Brief report

Imatinib mesylate (STI571) in the treatment of relapse of chronic myeloid leukemia after allogeneic stem cell transplantation

Eduardo Olavarria, Charles Craddock, Francesco Dazzi, David Marin, Sarah Marktel, Jane F. Apperley, and John M. Goldman

Donor lymphocyte infusion (DLI) can restore durable molecular remission in a high percentage of patients with chronic myeloid leukemia (CML) who have relapses after allogeneic stem cell transplantation, but for patients who do not respond survival is poor. Imatinib mesylate (STI571) is a specific inhibitor of BCR-ABL tyrosine kinase that can induce hematologic and cytogenetic remissions in patients with CML. We report here a male patient who had a relapse to chronic phase after stem cell transplantation for CML, did not benefit from treatment with DLI, and then was administered STI571 at a dose of 400 mg daily. There was a rapid, complete hematologic response, and complete restoration of donor-type hematopoiesis (100% 46, XX marrow metaphases) was achieved after 6 months of therapy, though RT-PCR studies still detected BCR-ABL transcripts in the blood at low level. This case demonstrates that imatinib mesylate can be highly effective in the management of patients who have relapses after allograft for CML.

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-SCT) is the only approach capable of curing patients with chronic myeloid leukemia (CML). One of the major causes of treatment failure after allo-SCT is relapse. The relapse rate is low for patients allografted in chronic phase with unmanipulated cells, but it is much higher when donor marrow cells are T-cell depleted. Approaches to treat patients with CML in relapse after allografting include interferon-α, chemotherapy, second SCT, and immunomodulation with donor lymphocyte infusion (DLI). Although DLI can restore durable molecular remissions in a high percentage of patients with CML in relapse after allografting, a significant proportion of patients do not benefit from DLI therapy because of disease progression or toxicity (namely, graft-versus-host disease [GVHD]) associated with the procedure.

The BCR-ABL oncoprotein is a constitutively activated tyrosine kinase now considered to be the principal cause of the chronic phase of CML. Imatinib mesylate inhibits the Ab1 tyrosine kinase and thus blocks the proliferation of CML cell lines and clonogenic CML progenitor cells. Imatinib mesylate (then called STI571) was first administered to patients with CML in the summer of 1998, and additional clinical trials recruited patients rapidly. The drug is given orally, is well tolerated, and has a manageable side-effect profile. Results from phase 2/3 trials suggest that complete cytogenetic remission (CCR) can be obtained in all phases of the disease.

Thus far, only a limited number of patients in relapse after allo-SCT have been treated with imatinib mesylate. We have reported the reappearance of transient full donor chimerism in 4 patients who had relapses in blastic phase after allo-SCT treated with imatinib mesylate. Here we report a patient in hematologic relapse in the chronic phase of CML treated with imatinib mesylate after failure to respond to DLI.

Study design

A 40-year-old man was diagnosed with CML in December 1993. Interferon-α (IFN-α) administration failed to elicit a cytogenetic response. He underwent allogeneic SCT from an HLA-matched unrelated female donor in October 1997. Conditioning included cyclophosphamide (120 mg/kg) and total body irradiation (14.4 Gy). Acute (grade 2) and chronic (limited) GVHD developed, necessitating immunosuppressive therapy with cyclosporine and prednisolone for 11 months after SCT. Despite full donor chimerism and complete cytogenetic remission soon after SCT, reverse transcription-polymerase chain reaction (RT-PCR) for BCR-ABL transcripts remained positive at variable levels after SCT. The patient satisfied our criteria for molecular relapse in January 1998 and was treated with escalating doses of DLI from September 1998. He progressed to cytogenetic relapse in September 1999 and to hematologic relapse in chronic phase in November 1999. He received interleukin-2-activated donor lymphocytes in December 1999 with no benefit. In August 2000, he was entered in the Novartis STI571-0113 study. At study entry, cytogenetic analysis showed 20/20 (100%) XY, t(9;22) metaphases with several other abnormalities, including del(13q), t(5;12), der(6), der(8), and nonclonal rearrangements. The patient commenced treatment with imatinib mesylate at 400 mg daily. No significant side effects were noted. Three months later his blood counts and marrow histology had normalized. Cytogenetics demonstrated 29/30 (97%) Philadelphia chromosome-negative metaphases of female origin and 1/30 (3%) Philadelphia chromosome positivity, with no additional chromosomal abnormalities. In February 2001, his bone marrow was 100% female (donor) by fluorescence in situ hybridization analysis and 100% 46,XX by conventional metaphase cytogenetics. Quantitative real-time PCR detected 650 BCR-ABL transcripts per 2.5 μL CDNA with a BCR-ABL/ABL ratio of 1%. This was repeated 9 and 12 months after treatment with imatinib mesylate started and showed BCR-ABL/ABL ratios of 0.3% and 0.2%, respectively (Table 1). The patient remains in good health and has had no recurrence of GVHD.

Results and discussion

This case illustrates the value of imatinib mesylate as treatment of relapsed CML after allo-SCT. Our patient did not respond to DLI. However, he responded rapidly to imatinib mesylate with normalization of the peripheral blood and bone marrow. Furthermore, after 3 months of treatment, there was evidence of a significant cytogenetic response that was complete by 6 months, with the total disappearance of...
Philadelphia chromosome–positive metaphases. PCR studies, however, still detected residual BCR-ABL transcripts at low levels. We believe this is the first report of the efficacy of imatinib mesylate in patients who have relapses in chronic phase after allo-SCT.

