Clinical pharmacology/phase I studies

923 ORAL

PHASE I STUDY OF TAXOL ADMINISTERED WEEKLY IN PATIENTS WITH PERSISTENT OVARIAN CANCER

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We commenced a Phase I study of Taxol administered weekly in pts with persistent ovarian cancer to assess feasibility, toxicity and schedule dependency. Cumulative hematologic toxicity has been uncommon with this schedule. *In vitro* studies with Taxol have suggested that fractionated brief infusion schedules would be more effective than standard 24 H infusion every 21 days. All pts had received prior platinum-based chemotherapy in addition to at least one regimen with Taxol. Pts with a history of grade 3–4 neuropathy were ineligible. *Methods:* Taxol dose levels of 40, 50, 60, 80 and 100 mg/m^2 per week were studied. Treatment was administered in the ambulatory clinic with standard Taxol premedication. *Results:* 18 pts enrolled, 17 evaluable for toxicity. Overall response in 3/14 (21.4%) pts evaluable, 2 pts with stable disease. Total of 170 Taxol cycles delivered, median 8 per pt (1–18). 166/170 cycles delivered on schedule. Mean WBC nadir following Taxol cycles was 3.8 (0.8–10.4) $\times$ 10^9/L. No cumulative hematologic toxicity has been noted. No alopecia noted. 11 pts entered study with neuropathy, 7 with grade I, 4 with grade II. No grade III neuropathy noted. In spite of Taxol 100 mg/m^2/weekly, we have thus far failed to demonstrate dose-limiting toxicity. Dose escalation continues. *Conclusions:* 1) Weekly administration of Taxol on this dose and schedule is feasible. 2) This schedule does not result in cumulative myelosuppression.

924 ORAL

PHARMACOLOGY OF PACLITAXEL (P) AND METABOLITES IN PATIENTS WITH ALTERED LIVER FUNCTION

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Hepatic metabolism and biliary excretion play an important role in the plasma disappearance of P. A safety and pharmacokinetics (PK) study of a 3-hour P infusion was undertaken in patients with altered hepatic function. Pts were treated in 1 of 5 cohorts (C): CI, Transaminase (T) <2.6*N and Bilirubin (B) ≤1.25*N; CII, T 2.6–10*N and B ≤ 1.25*N; CIII, T < 10*N and B 1.26–2.0*N; CIV, T < 10*N and B 2.1–3.5*N; CIV, T < 10*N and B 3.6–10*N. The dose of cohort I–III was 175 mg/m^2, 135 mg/m^2 in cohort IV and 90 mg/m^2 in cohort V. PK were performed during the first and second cycle of P administration. Twelve PK curves (n = 12) from 8 patients are available so far. PK of P, 6α-hydroxypaclitaxel (6-OHP), 3′-p-hydroxypaclitaxel (3-OHP) and 6α,3′-p-dihydroxypaclitaxel (6,3-DOHP) of the first three cohorts were:

Cohort	P:AUC0$\rightarrow\infty$ (μM.h)	P:C_{max} (μM)	6-OHP: AUC (μM.h)	3-OHP:AUC (μM.h)	6.3-DOHP:AUC (μM.h)
I (n = 6)	16.7 (13.3–21.8)	4.4 (3.6–4.9)	1.05 (0.5–1.8)	0.86 (0.30–2.35)	1.03 (0.23–3.26)
II (n = 5)	21.8 (17.9–31.8)	5.9 (5.1–7.0)	3.7 (0.2–8.8)	0.61 (0.09–1.66)	0.91 (0.00–2.19)
III (n = 1)	26.7	5.7	16.6	4.17	6.79

No dose limiting toxicity occurred in the first 12 patients. There is a clear reduction in systemic clearance of both P and 6-OH as indicated by the higher AUC levels and the prolonged circulation time of 6-OH (median 9.3 h, range 3.4–25.2 for cohort I; 22.6 h, range 2–46.7 for cohort II). There were no clear indications for reduced clearance of the two other metabolites. P could be given safely to pts with mild liver function disturbances at a dose of 175 mg/m^2 as found for cohort I and II.

