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Clinical and Epidemiologic Research

Phase I Trial Indicates That Gene Therapy for Soft Tissue Sarcoma Is Well Tolerated

Researchers from the University of Chicago presented the results of a collaborative phase I trial of a second-generation adenovector carrying the gene for human TNFalpha, TNFerade™ (GenVec, Gaithersburg, MD), used in combination with radiation for patients with soft tissue sarcoma. The dose of TNFerade was escalated from 4 x 10^9 to 4 x 10^11 pu and given by intratumoral injection twice weekly for one week and then once weekly for two to five weeks concurrent with radiation (50 Gy). Six patients were evaluated in the study and received either TNFerade plus radiation preoperatively (n = 4) or TNFerade plus radiation for palliation (n = 2). No dose-limiting toxicities and no drug-related serious side effects occurred. Of those who received the treatment preoperatively, three had a complete response and one showed more than 95% necrosis. The other two patients had either partial regression or stable disease. The study suggested that TNFerade is well tolerated and has potential as an effective agent for soft tissue sarcomas in combination with radiation.

rViscumin Found to Target Solid Tumors in Phase I Trial

rViscumin (aviscumine) is a type II ribosome-inactivating protein that has demonstrated antitumor activity in animal models. The protein currently is under investigation in a dose-escalating phase I trial under the direction of the New Drug Development Early Clinical Studies Group in Hannover (Germany) and Nantes (France). Researchers from Medical School Hannover reported information from this ongoing trial. Patients included in the study had solid tumors that were refractory to conventional treatment. rViscumin was given via IV twice weekly over one hour. Pharmacokinetic samples were obtained at 0, 1, 1.25, 1.5, 2, 4, 8, and 24 hours after the first and eleventh treatments. Immunoplotterase chain reaction was used to detect the intact rViscumin protein and its metabolites. Twenty-six patients have entered the trial thus far, and tolerated doses have ranged from 10–4,800 ng/kg per treatment. The terminal half-life of the protein is estimated to be about 24 hours, and no evidence exists of drug accumulation. Plasma concentrations reached levels that were effective in preclinical animal models. Additional phase I trials are being considered.

SU011248 Inhibits Tyrosine Kinase Activity With Good Oral Availability in Phase I Trial

SU011248 inhibits tyrosine kinase activity via several different receptors, including vascular endothelial and platelet-derived growth factor receptors as well as c-kit. SU011248 previously has demonstrated inhibiting growth of human xenografts in mice. Researchers from Institut Gustave Roussy in Villejuif, France, presented results from a clinical trial with escalating doses of oral SU011248 administered to patients with advanced malignancies refractory to conventional chemotherapy. Seventeen patients received treatment for 28 days, followed by a two-week rest period. The starting dose was 30 mg/m² every other day, then daily 30 mg/m², 42 mg/m², and 59 mg/m². At 42 mg/m², SU011248 toxicities were grade two asthenia (n = 4), grade two thrombocytopenia (n = 1), grade two neutropenia (n = 1), and grade two diarrhea (n = 1). At the highest dose, grade two sore tongue and mouth occurred. A dose-dependent “tanned gold” coloration of the skin was observed at the highest doses, as was progressive hair discoloration. Good oral bioavailability was found with modest inter- or intrapatient variability. The target preclinical plasma concentrations were achieved. Objective responses were achieved in four patients. The dose escalation is continuing with 59 mg/m² to determine the maximum tolerated dose.

Cyclooxygenase-2 Upregulated in Precancerous and Malignant Oral Mucosa May Predict Genetic Risk

Researchers from the Norwegian Radium Hospital in Oslo, Norway, presented results from a study measuring cyclooxygenase-2 (COX-2) expression in oral tissues. Previous studies suggested that genetic instability and upregulation of COX-2, an enzyme involved in prostaglandin biosynthesis, might be correlated. Therefore, COX-2 expression might be a predictor of genetic risk for oral cancer, and selective treatment with COX-2 inhibitors may prove to be useful. In this study, levels of COX-2 and DNA ploidy status in healthy, premalignant, and cancerous tissues were compared. Samples were analyzed using in situ hybridization for messenger ribonucleic acid levels or Western blotting for protein levels. Only 1 of 30 healthy people demonstrated COX-2 expression in oral mucosa. DNA content was normal in all the healthy samples. By contrast, COX-2 expression was found in 26 of 29 patients with oral carcinomas, and aneuploidy was found in 25 patients. Of 22 patients with precancerous lesions, COX-2 was expressed in a subset of high-risk patients (n = 9) who also had aberrant DNA content in their lesions. Six of these nine patients developed oral carcinoma within five years.

Basic Research

STI571 Is Synergistic With Common Chemotherapeutic Agents in Squamous Cell Carcinoma Cell Cultures

STI571 (Gleevec™, Novartis Oncology, East Hanover, NJ) inhibits tyrosine kinases, including platelet-derived growth factor receptor and c-kit, involved in signaling proliferation of cells. C-kit has been demonstrated to be present in 90% of adenoid cystic carcinomas (ACCs) of the head and neck. A study presented by researchers from the Paterson Institute for Cancer Research in Manchester, UK, explored the interaction of Gleevec with common chemotherapeutic agents for inhibiting proliferation of squamous cell carcinoma (SCC) cell lines and primary cell cultures of ACC and SCC. In SCC cell lines, Gleevec was synergistic with several agents but antagonistic with gemcitabine. Similar effects were found with the ACC cell lines. Gleevec alone has significant growth inhibitory properties in