dose of 175 mg/m^2/day and showed clinical activity. We report a multiple sch, parallel, dose intensity-guided phase I trial.
Methodology: Patients (pts) with solid tumours refractory to standard therapy received CP-4055 over 2 hours through a central venous catheter according to three sch: Days (D) 1, 8 q3w (sch A); D 1, 15 q4w (sch B); D 1, 8, 15 q4w (sch C). Dose escalation with dose levels (DL) defined according to dose intensity (DI) was used, DL1: 80 mg/m^2/w, DL2: 160 mg/m^2/w, DL3: 240 mg/m^2/w, DL4: 320 mg/m^2/w, DL5: 400 mg/m^2/w, DL6: 440 mg/m^2/w. Standard definitions of dose limiting toxicity (DLT) were used, including treatment delay >2w in the first 2 cycles. Inclusion is ongoing.
Results: 37 pts are treated to date at 6 DLs in 4 European centres between June 2004 and May 2005. Seven pts are still on treatment while 28 have discontinued due to progressive disease (PD) and 2 due to refusal. *Pt characteristics*: male/female: 20/17, median age 56 (range 35–72); WHO PS; 0: 12 pts, 1: 23 pts, 2: 2 pts. Principal tumour types: soft tissue and bone sarcoma, breast, colorectal, head and neck and GI; median of 3 lines of prior chemotherapy (range 1–5). *MTD*: No DLT has been observed. *Safety* (NCI-CTCAE ver 3): 32 pts assessed. The main toxicity, reported in all sch, is grade 1–2 anaemia (75% of pts; of these 25% had anaemia at baseline). Grade 1–2 nausea-vomiting is observed in 59% of all pts. Short lasting grade 3 neutropenia is observed in 2/17 pts at DL4 and DL5. No dose reduction required due to toxicity. *Efficacy*: Four sustained disease stabilizations (>3 months); breast cancer, prostate cancer, rectum cancer (sch A) and lung carcinoid (sch B).
Conclusion: Intermittent weekly or biweekly dosing of CP-4055 is well tolerated up to DI equal to 400 mg/m^2/w in the 3 sch tested. Patient accrual is ongoing at DL6 (440 mg/m^2/w)

1484 PUBLICATION

A metronomic treatment with oral vinorelbine in poor performance status patients with pretreated solid tumors

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Background: The safety profile and activity of oral vinorelbine (O-VNR) are comparable to that observed with i.v. formulation. It is known that the continuous infusion of drugs has possible advantages: administration of higher total dose; better tolerability; efficacy for a wider range of cell populations. An oral formulation can mimic the continuous infusion since the metronomic schedule implies the administration of low and repeated doses of drug.
The aim of this pilot study is to evaluate the faesibility of a metronomic schedule of O-VNR in poor performance status (PS) patients (pts) with pretreated solid tumors.
Patients and methods: From May 2004 till May 2005, 25 pts received O-VNR 30 mg fixed dose every other day for 12 weeks. Pts with tumor response or stable disease received another 12-week treatment until disease progression or toxicity or patient's refusal.
Pts' characteristics: median age 70 y (range 46–86); gender M/F 13/12; ECOG PS 2–3; tumor types: non small cell lung cancer 12, breast 3, unknown primary 2, sarcoma 3, prostate 1, ovary 2, kidney 1; rectum 1; metastatic sites were mainly viscera, soft tissue, brain; median number of previous lines 2.4 (range: 1–7).
Results: No WHO grade (G) 3–4 haematological or non-haematological toxicities have been recorded during 250 weekly treatments; vomit G1 has been reported in 3 pts.
Even if the activity was not a primary objective of the study, among the 11 pts who completed 12 weeks of O-VNR, 2 pts achieved partial response (breast, unknown primary tumor), 3 stable disease (lung, ovary) and 6 progression (kidney, sarcoma, lung and rectum).
Conclusions: In our preliminary experience the metronomic schedule of O-VNR is manageable: no significative toxicities have been recorded and no anti-emetic prophylaxis needed. This schedule might be used in phase II studies for malignancies, such as pretreated lung and breast carcinoma, where O-VNR showed activity and in poor PS pts even in early stages.

