due to drug-drug interactions. However, PK testing revealed an adequate plasma imatinib concentration of 1342 ng/mL. These patients illustrate that monitoring plasma imatinib concentrations is useful for guiding therapeutic decisions when excessive or inadequate drug concentrations are suspected clinically. Even if the results do not lead to dose adjustment, they provide important reassurance for patients and physicians. Once testing is more widely available, drug monitoring may become an integral part of clinical management of patients on imatinib.

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Contribution: C.B. helped with patient care, data retrieval, and drafting the manuscript; M.J.E. developed the imatinib assay, reviewed all imatinib patient data, and helped with writing; T.F.L. analyzed the patient plasma samples; B.J.D. contributed to patient care, study design, and writing; and M.W.D. helped with data collection and study design and wrote the manuscript.

Response:

Use of therapeutic drug monitoring in CML patients on imatinib

Pharmacokinetic monitoring is widely used in different medical specialties, such as neurology, cardiology, and psychiatry, but it has rarely been applied in clinical oncology practice. However, monitoring of imatinib would probably be most beneficial to physicians managing patients with Philadelphia chromosome-positive (Ph+)-chronic myelogenous leukemia (CML). 1,2 We have recently demonstrated that trough imatinib plasma levels are associated with both cytogenetic and molecular response to standard-dose imatinib in CML, with a plasma imatinib threshold of 1002 ng/mL in vivo. 3 Our results suggest monitoring imatinib plasma levels to adjust treatment strategies in CML patients, and, as reported by Blasdel et al, imatinib plasma concentration determination helped us in specific clinical situations.

The first case regards a 50-year-old woman with de novo chronic-phase CML with a high-risk Sokal score. After 3 months with imatinib treatment (400 mg/day), a complete hematologic response (CHR) was not achieved. The lack of CHR was confirmed at 6 months and the patient was considered in failure. No mutation in kinase domain was found. However it was decided to check the trough plasma concentration of imatinib, which was lower than 10 ng/mL at 3, 6, and 9 months despite the imatinib dose escalation to 600 mg between 3 and 6 months and to 800 mg between 6 and 9 months. The patient declared having taken the drug, but after careful questioning she acknowledged that she forced herself to vomit after intake. This case illustrates that the problem of adherence (compliance) for chronic treatment with oral-route drugs remains important, even for cancer therapeutics.

The second case regards a 56-year-old woman who was treated for CML with interferon alpha and hydroxyurea over a period of 10 years. Imatinib treatment (400 mg/mL) was started in 2001 because of an intolerance to interferon and a lack of cytogenetic response. Dose escalations of imatinib to 600 mg were initiated in 2002 in the absence of cytogenetic response. In 2004, an unusual severe side effect (cryptogenic pneumonia) associated with a high plasma imatinib concentration (3819 ng/mL) led to imatinib discontinuation. The patient was treated successfully with corticosteroids for the cryptogenic pneumonia, and 2 months later her CML was treated with only hydroxyurea.

Imatinib is the first-line therapy for CML in chronic phase and according to the last published results of the IRIS study (International Randomized Study of IFN and STI571), 89% of such patients randomized to imatinib are still alive after 5 years of follow-up. 4 Achieving maximum benefit with imatinib therapy may require optimal dosing as well as adherence to therapy. Pharmacokinetic factors such as individual patient variation in drug absorption and metabolism, interactions between prescribed medications, or other patient-related factors can also affect drug exposure. Monitoring of imatinib is useful for physicians managing patients with Ph+ CML, particularly in the case of poor response or adverse drug reaction. Imatinib monitoring will benefit greatly from the determination of a therapeutic range that we are actively investigating in our laboratory.

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