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Abstract

Pharmacodynamic-guided, modified continuous reassessment method (mCRM)-based, dose finding study of rapamycin in adult patients with solid tumors

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Background: Pharmacodynamic (PD) studies, using either surrogate or tumor tissues, are frequently incorporated in Phase I trials. However, it has been less common to base dose selection, the primary endpoint in Phase I trials, in PD effects. We conducted a PD-based dose selection study with rapamycin (Rap). **Methods:** We used the modified continuous reassessment method (mCRM), a computer-based dose escalation algorithm, and adapted the logit function from its classic toxicity-based input data to a PD-based input. We coupled this design to a Phase I trial of Rap with 2 parts: a dose estimation phase where PD endpoints are measured in normal tissues and a confirmation phase where tumor tissue is assessed. Patients (pts) had solid tumors refractory to standard therapy. Rap was given starting at 2 mg/day continuously in 3-pt cohorts. The PD endpoint was pP70S6K in skin and tumor. Biopsies were done on days 0 and 28 of cycle 1, and a PD effect was defined as ≥ 80% inhibition from baseline. The first 2 dose levels (2 and 3 mgs) were evaluated before implementing the mCRM. The data was then fed to the computer that based on the PD effect calculated the next dose level. The mCRM was set so escalation continued until a dose level elicited a PD effect and the mCRM assigned the same dose to 8 consecutive pts, at which point the effect of that dose will be confirmed in tumor biopsies. Other correlates were PET-CT and pharmacokinetics. **Results:** Ten pts were enrolled at doses of 2 mg (n = 4), 3 mg (n = 3) and 6 mg (n = 3). Toxicity was anemia (4 G1, 1 G2), leucopenia (1 G1, 2 G2), low ANC (2 G2), hyperglycemia (2 G1, 1 G2), hyperlipidemia (4 G1), and mucositis (1 G1, 1 G2). PD responses were seen in 2 and 1 pt at 2 and 3 mg dose levels. Input of data to the mCRM selected a dose of 6 mg for the third cohort, where PD effect was seen in 1 pt, and thus a fourth dose around 9 mg will be tested. No responses by RECIST occurred, but 2 pts had a response by PET. The PK was consistent with prior data (t1/2 24.6 ± 10.2 h, CL 31.4 ± 12.0 L/h, vol of distribution 235 ± 65 L), and exposure increased with dose. Steady-state concentration were in the 5–20 nM range. **Conclusions:** mCRM-based dose escalation based on real-time PD assessment is feasible and permits the exploitation of PD effects for dose selection in a rational manner.

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