Impact of Post-transplant Imatinib Administration on Philadelphia Chromosome-positive Acute Lymphoblastic Leukaemia

SATOSHI NISHIWAKI1, KOICHI MIYAMURA1,2, CHIAKI KATO3, SEITARO TERAKURA1, KAZUTERU OHASHI4, HISASHI SAKAMAKI4, SHINJI NAKAO5, HIDEO HARIGAE2 and YOSHIHISA KODERA1

1Department of Hematology, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan; 2Department of Hematology/Immunology, Tohoku University School of Medicine, Sendai, Japan; 3Department of Hematology and Oncology, Nagoya University School of Medicine, Nagoya, Japan; 4Department of Hematology, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan; 5Cellular Transplantation Biology, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan

Abstract. To evaluate the effect of post-transplant imatinib administration, 34 Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ALL) patients were retrospectively analysed, with 7 receiving post-transplant imatinib administration. Overall survival was significantly better in patients with post-transplant administration (66.7% vs. 29.6% at 3 years, p=0.03), with no significant difference in leukaemia-free survival (0% vs. 29.6% at 3 years, p=0.29). The median duration of negative minimal residual disease (MRD) in patients with post-transplant imatinib administration was 6 months in the pre-emptive administration group, where imatinib was administered upon detecting MRD after allogeneic stem cell transplantation (allo-SCT). In the prophylactic administration group, imatinib was administered as soon as possible after allo-SCT, and the median duration of MRD was 12 months. In all patients whose observation periods were longer than one year, MRD became positive in both groups leading to haematological relapse. It is therefore concluded that post-transplant imatinib administration is not an ideal treatment for Ph+ALL patients whose MRD is positive at allo-SCT.

Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ALL) is associated with highly aggressive disease, and leukaemia-free survival (LFS) with intensive chemotherapy alone has remained low (1). Allogeneic stem cell transplantation (allo-SCT) is at present the only curative treatment option for Ph+ALL patients (2). Even with allo-SCT, haematological relapse remains a major obstacle. In the early 1990s, the detection of minimal residual disease (MRD) in Ph+ALL patients was performed using a polymerase chain reaction (PCR) (3, 4). An earlier study suggested that BCR-ABL chimeric messenger RNA (BCR-ABL) detected by PCR after allo-SCT indicates imminent haematological relapse (3). The previous study also found that MRD negativity just before allo-SCT suggested long-term LFS after allo-SCT (5).

Although it is ideal to perform allo-SCT under MRD-negative conditions, this is sometimes difficult to achieve, despite the administration of imatinib. There are some reports of post-transplant imatinib administration (6, 7), but its efficacy and administration methods are still controversial. In this study, a better treatment option for Ph+ALL with MRD-positive at allo-SCT was sought.

Patients and Methods

In this study, 34 Ph+ALL patients with positive MRD at allo-SCT were analysed. Two strategies for post-transplant imatinib administration were proposed. The first strategy was pre-emptive administration, whereby imatinib was administered upon detecting MRD after allo-SCT. The second strategy, which was initiated from 2005, was prophylactic administration, where imatinib was administered as soon as possible after allo-SCT. Imatinib was initiated at a daily oral dose of 400 mg that could be escalated by protocol-defined guidelines to 600 mg. The Ethics Committee of each institute approved the study, and all patients gave written informed consent. The study was performed in accordance with the guidelines of the Declaration of Helsinki (8). The data were analysed in July, 2008.

For monitoring MRD, real-time quantitative PCR was performed on an ABI PRISM 700 Sequence Detector, using ABI PRISM 7700 Sequence Detector Software 1.6 (Perkin Elmer/Applied Biosystems,
Foster City, CA, USA) under standard conditions (95°C for 10 min, 40 cycles at 95°C for 15 s, and 58°C for 60 s). Total RNA was extracted with STAT-60 (TELTEST, TX, USA) from 10⁶ to 10⁷ mononuclear cells. PCR primers and TaqMan probes (9) were designed to amplify and detect the BCR-ABL (p210 type and p190 type), β-actin and ABL sequences. The quantification of the starting copy number in unknown samples was determined by preparing a standard curve using serial dilutions of a known amount of standard plasmid. The quantity of BCR-ABL transcript for each sample was normalised to the absolute quantity of the β-actin gene transcript, and the result was expressed as the number of BCR-ABL transcripts in 1 μg of RNA. Haematological relapse was defined as either the presence of leukaemia blasts in the bone marrow peripheral blood, or evidence of Philadelphia chromosome on cytogenetic examination. MRD-positive or BCR-ABL-positive was defined as >50 copies of BCR-ABL mRNA in 1 μg of total RNA. The relapse rates for patients classified by PCR test results at the stated time intervals were estimated by the cumulative incidence statistics. Overall survival (OS) and LFS were evaluated by Kaplan-Meier plots and log-rank tests.

