

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.

254

POSTER

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)

K.A. Gelmon¹, D. Stewart¹, D. Ayers¹, D. Fry¹, L. Douglas², L.W. McIntosh¹, L.K. Seymour¹. ¹NCIC Clinical Trials Group, Kingston, Canada; ²AstraZeneca, Mississauga, Canada

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 G-CSF 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.

255

POSTER

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

J.P. Stevenson¹, I.A. Blair¹, M. Redlinger¹, W. Sun¹, T. Oe¹, M. Koehler², D.W. Roberts³, M.D. Malone¹, P.J. O'Dwyer¹. ¹University of Pennsylvania, Philadelphia, PA; ²AstraZeneca, Wilmington, DE, USA; ³AstraZeneca, Alderley Park, UK

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/m² (1 pt; 6 cycles), 150 mg/m² (1 pt; 5 cycles) and 180 mg/m² (5 pts; 2 cycles [median], range 1-4). ZD0473 had a manageable safety profile: pts receiving 120 or 150 mg/m² 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/m². Of pts receiving 180 mg/m² ZD0473, 2 experienced DLT (G4 thrombocytopenia or G3 non-hematologic toxicity). Other toxicities at 160 mg/m² 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/m² (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 interpatient variability.

256

POSTER

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

E. Raymond¹, J. Alexandre², E. Brain³, S. Faivre¹, M. Ould Kaci⁴, S. Vignot³, S. Smith⁵, S. Lagree⁴, K. Vanderbilt⁵, J.L. Misset². ¹Institut Gustave Roussy, Villejuif, France; ²Hôpital Paul Brousse, Villejuif, France; ³Centre René Huguenin, Saint Cloud, France; ⁴C.A.C., Kremlin-Bicêtre, France; ⁵MGI Pharma, Minnesota, USA

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 (t_{1/2} 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