Metabolically active cytochrome P450 CYP1B1 in solid tumours: a novel target for chemotherapeutic intervention.

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kinetics (C_{max} and $AUC_{(0\text{-}Inf)}$) over the dose-range evaluated. Estimated PK parameters: $t_{1/2}$=50.4±42.7 hour; V_{ss}=795.4±331.5 L/m^2; Cl=23.9±15.2 L/hr/m^2. The erythromycin breath test did not predict drug clearance. Accrual continues at 25 mg/m^2/wk (HP) and 30 mg/m^2/wk (MP) to define safe dose schedules for MP and HP patients. **Conclusion:** This weekly schedule of BMS247,550 has clinical anticancer activity and warrants broad disease-oriented testing in phase II studies

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METABOLICALLY ACTIVE CYTOCHROME P450 CYP1B1 IN SOLID TUMOURS: A NOVEL TARGET FOR CHEMOTHERAPEUTIC INTERVENTION.

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Cytochrome P450 CYP1B1 is a member of a superfamily of haemoproteins which are central to the oxidative metabolism of a wide variety of endogenous and exogenous compounds. Several of these enzymes have an established role in the metabolic bio-transformation of a variety of anti-cancer drugs. We have previously shown that CYP1B1 is a tumour-specific form of cytochrome P450 highly expressed in a variety of malignant tumours localised specifically to tumour cells[1]. In contrast CYP1B1 protein is un-detectable in corresponding normal tissue. Recently we have identified several anti-cancer drugs that are substrates for CYP1B1[2]. Moreover, our *in vitro* studies have shown that the presence of CYP1B1 reduces the efficacy of some of these neoplastic agents[3]. Cytochrome P450 enzymes require the presence of cytochrome P450 reductase (CPR) for optimal metabolic activity. Since CYP1B1 metabolises anti-cancer drugs in tumour cells it is important to determine the level of active CYP1B1 and CPR in tumours. In this study we demonstrated both CYP1B1 and CPR activity in the microsomal fraction of ovarian (n=9) and kidney tumours (n=24). The Ortho-deethylation of ethoxyresorufin to resorufin was used to measure CYP1B1 activity. We have found CYP1B1 activity in the 100,00g fraction in both ovarian and kidney tumours (100-800 fmol/min/mg of protein). Co-incubation with the CYP1B1 inhibitor alpha-naphthoflavone inhibited this activity. No CYP1B1 activity was observed in any of the normal kidney samples examined (n=8). CPR activity was determined spectrophotometrically by measuring the reduction of cytochrome c at 550nM. CPR activity was detected in all normal and tumour samples (0.04-3nmol/min/mg protein). The presence of CYP1B1 which is capable of metabolising anti-cancer drugs and which is active only in tumour cells highlights a novel target for chemotherapeutic intervention.

References

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