was interrupted for hydrocephalus and hearing loss in 1 patient each, although toxicities were not directly attributed to the agent. In their letter, Chamberlain and Glantz comment on the neurologic syndromes we reported and question attribution to liposomal cytarabine. Our attributions were based on 15-year experience in nearly 500 adults with acute lymphoblastic leukemia without central nervous system (CNS) disease, treated with hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) and standard CNS prophylaxis (methotrexate 12 mg day 1; cytarabine 100 mg day 7 for 3-8 cycles). In this setting, seizures are extremely uncommon (3 of 482 patients [0.006%]). The long half-life of liposomal cytarabine made attribution plausible in patient 1, given absence of discernable metabolic or other etiology. We have not observed hydrocephalus with standard CNS prophylaxis. Obesity and corticosteroids contribute to pseudotumor cerebri. Patient 2 was not obese, and dexamethasone dosing was only slightly increased. Investigators in our Department of Neuro-Oncology have also attributed anecdotal hydrocephalus cases to liposomal cytarabine (Morris D. Groves, M. D. Anderson Cancer Center, written personal communication, March 22, 2007). These data, taken in aggregate with the case in the lymphoma trial, raise the question whether association of hydrocephalus with liposomal cytarabine has been unrecognized or underreported.

Findings for patient 3 are better described as partial cauda equina syndrome or sacral radiculopathy. Although Chamberlain and Glantz suggest any chemotherapy given via lumbar puncture (LP) could cause such neurologic sequelae, we have not observed this after standard CNS prophylaxis given almost exclusively via LP. Decreased perineal sensation and lower-extremity paresthesias in patient 4 were also consistent with sacral radiculopathy. Standard intrathecal chemotherapy was delayed until 4 months later. The morbidity of urinary and/or fecal incontinence associated with these syndromes in 2 of 31 patients was considered unacceptable. Encephalopathy is more appropriate terminology for patient 5; encephalitis implies an inflammatory process. Encephalopathy related to high-dose systemic methotrexate-cytarabine usually manifests during administration or immediately thereafter, not on day 15, in this case approximately 36 hours after liposomal cytarabine. An exhaustive evaluation was unable to discern any other etiology for the neurotoxicity, which led to the patient’s demise. To what degree each agent contributed is an unanswerable question but does not preclude an association.

The character, constellation, and severity of neurotoxicity was concerning in potentially curable patients. We felt it prudent to alert other investigators of the need for monitoring and reporting of neurotoxicity if this agent was used in a similar manner. The absence of similar neurotoxicity in the 56 patients treated with standard CNS prophylaxis since terminating the liposomal cytarabine trial further supports our conclusions.

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Research grant support and drug were provided by Enzon Pharmaceuticals and Syke Pharma.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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References

To the editor:

Therapeutic drug monitoring in CML patients on imatinib

Imatinib dosing in patients with chronic myeloid leukemia (CML) is flat, as pharmacokinetic (PK) studies showed that plasma trough concentrations are correlated with dose, whereas body weight or body surface area are of minor importance.1,2 However, there is considerable interindividual variability. In a recent study, Picard et al3 reported that the median imatinib plasma concentration at steady-state is higher in patients with a major molecular response (MMR) than in patients without MMR, suggesting that therapeutic drug monitoring may be useful for optimizing therapy. We have measured imatinib plasma concentrations in selected patients in specific clinical situations (Table 1). In patients nos. 1 to 3, unusually severe toxicity raised the question of higher than expected imatinib plasma concentrations. All 3 patients were treated with a starting dose of 300 mg imatinib twice a day because of high Sokal risk or an initial delay in commencing therapy. Dominant side effects were grade 3 myalgia in patient no. 1, transfusion-dependent erythropoietin-refractory anemia (associated with bone marrow hypoplasia) in patient no. 2, and diffuse pulmonary infiltrates in patient no. 3. Plasma trough concentrations on the initial dose of imatinib (patient nos. 1 and 2) or on 400 mg imatinib daily after transient escalation to 400 mg twice a day were considerably higher than expected from the phase 1 data (Table 1).4 After dose reduction, myalgia improved in patient no. 1 and patient no. 2 became transfusion independent. Repeat PK studies showed plasma concentrations that were similar to or slightly above the concentrations observed in the phase 1 study, providing reassurance that after dose reduction drug concentrations were still in a therapeutic range. In patient no. 3, imatinib was permanently discontinued, as the risk of further aggravating her side effects was felt to be unacceptable.

