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Phase I study of MGI 114 (irofulven) exploring 3 different iv schedules (SCH) as a 5 minute infusion in advanced solid tumors (AST): final results

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Purpose: Irofulven (illudin S analog) IV 5 min daily x5 q4w phase I/II studies had delayed thrombocytopenia (T), nausea-vomiting (N/V), asthenia as treatment (Tt) limiting toxicities. Tolerance issues and T recovery led to reTt delays and reduced dose intensity (DI).

Methods: We performed a DI based escalation phase I in AST exploring 3 dosing sch at 3 dose levels (DL), Sch A: D1,8,15 q4weeks (w), DL1 [mg/m2/d]: [13.3], DL2 [16] and DL3 [18.6]; Sch B: D1,8 q3w DL1 [16], DL2 [18], DL3 [21]; Sch. C: D1,15 q4w DL1 [20], DL2 [24], DL3 [28]. Maximal tolerated dose was based on standard dose limiting toxicity (DLT) criteria and toxicity-related Tt delays in the first 2 cycles (cy). Starting DI was 75% of the daily x5 sch RD (10mg/m2/w) with DI increased by 2mg/m2/w at successive DL if <50% of = or <6 pts (pts)/DL experienced DLT. Irofulven was given over 5 min with anti 5-HT3, steroids and 1000cc hydration. ReTt was allowed with = or >90.000 platelets/mm3 and = or >1.000 neutrophils/mm3.

Results: As of 12/2000, 60 pts (M/F: 34/26), median age: 54.5 (20-79) had received 128 cy over 3 DL. Sch A: DL1 (6pts), DL2 (9pts) and DL3 (6pts). Sch B: DL1 (3pts), DL2 (9pts), DL3 (6pts). Sch C, DL1: (3pts), DL2: (9pts), DL3: (6pts). Mild (Gr 1-2) N/V, diarrhea, asthenia and T were prevalent in all 3 sch at all DLs without cumulative effects. There was no N/V or asthenia = or > Gr 2 at DL1 and 2. Gr 3/4 T was seen in 2, 1 and 2 pts at DL1, 2 and 3 respectively with nadir at day 28-35, resolving within 7 days in most cases, brief neutropenia Gr 3/4 was seen in 3, 6 and 3 pts at DL1, 2 and 3 respectively. Gr 2 transient visual disturbance (modification of the vision of colors/contrast with normal acuity) was seen in 4 pts at DL3 only. DLTs were seen in sch A in 1, 2 and 3 pts at DL 1, 2 and 3 respectively, and in 1 pt each in sch B and C, both at DL3. Median given DI over 2-3 cy was greater with the present weekly or q2w sch than with the daily x5 sch. Activity: 53 pts evaluable, 1 CR (ovarian carcinoma), 1 PR (sarcoma), 1 MR (prostate), 12 pt SD = or >3 cy.

Conclusion: Superior DI with a better toxicity and tolerance profile are obtained with these new (weekly or every 2 week) sch than daily x5 sch along with objective antitumor activity. D1,15 (24 mg/m2/d) q4w sch at DL2 was chosen as the RD for ongoing single agent phase II/III trials.

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Phase I study of amifostine (A) as a cytoprotector of the gemcitabine/cisplatin (GP) combination

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Purpose: Myelosuppression is a frequent dose-limiting toxicity (DLT) of GP. We evaluated the role of A as a cytoprotector of patients with solid tumors administered the GP combination.

Patients and Methods: A two-period cross-over design was utilized: patients (pts) were randomized to GAP or GP (C1) and then were crossed over to the other treatment (C2). A at 740 mg/m2 was administered just prior to the GP drugs, which were administered together, for 2 consecutive weeks, every 4 weeks. Two doses of GP were studied: G 1000 mg/m2 and P 40 mg/m2 d1, 8 (high dose), and G 800 mg/m2 and P 30 mg/m2 d1, 8 (low dose).

