serine 727 phosphorylation of STAT1, which is required for maximal transcriptional activation of STAT1. STAT1 activation is generally associated with cell cycle arrest and apoptosis. In this regard, treatment of cells with IFNg together with either doxorubucin or mitoxantrone, synergized in enhancing cell cycle arrest, initially suggested by enhanced expression of the cell cycle inhibitory protein, p21. Enhanced cell death (apoptosis) was also observed as measured by potentiation of caspase-3 cleavage (apoptosis). These phenotypes were confirmed by flow cytometric analysis and MTT assays respectively. Analysis of the pattern of Stat1 target gene regulation has revealed that a novel mechanism exists whereby clinically used anti-cancer drugs enhance cell death by modulation of Stat transcriptional activity. Our data illustrate how potentiation or attenuation of STAT activation may be a component of pro- or anti-apoptotic responses determining cell survival following drug treatment, and furthermore, support addressing their role as potential targets for therapeutic intervention in the treatment of cancer.

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570

A phase 1 and pharmacodynamic study of PX-12, a thioredoxin inhibitor, in advanced malignancies

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PX-12 is a small molecule inhibitor of thioredoxin, and the first agent of this class to be tested in clinical trials. It is a potent stimulator of apoptosis and had been found to have good anti-tumor activity in a variety of human tumor xenografts in animal models. Thioredoxin inhibits apoptosis, stimulates cellular proliferation and has been found to be over expressed in a number of human tumors, including lung, colon and gastric. High levels of thioredoxin in human biopsies have been found to be associated with poor patient prognosis. The objectives of this Phase I trial are to determine the maximum tolerated dose (MTD), safety and dose limiting toxicities (DLTs) of PX-12 and to assess its pharmacokinetic and pharmacodynamic profiles. Patients with advanced solid tumors who had failed standard therapy were eligible and eligibility criteria were standard. PX-12 was delivered in 250 ml D5W over 1 hr daily for 5 days every 21 days. The starting dose was 9 mg/m^2/day and was 1/10th of the severely toxic dose in rats, which are the most sensitive species, with 3 patients entered at each cohort. Escalation was 100% to 72 mg/m^2/day after which a modified Fibonacci scheme will be used. Intradose escalation has been permitted when the next cohort completed successfully. DLTs were defined as grade 4 hematologic or grade 3 non-hematologic toxicity in 2 or more patients in a cohort. As of June 2002, 13 patients have been enrolled and the 72 mg/m^2/day cohort has been completed with only 1 grade 2 drug related cough noted. Pharmacokinetic and dynamic samples have been collected and the thioredoxin lowering activity of PX-12 in plasma samples is being assessed. One patient with refractory colon cancer has experienced a minor response and has completed 10 cycles of therapy starting with 9 mg/m^2/day and escalating to 36 mg/m^2/day. The therapy of this patient is continuing at this time. To date, two patients have received 7 cycles of therapy, one patient 5 and one patient 4 cycles. Accrual is ongoing.

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