Impact of early molecular response in children with chronic myeloid leukemia treated in the French Glivec phase 4 study

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**Key Points**

- Early molecular response at 3 months can predict outcome in children treated with imatinib for CML.
- Children with CML may be less likely to achieve an early molecular response to imatinib than adults with CML.

**Studies in adults have shown that an early molecular response to imatinib predicts clinical outcome in chronic myeloid leukemia (CML).** We investigated the impact of the BCR-ABL1 transcript level measured 3 months after starting imatinib in a cohort of 40 children with CML. Children with a BCR-ABL1/ABL ratio higher than 10% at 3 months after the start of imatinib had a larger spleen size and a higher white blood cell count compared with those with BCR-ABL1/ABL ≤10%. Children with BCR-ABL1/ABL ≤10% 3 months after starting imatinib had higher rates of complete cytogenetic response and major molecular response at 12 months compared with those with BCR-ABL1/ABL >10%. With a median follow-up of 71 months (range, 22-96 months), BCR-ABL1/ABL ≤10% correlated with better progression-free survival. Thus, early molecular response at 3 months predicts outcome in children treated with imatinib for CML. This trial was registered at [www.clinicaltrials.gov as #NCT00845221](http://www.clinicaltrials.gov) ([Blood. 2014;124(15):2408-2410](http://Blood.2014;124(15):2408-2410)).

**Introduction**

Although imatinib is effective for the majority of children with chronic myeloid leukemia (CML),1,2,3 13% to 25% of children have a poor response.4,5 Reports in adults indicate that measurement of BCR-ABL1 transcripts 3 months after starting imatinib can predict outcome with better overall survival in patients with a BCR-ABL1/ABL ratio of <10% at this time point.6 In order to address the relevance of this cutoff in the pediatric population in terms of cytogenetic and molecular responses and outcome, we reanalyzed the French Glivec phase 4 study data.3

**Study design**

This study was approved by the institutional review board of the University Hospital of Poitiers (Poitiers, France) and participants provided informed consent in accordance with the Declaration of Helsinki. Between March 2004 and December 2008, 44 consecutive patients younger than 18 years of age with newly diagnosed CML in chronic phase were enrolled in the prospective Glivec phase 4 study from 16 French university hospitals. Patient eligibility and trial design were previously described.7 Patients received imatinib 260 mg/m² daily.8 Bone marrow assessment including morphology, cytogenetics, and molecular analysis was performed at diagnosis, 3 months, and 12 months after the start of imatinib. Complete cytogenetic response (CCyR) was defined by the absence of Ph-positive metaphases among at least 20 analyzed metaphases in bone marrow. Determination of BCR-ABL1 transcript level in the blood was performed at 3-month intervals using quantitative reverse transcription–polymerase chain reaction independently aligned on the International Scale (IS) by specific conversion factors as described previously.5,9 Major molecular response (MMR) was defined as a BCR-ABL1 IS ≤0.1%, molecular response (MR) ≤0.1% and MR ≤0.01% were defined as either detectable disease with BCR-ABL1 IS ≤0.01% and ≤0.0032%, respectively, or undetectable disease with ≥10 000 and ≥32 000 ABL1 copies, respectively, in the same volume of complementary DNA used to test for BCR-ABL1. Complete molecular response (CMR) was defined by no detectable transcripts in 2 consecutive samples, with ≥32 000 ABL1 copies. BCR-ABL1 transcript levels (≤1%, >1% to ≤10%, >10%) 3 months after starting imatinib were used to assess the association between early molecular response and the rates of CCyR and MMR 1 year after the start of imatinib.
of imatinib as well as the association between early molecular response and progression-free survival (PFS). PFS was defined by absence of accelerated phase, blast crisis, and death from any cause.\textsuperscript{10}

Comparisons between groups were performed using the \( \chi^2 \) test or the nonparametric Fisher exact test and Wilcoxon test, as appropriate. PFS from the onset of imatinib was estimated by the Kaplan-Meier method and was compared within groups by log-rank test. All analyses were 2-sided and were performed on starting imatinib and were excluded from landmark analyses if a missing polymerase chain reaction assessment 3 months after starting imatinib.

Results and discussion

Four of the 44 patients enrolled in the Gleevec phase 4 study had a missing polymerase chain reaction assessment 3 months after starting imatinib and were excluded from landmark analyses performed on \( \text{BCR-ABL} \) transcript levels. Hence, the patient population consisted of 40 children. Because of severe side effects, 1 of them was switched to a second-generation tyrosine kinase inhibitor (TKI) 2 months after starting imatinib and was included in the intention-to-treat analysis. Patient characteristics are reported in Table 1. A high Sokal risk score (for patients younger than 45 years of age)\textsuperscript{9} was reported.

