Extended Follow-up of Patients Treated with Imatinib Mesylate (Gleevec) for Chronic Myelogenous Leukemia Relapse after Allogeneic Transplantation: Durable Cytogenetic Remission and Conversion to Complete Donor Chimerism without Graft-versus-Host Disease


ABSTRACT

Purpose: Over the last several years, donor lymphocyte infusions have become the standard approach for patients with chronic myelogenous leukemia (CML) who relapse after allogeneic stem cell transplantation (SCT). Recent reports indicate that imatinib mesylate (Gleevec) can induce remissions in these patients as well. Less is known about the extent and durability of these responses.

Experimental Design: We studied 15 patients treated with imatinib for recurrent CML after SCT, 10 patients with stable phase CML (SP-CML), 1 with accelerated phase (AP-CML), and 4 with blast phase (BP-CML). The dose of imatinib was 600 mg (n = 10) or 400 mg (n = 5) daily. Patients were followed for hematological, cytogenetic, and molecular response. A subset of responders was followed for changes in donor-derived hematopoietic chimerism.

Results: Of the 10 patients with SP-CML, all achieved a hematological response. Within 3 months, five of these patients had achieved a complete cytogenetic response (CCR). By six months, 9 of 10 patients had achieved CCR. The BCR-ABL transcript could not be detected by reverse transcription-PCR in 7 of 9 patients. Patients who achieved CCR showed evidence of conversion to complete donor chimerism. No patient developed graft-versus-host disease. With a median follow-up of 25 months, all patients are alive and 9 of 10 patients remain in CCR. Only one of the 5 patients with AP/BP-CML achieved a complete cytogenetic response.

Conclusions: We find that imatinib is well tolerated in patients with SP-CML who relapse after SCT. Responses were rapid, durable, and associated with conversion to full donor chimerism without graft-versus-host disease. Imatinib was far less effective in patients who relapsed with AP/BP-CML. Imatinib should be evaluated as either an alternative or as an adjunct to donor lymphocyte infusions for patients with SP-CML who relapse after SCT.

INTRODUCTION

Until the introduction of donor lymphocyte infusions (DLI) into clinical practice 10 years ago, the therapeutic options available to patients who relapsed after allogeneic stem cell transplantation (SCT) were extremely limited. Second allogeneic transplants were performed with some reported success. However, these second transplants had been associated with significant treatment-related morbidity and mortality. The options for patients who relapsed after transplantation improved considerably with the advent of DLI, especially for those patients with chronic myelogenous leukemia (CML; Ref. 1 and 2). Reports have suggested that durable responses can be achieved in 70–80% of patients with CML who relapse with stable phase disease (SP-CML) although remissions in advanced CML are rare (3, 4). Unfortunately, DLI can be complicated by potentially life-threatening graft-versus-host disease (GVHD) and pancytopenia (1). Therefore, novel safe and effective treatment modalities for relapse after transplantation are still needed.

Imatinib mesylate is a potent inhibitor of the BCR-ABL fusion gene product and is able to interrupt many of the proliferation and antiapoptotic signals engineered by this transgene (5–7). Imatinib mesylate can safely induce high rates of both hematological and cytogenetic responses in newly diagnosed patients with stable phase CML and those who are refractory to or intolerant of IFN (8–10). There have been recent reports of promising activity of imatinib mesylate in patients with CML relapsing after allogeneic transplantation (11–18). We report extended follow-up of 10 patients treated with imatinib mesylate for relapse of SP-CML after allogeneic transplantation. We have observed rapid and durable cytogenetic and molecular responses without any apparent adverse effects. After treatment with imatinib, all responding patients experienced conversion from mixed to full donor chimerism without the development of GVHD.
MATERIALS AND METHODS

Patient Population. All patients who received imatinib mesylate had previously undergone an allogeneic bone marrow transplant for SP-CML. The transplant conditioning regimen consisted of cyclophosphamide and total body irradiation. Primary GVHD prophylaxis was cyclosporine/methotrexate in seven patients and T-cell depletion (anti-CD6 monoclonal antibody) in eight patients (19). All patients had evidence of either cytogenetic or hematological relapse after transplantation. At the time of initiation of imatinib mesylate, patients had no evidence of active infection or organ dysfunction.

SP-CML was defined by the presence of all of the following: <15% blasts, <20% basophils, and <30% blasts plus promyelocytes in the peripheral blood or bone marrow as well as a platelet count of at least 100,000/ml. The presence of additional cytogenetic abnormalities without other signs of accelerated phase disease were not considered accelerated phase disease (AP-CML), and for the purposes of this study these patients were included in the SP-CML group.

