Published in final edited form as:

Clin Pharmacol Ther. 2009 February ; 85(2): 208–211. doi:10.1038/clpt.2008.242.

Pharmacokinetic Considerations for New Targeted Therapies

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Abstract

Targeted therapies are increasingly being incorporated into standard treatment regimens for cancer. Tyrosine kinase inhibitors represent one class of targeted agents, with eight drugs receiving approval for the treatment of cancer in recent years. Although they hold the promise of being more effective and less toxic to normal cells than conventional cytotoxic chemotherapy, tyrosine kinase inhibitors are associated with different adverse effects, sometimes severe, as well as wide pharmacokinetic variability. Thus, a “therapeutic window” may exist for these agents.

Clinical Pharmacology of Tyrosine Kinase Inhibitors

The majority of tyrosine kinase inhibitors approved for the treatment of cancer have selective activity in certain populations such as imatinib, dasatinib, and nilotinib in patients with Philadelphia chromosome-positive (Ph⁺) chronic myelogenous leukemia (CML) with the Bcr-Abl oncogene,^{1, 2} sunitinib in patients with gastrointestinal stromal tumors and activating mutations in the tyrosine kinase c-Kit,^{3, 4} and the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors gefitinib and erlotinib in patients with non-small cell lung cancer (NSCLC) harboring EGFR mutations.⁵ However not all patients in these selected populations respond and emerging drug resistance becomes a clinical problem. Although life-threatening myelosuppression is less frequent with many of the approved kinase inhibitors, they are associated with other adverse effects such as fatigue, nausea, diarrhea, rash and hand-foot syndrome, mucositis, as well as newly recognized ones such as cardiotoxicity and hypothyroidism.⁶⁻¹⁰ Since these drugs are administered daily and for some diseases are given for years until disease progression, toxicities can greatly affect patient quality of life and may lead to treatment cessation and relapse.

Tyrosine kinase inhibitors registered for the treatment of cancer are administered orally and generally exhibit similar pharmacokinetic characteristics to each other. They are highly bound in human plasma (>90%), they undergo extensive metabolism by cytochrome P-450 3A (CYP3A), and are substrates for and/or inhibitors of transporters in the intestinal epithelial cells and hepatocytes. Variation in drug metabolizing enzymes and transporters contribute to systemic pharmacokinetic variability, but they are also localized in cancer cells and can contribute to intracellular pharmacokinetic variability and drug action. Figure 1 illustrates the concept of how variable expression of solute carriers (involved in drug uptake), ABC transporters (involved in drug efflux), and drug-metabolizing enzymes can affect systemic and intratumoral exposure to orally administered drugs. Similar to most drugs that undergo extensive metabolism, tyrosine kinase inhibitors exhibit wide pharmacokinetic variability. For example, steady-state trough concentrations of gefitinib varied 20-fold in 14 adult cancer

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Conflict of Interest: The authors declared no conflict of interest.

patients receiving 250 mg once daily.¹¹ The extent of pharmacokinetic variability is often not fully appreciated until the drug is evaluated in a larger population of patients. To that end, the clearance of imatinib was shown to vary 60-fold in 82 adult patients with gastrointestinal stromal tumors.¹²

Like targeted therapies used for the treatment of other human disease, the wide pharmacokinetic variability observed for orally administered tyrosine kinase inhibitors is likely to affect clinical outcomes, both toxicity and efficacy. This has been demonstrated for imatinib, the first tyrosine kinase inhibitor registered for the treatment of CML. Two independent studies in patients with CML have shown that imatinib trough total plasma concentrations were higher (mean, approximately 1000 ng/mL [~ 2 μ M]) in patients achieving a complete cytogenetic response (CCyR) and major molecular response (MMR) than those who did not (mean, approximately 800 ng/mL).^{13, 14} In the IRIS phase III trial,¹³ patients with higher imatinib exposure had better rates of CCyR ($p = 0.005$), MMR ($p = 0.008$) and event-free survival ($p = 0.16$). Regarding exposure-toxicity relationships, associations have been observed between elevated imatinib trough concentrations (> 1500 ng/mL) and severe side effects, with improvement in toxicities following dose reductions to achieve concentrations of 1000 ng/mL.^{13, 15} Combined, these studies suggest that therapeutic drug monitoring to obtain effective imatinib concentrations may provide clinical benefit to patients with CML.