Results: Forty patients were enrolled in the study. Diagnoses included lung (14 pts), cervix (2), gastric (10), ovarian (5), colorectal (2), esophageal (1), thyroid (1), head and neck (1), and adenocarcinoma of unknown primary (4) cancers. The average age was 56, and the median ECOG performance status was 1. All but 8 pts had ~1 prior treatment. Of the 19 pts treated with high-dose GP, 11 (9 pts GP in C1 and GAP in C2, 2 pts GAP in C1 and GP in C2) completed 2 cycles of therapy and were thus evaluable. Of the 21 pts treated with low-dose GP, 15 (8 pts GP in C1 and GAP in C2, 7 pts GAP in C1 and GP in C2) were likewise evaluable. Among the 14 non-evaluable pts, 1 withdrew consent prior to treatment, and 1 had the d8 dose withheld due to grade 1 renal insufficiency; the remaining non-evaluable pts (12) came off study during C2, which occurred more frequently for pts treated with GAP in C1 and GP in C2 than those treated with GP in C1 and GAP in C2 (high dose: 7/9 pts versus 1/10 pts, p=0.03; and low dose: 4/11 pts versus 2/10 pts, p=0.64). Grade 3/4 hematologic toxicities were similar for GP and GAP during the first 2 cycles of treatment; these included (C1 and C2 combined) neutropenia in 2/1 pts for GP and 3/0 pts for GAP, thrombocytopenia in 1/2 pts for GP and 4/1 pts for GAP, and anemia in 0/0 pts for GP and 1/0 pts for GAP in the high-dose group; and neutropenia in 2/0 pts for GP and 0/0 pts for GAP, thrombocytopenia in 2/0 pts each for GP and GAP, and anemia in 1/0 pts for GP and 0/0 pts for GAP in the low-dose group.

Conclusion: A, at a dose of 740 mg/m2, does not lead to less myelosuppression when combined with GP.

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Phase I trial of the novel platinum analog ZD0473 in combination with gemcitabine in patients with advanced cancer

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Aims: ZD0473 is a new generation platinum compound designed to deliver an extended spectrum of antitumor activity and overcome platinum resistance mechanisms. Single-agent Phase I evaluation of ZD0473 reported activity and manageable toxicity in platinum-pretreated patients. Combination of ZD0473/gemcitabine (GEM) is of particular interest, due to the distinct mechanisms of action of the agents, differing toxicity profiles and evidence of preclinical synergistic activity. This study aimed to determine the recommended dose, antitumor activity and safety of ZD0473 in combination with GEM.

Methods: In this Phase I trial, patients with advanced cancer received ZD0473 (60-120 mg/m2) as a 1-h iv infusion on day 1 followed 30 min later by GEM (600-750 mg/m2) as a 30-min infusion on days 1 and 8, repeated every 21 days.

Results: To date, 35 patients (age range 41-79 yrs) with a range of tumor types (non-small cell lung [13 patients], pancreatic [6], sarcoma [5], ovarian [3], others [8]) have been enrolled. All had excellent performance status. Patients received ZD0473/GEM at doses of 60/750 (7 patients), 90/600 (4), 90/750 (10) and 120/750 (5) mg/m2. A total of 124 treatment cycles have been administered (median cycles per patient 3). At 90/750 mg/m2 ZD0473/GEM, there was 1 DLT (thrombocytopenia); other hematological effects included G3/4 neutropenia (6 patients) and anemia (2). At 120/750 mg/m2 ZD0473/GEM, 2 of 4 patients had dose-limiting thrombocytopenia. Separate patient cohorts were then accrued to the lower dose levels to define Phase II doses for minimally pretreated (no more than one prior regimen) and heavily pretreated populations. The 90/750 level was well tolerated in minimally pretreated patients (1 DLT/9 patients), while 60/600 was in excess of MTD for heavily treated patients (2 DLT/4 patients). Other toxicities were mainly G1/2 and included nausea, vomiting and fatigue. No nephrotoxicity or neurotoxicity was observed. Evidence of activity included 2 partial responses (leiomyosarcoma and refractory ovarian cancer) and 16 patients with stable disease.

Conclusion: The combination of ZD0473/GEM on this schedule is well tolerated and the recommended Phase II ZD0473/GEM dose in minimally pretreated patients is 90/750 mg/m2.

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A phase I study of weekly Oxaliplatin (OXA), 5-fluorouracil (5-FU) continuous infusion and preoperative radiotherapy in locally advanced rectal cancer

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Oxaliplatin (OXA) significantly enhanced the antitumor activity of fluorouracil (FU) in patients with advanced colorectal cancer and displayed radiosensitizing properties in both cell culture and xenografts experiments. The addition of Oxaliplatin to infusional FU might thus increase the activity of neoadjuvant chemoradiation for locally advanced rectal cancer.

A weekly schedule of Oxaliplatin administration may be optimal both to reduce acute toxicity (thanks to dose fractionation) and to maximize the

inhibition of sublethal radiation-induced DNA damage repair (advocated as the main mechanism for the radiosensitizing effect of Oxaliplatin).

