Unplanned discontinuation of tyrosine kinase inhibitors in chronic myeloid leukemia

YUTAKA TSUTSUMI¹, SHINICHI ITO¹, HIROYUKI OHIGASHI¹, SOUICHI SHIRATORI¹ and TAKANORI TESHIMA²

¹Department of Hematology, Hakodate Municipal Hospital, Hakodate, Hokkaido 041-8680; ²Department of Hematology, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido 060-8638, Japan

Received March 31, 2015; Accepted September 18, 2015

DOI: 10.3892/mco.2015.653

Abstract. This study was conducted to investigate the outcomes of patients with chronic myeloid leukemia (CML) who discontinued tyrosine kinase inhibitor (TKI) treatment. A single-center retrospective analysis was performed, including 46 chronic-phase (CP) CML patients who achieved complete molecular response (CMR) with TKIs. TKI treatment was discontinued in 13 patients based on their requests. The BCR-ABL transcript levels were monitored in the peripheral blood by quantitative polymerase chain reaction analysis following treatment discontinuation. Of the 13 patients who discontinued TKI treatment, 7 remained in CMR, with a median follow-up of 26 months (range, 10-60 months). The remaining 6 patients lost CMR following TKI discontinuation; 2 of these patients achieved a second CMR following re-administration of TKIs, 2 patients spontaneously achieved CMR and 2 remained in complete hematological response (CHR) without TKI treatment with a median follow-up of 29.5 months (range, 10-52 months). In conclusion, the survival of patients who lost CMR following TKI discontinuation may not be affected, even without re-administration of TKIs. Vigilant observation is recommended for such patients. The limitations of this study included the small patient sample, retrospective design and patient heterogeneity. Therefore, the results must be interpreted with caution.

Introduction

The emergence of tyrosine kinase inhibitors (TKIs) has significantly changed chronic myeloid leukemia (CML) treatment (1-3). With imatinib, ~40% of chronic-phase (CP) CML patients achieve a complete molecular response (CMR) within 5 years, as determined by the sensitive reverse transcription quantitative polymerase chain reaction (qPCR) analysis (4, 5). The estimated overall survival (OS) rate of CML patients treated with imatinib was reported to be 89 and 85% at 5 and 8 years, respectively (6). Next-generation TKIs have also been found to be effective for CML (7, 8). Although CML patients primarily require lifelong treatment with TKIs, recent clinical studies demonstrated that approximately half of the patients in CMR who discontinued TKIs remained in CMR, whereas the remaining patients lost CMR (9-11).

The high cost of TKIs may be prohibitive for their administration (12). A significant proportion of patients have decided to discontinue TKI treatment, but their outcomes have not been reported. The aim of this study was to investigate the natural course of patients who voluntarily discontinue TKI treatment.

Patients and methods

Patients. The medical records from the Hakodate Municipal Hospital were reviewed to identify all Philadelphia chromosome-positive CP-CML patients aged ≥18 years who achieved CMR with TKIs, such as imatinib, nilotinib and dasatinib, between August, 2002 and March, 2013. Certain patients had a history of prior treatment with interferon, hydroxyurea or busulfan. Our study protocol was approved by the Hakodate Municipal Hospital Institutional Review Board. Based on the Declaration of Helsinki, written informed consent was obtained from all participating patients.

Treatment. The patients were treated according to the European LeukemiaNet recommendations (13). We monitored the BCR-ABL transcript levels in the peripheral blood based on the recommendations of the Europe Against Cancer Program (14). CMR was defined as no detection of BCR-ABL/ABL transcript. The limit of detection with this method was <2×10³ copy/µgRl. A complete hematological response (CHR) was defined as a white blood cell count of <1.0×10⁹/l, a platelet count of <450×10⁹/l, a proportion of basophils ≤5%, with no blast cells in the peripheral blood and no splenomegaly. qPCR analysis of the peripheral blood was performed once a month for 2 years after the initiation of TKI therapy and once every 3 months thereafter. Following TKI discontinuation, qPCR analysis was performed once a month.

Correspondence to: Dr Yutaka Tsutsumi, Department of Hematology, Hakodate Municipal Hospital, 1-10-1 Minato-cho, Hakodate, Hokkaido 041-8680, Japan
E-mail: yutsutsu@shore.ocn.ne.jp

Key words: chronic myeloid leukemia, tyrosine kinase inhibitors
The OS was defined as the time from the initiation of TKI treatment until death from any cause or the date of the last follow-up. In patients who discontinued TKI treatment, event-free survival (EFS) was defined as the time from TKI discontinuation to molecular relapse (loss of CMR) or the date of the last molecular evaluation. These values were estimated using the Kaplan-Meier method. Statistical analysis was performed using the log-rank test. A P-value of ≤0.05 was considered to indicate statistically significant differences.

