Pharmacokinetically Guided Dosing of Oral Drugs: True Precision Oncology?

Moshe C. Ornstein and Brian I. Rini

Higher plasma concentrations of tyrosine kinase inhibitors (TKI), such as pazopanib, are associated with improved clinical outcomes. However, TKI pharmacokinetics exhibit significant interpatient variability, resulting in inconsistent and unpredictable plasma drug levels. An individualized dosing approach based on patient pharmacokinetics data and toxicity can potentially optimize plasma concentrations of pazopanib. Clin Cancer Res; 22(23): 1–3. ©2016 AACR.

See related article by Verheijen et al., p. 5738

In this issue of Clinical Cancer Research, Verheijen and colleagues report the results of a prospective clinical study of 30 patients treated with pazopanib on a pharmacokinetically driven dosing schema in which patients were dose titrated based on plasma trough levels (C_min) of pazopanib and toxicity (1). Several interesting findings emerged, including the wide range of final doses, variable toxicity, and the potential for improved clinical outcomes. Most importantly, this study incorporates a design that should be employed at the earliest stages of drug development.

Tyrosine kinase inhibitors (TKI) are a heterogeneous class of oral small molecules that bind to the catalytic domain of a variety of oncogenic tyrosine kinases, thereby suppressing cellular proliferation and growth. Although they have demonstrated safety and efficacy in multiple cancers, a primary challenge in the delivery of these oral small molecules is the interpatient variability in plasma drug concentration (2, 3). This is especially relevant as TKIs generally exhibit linear pharmacokinetics with higher doses resulting in increased plasma concentrations, which have been associated with improved clinical outcomes (4, 5).

Pazopanib is a VEGFR TKI approved for treatment of metastatic renal cell carcinoma (mRCC) and soft tissue sarcoma (STS; refs. 6, 7). In the accompanying article, Verheijen and colleagues investigated the administration of pazopanib using an individualized dosing schema based on plasma trough levels (C_min, ref. 1). Thirty patients with previously treated solid tumors (15 tumor types; 7 patients with STS) were treated with pazopanib initiated at the standard starting dose of 800 mg daily. C_min levels were collected weekly for the first 8 weeks and subsequently every 4 weeks. On the basis of prior retrospective pharmacokinetic analyses, the target C_min was ≥20 mg/L, and patients who had C_min <20 mg/L and no grade 3 or above toxicities at weeks 3, 5, and 7 underwent dose escalation.

Of the 30 patients enrolled in the study, 17 patients had at least one C_min <20 mg/L and 13 patients had C_min ≥20 mg/L at week 3, 5, or 7. Seven of the 17 patients with a subtherapeutic C_min were ineligible for dose titration due to toxicity. The 10 patients who underwent dose escalation experienced a significant increase in their C_min [mean (CV%)] from 13.2 mg/L (38%) to 22.9 mg/L (44.9%). Of the 13 patients who had a C_min ≥20 mg/L, 9 patients (69%) had at least one grade 3 toxicity and required dose reduction. The median C_min in these patients was 51.3 mg/L (45.1%) and, with dose reduction, remained in the prespecified therapeutic range at 28.2 mg/L (25%).

The authors should be applauded for the thoughtful and nuanced design in which they combined the use of pharmacokinetics and drug-related toxicities to modify pazopanib dosing. However, the strength and impact of this trial rest less with the actual conclusions (i.e., that dose titration leads to higher C_min levels and less plasma concentration variability) and more with the study design and concept. The current design of early-phase trials focuses on finding a single dose that can be applied to a large group of patients. However, using a model similar to that of Verheijen and colleagues, early-phase clinical trials should result in a titration schema for each individual patient and not just one dose to be applied across all patients (Fig. 1). The current dosing of pazopanib based on STS and mRCC clinical trials is 800 mg daily, with dose reductions to 600 and 400 mg for toxicities (6, 7). However, in the current study, the dose range was 400 to 1,800 mg. Patients with low drug exposure and limited toxicities received doses ranging from 1,000 to 1,800 mg daily, with a mean dose of 1,378 mg per day. Using current dosing standards, thus, results in a drastically underdosed subset of patients who, from a toxicity perspective, could tolerate doses up to more than twice those currently recommended. Focusing on an individualized, patient-tolerated maximum dose, as described in this study, would likely result in higher plasma concentrations. However, it is important to note that despite higher drug levels in this study, the impact on clinical outcome remains uncertain and needs to be evaluated in larger, histology-specific clinical trials.