### Results

Patient characteristics are shown in Table I. Twenty patients received allo-SCT from related donors and 14 from unrelated donors. The median age of the patients was 40 years (range, 7-62). Seven patients received a post-transplant administration of imatinib, 4 of which were pre-emptive, where imatinib was administered upon detecting MRD after allo-SCT, and 3 prophylactic, where imatinib was administered as soon as possible after allo-SCT.

The incidence of graft failure was 0%, with grade II-IV graft- versus-host disease (GVHD) developing in 8 out of 29 evaluable patients, and chronic GVHD in 17 out of 27 patients at risk. A total of 9 patients died of transplant-related mortality (TRM) and 11 of leukaemia. For all patients, OS, LFS, and relapse rates were 45.3%, 38.7% and 45.8% at 1 year and 37.8%, 35.2% and 45.8% at 2 years, respectively. OS at 1 and 2 years after allo-SCT was 100% and 66.7%, respectively, in the post-transplant imatinib administration group compared to 33.3% and 29.6%, respectively, in the non-administration group (p=0.03), while LFS was 55.6% and 55.6% at 1 year and 33.3% and 29.6% at 2 years, respectively (p=0.29) (Figure 1A).

The details of MRD in patients given post-transplant imatinib administration are shown in Figure 1B. The duration of negative MRD was 6 months, 9 months, and at least 2 months in the pre-emptive administration group (the details of MRD were unknown in 1 patient who survived 324 days), while in the prophylactic administration group it was 29 months, 12 months, and at least 9 months. It seems that the duration of negative MRD was longer in the prophylactic administration group. However, in all patients whose observation periods were longer than 1 year, MRD became positive in both groups and resulted in haematological relapse.

### Discussion

The OS of Ph⁺ALL patients was improved by the post-transplant administration of imatinib. This has some advantages, considering that those patients who survived after allo-SCT, even without a complete cure, could potentially benefit from newly developed drugs, given the striking progress made since the introduction of imatinib. Meanwhile, the fact that post-transplant imatinib administration exerted no significant effect on LFS reveals the limitation of imatinib administration after allo-SCT. This study proposes two strategies for post-transplant imatinib administration, namely, pre-emptive and prophylactic; the latter, contrary to expectations, had only a limited effect on relapse. Although it is a considerable achievement to prolong the duration of negative MRD, post-transplant imatinib administration might not be regarded as a fundamental solution for Ph⁺ALL patients with positive MRD at allo-SCT.

These data indicate that post-transplant imatinib administration seems inadequate to achieve long-term LFS of Ph⁺ALL patients, thus highlighting the need for a further improvement in therapeutic strategies. In terms of a cure for Ph⁺ALL, MRD at allo-SCT may produce a profound impact on long-term LFS, indicating that post-transplant intervention seems to have serious limitations. In cases where imatinib is inadequate to achieve negative MRD, it seems better to achieve negative MRD before performing allo-SCT by using other drugs such as dasatinib, a dual SRC/ABL inhibitor (10).

In conclusion, post-transplant imatinib administration improved OS of Ph⁺ALL patients with positive MRD at allo-SCT. However, LFS could not be improved, suggesting a major limitation of post-transplant imatinib administration. Positive MRD at allo-SCT seems to have a strong impact on the negative outcome of Ph⁺ALL, confirming that MRD-based strategies are essential for the cure of Ph⁺ALL.

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**Table I. Patient characteristics.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Gender, male/female</td>
<td>18/16</td>
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<tr>
<td>Median age at allo-SCT, years (range)</td>
<td>40 (7-62)</td>
</tr>
<tr>
<td>Type of BCR-ABL, p190/p210</td>
<td>21/13</td>
</tr>
<tr>
<td>Disease status, CR1/CR2/relapse or refractory</td>
<td>15/3/16</td>
</tr>
<tr>
<td>Donor, unrelated/sibling/other relatives</td>
<td>14/17/3</td>
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<tr>
<td>HLA, match/mismatch</td>
<td>28/6</td>
</tr>
<tr>
<td>Graft, BM/PB/CB</td>
<td>26/7/1</td>
</tr>
<tr>
<td>GVHD prophylaxis, CyA+sMTX/FK+sMTX</td>
<td>26/8</td>
</tr>
<tr>
<td>Conditioning, TBI/non TBI</td>
<td>29/5</td>
</tr>
</tbody>
</table>

Allo-SCT: allogeneic haematopoietic stem cell transplantation; CR1, first complete remission; CR2, second complete remission; BM, bone marrow; PB, peripheral blood; CB, cord blood; CyA, cyclosporine; sMTX, short-term methotrexate; FK, tacrolimus; TBI, total body irradiation.
Figure 1. Impact of post-transplant imatinib administration. A: Overall survival and leukaemia-free survival according to the status of post-transplant imatinib administration. B: The results of longitudinal MRD analyses. ■, Positive MRD; □, negative MRD; △△, imatinib administration; △△△, dasatinib administration; R, relapse; A&W, alive and well; D, dead.
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Conflicts of Interest

The Authors declare no conflict of interest.

References


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