Donor lymphocyte infusions have become the treatment of choice for patients in relapse after allo-SCT. Results in patients who have relapses in the advanced phase are poor, but durable, complete remissions can be achieved in most patients in chronic-phase or cytogenetic relapse. GVHD and marrow aplasia remain the 2 most important complications of DLI, but when an escalating dose schedule is used, these problems are greatly reduced. In a recent European Group for Blood and Marrow Transplantation (EBMT) study, survival after relapse was related to 5 factors: time from diagnosis to transplantation, disease phase at transplantation, disease phase at relapse, time from transplantation to relapse, and donor type. The effects of individual adverse risk factors were cumulative so that patients with 2 or more adverse features had significantly reduced survival rates (35% vs 65% at 5 years). Furthermore, DLI was less effective in patients in whom GVHD developed after SCT. According to these data, our patient was in the group likely to survive long-term, despite remaining in chronic phase at relapse.

Imatinib mesylate binds to the adenosine triphosphate–binding site of the ABL and BCR-ABL tyrosine kinases and maintains them in an inactive conformation. It is also capable of inhibiting at least 2 other tyrosine kinases, c-kit and platelet-derived growth factor receptor. Although in vitro studies have demonstrated selective killing of CML hematopoietic cells, presumably resulting from BCR-ABL kinase inhibition, its precise mechanism of action in vivo is still unclear. However, clinical trials have shown remarkable, though preliminary results. In an ascending-dose phase 1 study, imatinib mesylate induced substantial and durable hematologic responses with minimal toxicity in nearly all patients with chronic-phase CML. In phase 2 trials, it has produced major cytogenetic remissions in nearly 50% of patients in chronic-phase disease resistant to interferon. In one third of patients, the cytogenetic response has been complete. Follow-up remains relatively short, but responses seem durable. In virtually all patients in CCR, residual BCR-ABL transcripts are detected by RT-PCR at variable levels. In our institution, a review of 31 patients in CCR revealed a median BCR-ABL/ABL ratio of 0.052% (range, 0.017%–0.7%). One patient had a single negative determination, and in 4 more patients the BCR-ABL/ABL ratio was more than 0.001% (data not published). The RT-PCR tests in the patient reported here showed ratios of 0.3% and 0.2%, consistent with our findings.

Our patient did not respond to DLI. Survival for patients resistant to DLI is poor. In the EBMT report, up to one third of patients had 2 or more adverse prognostic factors for response to DLI. Despite recent progress in the treatment of relapse of CML after allo-SCT, there is still a need for alternative therapies for a significant proportion of patients. Our findings suggest that there could be a role for imatinib mesylate in the management of these patients. It is also possible that the combination of imatinib mesylate and DLI will prove beneficial in some cases, thus reducing the need for higher doses of DLI and reducing the risk for complications. Finally, a new strategy may emerge from these observations—the use of imatinib mesylate immediately after SCT may prevent relapse and increase the efficacy of reduced-intensity conditioning allo-SCT in the future.

Table 1. Cytogenetic and molecular evolution

<table>
<thead>
<tr>
<th>Date</th>
<th>Disease status</th>
<th>Treatment</th>
<th>Cytogenetics</th>
<th>FISH</th>
<th>RT-PCR BCR-ABL/ABL ratio (%)</th>
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</thead>
<tbody>
<tr>
<td>Oct 1997</td>
<td>Chronic phase</td>
<td>Allo-SCT</td>
<td>100% XY t(9;22)</td>
<td>ND</td>
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<td>Sep 1998</td>
<td>Molecular relapse</td>
<td>DLI</td>
<td>100% XX</td>
<td>100% XX</td>
<td>10</td>
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<tr>
<td>Sep 1999</td>
<td>Cytogenetic relapse</td>
<td>DLI</td>
<td>92% XY t(9;22)</td>
<td>ND</td>
<td>80</td>
</tr>
<tr>
<td>Dec 1999</td>
<td>Hematologic relapse</td>
<td>DLI (+ IL-2)</td>
<td>100% XY t(9;22)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Aug 2000</td>
<td>Hematologic relapse</td>
<td>DLI</td>
<td>100% XY t(9;22)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Nov 2000</td>
<td>Remission</td>
<td>STI571</td>
<td>97% XX</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Feb 2001</td>
<td>Remission</td>
<td>STI571</td>
<td>97% XX</td>
<td>100% XX</td>
<td>1</td>
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<tr>
<td>May 2001</td>
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<td>STI571</td>
<td>100% XX</td>
<td>100% XX</td>
<td>0.3</td>
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<tr>
<td>Aug 2001</td>
<td>Remission</td>
<td>STI571</td>
<td>100% XX</td>
<td>100% XX</td>
<td>0.2</td>
</tr>
</tbody>
</table>

FISH indicates fluorescence in situ hybridization; STI571, imatinib mesylate; ND, not done.
*Plus del(13q), t(5;12), der(6), der(8), and nonclonal rearrangements.

References

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