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Carboplatin Dosing in Obese Patients. *P. R. Hutson, K. D. Tutsch, M. Pomplun, H. I. Robins, C. L. Tiggelaar, D. B. Alberti, C. A. Feierabend, N. Rieck, R. Arzoomanian, G. Wilding; UW Sch of Pharmacy, Madison, WI; UWCCC, Madison, WI*

The Calvert or Chatelut equations are commonly used to estimate carboplatin clearance and thus the dose needed to establish a target AUC. The accuracy of sequentially using the Cockroft-Gault (CG) and Calvert equations to respectively estimate creatinine (Clcr) and carboplatin clearance in obese patients was retrospectively examined in two Phase I trials of carboplatin combined with thymidine (THY) and with hyperthermia (WBH). Neither THY or WBH affected carboplatin pharmacokinetics. Unbound carboplatin AUC was measured by atomic absorption spectrometry in 59 subjects receiving an average of 390 mg/m^2 carboplatin (range 100–576 mg/m^2) with an average body mass index of 26.6 kg/m^2 (range 17.9–40.4; values > 25 are considered obese). Ideal body weight was estimated as (50kg male ; 45kg female) + 2.3kg * (Height (inches)-60). The effects of various weight adjustments for CG/Calvert or Chatelut equations are shown in the following table. Prediction bias was measured as mean prediction error (MPE) = (calculated AUC - measured AUC). Accuracy was measured using root mean squared prediction error (RMSE). Minimization of both parameters to zero is optimal:

Weight used in Equation	CG/Calvert		Chatelut	
	MPE	RSME	MPE	RSME
Actual Wt (ABW)	0.36	1.44	-2.85	3.62
Ideal Wt (IBW)	1.18	1.98	-0.82	2.42
Ideal + 40% Fat	0.79	1.61	-1.18	2.50
Mean (ABW & IBW)	0.70	1.55	-1.25	2.53
Measured Clcr	0.12	1.41	n/a	n/a

Conclusion: Carboplatin AUC-targeted dosing using the Calvert equation in obese patients can use actual weight, even for very obese patients; no substantive improvement is obtained by using lean weight or intermediate values. Use of ideal or lean weight appears to optimize the Chatelut equation. Supported by NIH UO1-CA62491 and GCRC grant MO1-RR03186.

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CCI-779, a Rapamycin Analog and Multifaceted Inhibitor of Signal Transduction: a Phase I Study. *M. Hidalgo, E. Rowinsky, C. Erlichman, R. Drengler, B. Marshall, A. Adjei, L. Hammond, L. Speicher, E. Galanis, T. Edwards, J. Boni, G. Dukart, J. Buckner, A. Tolcher; Institute for Drug Development, San Antonio, TX; Mayo Clin, Rochester, MN; Wyeth-Ayerst, Radnor, PA*

CCI-779, an ester analog of rapamycin which is being developed for cancer therapy, inhibits the transduction of several critical proliferative signals. CCI-779 binds to FKBP-12 intracellularly, forming a complex that inhibits the kinase activity of mammalian target of rapamycin (mTOR). This action interferes with key signal transduction pathways, including those regulated by the p70s6 kinase and PHAS-I protein resulting in the inefficient translation of proteins involved in cell cycle progression and produces cell cycle arrest at the G1-S boundary. CCI-779 demonstrated growth inhibitory properties in preclinical models. This study is evaluating the feasibility, pharmacokinetics (PK) and biological effects of escalating doses of CCI-779 administered as a 30-minute IV infusion daily x 5 every 2 weeks as a single agent in patients (pts) with solid neoplasms. To date, 35 pts have received 167 courses (median 4, range 1–12) at doses ranging from 0.75–11.3 mg/m2/d. Isolated, asymptomatic, grade 3 hypocalcemia at the 2.16 mg/m2/d dose level has been the only dose-limiting toxicity noted to date. Other generally mild-moderate toxicities noted, some over a broad dose range, are neutropenia, thrombocytopenia, rash, mucositis, hypertriglyceridemia, and allergic phenomena. In 17 pts receiving doses of 0.75 to 3.12 mg/m2/d, CCI-779 exhibited increasing peak concentrations with increasing dose, preferential red blood cell partitioning, and a median terminal half-life of 15.2 h. Lymphocyte subset and mitogen proliferation assays have not shown any consistent pattern, and it is projected that they will not be useful as pharmacodynamic surrogates. Minor antitumor responses and/or prolonged (> 4 months) stable disease have been noted in several drug-refractory cancers including: soft-tissue sarcoma (2), and cervical (1), uterine (1), non-small cell lung (1), and renal cell (4) carcinomas. CCI-779 dose escalation is ongoing. However, the tolerance and antitumor activity observed to date, associated with plasma concentrations that portend biological activity in vitro, are encouraging.