This phase I study was thus started to determine the maximum tolerated doses of OXA (25-35-45 and 60 mg/m2, weekly for 6 times) and continuous infusion FU (200-225 mg/m2/die, d 1-38) in combination with standard pelvic radiotherapy (50.4 Gy - 28 fractions).

Since April 2000, 24 patients with locally advanced (cT3-T4 and/or N+) or recurrent rectal cancer were accrued (16 males, 8 females; median age 59, range 34-71 years).

Overall, 102 out of 108 courses of chemotherapy were delivered as planned. Three courses were omitted and two were delayed (1 day- 2 days) because of toxicity, while one course was given without FU (CVC dislocation). Only one patient did not complete the treatment program because of toxicity (grade III diarrhea leading to Oxaliplatin discontinuation after four doses). The first 13 patients had surgery as scheduled (6-8 week following completion of chemoradiation).

No grade IV toxicity was observed at the first four dose levels (OXA 25/FU 200; OXA 35/FU 200; OXA 45/FU 200; OXA 60/FU 200). Three episodes of grade III diarrhea were observed: two at OXA 25/FU 200, one at OXA 60/FU 200. Nine patients complained of grade I-II neurotoxicity (OXA 45/FU 200: 1; OXA 60/FU 200: 8).

All the patients had substantial tumor shrinkage with primary tumor and nodes down-staging observed in 11/13 and 6/7 cases respectively. Among 13 patients for whom final pathologic reports are available, 5 pCR were reported.

These results demonstrate that the combination of weekly OXA, continuous infusion FU and pelvic radiotherapy is feasible, well tolerated and has promising antitumor activity. The MTD has not been reached up to the dose of 60 mg/m2/week of Oxaliplatin. The study is now accruing patients at this OXA dose combined with FU 225 mg/m2/die.

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A phase I study of ZD0473 and Docetaxel given once every three weeks in patients with advanced refractory cancer. A National Cancer Institute of Canada-Clinical Trials Group Study (NCIC CTG-IND 131)

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ZD0473 is a new generation platinum compound with significant activity against a wide range of cultured human tumour cell lines and against a panel of human ovarian xenografts, including cisplatin- and carboplatin-resistant cell lines. Phase I and II studies reported activity in several solid tumours. As platinum agents are often combined with taxanes in a number of solid tumours, NCIC-CTG initiated a phase II study in of the combination of ZD0473 and docetaxel in advanced refractory cancers to define the toxicity, maximum tolerated dose (MTD), recommended phase II dose (RD) and pharmacokinetics. 17 patients (pts) have been enrolled on three dose levels (DL). 14 pts are evaluable for toxicity and 7 for response at this time. Eligibility criteria included pts with histologically advanced incurable cancer, performance status (ECOG 0-2), adequate organ function, and informed consent. All pts at DL1 (80 mg/m2 ZD0473 and 60 mg/m2 docetaxel), experienced grade (gr) 4 granulocytopenia; 1 pt was treated with GCSF after 4 days and was considered a possible DLT; the DL was expanded with 4 additional pts: no further DLTs were observed. Four pts were entered at DL2 (80 mg/m2 ZD0473 and 75 mg/m2 docetaxel); toxicities included gr 4 granulocytopenia lasting < 7 days (3 pts). 1 DLT of febrile neutropenia was seen and thus the DL was expanded with 2 more pts but no further DLT was seen. Toxicity data is currently pending for the 3 patients entered at the third DL of ZD0473 100 mg/m2 and docetaxel 75 mg/m2. Other related toxicities included 3 gr 3 infections (1 fatal), 2 gr 3 fatigue, and 1 gr 3 vomiting. Hematological toxicity included four gr 3 anemia, one gr 3 thrombocytopenia, and nine gr 4 granulocytopenia which was associated with febrile neutropenia in only two cases. 8 serious adverse events have been reported, 5 related fever and/or infection; 1 pain control; 1 unrelated bowel obstruction and 1 possibly related GI bleed. DLT is likely to be hematological and MTD is likely to be close to the current dose level. Median number of cycles is 6 at DL 1 and 3 at DL 2. It is too early to definitively assess activity, but this combination appears active and may have future potential in tumours that are responsive to taxane/platinum combination. The updated results of this phase I trial with pharmacokinetics will be reported.

