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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

J. Alexandre[1], S. Chieze[2], E. Raymond[2], E. Brain[3], M. Ould Kaci[4], S. Smith[5], S. Lagree[4], K. Vanderbilt[5], E. Cvitkovic[4], C. Kahatt[1]. [1]Hôpital Paul Brousse, Villejuif, France; [2]Institut Gustave Roussy, Villejuif, France; [3]Centre René Huguenin, Saint Cloud, France; [4]C.A.C., Kremlin-Bicêtre, France; [5]MGI Pharma, Minnesota, USA

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

F. Muggia, M. Haigentz, H. Hochster, M. Macapinlac, D. Mirchandani, J. Sorich, J. Lee, S. Sewak, M. Kim, A. Hamilton. *New York University School of Medicine, Kaplan Comprehensive Cancer Center, New York, NY, USA*

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

P. O'Dwyer[1], J. Stevenson[1], M. Redlinger[1], W. Sun[1], B. Giantonio[1], S. Hahn[1], K. Algazy[1], M. Burnite[1], M. Koehler[2]. [1]University of Pennsylvania Cancer Center, Philadelphia, USA; [2]AstraZeneca, Wilmington, USA

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

C. Aschele[1], M. Friso[2], S. Pucciarelli[3], G. Fabris[3], B. Martella[3], G. Da Dalt[3], E. Urso[3], D. Neri[3], O. Lora[2], S. Monfardini[1]. [1], Padova University Hospital, Dept of Medical Oncology, Padova, Italy; [2], Padova University Hospital, Dept of Radiotherapy, Padova, Italy; [3], Padova University Hospital, Depts of Surgery, Padova, Italy

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