Individualizing Dosing of Irinotecan

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Individualized drug dosing is a longstanding goal of clinical pharmacologists. Given the narrow therapeutic index of most anticancer agents, it is plausible that this approach would be of particular value in oncology. Irinotecan is an interesting agent for individualized dosing, given its complex metabolism and increasing knowledge of its pharmacokinetics predictors.

In this issue of *Clinical Cancer Research*, van der Bol and colleagues (1) report the results of a small randomized trial investigating the use of a pharmacokinetic model based on midazolam phenotyping (also including height and γ-glutamyltransferase) to individualize irinotecan therapy. The report confirms the group’s prior study of this approach in that there was a significant correlation between predicted and observed irinotecan clearance. However, the authors’ prespecified hypothesis, a 50% decrease in interindividual variability (IVV) through this approach, was not shown, as the reduction in IVV was only 19%. It is somewhat surprising that this study has shown a benefit of CYP3A4 phenotyping for irinotecan, given that only 12% of irinotecan was converted to CYP3A4-mediated inactive metabolites in a small mass balance study (2).

Of particular interest in this study was the ability to safely administer doses of more than 1,000 mg to two patients whose predicted irinotecan clearance was high. In addition, the use of the model-based dosing was associated with a lower rate of grade 3 to 4 neutropenia, despite similar doses between the two groups. (However, no data are presented on the relationship of irinotecan or SN-38 exposure to neutropenia, which could provide support for the authors’ hypothesis relating midazolam phenotyping to IVV in pharmacokinetics and neutropenia.) What is unclear is why the predicted irinotecan clearance was so high in several of the patients, in the range of that observed in patients on dexamethasone and enzyme-inducing anticonvulsants (3). This result suggests that these patients, unbeknownst to the investigators, were on concomitant agents that are inducers of CYP3A4 (and thus had a much greater proportion of plasma clearance mediated by CYP3A4), because patients on known inducers were excluded from the study.

This finding is not surprising, given the large number of herbal supplements and commonly administered agents that can induce CYP3A4 via activation of pregnane x receptor (PXR) and/or constitutive androstane receptor (CAR). We have not observed similar patients with very high irinotecan clearance, suggesting that this may be a phenomenon unique to Rotterdam, or potentially the Netherlands. Speculating further, this may represent use of a local herbal supplement, or alternatively prescription of methadone (a recently identified inducer) for chronic pain.

Individualized dosing, also known as adaptive control (with or without feedback), has been under investigation for decades (4). In order to truly optimize dosing of irinotecan, one needs to know the relationship of plasma concentrations of irinotecan and its active metabolite, SN-38, to toxicity and efficacy (Fig. 1). To further complicate the situation, the pharmacodynamics of myelosuppression are distinct from the pharmacodynamics of diarrhea, as the former has been associated with plasma SN-38 exposure (5), whereas the latter has been suggested to be associated with SN-38 exposure within the intestinal lumen (6). In contrast, little is known about the relationship of plasma concentrations of irinotecan or SN-38 to efficacy, although there is some evidence that the intratumoral formation of SN-38 may be the most important determinant of efficacy (7), consistent with the concept of irinotecan as a selective camptothecin prodrug.

If the optimal irinotecan and SN-38 exposure were known, dosing could be individualized accordingly. Alternatively, an attempt can simply be made to administer the maximal dose that does not result in dose-limiting toxicity, an approach that was used previously for aminoflur (6). In either context, the initial dose can be determined on the basis of patient covariates, genotyping, and/or phenotyping with a probe drug. The standard approach to irinotecan dosing is to use estimated body surface area, a composite of height and weight, even though there is no evidence to support this approach (8). UGT1A1 genotyping can identify patients at increased risk for myelosuppression owing to increased SN-38 exposure, and UGT1A1 genotyping-driven approaches of dose escalation have already proven to be successful in safely delivering higher doses of irinotecan in FOLFIRI (9). There is also evolving evidence on the importance of polymorphisms in SLCO1B1, a major hepatic uptake transporter (10). We can now add midazolam phenotyping to the list of tools to individualize the initial dose of irinotecan.
Subsequent doses can be based on observed toxicity, repeat phenotyping, measured plasma concentrations, or pharmacodynamic biomarkers. The standard approach in oncology is to reduce doses subsequent to dose-limiting toxicity, although dose escalations for minimal toxicity have only rarely been used. Adaptive control with feedback, as used for etoposide (11), could also be considered to guide dosing. Although measurement of pharmacodynamic biomarkers has not been used for irinotecan, this approach has been proposed for other agents (e.g., ambulatory blood pressure for sorafenib).

However, in an era of cost sensitivity, we should focus our efforts on approaches that are likely to have the greatest impact. As genotyping costs are rapidly decreasing, it is likely that a genomic prescribing system will be routinely incorporated in the foreseeable future, at readily affordable lifetime costs (12). We will then need to ask whether expensive phenotyping approaches, requiring real-time measurement of drugs and metabolites, are a good use of limited health care resources.

Disclosure of Potential Conflicts of Interest

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References