Blast phase (BP) disease was defined as the presence of at least 30% blasts in the peripheral blood or bone marrow or the presence of extramedullary blastic disease. Accelerated phase disease was defined by the presence of one of the following: (a) 15–29% blasts in the blood or bone marrow, (b) at least 30% blasts plus promyelocytes in the blood or bone marrow but not making the criteria for BP disease, or (c) at least 20% basophils in the blood or bone marrow.

Treatment Program. Five patients with SP-CML were initiated at a dose of 600 mg daily, and five patients were started at a dose of 400 mg daily. Patients did not receive concurrent administration of either cytotoxic or biological therapy. Before starting imatinib mesylate, patients were off of all immunosuppressive agents, and there were no clinical signs or symptoms of either acute or chronic GVHD. All five patients with BP-CML or AP-CML received imatinib at a dose of 600 mg/ day. All patients signed an internal review board approved consent form before initiating treatment.

Treatment Evaluation. Complete blood counts and metabolic profiles were performed weekly for 1 month and then monthly thereafter. To assess response, bone marrow evaluations with karyotypic and molecular analyses were initially performed every 3 months after starting therapy. A complete hematological remission was defined by a white cell count < 10 × 10^9/ml; platelet count < 450 × 10^9/ml but > 100 × 10^9/ml; the presence of <5% myelocytes and metamyelocytes in the peripheral blood; <20% basophils in the peripheral blood or bone marrow; the absence of blasts and promyelocytes in the peripheral blood; and the absence of extramedullary involvement.

A major cytogenetic response was classified as either complete (0% Ph+–cells in metaphase in the bone marrow) or partial (1–35% Ph+–cells in metaphase in the bone marrow). Other categories of cytogenetic response were minor response (36–65% Ph+–cells in metaphase in the bone marrow), minimal response (66–95% Ph+–cells in metaphase in the bone marrow), and no response (>95% Ph+–cells in metaphase in the bone marrow). Evaluation of the cytogenetic response was based on the examination of at least 20 cells in metaphase in bone marrow aspirate samples.

RNA was isolated from ficolled blood or bone marrow by a standard guanidinium isothiocyanate technique (20, 21). Reverse transcription (RT)-PCR analysis to detect bcr-abl chimeric mRNA was performed in duplicate by parallel assays on separate RNA isolates. This qualitative multiplex assay uses a set of nested primers to BCR exons e1 and b2 and to ABL exon 2. A nested parallel control assay for abl mRNA was used to assure that RNA was isolated and that the reverse transcriptase reaction worked appropriately. The PCR products from both reactions were size-fractionated on a 2.5% agarose gel. The sensitivity of detecting a gene product is estimated at 1 in 10^6.

To assess the response to imatinib at a molecular level, a qualitative 3-step “nested” RT-PCR assay was performed to amplify the chimetic bcr-abl in at least duplicate assays on EDTA anticoagulated fresh blood or bone marrow specimens (21). A minimum of 5 ml of peripheral blood or 2 ml of bone marrow was ficolled, and the mononuclear layer was separated into three separate aliquots. RNA was isolated by a standard guanidinium isothiocyanate technique from each aliquot. Total RNA (0.5–1 μg) was converted to cDNA in a 40-μl reaction mix of 10 pmol abl-specific primer (abl-1), 50 μM Tris-HCL (pH 8.3), 75 μM KCL, 3 μM MgCl2, 500 μM/l deoxynucleoside triphosphates, 10 μM DTT, 10 units RNAsin (Promega Corp., Madison, WI), 200 units Superscript II RNAase H–RT (Invitrogen, Carlsbad, CA), and diethyl pyrocarbonate H2O. The reaction mix was incubated at 37 °C for 60 min and then 95°C for 5 min. Eighteen μl of the RT reaction was transferred to a separate tube containing 20 pmol each of primers abl-1, mbc-1, and Mbcr-1; 10 μM Tris-HCL (pH 8.3); 50 mM KCL; 1.5 mM MgCl2; 1.25 units Taq polymerase (Amplitaq, Applied Biosystems, Foster City, CA); and diethyl pyrocarbonate H2O in a 50-μl reaction. The reaction mix was incubated in a preheated thermocycler for an initial denaturation step at 94°C for 4 min, then 26 cycles of amplification at 94°C for 1 min, 61°C for 1.5 min, followed by a final elongation at 72°C for 10 min. Ten microliters of a 1:100 dilution of the first round of PCR was transferred to a tube containing fresh PCR reagents of 20 pmol each of “nested” primers abl-2, mbcr-2, and Mbcr-2; 10 μM Tris-HCL (pH 8.3); 50 mM KCL; 1.5 mM MgCl2; 200 μM/l deoxynucleoside triphosphates; 1.25 units Taq polymerase (Amplitaq; Applied Biosystems); diethyl pyrocarbonate H2O in a 50-μl reaction; and denatured and amplified for 35 cycles in conditions identical to the first round. After amplification, 20 μl of the final PCR product was electrophoresed through an ethidium-bromide-stained 2.5% agarose gel and photographed.

