kinase inhibitor that interrupts signaling in proliferating cells. The drug has been approved for patients who do not respond to standard interferon therapy and patients who are in accelerated phase or myeloid blast crisis. In this study, 1,106 patients from 16 countries were randomized into groups receiving either imatinib 400 mg per day or interferon (target dose 5 MIU/m^2 per day) plus cytarabine (20 mg/m^2 per day for 10 days per month). After six months of therapy, the rates for major and complete cytogenetic responses were 63% and 40% for the imatinib group and 10% and 2% for the interferon group ($p < 0.001$). The disease progressed in eight patients taking imatinib compared to 57 patients taking inteferon. Furthermore, 75% of the patients in the imatinib group showed a significant decrease in the number of cancer cells in their bone marrow compared to 15% in the interferon group. The study results indicated that imatinib mesylate appears to be well tolerated and more effective than standard treatment with interferon.

Patients With Rare Stomach Tumors Benefit From Imatinib Mesylate

Researchers from Fox Chase Cancer Center in Philadelphia, PA, and collaborators presented the results of a phase II trial of imatinib mesylate (Gleevec™, Novartis Pharmaceuticals, East Hanover, NJ) for patients with nonresectable or metastatic gastrointestinal stromal tumors. Imatinib mesylate is a tyrosine kinase inhibitor that targets receptors for growth factors that stimulate tumor cell proliferation. Patients (N = 147) were randomized into one of two imatinib groups (400 or 600 mg imatinib mesylate per day). At the time of the study presentation, the patients had been followed for more than six months and 82% had remained in the study. The overall rate of partial response was 54%, and 28% had either minor response or stable disease. Disease progression occurred in 14% of patients. Most (90%) of the adverse effects were mild to moderate, including grade 1 or 2 nausea (54%), diarrhea (51%), periorbital edema (48%), muscle cramps (42.2%), fatigue (38.8%), headache (30.6%), and dermatitis (26%). Severe adverse events (i.e., grade 3 or 4) included edema (3%), gastrointestinal or tumor hemorrhage (5%), abdominal pain (6%), neutropenia (5%), and fluid retention (5%). The researchers concluded that imatinib was effective in treating these patients and the safety profile is acceptable.

Improved Responses Occur With HuM195 Plus Chemotherapy for Patients With Acute Myeloid Leukemia

The results of a collaborative, phase III trial of HuM195, an anti-CD33 antibody, were presented by researchers from Weill Medical College of Cornell University in Ithaca, NY. HuM195 targets CD33 receptors on the cell surface of myelomonocytic cells. In this study, 191 adults with acute myeloid leukemia (AML) who were either refractory to standard therapy or had relapsed were randomized to receive mitoxantrone, etoposide, and cytarabine with or without HuM195. HuM195 12 mg/m^2 was administered as a four-hour infusion on days 7–10 and 19–22. For those treated with HuM195, an overall response rate of 43% resulted, compared to 26% for those who received chemotherapy alone ($p = 0.015$). Induction mortality rates were 15% and 13% for the HuM195 and control arms, respectively. Toxicities related to HuM195 were mild to moderate fever and chills. Other toxicities were found in both arms of the study: mucositis and diarrhea and hepatic, cardiac, and renal dysfunction. The combination of HuM195 with standard chemotherapy can be safely given and may improve the response for patients with poor prognosis refractory AML.

Anti-VEGF Antibody Slows Disease Progression in Patients With Metastatic Renal Cancer

Researchers from the National Cancer Institute in Bethesda, MD, and Genentech, Inc., in San Francisco, CA, examined the effectiveness of an antibody raised against vascular endothelial growth factor (VEGF) for patients with metastatic renal cancer. VEGF is dysregulated and oversecreted because of a genetic mutation in renal carcinoma. As a result, blood vessel growth is enhanced and contributes to tumor growth. Anti-VEGF therapy (bevacizumab) was designed to neutralize VEGF and block tumor cell proliferation. A prospective, double-blind, three-arm trial was initiated to compare the effectiveness of the placebo, low-dose anti-VEGF (3 mg/kg), and high-dose anti-VEGF (10 mg/kg) given every two weeks. A total of 110 patients with renal cell carcinoma were randomized into the three arms. A highly significant prolongation of time to disease progression was found with the high-dose arm compared to the placebo (hazards ratio = 2.3, $p = 0.001$). The difference between the low dose and placebo showed only borderline significance. Partial response occurred in only three patients (8%, high-dose regimen). At the time of the presentation, 58% of the patients still were living. Both doses of the antibody resulted in minimal toxicity; the most common toxicities were hypertension and asymptomatic proteinuria. This study demonstrated biological activity of bevacizumab as an antiangiogenic agent and suggested that trials with similar agents may be promising.