**Results**

**Patient characteristics.** We evaluated a total of 46 newly diagnosed CML-CP patients who were treated with various TKIs and achieved CMR (Table I). The first-line TKI treatment was imatinib in 38, dasatinib in 6 and nilotinib in 2 patients. Prior to TKI treatment, additional cytogenetic abnormalities were detected by G-band analysis in 2 patients. With a median follow-up of 66 months, the 8-year OS rate of all the patients was 83% (Fig. 1). There was no significant difference in the OS rate between patients who continued (86%) and those who discontinued TKI treatment (100%).
Characteristics of patients who discontinued TKI treatment. In patients who discontinued TKIs, the median duration of the treatment until discontinuation was 74 months (range, 27-158 months) (Table II). The reasons for treatment discontinuation were as follows: A total of 5 patients were unable to receive TKIs due to surgery (1 for a traffic accident and 4 for malignancy) and refused TKI treatment after recovery. The remaining 8 patients declined TKI treatment due to their high cost.

Table III. Patient outcome.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>On TKIs (n=33)</th>
<th>Off TKIs (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up, months (range)</td>
<td>34 (1-143)</td>
<td>107 (44-177)</td>
</tr>
<tr>
<td>Median follow-up after TKI discontinuation, months (range)</td>
<td>-</td>
<td>28 (10-60)</td>
</tr>
<tr>
<td>Disease status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First CMR</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Second CMR</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>CHR</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Disease progression</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary infarction</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Uterine cancer</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CML blast crisis</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

TKI, tyrosine kinase inhibitor; CMR, complete molecular response; CHR, complete hematological response; CML, chronic myeloid leukemia.

Patient outcomes. The median follow-up of the patients after TKI discontinuation was 28 months (range, 10-60 months) (Table III). The 5-year EFS was 67% and the median duration of CMR was 20 months (range, 1-60 months) (Fig. 2).

Of the 13 patients who discontinued TKIs, 7 remained in CMR with a median follow-up of 26 months (range, 10-60 months) (Table III), whereas the remaining 6 patients lost CMR, with a median follow-up of 29.5 months (range, 10-52 months). The median time to CMR loss after TKI discontinuation was 6.5 months (range, 1-20 months). The BCR-ABL levels after TKI discontinuation are presented in Fig. 3. Of the 6 patients who lost CMR, 2 were re-treated with TKIs and attained a second CMR; 2 spontaneously attained a second CMR without retreatment; and the remaining 2 patients lost CMR but remained in CHR without any treatment for 43-126 months. A total of 4 patients on TKI treatment who succumbed to the disease were aged >75 years, of whom 2 patients had solid cancers (lung cancer, n=1; and uterine cancer, n=1); for these 2 patients, the spleen size was not measured at diagnosis, so the Sokal or Hasford scores could not be calculated. The remaining 2 patients were classified as a high-risk Sokal score group; in 1 patient, severe thrombocytosis was found at diagnosis and led to pulmonary infarction and death; the other patient was unresponsive to all types of TKIs, developed a blast crisis and succumbed to CML. There were no mortalities among patients who discontinued TKI treatment.

Discussion

TKI discontinuation has been investigated in a number of clinical trials in CML patients who have been in CMR. In a study by Rousselot et al (9), where imatinib was discontinued in patients who had been in CMR for >2 years (range, 26-45 months), approximately half of the patients experienced a molecular relapse within 6 months following discontinuation.
No late relapse was observed 4 years after TKI discontinuation. In the Stop Imatinib (STIM) study, 61% of the patients lost CMR, mostly within the first 6 months following treatment discontinuation (15). The predictive factors for treatment-free remission are the Sokal score and the length of the imatinib treatment (12,15-17). However, the Sokal score could not be analysed, as the spleen size on admission was not recorded for all the patients in this study.

In our study, the probability of CMR persistence was 41%. The OS in patients who discontinued TKI treatment in our study almost equaled that in prospective TKI stop studies (15,18-20). Interestingly, no statistical differences in OS were observed between patients who continued and those who discontinued TKI treatment in our analysis, suggesting that survival was not always compromised by molecular relapse following TKI discontinuation, even without TKI re-treatment.

A total of 2 patients spontaneously attained a second CMR without TKI treatment, and 2 patients remained in CHR without any treatment for 43 and 126 months. These findings suggest that immediate re-treatment with TKIs may not always be necessary for patients who had been in CMR for >2 years and lost CMR following TKI discontinuation. This study was conducted retrospectively using a single-center analysis, which raises the risk of bias; thus, additional investigation is required to elucidate this issue.

References