Pharmacokinetics and pharmacodynamic biomarkers in early oncology drug development

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An integrated clinical pharmacology strategy is an essential part of any drug development programme. However, the modern era of oncology therapeutics with its inherent emphasis on molecularly targeted strategies requires a rethinking of our traditional strategies. The growing emphasis on the incorporation of biomarkers into early clinical development programmes is altering the pharmacokinetic (PK) and pharmacodynamic (PD) strategies for the conduct of our early clinical trials. While traditional descriptive PK profiling remains an important endpoint for any first-in-human study, PDs for molecularly targeted therapies have increased in complexity and sophistication. In our current development programme, major resources are devoted to the development of clinically relevant biomarkers indicative of a drug's pharmacodynamic mechanism of action, so called PD/MoA biomarkers. These laboratory correlative assays are subsequently integrated into the PK-PD monitoring strategy in early clinical trials to understand if a new therapeutic is acting on its molecular target in the expected manner. This review discusses the challenges and potential rewards for this scientific approach and will describe a general strategy for integrating PK-PD and biomarker studies into early oncology drug development programmes for targeted therapeutics. This review will not emphasise the extremely important use of predictive biomarkers to select patients for therapeutic intervention, which remains beyond the scope of the current discussion.

The major goal for PK-PD studies in early drug development is to understand and characterise an agent's pharmacological behaviour in the clinical setting. Because this effort bridges the gap between our understanding of a drug's activity in the preclinical setting and in the clinic, it meets the exact definition of translational research. Nonetheless, a recent critical review of the current state of the art of the use of PD/biomarkers in oncology drug development found major shortcomings [1]. Most clinical trials of targeted agents do not utilise PD/MoA biomarkers to make critical drug development decisions, leading to major criticisms of this entire approach [2]. In an attempt to improve strategic thinking in this area, Paul Workman developed the Pharmacological Audit Trail (PhAT) as a tool to guide the development of a novel, targeted oncological therapeutic [3]. The PhAT is a series of sequential questions addressed in early drug development in an attempt to define the relationships between molecular target status, pharmacokinetics, pharmacodynamics, biomarker changes, and ultimately, clinical outcomes. With some modification, our development programme has adopted the PhAT as a means to improve the quality of decision-making at these early stages of the drug development (Table 1).

Adoption of the PhAT approach has multiple ramifications for various stages of drug development. At the preclinical stage, extensive experimental studies are required to define the critical benchmarks for assessing the audit trail points in clinical trials. These include animal PK studies to define the kinetic profile for a new drug. Animal kinetics may poorly predict findings in humans; however, these studies still provide valuable information about drug exposure and toxicity and efficacy relationships. Preclinical PK studies also provide the first opportunity to develop key analytical

Table 1
The pharmacological audit trail (PhAT) originally developed by Workman [3] and modified by the author

1. Is the targeted expressed or activated?
2. Adequate drug dose and schedule?
3. Active concentrations in plasma?
4. Active concentrations in tumour?
5. Active against the molecular target?
6. Modulation of the downstream pathway?
7. Biological effect achieved?
8. Clinical response or benefit?
9. Predictive biomarkers of activity?

assays for monitoring the drug of interest and any anticipated metabolites.

Preclinical *in vivo* efficacy models also provide the opportunity to conduct comprehensive PK and PD/MoA biomarker studies that relate systemic drug exposure to biomarker changes associated with anti-tumour activity [4]. The data generated from these studies are essential for developing preclinical PK–PD models to define critical performance criteria for each of the audit trail points evaluated in the clinical setting. In a comprehensive PK and PD biomarker study performed in animals bearing human xenografts, the drug concentrations in plasma and tumour tissues associated with antitumour activity can be estimated [5]. This provides a benchmark for target PK exposures in clinical studies. Mechanistic studies performed in these same *in vivo* systems can be used to develop and validate robust PD/MoA biomarkers for clinical use that inform about target interaction and downstream pathways. Ultimately, the degree of biomarker modulation can be related to tumour growth inhibition in animal studies in a quantitative manner using standard PK-PD modelling techniques. While the challenges of developing a comprehensive PK and PD/MoA biomarker model are not trivial, the ability to generate quantitative benchmarks is a tremendous asset for clinical testing.

Once a drug enters clinical testing, the careful evaluation of each point of the PhAT becomes a major priority. Extended pharmacokinetic monitoring is a hallmark of Phase I, first-in-human trials. This is the most common situation to obtain detailed pharmacokinetic data on a new agent. Collection of extensive PK sampling can be labour intensive and these are typically performed at selected institutions with prior Phase I experience. Analysis of the data collected during extensive PD monitoring can be used to calculate descriptive PK parameters that characterise a drug's kinetic behaviour and it can give an indication of the extent of intraindividual variability. Early analysis of covariates can give insight into the key clinical factors that underlie this variability.

The next stage of evaluation of the PhAT requires assessment of drug effects in tumour or surrogate tissues. Because biopsies of tumour tissues during treatment are challenging under most circumstance, drug related PD/MoA biomarker evaluation will often be implemented in more accessible tissues, such as skin or peripheral blood mononuclear cells. We have modified our current approach to Phase I trials performed in cancer patients to include a determination of the biologically active dose (BAD) for our agents in development whenever feasible. These new trial designs employ the use of PD/MoA biomarker-defined endpoints to define the BAD range for further clinical testing in Phase II studies. A detailed example will be provided in the presentation materials.

At the end of phase I the PK data set should allow for some understanding of the agents pharmacological behaviour. Modelling can provide information for the development of optimal and limited sampling strategies that can more readily be applied to larger scale clinical studies performed in Phase II and beyond. In Phase II trials, the primary endpoint remains antitumour activity. Within a specific drug development programme, the number of patients treated with the agent increases exponentially from this point forward. In addition, the pharmacodynamic readout in Phase II is much more focused on antitumour efficacy. Thus, it becomes more realistic to query the PhAT criteria that relate clinical activity to the treatment regimen. Pooling of data collected from all studies at this stage can be formally analysed using population PK methods such as non-linear mixed effect modelling or other methods. Finally, population PK-PD models developed at this time can be used to perform detailed clinical trial simulations that can greatly assist in the design and conduct of larger randomised trials.

Conclusions

Integrated PK and PD/MoA biomarker strategies can considerably enhance the early drug development process. However, the lack of investment in appropriate preclinical PK–PD studies and the ever-present concern about shortened timelines remain substantial obstacles. As a consequence, many programmes under utilise this approach, failing to use this information for critical decision-making. The PhAT concept developed by Workman [3] provides a scientific framework to address these issues in a scientifically rigorous manner and it deserves more widespread application in the oncology field.

Conflict of interest statement

Author is a full time employee of Ortho Biotech Oncology R&D, a member of the Johnson & Johnson family of companies and is a stock holder in Johnson & Johnson.

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