Anti-EGFR Antibody Plus Chemotherapy May Improve Response Rates for Head and Neck Cancer

Epidermal growth factor receptor (EGFR) commonly is overexpressed in squamous cell head and neck tumors. EGFR is involved in intracellular signaling that leads to cell proliferation and tumor growth. Therapies that target EGFR may, therefore, slow or stop tumor development. Researchers from Yale University School of Medicine in New Haven, CT, presented the results of a collaborative clinical trial by the Eastern Cooperative Oncology Group using C225 (Erbitux™, ImClone, New York, NY), an antibody directed against EGFR. One hundred twenty-one patients with squamous cell head and neck cancer that had not been cured by radiation or surgery were enrolled in the study. The participants had not received prior treatment for metastatic cancer. Patients were assigned randomly to one of two groups: cisplatin plus placebo or cisplatin plus C225 (test dose and

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then, if no hypersensitivity, 400 mg/m^2 over 120 minutes prior to cisplatin). Patients receiving the combined therapy (C225 plus cisplatin) had a response rate of 22.6% compared to 9.3% for the control group. No significant differences existed in overall survival. Toxicities included grade 3 or 4 hypersensitivity (6%), neutropenia (17%), and rash or desquamation (11%). The median overall survival for all the patients was 7.2 months.

Temozolomide May Improve Survival for Patients With Oligodendroglial Tumors

The results of a European Organization for Research and Treatment of Cancer prospective, multicenter trial of temozolomide (TMZ) for treating oligodendroglial tumors were presented by researchers from the University Hospital Rotterdam in the Netherlands. TMZ is an alkylating agent shown to be effective in treating astrocytic tumors. In this study, 39 patients with recurrent oligodendroglial tumors greater than 1 cm in diameter who had not had prior chemotherapy were treated with 200 mg/m^2 TMZ on days one through five every 28 days. Of the 39 patients enrolled in the study, 35 were able to be evaluated for response. Data analysis showed a 54% objective response rate, and at 12 months, 49% of the patients showed no disease progression. The primary toxicity was hematologic—grade 3 leukopenia or thrombocytopenia (n = 7). In addition, patients experienced grade 3 nausea and vomiting (n = 2), lethargy or malaise (n = 1), and hypertension (n = 1). In summary, TMZ demonstrated significant activity as first-line chemotherapy with an acceptable toxicity profile.

Epidemiologic Research

Women Surviving Hodgkin's Disease May Have Increased Risk for Bilateral Breast Cancer

A prospective study of 398 women younger than age 19 who were treated for Hodgkin's disease was carried out from 1960–1990 at Harvard University in Cambridge, MA, St. Jude Children's Research Center in Memphis, TN, Johns Hopkins Hospital in Baltimore, MD, the University of Florida in Gainsville, and the University of Rochester in New York. The median duration of follow-up was 14.5 years. The data from these patients were compared with expected rates of breast cancer using age-specific data from the National Cancer Institute's Surveillance, Epidemiology, and End Results study. The risk of breast cancer increased 45-fold in these patients, and the likelihood of bilateral disease also increased. All patients who developed breast cancer had early-stage Hodgkin's disease. Recommendations from this study were that (a) survivors of Hodgkin's disease should be counseled regarding the probability of breast cancer and screening should begin no later than nine years after diagnosis of Hodgkin's disease, (b) lowering the dose field of radiation may be useful in some cases, and (c) options, such as prophylaxis with tamoxifen, may be considered. Prophylactic mastectomy also may be considered when breast cancer is discovered in one breast, because the risk of bilateral breast tumors increases.

Recommended Frequency of Prostate Cancer Screening May Vary Based on Findings

Researchers from the University of Colorado Health Sciences Center presented an analysis of data from the National Cancer Institute's nationwide prostate, lung, colorectal, and ovarian cancer screening trial. Data from 26,863 men aged 55–74 (90% had initial prostate-specific antigen [PSA] levels in the normal range [less than 4 ng/ml]) were analyzed using a statistical model that predicted changes in PSA over five years. They found that 98.6% of men with initial levels less than 1 ng/ml continued to have normal levels over the next four years. In addition, 98.8% who had levels from 1–2 ng/ml had normal levels the next year. For men with PSA levels from 3–4 ng/ml, 24% had elevated levels within one year and 83% had elevated levels within four years. These findings may be useful in developing PSA screening guidelines.