In 2 patients, PK studies were done because of concerns about inadequate imatinib plasma concentrations. Patient no. 4, a 9-year-old girl, achieved a complete cytogenetic response but not MMR after 11 months on 300 mg of imatinib. Dose escalation to 400 mg/day failed to improve on the molecular response, which raised the issue of inadequate drug concentrations. However, the plasma imatinib concentration was higher than expected at 2341 ng/mL.5 Based on this, the dose was not escalated because of concerns about side effects. Patient no. 5 failed to attain a complete hematologic response (CHR) on 400 mg imatinib daily. Replacement of carbamazepine with valproic acid for suspected drug interaction and dose escalation to 600 mg/day led to CHR but without any cytogenetic response. Sequencing of BCR-ABL did not reveal a kinase domain mutation. Given multiple comedications, low plasma imatinib concentrations were suspected.

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Table 1. Patient characteristics and PK data

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age at diagnosis, y</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>Body mass index</th>
<th>Phase at starting imatinib</th>
<th>Concomitant medications*</th>
<th>Side effects</th>
<th>Indication for PK</th>
<th>Imatinib dose, mg</th>
<th>Observed trough concentration(s), ng/mL observed in the phase 1 study</th>
<th>Clinical consequences</th>
<th>Best response</th>
<th>Last follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>12</td>
<td>161</td>
<td>50</td>
<td>19.2</td>
<td>CP1, newly diagnosed</td>
<td>Odansetron, esomeprazole, ziprasidone</td>
<td>Nausea, fatigue, arthralgia, myalgia</td>
<td>Unusually severe side effects</td>
<td>300 BID</td>
<td>1937</td>
<td>972 ± 317 NA</td>
<td>Dose reduction 2.2-log reduction in BCR-ABL transcripts</td>
<td>Switched to dasatinib</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>50</td>
<td>158</td>
<td>63</td>
<td>25.2</td>
<td>CP1, newly diagnosed</td>
<td>Levetiracetam, desferroxamine, desloratadine fluticasone</td>
<td>Myalgia, transfusion dependent anemia, transfusion dependent anemia, transfusion dependent anemia, transfusion dependent anemia, transfusion dependent anemia</td>
<td>Unusually severe side effects</td>
<td>300 BID</td>
<td>1997, 1990, 1890, 2250</td>
<td>972 ± 317 NA</td>
<td>Dose reduction CMR</td>
<td>Continuation on alternating 300/200 mg QD</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>49</td>
<td>163</td>
<td>74</td>
<td>27.8</td>
<td>CP1, IFN failure</td>
<td>Prednisone, pantoprazole, diltiazem, L-thyroxine, azathioprine, zolpidem</td>
<td>Pulmonary infiltrates when increased to 400 BID</td>
<td>Unusually severe side effects</td>
<td>400 QD</td>
<td>2344</td>
<td>1216 ± 750*</td>
<td>Discontinuation CMR</td>
<td>Off therapy</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>9</td>
<td>133</td>
<td>30</td>
<td>16.9</td>
<td>CP1, newly diagnosed</td>
<td>Lansoprazole</td>
<td>Dyspepsia</td>
<td>qPCR plateau</td>
<td>400 QD</td>
<td>2341</td>
<td>1216 ± 750*</td>
<td>Reassurance and continuation of current dose</td>
<td>Continue on 400 mg QD</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>47</td>
<td>173</td>
<td>132</td>
<td>44.1</td>
<td>CP1, IFN failure</td>
<td>Quinapril, valproic acid, gabapentin, metformin, glipizide, hydrocodone, spirin, fentanyl, furosemide, allopurinol</td>
<td>Myalgia</td>
<td>Cyto genetic refractoriness</td>
<td>600 QD</td>
<td>1342</td>
<td>1214 ± 817</td>
<td>Switch to dasatinib considered CHR</td>
<td>CHR, switch to dasatinib planned</td>
</tr>
</tbody>
</table>

BID indicates twice daily; CcyR, complete cytogenetic response; CHR, complete hematologic response; CMR, complete molecular response; CP1, first chronic phase; IFN, interferon-alpha; NA, not applicable; PK, pharmacokinetic; QD, daily; *979 plus or minus 530 were reported in the IRIS trial.
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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Conflict-of-interest disclosure: The authors declare no competing financial interests.

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This work was supported in part by National Heart, Lung, and Blood Institute (NHLBI) grant HL082978-01 (M.W.D.), Doris Duke Charitable Foundation (B.J.D.), and the Leukemia and Lymphoma Society (B.J.D., M.W.D.). The M.J.E. laboratory was financially supported by Novartis Pharma to perform the PK studies.

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.

References


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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Conflict-of-interest disclosure: The authors recently received a grant from Novartis Pharma to perform and determine imatinib plasma level in French patients treated with imatinib.

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References

Therapeutic drug monitoring in CML patients on imatinib

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