925 ORAL

DOSE-FINDING STUDY OF TAXOL (T) AND CYCLOPHOSPHAMIDE (C) IN ADVANCED BREAST CANCER (ABC)

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Phase I studies demonstrated that relevant doses of T and C can be safely given to heavily pretreated patients (pts) with ABC. Aim of this study is to determine the MTD for T (over 3 hour) followed by C q3wks, with or without G-CSF. Eligibility was restricted to pts who have not received more than one prior chemotherapy (CT) as adjuvant therapy or for ABC. From Sept 92 to Feb 95, 38 pts (median age 52, median ECOG PS 0) have received 144 courses (cx). 31 pts were pretreated, (12 as adjuvant CT, 11 for ABC and 8 for both), 23 of which with doxorubicin-containing regimens. Starting doses were T 135 mg/m^2 and C 750 mg/m^2. G-CSF was added in pretreated pts at T 200 mg/m^2 and C 1000 mg/m^2 allowing further dose escalation of C to 1250 mg/m^2, while in non-pretreated pts the current dose level is T 200 mg/m^2 and C 1000 mg/m^2 without G-CSF.

T/C mg/m^2	Pts/cx	ANC < 500% cx/avg length	G2–3 neurotox/% pts
175/750*	5/17	76% (5 days)	-
175/750	2/18	11% (3.5 days)	-
200/750*	7/34	55% (5 days)	11%
200/750	2/9	22% (6 days)	11
200/1000*	4/13	38% (5 days)	57%
200/1000	3/10	80% (4.5 days)	57

* prior CT

Three non-pretreated pts achieved good partial responses at the highest dose level. Preliminary data seem to allow further dose escalation.

926 ORAL

PHARMACOKINETICS (PK), CLINICAL PHARMACODYNAMICS (PD) AND SAFETY OF CHRONIC ORAL TOPOTECAN (T), IN A PHASE I STUDY

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PK and PD of T and lactone ring-opened hydroxy-acid (HA) were determined in a phase 1 study with oral T b.i.d., day 1–21, q 4 weeks. To date, 26 patients (pts) have been entered, 10 males and 16 females, age range of 33–73 yrs and ECOG performance score of 0–2. Colorectal cancer was the most common tumor type enrolled (10/26). Dose levels (number of pts) studied were 0.15 (4), 0.3 (7), 0.4 (7), 0.5 (4) and 0.6 (4) mg/m^2, twice daily. A total of 40 courses are presently evaluable. Dose-limiting toxicity is diarrhea. CTC grade 3 diarrhea was seen in 1 pt at 0.3 mg/m^2 and grade 4 in 5 pts (mainly at the higher dose levels). The onset was rapid after 10–17 days, it could not be adequately reversed by loperamide and lasted 7–10 days. Two pts developed grade 3 granulocytopenia (1 at 0.15 and 1 at 0.3 mg/m^2 and the latter coincided with grade 3 thrombocytopenia). The MTD is 0.6 mg/m^2. To date, 1 PR in colorectal cancer has been observed. PK were determined twice during course 1 on day 1 and 8 or 21, using HPLC and noncompartmental methods. The AUC of T and HA showed substantial variation. As a measure of variability Dose/AUC of T was calculated, which was 3.7 ± 2.2 on day 1 and 2.5 ± 2.2 l/min on day 8 ($P < 0.05$). Interpatient variability (%CV) in Dose/AUC of T was 59%. A significant correlation was found between the AUC of T on day and 8 or 21 (R = 0.64). AUC of T and HA were consistently higher on day 8 or 21 compared to day 1. The correlation between Dose and AUC of T was 0.82 ($P < 0.01$). The ratio between AUC of T/HA was constant between day 1 and 8 or 21 (R = 0.90). There was a significant correlation between the AUC of T and CTC-grade myelotoxicity and diarrhea (Spearman rank R = 0.88, $P <$ 0.001). Substantial interpatient variation in systemic exposure was observed. Systemic exposure appeared to be correlated to toxicity. Further data are required to assess the PK/PD of oral T and its clinical utility.