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Phase I study of Xyotax (CT-2103) and cisplatin in patients with solid tumors: preliminary data

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Xyotax (CT-2103) is a macromolecular poly-L-glutamate water-soluble conjugate of paclitaxel. A 2-center, phase I study was designed to determine the maximum tolerated dose of Xyotax/cisplatin in patients with solid tumors. Escalating doses of Xyotax with cisplatin 75 mg/m^2 are being administered to patients (pts) with tumors refractory to conventional therapy or for which no conventional therapy exists. Xyotax is administered as a 10-min IV infusion every 21 days followed by a 3-hr IV infusion of cisplatin. Toxicity and response are assessed according to the NCI CTC and RECIST. Blood is obtained to evaluate pharmacokinetic and pharmacodynamic parameters. Thirteen pts (10 women) have been treated, and data are available for 12. Study pts have ovarian or primary peritoneal (5 pts), thyroid (3), unknown primary peritoneal (1), or uterine (1) carcinomas or sarcoma (2). Pts had 0 to 3 prior chemotherapy regimens (median, 2). To date, pts have received 1 to 13+ cycles at doses of 175 mg/m^2 (3 pts), 210 mg/m^2 (6), and 225 mg/m^2 (4). PR and SD were obtained in 10 pts: 5 have PR (3 ovarian, 1 uterine, 1 malignant schwannoma) and 5 have SD (2 ovarian, 2 thyroid, 1 myxoid chondrosarcoma). Time to progression in pts with PR was 10, 5+, 5.5+, 5.2 and 3+ mo and in pts with SD was 4.8+, 3, 6.3, 5+ and 2+ mo. CA-125 values in the pts with ovarian cancer were normalized in those with PR and reduced in those with SD. Thus, PR and SD were obtained in 10 of 12 pts to date. Grade 3 or 4 regimen-related toxicities to date are neutropenia (10 pts), nausea/vomiting (3), fatigue (3), anemia (2), dehydration (2), febrile neutropenia (2), and peripheral neuropathy (1 pt withdrew after 7 cycles). Neutropenia was responsive to growth factor therapy and did not cause withdrawal. Preliminary pharmacokinetic data suggest that unconjugated paclitaxel represented <6% of the total plasma paclitaxel, confirming the stability of the conjugated polymer. Xyotax/cisplatin shows encouraging efficacy and manageable toxicity. This study is continuing with 250 mg/m^2 Xyotax:75 mg/m^2 cisplatin.

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Phase II study of Xyotax (CT-2103) in patients with colorectal cancer having recurrent disease after treatment with a 5-fluorouracil-containing regimen

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Xyotax (CT-2103) is a polymer-bound form of paclitaxel that shows selective distribution to tumors that have a leaky vascular endothelium. Xyotax, soluble in aqueous solution, exposes normal organs to conjugated paclitaxel, which is nontoxic *in vitro*, thus minimizing overall toxicity. Xyotax shows enhanced efficacy compared with paclitaxel/Cremophor in syngeneic and xenogeneic *in vivo* tumor models of colorectal tumors and other paclitaxel-resistant cell lines (data on file, CTI). An ongoing, open-label, multicenter phase II study is currently enrolling patients with advanced, measurable colorectal cancer who have progressive disease after first-line therapy or relapse within 6 mo of adjuvant therapy. In this study, patients receive a paclitaxel-equivalent dose of Xyotax 210 mg/m^2 as a 10-min IV infusion every 21 days. Safety assessments are made using the NCI CTC (version 2), and dose reductions for defined toxicities are allowed in subsequent cycles. Efficacy assessments made using RECIST criteria are done after every second cycle. Preliminary unmonitored data are now available. Sixty patients (pts) age 38-84 yr (median, 62.5 yr) have been treated. Before entering this study, >85% progressed on treatment or relapsed within 6 mo of initiation of adjuvant therapy and 60% received second-line chemotherapy (oxaliplatin, gemcitabine, doxorubicin) or investigational agents (UFT, SU5416, vascular endothelial growth factor). Forty-two pts are currently evaluable for response. Fourteen pts (33%) achieved disease control (1 PR and 13 SD). Twenty-five percent have received > or = 4 cycles of therapy. With a median follow-up of 7 mo, 38/60 patients are alive and median survival has not been reached. Grade 4 drug-related adverse events have been reported in 3 patients to date: 1 pt had sepsis, mucosal inflammation, and febrile neutropenia; 1 pt had febrile neutropenia, and 1 patient had neutropenia. Grade 3 neuropathy has been reported in 3 patients. Xyotax showed encouraging signs of antitumor activity and manageable toxicities in this heavily pretreated population. This study will continue until an additional 30 patients who have received no more than 1 prior therapy have been treated.