Data are emerging showing associations between exposure and treatment-related outcomes for gefitinib and erlotinib. In a population pharmacokinetic analysis of erlotinib involving 339 patients with NSCLC enrolled to the BR.21 phase III trial, a correlation was observed between steady-state area under the concentration-time curve and maximal plasma concentrations values and the toxicity skin rash ($p < 0.05$) but not diarrhea.¹⁶ Although the data suggest an association between higher exposure and higher grade of toxicity, there was significant overlap in the range of values for each pharmacokinetic parameter within each toxicity grade group between the patients who had no toxicity versus those that did. In a population pharmacokinetic analysis of gefitinib involving 27 patients with advanced cancer, steady-state trough concentrations were associated with the probability of experiencing the side effect diarrhea ($p < 0.05$), but not skin rash.¹¹ In this analysis, unbound gefitinib concentrations > 0.05 μ M were associated with a probability > 0.8 to experience diarrhea. Based on *in vitro* data,¹⁷ the IC_{50} for inhibiting cellular proliferation in cells with mutant EGFR is 0.015 μ M and in cells with wild-type EGFR, 0.1 μ M. Theoretically, adjusting gefitinib doses to achieve unbound plasma concentrations capable of inhibiting wild-type EGFR *in vitro* would also increase the probability of experiencing diarrhea. Although these studies are preliminary, they highlight the need for continued pharmacokinetic investigations to determine if a therapeutic range exists for this class of agents.

Implications for Drug Development and Clinical Translation

The biggest challenge for developing targeted therapies involves finding which sub-populations of patients will respond to drug treatment, such has been done with imatinib in patients with Ph^+ CML and the Bcr-Abl gene. After selection of the appropriate drug for a patient, consideration needs to be given towards selecting the right dose for the individual to achieve effective concentrations and avoid treatment failure, but also to avoid high concentrations associated with excessive toxicity, which alone faces many challenges.

To begin this process, before a drug enters clinical trials, preclinical *in vitro* and *in vivo* pharmacokinetic data can be used to guide dose escalation and ensure that effective concentrations are being achieved clinically. For example, concentrations that produce desired biological and antitumor effects in cell-based models can be used to establish a starting target exposure in animal and human studies. If a drug is highly bound in human plasma,

concentrations should be corrected for protein binding *in vitro* (e.g., cell culture media) and *in vivo* (e.g., human plasma) for comparison of equivalent unbound concentrations. Using microequilibrium dialysis as described previously,^{18, 19} the binding of seven tyrosine kinase inhibitors at varying concentrations was assessed in human donor plasma and cell culture media. Binding was independent of drug concentration and values are shown as an average of all concentrations in Table 1. The data show differences in unbound fraction (fu) in human plasma and cell culture media among the different kinase inhibitors. A correction factor was calculated (see footnotes to Table 1), which can be used to relate IC₅₀ values in cell culture medium to plasma steady-state exposures in humans. For example, the binding of sorafenib in human plasma and cell culture medium (fu, 0.59% and 1.2%, respectively) was substantially more than that for sunitinib (fu, 38% and 8.5%, respectively), and differences in binding between cell culture and plasma were less for sorafenib. After correction for binding differences, a sorafenib concentration of 7.4 μM *in vitro* would be comparable to a steady-state plasma concentration of 15 μM in humans (2-fold less). However, for a drug like sunitinib where binding differences are greater between culture medium and plasma, an *in vitro* concentration of 0.022 μM would be comparable to a steady-state plasma concentration of 0.10 μM (4.5-fold less). For planning preclinical *in vivo* studies, binding in mouse plasma can be determined and similar comparisons to exposure *in vitro* and in humans can be made.

Identifying drug exposure that produces optimal target inhibition does not necessarily translate into optimal tumor response, and thus drug exposure-efficacy relationships should ultimately be determined and confirmed in clinical trials. Through this process, a therapeutic window can be identified. For drugs like imatinib that exhibit high response rates in Ph⁺ CML, this can be done with a relatively small number of patients. However, for drugs like gefitinib with response rates of approximately 10% in Caucasian populations, pharmacokinetic studies would be required in large populations to derive a therapeutic window. Ideally, these studies should be incorporated in pivotal registration trials to minimize costs and use of patient resources.

Once a therapeutic range has been identified, strategies for dosage adjustment to achieve a target concentration is then required. The concept of therapeutic drug monitoring has been described above for imatinib. Other strategies include the use of phenotyping and genotyping strategies to *a priori* select an optimal dose based on an individual's activity of liver drug metabolizing enzymes and/or transporters. One study administered oral midazolam as a phenotypic probe for intestinal and liver CYP3A to 27 patients with advanced cancer receiving gefitinib. Population pharmacokinetic modeling indicated that CYP3A activity was significantly associated with gefitinib clearance ($R^2 \geq 0.6$) and accounted for approximately 50% of pharmacokinetic variability.¹¹ Further calculations using the population model pharmacokinetic parameter estimates were performed to demonstrate that patients with high midazolam clearance (e.g., ≥ 100 L/h) would require higher gefitinib doses (e.g., 500 mg or 750 mg) to inhibit wild-type EGFR *in vitro*. A study in a separate population of 124 patients with NSCLC receiving gefitinib 250 mg demonstrated that patients carrying one allele of a common reduced function variant of the efflux transporter ABCG2 (BCRP) at codon 141 (Q141K), was associated with the occurrence of diarrhea (grade ≥ 0).²⁰ The incidence of diarrhea was also associated with better survival in this same patient population expanded to 175 patients (hazard ratio, 2.1 [p = 0.0058] for grade 0 diarrhea), indicating that some degree of toxicity may be necessary for optimal long-term outcome in NSCLC following treatment with gefitinib.²¹ Combined, these studies suggest that patients with high CYP3A phenotypic activity and/or patients lacking a variant allele at ABCG2 codon 421 may benefit from a higher dose of gefitinib.

