toxicity was mild; only 1 pt developed neurotoxicity grade 2 while 4 pts fatigue grade 2. The study is now ongoing at the DLT level with G-CSF support.

1181 PUBLICATION

Phase I clinical trials of intravenous 2′-deoxycytidine-2′-fluoromethylene (FMdC) in patients with advanced solid tumors

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Purpose: To assess the clinical safety, tolerability, and pharmacokinetics of the nucleoside analogue, FMdC, a ribonucleotide reductase inhibitor and DNA chain terminator shown to have potent activity against a broad range of murine and human tumor cell lines in preclinical studies.

Methods: Four open-label, dose-escalation trials were conducted in patients with a variety of advanced solid malignancies. Dose levels: 16 to 670 mg/m^2; dosing schedules: 2×/wk × 3 wk + 1–2 wk rest to 1×/3 wk.

Results: 70 patients were evaluable. Pharmacokinetics were generally linear over a wide dose range. 86% of the dose was recovered in the urine within 24 h of administration; 23% of this amount was parent compound, and 64% was uridine metabolite. C_{max} occurred 4 h after dosing; then drug disappeared monophasically. The most common treatment-related adverse events (AEs) included transient fever (96%, 67/70), leukopenia (71%, 50/70), neutropenia (69%, 48/70), nausea (40%, 28/70), asthenia (39%, 27/70), and vomiting (27%, 19/70). Duration of leukopenia and neutropenia was brief (grade 4, 1–2 d and 1–8 d, respectively), and recovery was prompt. 27 patients accounted for 49 serious treatment-related AEs, of which 9 prompted discontinuation of the drug. One patient (metastatic colon cancer, 200 mg/m^2, 2×/mo) had a partial response after 4 cycles (4 mo) which was maintained for 5 mo. One patient with metastatic cholangiocarcinoma (32 mg/m^2, 2×/mo) had stable disease for 18 treatment cycles and progressed after 20 cycles (19 mo).

Conclusion: FMdC was generally well tolerated and showed objective anticancer activity. Phase II studies will be initiated in non-small-cell lung carcinoma, colorectal cancer, and ovarian cancer.

1182 PUBLICATION

A phase I study of weekly one hour escalating dose of paclitaxel infusion in conjunction with amifostine in patients with advanced cancer

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Background: Weekly infusion of paclitaxel is an active, well tolerated treatment under extensive investigation. Using standard premedications for the control of hypersensitivity reaction and colony stimulating factors to prevent myelosupression, neurotoxicity is the principal non-hematological toxicity of paclitaxel. Much higher doses of paclitaxel have been given using weekly instead of three week schedule. Dose limiting toxicities are noted between 80–100 mg/m^2 for previously treated patients. Amifostine protect normal tissue against ionizing radiation and chemotherapeutic agents without affecting the anti tumor effect. Many clinical trials have shown the decrease incidence of chemotherapy related toxicities including neuropathy, nephrotoxicity and myelotoxicity. Limited published data is available assessing its use in combination with paclitaxel.

Objective: To ascertain the maximum tolerated dose of weekly one hour paclitaxel infusion in conjunction with amifostine.

Methods: Phase I non randomized non-comparative, prospective study. Patients received granisetron 2 mg orally and dexamethasone 20 mg orally 2 hours before and cimetidine 300 mg with diphenhydramine 50 mg IVSS in 50 cc of NS 30 minutes before the chemotherapy and NS 250 cc over 1/2 hour. Each cohort has fixed amifostine dose of 740 mg/m^2 infused over 3–5 minutes immediately after hydration and escalating doses of paclitaxel infused over 60 minutes, 5 minutes after amifostine infusion, starting from 90 mg/m^2. In addition to routine evaluation, all patients have neurologic examination, nerve conduction studies, quantitative sensory testing with CASE IV and FACT neurotoxicity questioner.