This study also highlights many of the challenges in TKI dosing. It is well established that oral TKIs generally follow linear pharmacokinetics with relationships among dosing, plasma concentrations, toxicities, and outcomes. These relationships, although often true for a population, are not always accurate in individual patients. This study highlights one such example. Within the subgroups of patients with C_min ≥20 mg/L or C_min <20 mg/L,
there is a trend toward increased toxicity with higher $C_{\text{min}}$. However, when the groups are compared side by side ($C_{\text{min}} \geq 20$ vs. $<20$ mg/L), the same conclusion does not hold true. Furthermore, not all clinical efficacy variability is due to pharmacokinetics variability (i.e., a subset of patients will not experience benefit even at the highest tolerable drug levels). These data support the hypothesis that although pharmacokinetics influences toxicity and efficacy, it is only one of many possible components of drug dose optimization. Other components (toxicity as a marker of efficacy, not just as a limiting factor for titration, blood- or tissue-based biomarkers, imaging, etc.) may be important in certain clinical contexts.

Despite the impressive design, the study is not without limitations, including multiple disease types and small sample size/subsets. The authors measured $C_{\text{min}}$ weekly for 8 weeks and then every 4 weeks thereafter, with dose titration only at weeks 3, 5, and 7. It is conceivable that there would be an additional benefit to either titrating weekly based on pharmacokinetics results and/or titrating throughout the duration of therapy, given the study's findings that patients who were not titrated (group 2a) showed a decline in plasma concentrations over time. Indeed, a recent retrospective analysis demonstrated that 78% of patients with mRCC who undergo TKI dose titration at RECIST-defined progression have a reduction in tumor burden (8), suggesting that TKI drug levels may decline over time and there may thus be a benefit to pharmacokinetic monitoring for the duration of therapy. Furthermore, when considering dose titration based on toxicities, it is important to remember that not all adverse events (AE) are of equal relevance. For example, in this study the most common grade 3 AE was hypertension (37%), and it accounted for 50% of the toxicity that limited further titration. However, hypertension should not necessarily be dose limiting, given variability in the definition of grade 3 hypertension and the generally asymptomatic and manageable nature. Similarly, liver function test abnormalities accounted for 25% of the limiting grade 3 toxicities but, as noted by the authors, may not be related to pharmacokinetics, and, thus, further titration may be possible after dose interruption. On that note, an alternative strategy to mitigate toxicity but maintain daily dose intensity is dose interruptions, although this has not been studied prospectively. A study design that reserves dose-limiting AEs to those insufficiently resolved with medications and of importance to patients (e.g., fatigue, diarrhea, hand–foot syndrome, etc.) could further optimize individual dosing.

In summary, more nuanced and patient-specific clinical trials are needed to optimize dosing of TKIs. Pharmacokinetically guided individualized dosing methods, such as those described by Verheijen and colleagues (1), provide a promising prospective model for future clinical trial designs that could potentially lead to improved clinical outcomes.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: M.C. Ornstein, B.I. Rini
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): B.I. Rini
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): B.I. Rini
Writing, review, and/or revision of the manuscript: M.C. Ornstein, B.I. Rini
Study supervision: B.I. Rini

Received August 12, 2016; accepted August 27, 2016; published OnlineFirst September 23, 2016.
References


Clinical Cancer Research

Pharmacokinetically Guided Dosing of Oral Drugs: True Precision Oncology?

Moshe C. Ornstein and Brian I. Rini

Clin Cancer Res  Published OnlineFirst September 23, 2016.

Updated version

Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-16-1833

E-mail alerts

Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions

To request permission to re-use all or part of this article, use this link http://clincancerres.aacrjournals.org/content/early/2016/11/17/1078-0432.CCR-16-1833. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.