1485 PUBLICATION

The effect of rifampin on the pharmacokinetics of sunitinib malate (SU11248) in Caucasian and Japanese populations

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Background: Sunitinib malate is an oral multitargeted tyrosine kinase inhibitor which specifically inhibits VEGFR, PDGFR, KIT, RET and FLT3 and has demonstrated single agent antiangiogenic and antitumour activity in phase I and phase II clinical trials in a variety of advanced solid tumours, including gastrointestinal stromal tumour, metastatic renal cell carcinoma and metastatic breast cancer. Sunitinib is metabolised by cytochrome P450 (CYP) 3A4 to SU12662, an equipotent metabolite that is further metabolised by CYP34A. Thus, co-administration of sunitinib and drugs that induce CYP3A4 could lead to a reduction in sunitinib exposure.
Materials and methods: The pharmacokinetics (PK) of sunitinib were assessed in the presence and absence of rifampin (a potent CYP3A4 inducer) in an open-label, 2-way cross-over study in healthy male volunteers. Caucasian (n = 13) and Japanese (n = 15) volunteers were enrolled to enable a preliminary assessment of any effects of race. Volunteers were randomized to initial treatment with either Treatment A (a single oral dose of sunitinib 50 mg) or Treatment B (17 daily oral doses of rifampin 600 mg/day combined with a single dose of sunitinib 50 mg on Day 8); the alternative treatment regimen was administered following a 2-week washout period. Concentrations of sunitinib and SU12662 in plasma were determined using validated methods.
Results: Compared with administration of sunitinib alone, co-administration of sunitinib and rifampin resulted in a 4.8- and 4.7-fold reduction in sunitinib AUC_{last} and $AUC_{0-\infty}$, respectively, and a 2.3-fold reduction in sunitinib C_{max}. In terms of the active metabolite, a 1.3-fold increase in SU12662 AUC and a 2.4-fold increase in SU12662 C_{max} were observed following co-administration of sunitinib and rifampin. The PK results with and without co-administration of rifampin were similar in both ethnic groups.
Conclusions: The reduction in sunitinib exposure when the drug was co-administered with rifampin indicates that concomitant treatment of sunitinib with drugs that induce CYP3A4 should be avoided. The lack of racial differences supports the use of a common sunitinib starting dose and schedule in Caucasian and Japanese populations.

1486 PUBLICATION

A phase I combination study of split-dose short infusion trabectedin and doxorubicin administered every 21 days in patients with solid tumors

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Background: Trabectedin (YONDELIS™) is a minor groove binder with single agent activity in soft tissue sarcomas and ovarian carcinoma (OC) at doses of 1.3–1.5 mg/m^2 infused over 3 or 24 h every 3 weeks (Q3W). In combination with a standard dose of doxorubicin (DOX) trabectedin Q3W in 3 h could not be administered at dose higher than 0.8 mg/m^2 because of dose limiting neutropenia. This trial explores if a more frequent dosing allows to increase the trabectedin dose per cycle in combination with DOX.
Methods: 35 patients (pts) with advanced solid tumors were accrued into a multicenter phase I study delivering trabectedin in escalating doses on days 1& 8 and DOX (50 mg/m^2) on day 1Q3W. Dexamethasone (IV & OS) was given during and after trabectedin. Selection criteria were: $\leqslant$1 prior chemotherapy; maximum prior DOX 300 mg/m^2 and adequate renal, liver and hematologic function.
Results: 34 pts were treated with 103 cycles of the combination at trabectedin doses ranging from 0.3 to 0.8 mg/m^2. Median age was 56 yrs (range 32–71), PS was 0 in 74%, tumor type was (registered pts): OC, N = 26, sarcomas, N = 7, endometrial ca, N = 2. At the maximum trabectedin administered dose of 0.8 mg/m^2, 2 of 3 pts had acute hematologic dose limiting toxicity (DLT). The MTD was defined at 0.7 mg/m^{2}with 3 of 8 pts having DLT (2 hematologic, 1 liver). At 0.6 mg/m^2, 6 pts were entered in the dose escalation phase and 1 liver DLT observed (ALT > 2.5 x UNL on day 8). At trabectedin $\geqslant$0.5 mg/m^2 48% of cycles required dose reduction, delay or both, mainly because of neutropenia or delayed hematologic recovery. The combination was otherwise well tolerated: 1 pt had G4 reversible ALT ?, G3 nausea/vomiting, asthenia and reversible transaminase ? occurred in 9, 12 and 15% of pts, respectively. Of 25 treated OC pts relapsing after platinum-taxane therapy, 3 responded (12% 3–31 95% CL).
Conclusions: A higher total dose/cycle can be delivered with DOX Q3W when trabectedin is given on days 1&8 instead of 3-weekly, but this increase cannot be maintained beyond cycle 1 because of hematologic toxicity. Substituting DOX with a less neutropenic anthracycline might decrease the myelosuppressive interaction of the combination. A phase I trial with liposomal DOX is currently ongoing.