Unexplored Pharmacokinetic Opportunities with Microdosing in Oncology

Commentary on Boddy et al., p. 4164

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The publication of the U.S. Food and Drug Administration’s “Critical Path” document highlights the importance of translational research and the development of new concepts and tools that may help provide more confidence in the selection of drug candidates early in clinical development.\(^1\) One type of exploratory study, the so-called phase 0 trial, allows dosing to pharmacologic response and limited multiple dosing of investigational agents in patients with cancer. This strategy has the potential to reduce attrition in clinical drug development, although its value as a major retooling of the drug development process has been questioned by some (1). Phase 0 trials are currently being perceived and explored mainly as a platform to establish the feasibility of assays for target modulation in human samples as well as to evaluate biomarkers for effects of molecularly targeted agents (2).

Another type of exploratory investigation supported by both European and U.S. regulatory agencies is a microdose study, which involves the administration of a compound in humans given at a dose that is less than 1/100 of the (predicted) therapeutic dose, up to a maximum of 100 \(\mu\)g. The principal applications of this microdosing concept have been to assist in the selection process when multiple new chemical entities are available, to obtain preliminary pharmacokinetic information for investigational new drugs early in the development process, and to confirm in vitro or in silico metabolic pathways in humans (3, 4). Beyond being a potential tool in the selection of drug candidates, microdosing has been widely used to obtain phenotypic information on enzyme or transporter activity, for drug candidates, microdosing has been widely used to obtain pharmacokinetic information on enzyme or transporter activity, for drug candidates.

In the present issue of the Clinical Cancer Research, Boddy et al. (6) describe an example of the use of microdosing to study the pharmacokinetics and metabolism of imatinib in patients on long-term therapy for chronic myelogenous leukemia. This is possibly the first human study involving an anticancer drug that investigates the pharmacokinetic profile of an individual dose under steady-state conditions. The successful application of an ultrasensitive analytic method, based on accelerator mass spectrometry used in conjunction with tracer amounts of carbon-14–labeled imatinib (\([^{14}C]\)imatinib), in this context, opens up possibilities to further mechanistically understand the contribution of interindividual pharmacokinetic variability and time-dependent kinetics to treatment outcome (7). Furthermore, this work not only has direct relevance to imatinib but is also of importance as an example of how accelerator mass spectrometry analyses and microdosing can be implemented in studies to further understand basic pharmacokinetic data on other Food and Drug Administration– approved drugs that are to be administered continuously.

One limitation of the use of microdosing commonly raised by skeptics is the potential for poor predictability of pharmacokinetic information obtained with a microdose versus a therapeutic dose due to the occurrence of nonlinear absorption or disposition. Although no exhaustive data are currently available, however, it has been suggested recently that for the majority of prescription drugs an acceptable degree of concordance can be anticipated (8). Indeed, a direct comparison of plasma concentrations determined by accelerator mass spectrometry for a microdose of \([^{14}C]\)imatinib with those derived from liquid chromatography-mass spectrometry for a simultaneously administered conventional dose of unlabeled imatinib provided roughly similar estimates for the average area under the curve (6).

Previous in vitro studies have shown that cytochrome P450 3A4 is the major enzyme involved in the biotransformation of imatinib and that the apparent oral clearance of imatinib following a single dose is sensitive to concurrent administration of typical inhibitors of this enzyme (9). The potential of imatinib to pharmacokinetically interact with other drugs through this mechanism and the degree to which this occurs at steady state, however, is currently unknown. Because imatinib itself is a potent inhibitor of cytochrome P450 3A4 (10), we have argued previously that it is theoretically plausible that, at steady state, imatinib may inhibit its own primary oxidation pathway, that metabolism is shunted to alternative routes, and that overall elimination may be essentially insensitive to further chemical inhibition of cytochrome P450 3A4 (11). The demonstration by Boddy et al. (6) that accelerator mass spectrometry can be applied to investigate the pharmacokinetics of a single dose of

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### References

imatinib in the context of chronic therapy now provides a unique opportunity to revisit and reevaluate the drug interaction potential of imatinib at steady state. Similar approaches can also be applied using a radiolabeled intravenous tracer dose of imatinib administered simultaneously with a nonlabeled oral dose (12) to determine absolute bioavailability in individual patients and discriminate between absorption and elimination as a potential cause for the occurrence of pharmacokinetic resistance to imatinib treatment.

Another currently unexplored opportunity is the utility of microdosing to evaluate the contribution of germ-line variants in genes with a confirmed or suspected role in the pharmacokinetics of oncology drugs. Identification of genetic and environmental factors associated with interindividual variability in the absorption and disposition of such drugs is vital to predicting or eventually adapting appropriate, individualized doses. Traditionally, pharmacogenetic studies in oncology, however, have been mostly retrospective, uncontrolled, expensive, contradictory, and underpowered because of the limited number of patients evaluated that carry the variant genotypes of interest (13). This is an unsustainable situation in need of an appropriate and cost-effective solution. The low (radioactive) systemic exposure to anticancer drugs associated with a single microdose enables new trial designs for preliminary, exploratory pharmacogenetic studies using matched groups of healthy volunteers with a predefined genotype of the desired signature. The implementation of such proof-of-principle approaches may not only unequivocally establish genotype-phenotype associations, or the lack thereof, in a statistically sound and unbiased fashion but the information could also be obtained faster and could save a lot of resources.

Because lack of efficacy and/or inadequate safety of investigational agents are currently the primary reasons for attrition (14), with poor pharmacokinetic properties representing only less than 10% of total attrition, microdose studies may have a limited effect on the overall efficiency of new drug development (15). Microdosing, however, should become an integrated approach to human studies aimed at understanding basic pharmacokinetic properties of (approved) oncology drugs that require continuous dosing. It is anticipated that in the near future microdosing will make a significant contribution in determining the relative role of genetic variation and environmental factors in the absorption and disposition of a wide variety of agents. It is hoped that the results presented by Boddy et al. (6) and the recent application of positron emission tomography in a pharmacokinetic study with [11C]imatinib (16) will encourage investigators to do similar trials to further explore microdosing as a potential tool to gain insight into the mechanisms underlying interindividual pharmacokinetic variability of imatinib and other anticancer drugs.

References
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