Results: To date 9 patients with advanced metastatic cancers received 49 cycles of paclitaxel. Transient grade 2 neutropenia noted in 2/49 cycles in one patient. 5/49 cycles in 3 patients had grade 2 vomiting, after amifostine infusion. Although asymptomatic transient drop in blood pressure is common, only 1/49 cycles required hydration. Grade 3 neurotoxicity developed in 1/49 cycles in one patient after 11 doses of paclitaxel 100 mg/m^2, at the same time patient was noted to have multiple brain metastatic lesions from his small cell lung cancer.

Conclusion: Combination of amifostine and weekly paclitaxel in this current trial is tolerable with acceptable toxicities. Trial is ongoing with paclitaxel dose of 110 mg/m^2.

1183 PUBLICATION

In vitro concentration response studies of gemcitabine as experimental base for regional chemotherapeutic studies

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Purpose: To improve the theoretical background and to find out the potential benefit of gemcitabine for regional chemotherapy.

Methods: Dose- and time-dependent cytotoxicity of gemcitabine was analyzed in the human colorectal (HT29 and NMG 64/84) and pancreatic (PaCa-2 and PMH 2/89) cancer cell lines using the human tumor colony-forming assay (HTCA). Dose-dependent cytotoxicity was also generated in tumor cell suspensions, 1/99 and 3/99, isolated from colorectal liver metastases of 2 patients.

Results: Gemcitabine exerted a significant dose- and time-dependent cytotoxicity in all 4 cell lines with IC_{50} values of 100 μg/ml, 1.15 μg/ml, 18 μg/ml, and 1.5 μg/ml (2 h), 45 μg/ml, 0.5 μg/ml, 1.5 μg/ml, and 0.4 μg/ml (4 h), and 2 μg/ml, 0.1 μg/ml, 0.15 μg/ml, and 0.15 μg/ml (24 h) for HT29, NMG 64/84, PaCa-2, and PMH 2/89, respectively. Gemcitabine (2 h) resulted also in dose-dependent cytotoxic effects with an $IC_{50} > 100$ μg/ml and 2.5 μg/ml in 1/99 and 3/99, respectively.

Conclusions: Cytotoxicity varied more than 60-fold between the individual cell lines and tumor cell suspensions suggesting that response to gemcitabine is dependent on individual factors of each tumor. Dose- and time-dependent cytotoxicity *in vitro* moreover implies that gemcitabine may be qualified for regional chemotherapy.

1184 PUBLICATION

Inhibition of CYP3A4 does not influence Aromasin® (exemestane, EXE) pharmacokinetics (PK) in healthy postmenopausal volunteers (HPV)

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EXE is a novel oral irreversible aromatase inactivator effective in the treatment of advanced breast cancer and is extensively metabolised also by cytochrome P-450 3A4 (CYP3A4). The effect of the inhibition of CYP3A4 on the PK of EXE has been evaluated in five HPV following single doses of EXE (10 mg) before and after ketoconazole administration (200 mg daily for 6 days), a treatment known to selectively inhibit CYP3A4. The volunteers were phenotyped as extensive metabolisers of CYP2C19 and CYP2D6 substrates. To assess the inhibitory effect of ketoconazole, the ratio of urinary excretion of 6-β-hydroxicortisol/cortisol, a marker for CYP3A activity, was calculated. EXE in plasma was evaluated using HPLC-RIA; urinary mounts of 6-β-hydroxicortisol and cortisol using ELISA and RIA assay, respectively. No significant differences were observed in the pharmacokinetic parameters of EXE (mean ± SD) before and during ketoconazole repeated administration, being AUC 31.33 ± 8.95 and 28.37 ± 5.07 ng.h/mL, C_{max} 15.26 ± 10.17 and 9.16 ± 2.77 ng/mL, CL/F 351 ± 142 and 360 ± 53 L/h, V_z/F 12507 ± 6163 and 22258 ± 15312 L. The inhibition of CYP3A4 activity, confirmed by the significant decrease in the ratio of 6-β-hydroxicortisol/cortisol, does not affect the bioavailability and the metabolism of EXE. This suggests that the multiplicity of metabolic pathways for EXE might compensate *in vivo* for the inhibition of the CYP3A4 pathway.