Conclusions

Substantial progress has been made in recent years toward an understanding of the clinical pharmacology of molecularly targeted drugs, in particular for the tyrosine kinase inhibitors. Although these drugs offer a number of important advantages over conventional cytotoxic chemotherapeutic agents, it is increasingly recognized that they are affected by some of the same problems, including an extensive interindividual pharmacokinetic variability. Further understanding of the underlying causes for this variability and exploration of the associations of measures of systemic exposure with toxicity and efficacy will likely have significant impact on future attempts to optimize the treatment of cancer with these agents. Regardless of the approach used for dosage adjustment, the clinical utility of dose individualization to achieve optimal drug exposure will ultimately be based on improving patient outcomes through prospective evaluation.

Acknowledgements

We thank Shelley Orwick (St. Jude Children's Research Hospital, Memphis, TN) for generating the *in vitro* protein binding data. This work was supported by the United States Public Health Service Cancer Center Support Grant 3P30CA021765 and the American Lebanese Syrian Associated Charities (ALSAC).

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Figure 1. Scheme for the involvement of solute carriers (SLC), ATP-binding cassette transporters (ABC), and drug-metabolizing enzymes (CYP) in the absorption and disposition of orally administered tyrosine kinase inhibitors. RTK, receptor tyrosine kinase.

Table 1
Binding of tyrosine kinase inhibitors in human plasma and cell culture media.

	Sorafenib	Midostaurin ^j	Erlotinib	Dasatinib	Gefitinib	Sunitinib	Imatinib
C _{ss,ave,total} (μM) ^a	15	1.0	4.0	0.10	1.0	0.10	3.0
C _{in vitro,total} (μM)	15	1.0	4.0	0.10	1.0	0.10	3.0
f _{u,plasma} (%) ^{b,c}	0.59 ± 0.072	0.62 ± 0.039	2.9 ± 0.85	4.1 ± 0.21	5.5 ± 0.48	8.5 ± 0.59	8.0 ± 0.41
f _{u,in vitro} (%) ^{d,e}	1.2 ± 0.18	2.9 ± 0.41	21 ± 7.4	29 ± 5.2	30 ± 4.3	38 ± 4.7	38 ± 6.0
C _{ss,ave,unbound} (μM) ^f	0.089	0.0062	0.12	0.0041	0.055	0.0085	0.24
C _{in vitro,unbound} (μM) ^g	0.18	0.029	0.84	0.029	0.30	0.038	1.1
CR ^h	0.49	0.21	0.14	0.14	0.18	0.22	0.22
Clinically relevant C _{in vitro,total} (μM) ⁱ	7.4	0.21	0.53	0.014	0.16	0.022	0.66

Abbreviations: fu, unbound fraction; C_{ss,ave}, average steady-state concentration; CR, correction factor.

^aMean C_{ss,ave} at the registered dose. 11, 16, 22-26

^bData are the mean ± standard deviation values from 8-32 measurements and 1-3 independent experiments.

^cBinding was evaluated in human donor plasma at the following concentrations (4 replicates per concentration): sorafenib (1.0 and 10.0 μM), midostaurin (2.0 and 10.0 μM), erlotinib (2.5 μM), dasatinib (0.1 μM), gefitinib (1.0 μM), sunitinib (0.1 μM), and imatinib (1.0 μM).

^dCell culture media consisted of RPMI + 10% fetal bovine serum.

^eBinding was evaluated in cell culture media at the following concentrations (4 replicates per concentration): sorafenib (0.01, 0.1, 1.0 and 10.0 μM), midostaurin (2.0 and 10.0 μM), erlotinib (2.5 and 10.0 μM), dasatinib (0.1, 1.0, and 10.0 μM), gefitinib (1.0 and 10.0 μM), sunitinib (0.01, 0.1, 1.0, and 10.0 μM), and imatinib (0.1, 1.0, and 10.0 1.0 μM).

^fCalculated as: C_{ss,ave,total} * f_{u,plasma}

^gCalculated as: C_{in vitro,total} * f_{u,in vitro}

^hCorrection factor was calculated as: 1 / [(C_{in vitro,total} * f_{u,in vitro}) / (C_{ss,ave,total} * f_{u,plasma})]

ⁱCalculated as C_{ss,ave,total} * CR

^jMidostaurin (PKC412) is not a registered drug but is in phase III evaluation for the treatment of acute myelogenous leukemia.