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Identification of Biochemical Parameters That Predict the Onset of Severe Toxicities in Patients Treated with ET-743. *J. Gómez, L. López Lázaro, C. Guzmán, A. González, J. L. Misset, C. Twelves, A. Bowman, K. Hoekman, M. Villalona, D. Ryan, L. Paz-Ares, J. Jimeno; Pharma Mar S A, Madrid, Spain; ET 743 Phase I group*

ET-743 is a novel marine compound that is under active phase II development.The potential limiting toxicities, pancytopenia-fatigue, at the proposed recommended dose (RD) have been consistently characterized. However 6/331 patients (1.81%; 95%CI: 0.67%–3.90%) treated with ET-743 have developed severe or multiorgan toxicities (MOT) including long lasting pancytopenia, renal and hepatic failure and rhabdomyolysis; three out of those six cases died. Therefore full clinical and pharmacokinetic (PK) data from 93 phase I patients treated at the RD or at the maximal tolerable dose among five phase I trials have been included in a multivariate analysis to identify factors that can anticipate the onset of MOT in order to improve patients safety. Results: Patients with intercycle peaks (IPK) of alkaline phosphatase (ALP) above normal values (NV), median apex intercycle day=15, in a given cycle had a high risk of severe or MOT in the following cycle than those without ALP-IPK: 24% vs. 4.7% ($p<0.001$). In addition data from 108 cycles were included in a stepwise logistic regression model. The following variables remained as the main predictors of severe or MOT: ALP-IPK > 1.1 NV p=0.0134, cycle baseline bilirubin > 0.6 NV p=0.0042 and AST-IPK > 5 NV p=0.0193.Other clinical, demographic and laboratory variables were not statistically significant. Moreover, an AUC > 70 h.mcg/l correlates to both severe or MOT and ALP-IPK, raising the possibility that intercycle peaks of ALP are a marker of subclinical cholangitis yielding to decreased elimination of ET-743. Conclusions: these findings indicate the need to monitor the biliary biochemistry (bib) at entry and during the intercycle period, performing one bib test within intercycle days 14–17. Patients with normal bib at baseline can be safely treated with the proposed RD of 1500 mcg/m2. A dose reduction to 1200 mcg/m2 is mandatory in case of ALP-IPK. A prospective identification of the RD in patients with impaired bib is warranted.

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CCI-779, a Rapamycin Analog with Antitumor Activity: A Phase I Study Utilizing a Weekly Schedule. *E. Raymond, J. Alexandre, H. Depenbrock, S. Mekhaldi, E. Angevin, A. Hanauske, E. Baudin, B. Escudier, J. Frisch, J. Boni, J. Armand; Gustave-Roussy, Villejuif, France; Onkologische Tagesklinik, Munich, Germany; Wyeth Ayerst/Genetics Institute, Munich, Germany*

Background: CCI-779, an ester analog of rapamycin, inhibits the protein kinase mTOR and has antitumor activity in animal models. Patients (pts) and Methods. CCI-779 was given as a weekly 30 min infusion in pts with advanced solid tumors. Dose escalations were made using the modified CRM as a guide. Results. 16 pts (M/F: 11/5) were treated at the doses of 7.5 (1 pt), 15 (2 pts), 22.5 (1 pt), 34 (3 pts), 45 (4 pts), 60 (1 pt), 80 (1 pt), 110 (1 pt), 165 (1 pt), and 220 mg/m^2/w (1 pt). So far, no dose limiting toxicity was observed. Grade (Gr) 1–2 skin toxicity was observed without any evidence of relationship to dose: dryness with mild itching (7 pts), eczema-like lesions (3 pts), sub-acute urticaria (1 pt), and aseptic folliculitis (10 pts). Skin biopsies from some patients with folliculitis showed superficial peri-capillar dermatitis. Five pts experienced reactivation of peri-oral herpes lesions. Gr1–2 mucositis was observed in 9 pts. All pts receiving ≥ 8 doses experienced Gr1 nails changes. Thrombocytopenia was observed in 3 pts treated at 34 (Gr3), 45 (Gr2) and 80 mg/m^2/w (Gr1), requiring treatment delay in 2 pts. Asymptomatic increases of triglyceride and cholesterol levels were observed in 8 and 4 pts, respectively. A reversible decrease in testosterone associated with increased levels of LH and FSH were observed in 5/6 men receiving more than 4 doses at dosages ≥ 15mg/m^2/w. Immunological analysis of blood showed no immunosuppression. Pharmacokinetic analysis in blood from 12 pts receiving up to the 60 mg/m^2/dose indicates an increasing of C_{max} and AUC of CCI-779 with increasing dose, a median half-life of 17.3 h, and a mean clearance of 22L/h. 15 pts were evaluable for efficacy: 1 partial response in a pt with a IL2-IFNα resistant metastatic renal cell carcinoma treated with 15 mg/m^2/w and 6 pts with disease stabilization ranging from 12% increase to 39% decrease of the tumor size in pts with bulky disease (2 renal carcinoma, 1 neuroendocrine tumor of the lung, 2 soft tissue sarcomas, 1 rectal, 1 adrenal cortical carcinoma, 1 melanoma). Conclusion. Current data show that CCI-779, a drug with a unique mechanism of action, has antitumor activity and mild toxicity at doses above 15 mg/m^2/w.