Exploring the potential of PK-PD modelling in early phase oncology drug development

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If one considers the approach to the development of cytotoxics and targeted therapies, clear differences are apparent. Conventional cytotoxic chemotherapies followed a well worn empirical course; dose escalation followed a fixed or semi-fixed scheme from a starting dose based on some multiple of a preclinical toxicity dose. Escalation continued until the maximally tolerated dose (MTD) was defined and this single dose was carried forward into later phase clinical trials. Toxicity such as myelosuppression, was often used as a biomarker of the desired cytotoxic effect in the tumour.

Pharmacokinetics was largely descriptive, body surface area dosing a substitute to individualized therapy, but without adequate understanding of the covariates (Gurney, 2002). In contrast, the early clinical development of targeted agents is driven by the need to assess the impact on the target which may occur in absence of clinically definable effect on the tumour or other tissues. Translation to clinical efficacy is more remote and hence more difficult to illicit in phase 1 studies. Dose escalation is more amenable to adaptive study design in which pharmacokinetics and pharmacodynamics play an increasingly important role. Biological effect rather than toxicity determines the subsequent range of doses which maybe taken into phase 2 studies.

New considerations have been introduced such as the degree and duration of target inhibition. Complete (100 %) inhibition indefinitely may adversely affect the margin of safety and may not be desirable for efficacy (Burgess and de Alwis, 2007). Two recent examples of developing a cytotoxic and a targeted agent within Eli Lilly & Company will be presented (Bueno et al., 2008). The cytotoxic agent exhibited a very high saturable protein binding, gender difference within a species and a species difference in toxicity. Total dose and total drug concentrations failed to explain a 30% mortality in male rats compared to a 3 % mortality in female rats given the same dose, however, incorporating protein binding and protein levels in a semi-mechanistic PK model explained these differences with predictions of unbound concentrations. This model also incorporated an in vitro bone marrow assay data to explain neutropenia differences between rat and dog. In another example, a preclinical model integrating PK, biomarkers, and tumour growth delay data described satisfactorily the mechanism of action of a TGF-β signal transduction inhibitor and provided a tool to investigate different experimental scenarios establishing levels of biomarker inhibition associated with efficacy, to assist in the design and description of the biologically effective dose range selection for the first in man study.