the true prevalence of biallelic JAK2 mutations in ET is approximately 5% to 10%.

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**Contribution:** P.A.B. designed and performed experiments, analyzed data, and cowrote the manuscript; C.A.O. and P.J.C. contributed to experimental design and reviewed the manuscript; and A.R.G. directed the research and cowrote the manuscript.

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**References**


To the editor:

**Poor outcome after reintroduction of imatinib in patients with chronic myeloid leukemia who interrupt therapy on account of pregnancy without having achieved an optimal response**

Since the introduction of imatinib as the first-line therapy in chronic phase chronic myeloid leukemia (CML), the prognosis for patients has dramatically improved. As female patients who wish to conceive are currently advised to discontinue imatinib during conception and pregnancy due to the recognized teratogenic effects of the drug, these patients are often without ideal therapy for a prolonged period of time. Responses to imatinib can be regained after prolonged cessation of therapy on account of side effects or pregnancy; however, the ideal degree of response that patients wishing to conceive should achieve before stopping therapy is not clear, nor is it clear whether a lengthy discontinuation of the treatment is safe in all the cases. Here we report the effect of discontinuing imatinib on the clinical response in 7 patients.

The median age was 32 years (range, 25-34 years). All patients received 400 mg of imatinib daily as initial therapy for CML in chronic phase. In 4 patients the imatinib was discontinued as soon as the pregnancy was confirmed, and 3 patients stopped imatinib to conceive. Before discontinuation, imatinib was received for a median time of 19 months (range, 7-42 months, Table 1), and all patients were still receiving 400 mg. The median period of drug interruption was 9 months (range, 6-23 months). All patients had lost their cytogenetic response, and 4 lost the complete hematologic response (CHR) before the imatinib was reintroduced, but only patient no. 3 required therapy (leukapheresis) during imatinib discontinuation.

Before imatinib discontinuation, patients 2, 3, 4, and 6 were suboptimal responders (Table 1). None of these 4 patients obtained an appropriate response when imatinib was reintroduced after the delivery. Patients 2, 4, and 6 (Table 1) failed to achieve complete cytogenetic response (CCyR) on subsequently restarting imatinib therapy. Patient 3 achieved CCyR but failed to achieve major molecular response (MMR) after 26 months of therapy. The 3 patients (nos. 1, 5, and 7) who had obtained an optimal response at the time of stopping imatinib regained at least MMR after restarting therapy (Table 1). None of the 7 patients had developed kinase domain mutations.

Our results demonstrate that an adequate response after restarting imatinib after discontinuation in pregnancy is seen only in patients who had an optimal response (MMR) before stopping the drug. Suboptimal responders to initial treatment with imatinib either demonstrated the same response after discontinuation or, more of concern, deterioration of the response eventually meeting criteria for imatinib failure. Indeed, it is not clear whether the poor results after reintroduction of imatinib occurred because the patients had not yet achieved an appropriate response before conception or because they were poor-risk patients. It is possible that the use of nilotinib or dasatinib in suboptimal responders to obtain MMR before therapy discontinuation may reduce the risk of treatment failure after the reintroduction of therapy. Our findings emphasize the importance of counseling patients about the possible consequences of therapy discontinuation. Although the role of kinase domain mutations in imatinib resistance remains to be fully elucidated, we report that none of the patients who achieved an optimal response before discontinuation had kinase domain mutations.
Table 1. Summary of patient data and outcomes

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sokal risk group</th>
<th>Months on imatinib prior to discontinuation</th>
<th>Clinical response at time of discontinuation</th>
<th>Clinical response at time of discontinuation according to ELN</th>
<th>Months without imatinib</th>
<th>WBC and cytogenetic response before reintroduction</th>
<th>Months of imatinib therapy after reintroduction</th>
<th>Clinical response after restarting imatinib (time to response, months)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Low</td>
<td>9</td>
<td>MMR</td>
<td>Optimal</td>
<td>9</td>
<td>7.3, no MCR</td>
<td>30</td>
<td>CMR (12)</td>
<td>Maintained CMR on imatinib therapy</td>
</tr>
<tr>
<td>2*</td>
<td>Low</td>
<td>42</td>
<td>CCyR</td>
<td>Suboptimal</td>
<td>9</td>
<td>48.2, no MCR</td>
<td>18</td>
<td>Failure to achieve MCR, subsequent lost of CHR</td>
<td>Imatinib increased to 600 mg after 8 o, then changed to dasatinib. The patient achieved CCyR at 12 mo</td>
</tr>
<tr>
<td>3</td>
<td>Low</td>
<td>21</td>
<td>CCyR</td>
<td>Suboptimal</td>
<td>13</td>
<td>88.81, no MCR</td>
<td>26</td>
<td>CCyR (24)</td>
<td>On imatinib; no MCR after 26 mo</td>
</tr>
<tr>
<td>4</td>
<td>Low</td>
<td>19</td>
<td>CCyR</td>
<td>Suboptimal</td>
<td>23</td>
<td>60.3, no MCR</td>
<td>29</td>
<td>no MCR</td>
<td>Failure to achieve any degree of cytogenetic response. Patient lost to follow-up after 29 mo</td>
</tr>
<tr>
<td>5</td>
<td>Low</td>
<td>14</td>
<td>MMR</td>
<td>Optimal</td>
<td>6</td>
<td>5.3, no MCR</td>
<td>90</td>
<td>MMR (9)</td>
<td>Patient remains in MMR</td>
</tr>
<tr>
<td>6</td>
<td>High</td>
<td>7</td>
<td>MCR</td>
<td>Suboptimal</td>
<td>8</td>
<td>79.4, no MCR</td>
<td>50</td>
<td>MCR (4)</td>
<td>Patient failed to regain MCR; the dose of imatinib was increased to 600 mg after 11 mo and then changed to dasatinib. Subsequently the patient achieved CCyR after 6 mo of dasatinib therapy</td>
</tr>
<tr>
<td>7</td>
<td>Low</td>
<td>50</td>
<td>MMR</td>
<td>Optimal</td>
<td>13</td>
<td>6.5, MCR</td>
<td>14</td>
<td>MMR (3)</td>
<td>Patient remains in MMR with a continuing decline in transcript levels</td>
</tr>
</tbody>
</table>

MCyR indicates major cytogenetic response; CCyR, complete cytogenetic response; MMR, major molecular response; and CMR, complete molecular response.

*Patient 2 had 2 pregnancies; the data shown in the table correspond to the second pregnancy. In the first pregnancy, imatinib was discontinued for 11 months after 3 months of therapy.
†Patient 3 required leukapheresis, which was started when the WBC rose above 100 × 10^9 cells/L.
need for further investigation into the effects of discontinuing imatinib therapy in those patients who wish to conceive.

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References


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