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Pharmacokinetic (PK)/pharmacodynamic (PD) trial of the new generation platinum compound ZD0473 administered as an iv infusion every 21 days

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Aims: ZD0473 is a new generation platinum drug designed to have an extended spectrum of antitumor activity and overcome platinum resistance mechanisms. Initial Phase I studies did not reveal a clear relationship between total plasma ultrafiltrate platinum (analyzed by atomic absorption spectroscopy) and toxicity. We aimed to better define a ZD0473 dose for further Phase II/III evaluation and to study PK/PD relationships.

Methods: In this ongoing multicenter, open-label, dose-escalating Phase I trial, ZD0473 was administered as a 1-h iv infusion q 21 days. The ZD0473 plasma ultrafiltrate concentrations were then determined by a novel stable isotope dilution liquid chromatography/tandem mass spectrometry assay.

Results: All 7 patients (pts) with refractory solid malignancies were minimally pretreated (no more than 1 prior chemotherapy regimen that included an alkylating agent) and had PS 0 or 1. ZD0473 doses were: 120 mg/m^2 (1 pt; 6 cycles), 150 mg/m^2 (1 pt; 5 cycles) and 180 mg/m^2 (5 pts; 2 cycles [median], range 1–4). ZD0473 had a manageable safety profile: pts receiving 120 or 150 mg/m^2 did not have dose-limiting toxicity (DLT). All toxicities were G1 or 2, and the only serious adverse event was G1 fever at 150 mg/m^2. Of pts receiving 180 mg/m^2 ZD0473, 2 experienced DLT (G4 thrombocytopenia or G3 non-hematologic toxicity). Other toxicities at 160 mg/m^2 included anemia (G3, 3 pts: G4, 1 pt) and thrombocytopenia (G3, 1 pt: G4, 3 pts). No adverse events were fatal or led to withdrawal from therapy at any dose tested. An evaluation of the preliminary PK data suggests that exposure in terms of $AUC_{(0-4)}$ and C_{max} increase with dose. The $t_{1/2}$, clearance, volume of distribution (V_{ds}) and mean residence times (MRT) were similar for all pts.

Pt	Dose (mg/m^2)	$AUC_{(0-4)}$ (ng/ml.h)	C_{max} (ng/ml)	$t_{1/2}$ (h)	Total clearance (l/h)	V_{ds} (l)	MRT (h)	Thrombo-cytopenia (grade)
1	120	9308	5772	0.90	23.94	29.70	1.01	0
2	150	12981	7228	1.02	20.14	27.46	1.32	1
3	180	19821	12137	1.11	15.16	20.38	1.29	4
4	180	17450	10117	1.23	18.15	26.70	1.38	3
5	180	15781	7655	0.98	21.44	30.33	1.38	3
6	180	19102	10373	1.01	18.67	24.09	1.26	3
7	180	14586	7580	1.11	19.12	26.52	1.33	4

Conclusion: The maximum tolerated dose in minimally pretreated pts was 180 mg/m^2 (2 of 5 pts with DLT). Using the more specific analytical method would enable us to define the PK/PD relationship more accurately. We await further data to determine if this specific assay will permit the description of a PD model for ZD0473 to account for interpt variability.

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Phase I study of MGI 114 (Irofulven) given as either D1, D8 q3 weeks or D1, D15 q4 weeks schedule (sch) as a 30 minute infusion in advanced solid tumors (AST): preliminary results

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Purpose: Pharmacokinetic (PK) analysis of Irofulven (DNA interacting acylfulvene illudin S analog) given as a 5 min infusion showed a short mean plasma half-life (t1/2 range 4 to 6 min), with substantial interpatient variability (ASCO 2001). Therefore, a steady state should be reached by the end of a 30 min infusion. With preliminary in vitro data showing that increasing cytotoxicity closely correlates with increasing time of exposure over the first hour after administration, a 30 min infusion was implemented to evaluate toxicity, optimize activity and reduce interpatient PK variability.

Methods: Patients (pts) with AST were treated with the same schedules (sch) previously explored with the 5 min infusion duration (B: D1, 8, q3w and C: D1, 15 q4w) using the following dosing levels (DL in [mg/m2/d]). Sch B: DL2 [18], DL3 [21]; Sch C: DL2 [24], DL3 [28]. Maximal tolerated dose was based on standard acute dose limiting toxicity (DLT) criteria and toxicity-related treatment delays in the first 2 cycles. Planned dose intensity (DI) was increased by 2mg/m2/w at successive DL if <50% of = or <6