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Phase I study of Xyotax (CT-2103) and carboplatin in patients with solid tumors: preliminary data

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Xyotax (CT-2103) is a macromolecular poly-L-glutamate water-soluble conjugate of paclitaxel, and in murine models, this agent is selectively concentrated in tumor tissues and shows synergistic antitumor efficacy when given in combination with carboplatin. We are currently performing a phase I study to determine the maximum tolerated dose of combination therapy with Xyotax and carboplatin (Cb) in patients with refractory solid tumors. In this study, Xyotax is administered at escalating doses per cohort of 3 patients every 21 days (10-min IV infusion) followed by a Cb 30-min IV infusion (1 of 2 dose levels per cohort). Twelve patients (median age, 56.4 yr) have been treated: NSCLC (n=2), esophageal adenocarcinoma (1), ovarian cancer (1), breast cancer (1), thyroid cancer (2), SCCHN (2), pancreatic cancer (1), colon cancer (1), renal carcinoma (1). Dose levels included: I, Xyotax 175 mg/m^2 / Cb AUC 5 (n=3); II, Xyotax 210 mg/m^2, Cb AUC 5 (n=3); Xyotax 210 mg/m^2 / Cb AUC 6 (n=6). Patients have received 1-8+ cycles on study. Disease assessment data are available for 9 pts. One patient with ovarian cancer had a PR (80% reduction) and continues on therapy after 8 cycles (24+ weeks); this patient's CA-125 has decreased steadily from 11,724 to 16/mL. This patient had previously failed a Cb/Taxol regimen. Five pts had SD for > or = 11 wk. Three had PD, and 3 are not yet evaluable. One patient with SD (NSCLC) had a 75% reduction in a brain metastasis but progressed to a lung metastasis after 4 cycles. Drug-related toxicities Grade 3 or greater include neutropenia (n=7), thrombocytopenia (5), anemia (3), leukopenia (1), and fatigue (1). No Grade 3 or greater peripheral neuropathy or hypersensitivity reactions were observed, and no alopecia has occurred. Xyotax combined with Cb is well tolerated; ongoing dose escalation continues, but evidence to date demonstrates anticancer activity.

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Post-irradiation carbogen breathing enhances the effectiveness of the bioreductive anticancer drug tirapazamine in SiHa but not SCCVII tumours in mice - a drug penetration phenomenon

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The penetration of anticancer agents into tumour tissue has recently attracted considerable attention. This study examines the effect of carbogen-breathing on the antitumour activity of tirapazamine combined with radiation therapy. Our hypothesis is based on the observation that the diffusion of tirapazamine through tissue is oxygen- tension dependent. We postulate that carbogen breathing might enhance the ability of tirapazamine to diffuse to hypoxic cells located distal to functional blood vessels in tumours.We first determined that carbogen-breathing caused no significant change in tirapazamine pharmacokinetics, suggesting that any effect of carbogen-breathing on the activity of tirapazamine is not attributable to pharmacokinetic modulation.Cell survival in SCCVII and SiHa tumours after 10 Gy X-rays alone was similar. However, when tirapazamine was administered 30 minutes after radiation treatment under air-breathing conditions, cell kill was greater in SCCVII compared to SiHa tumours. Carbogen-breathing during the exposure to tirapazamine did not change the cell survival in SCCVII tumours, but enhanced cell kill in the SiHa tumour. Interestingly, carbogen breathing during radiation treatment produced greater cell kill in the SiHa than the SCCVII tumour. The vascular architecture and type of hypoxia in the two tumours probably underlie the differences in the response of the two tumours. These findings suggest that the effectiveness of tirapazamine and other hypoxic cytotoxins may be tumour type dependent.