Table 1. Patient characteristics according to the \( \text{BCR-ABL} \) ratio 3 months after starting imatinib

<table>
<thead>
<tr>
<th>( \text{BCR-ABL} ) at 3 mo</th>
<th>≤10%</th>
<th>&gt;10%</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>25 (63)</td>
<td>15 (37)</td>
<td></td>
</tr>
<tr>
<td>Sex, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>14</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>11</td>
<td>4</td>
<td>.329</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>11.3 (0.8-16.7)</td>
<td>11.7 (1.9-17.3)</td>
<td>.561</td>
</tr>
<tr>
<td>Sokal risk score*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>13</td>
<td>12</td>
<td>.170</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>19 (76%)</td>
<td>14 (93%)</td>
<td></td>
</tr>
<tr>
<td>Spleen size, median (range), cm below the costal margin</td>
<td>5 (0-21)</td>
<td>13 (0-21)</td>
<td>.005</td>
</tr>
<tr>
<td>White blood cell count, median (range), ( \times 10^9/\text{L} )</td>
<td>252 (16-482)</td>
<td>378 (44-762)</td>
<td>.02</td>
</tr>
</tbody>
</table>

*As applied to patients younger than 45 years of age.\textsuperscript{9}

\textsuperscript{10}One patient with no conventional cytogenetic assessment at 12 mo achieved MR4.5 at this time point and was considered as having a CCyR.

Table 2. Rates of CCyR and MMR at 12 months and PFS at 36 and 48 months, according to the molecular response at 3 months, in 40 children with CML

<table>
<thead>
<tr>
<th>( \text{BCR-ABL} ) at 3 mo, %</th>
<th>( \text{BCR-ABL} ) transcript level at 3 mo*</th>
<th>CCyR at 12 mo (%)</th>
<th>MMR at 12 mo (%)</th>
<th>PFS at 36 mo (%)</th>
<th>PFS at 48 mo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10</td>
<td>( \leq 10 % )</td>
<td>19** (76)</td>
<td>12 (48)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>&gt;10</td>
<td>( &gt;10 % )</td>
<td>7 (47)</td>
<td>1 (7)</td>
<td>92</td>
<td>61</td>
</tr>
</tbody>
</table>

\( 95\% \text{ CI, 54-99} \) \( 95\% \text{ CI, 7-91} \)

\( P = .177 \) \( P = .0128 \) \( P = .028 \) (overall)

*As applied to patients younger than 45 years of age.\textsuperscript{9}

**This portion of the table shows that achieving a <10\% cutoff ratio at 3 mo is in favor of a higher rate of MMR at 12 mo. However, it is also documented that a delayed cutoff ratio achievement of this <10\% cutoff ratio at 6 mo with favorable outcome may exist. The small sample size of children does not allow providing robust rate estimates within subgroups.

***One patient with no conventional cytogenetic assessment at 12 mo achieved MR4.5 at this time point and was considered as having a CCyR.

With a median follow-up of 71 months (range, 22-96 months), a transcript level ≤10\% correlated with better PFS (Table 2). A high Sokal risk score at diagnosis but with a similar Sokal score distribution at diagnosis but with a larger spleen size and a higher white blood cell count compared with patients with a \( \text{BCR-ABL} \) ratio of ≤10\% (Table 1). The dose of imatinib administered within the first 3 months of treatment was similar \( (P = .209) \) in patients with a \( \text{BCR-ABL} \) ratio >10\% (median, 242 mg/m\(^2\); range, 132-381) and those with ≤10\% at 3 months (median, 250 mg/m\(^2\); range, 300-342). Two children progressed to blast phase 25 months and 42 months after the start of imatinib (1 of them was switched for a second-generation TKI before onset of progression) and 1 of them died. Both children had a \( \text{BCR-ABL} \) ratio of >10\% at 3 months after starting imatinib. No other death was reported.

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than the 24% to 28% of adults who fail to reach the ≤10% cutoff.6,14 This might be explained in part by the higher proportion of patients with bulky disease (large spleen, high leukocyte count) and a higher proportion of patients with a high Sokal risk score in our pediatric population compared with adult series.6 Consistent with this, Hughes et al showed that adult patients who failed to achieve a BCR-ABL1/ABL ≤10% 3 months after the start of imatinib also had a larger median spleen size and higher Sokal risk score than those who achieve an early molecular response.15 In the present study, the dose of imatinib administered during the first 3 months of treatment was similar in children who did or did not achieve an early molecular response, suggesting that treatment exposure was not an independent influencing factor.

In summary, given the limitation of the small number of patients and events, we show that BCR-ABL1 transcript level 3 months after starting imatinib can identify children with a lower rate of progression who might benefit from an alternative treatment strategy. The reliability of a cutoff of 10% at 3 months after the start of imatinib as a surrogate marker of response at 1 year and PFS remains to be confirmed in a larger cohort of children.

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Authorship

Contribution: F. Millot coordinated the study and wrote the manuscript; J.G. performed statistical analysis; A.B., A.P., Y.B., F. Mazingue, P.L., C.V., C.B., G.N., N.S., K.Y., C.S., V.G., Y.R., G.C., and F. Mechinaud provided patients; and J.M. performed the molecular review.

Conflict-of-interest disclosure: F. Millot received speaker fees from Novartis and Pfizer. The remaining authors declare no competing financial interests.

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References

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