For all PCR reactions, parallel-positive controls of RNA from K562 (b3a2) and SUP-B13 (e1a2) cell lines and negative controls of pooled normal blood RNA and “no-RNA” were run. The assay routinely detects a 10^-6 dilution of the positive cell line RNAs into Philadelphia-negative cell line RNA. For all patient samples, a separate “nested” PCR amplification was performed in parallel as a control for RNA integrity. Eighteen μl of the same RT reaction used for the bcr-abl PCR reactions was amplified using primers that detect normal abl mRNA [abl-1, c-abl 1A, c-abl 1B (first round); abl-2, c-abl 2 (second round)]. The thermocycling and gel electrophoresis conditions were identical to those used for bcr-abl detection.
Precautions to eliminate PCR carryover contamination included separate rooms for pre-PCR, amplification and post-PCR procedures, filter-containing disposable pipette tips, and normal RNA and no-nucleic acid PCR reactions in all runs. If negative control RNAs showed a PCR product, the entire assay was repeated. The nucleotide sequences of the PCR primers used were as follows: abl-1, 5’-TGATTATAGCCTAGAACCCGGA-3’; mbc-1, 5’ACCATGGTGGCGTCCCGAAGA-3’; mbc-1, 5’GAAGTGTTTCAGAAGCTTCTCC-3’; abl-2, 5’ATCTCCAC- TGGCCACAAATCATA-3’; mbc-2, 5’AGATCTGGCCC- AAGATGGCGGAGGG-3’; Mbc-2, 5’TGGAGCTGCAGATGCTGACCAATCG-3’; c-abl 1A, 5’ATCTGCGTAAGCTGG- TGGGCT-3’; c-abl 1B, 5’ GCAGCAGCTGGAAAGTACCTT-3’; abl-2, 5’AGTGGAGCGCTCGGTGGAATCCTCAA-3’; c-abl 2, 5’AGTGAAGCGCTCGGTGGAATCCTCAA-3’.

Using these primers, the alternate transcripts yielded PCR products of different sizes (b3a2 305 bp, b2a2 230 bp, e1a2 197 bp, normal abl 106 bp). A positive PCR test required appropriate results in the negative and positive controls as well as a correct size bcr-abl PCR product in duplicate parallel tests on paired cell aliquots. If there was discordance between aliquots, the third cell aliquot was assayed. Results were reported as a number of positive to number of cell aliquots tested. A negative test required the absence of a bcr-abl PCR product in duplicate parallel aliquots as well as appropriate results in the negative and positive controls.

**Chimerism Evaluation.** Cryopreserved peripheral blood mononuclear cells were available from six patients and their donors before allogeneic stem cell transplantation, before imatinib mesylate administration, and 3–6 months after initiation of imatinib mesylate therapy. Cryopreserved cells were thawed and genomic DNA was extracted from 3–10 × 10^6 cells using the QiAamp DNA Blood Mini kit (Qiagen Inc., Valencia, CA) according to the manufacturer’s instructions. Before PCR amplification, DNA concentration in all samples was determined by UV spectrophotometry and adjusted to a concentration of 0.03 μg/μl with sterile distilled water. PCR was performed on each sample, and the percentage of hematopoietic chimerism was determined by the PSQ96 Allele Discrimination Software (Pyrosequencing AB) for informative single nucleotide polymorphisms (22). Chimerism analysis on the patient with a sex mismatched donor was assessed by fluorescent in situ hybridization.

**RESULTS**

**Patient Characteristics**

A total of 15 patients were treated with imatinib for relapsed CML after an allogeneic SCT. Patient demographics for patients treated for SP-CML with imatinib are detailed in Table 1. All ten patients were fully matched with their donors. The median interval from a documented relapse and the initiation of imatinib mesylate therapy was 21 months (range, 11 months to 7 years) for the patients treated with SP-CML and 9.2 months (range, 2–12 months) for the patients treated with either AP or BP-CML. The median interval between bone marrow transplantation and the first documented evidence of relapse was 30 months (range, 11 months to 7 years) for the patients treated with SP-CML and 9.2 months (range, 2–12 months) for the patients treated with either AP or BP-CML. All the patients with SP-CML had stopped their immune suppression >12 months before starting imatinib mesylate. Four patients had received DLI previously. In two cases, a complete response had been obtained followed by subsequent relapse. In all cases DLI was administered >12 months before starting imatinib mesylate. No patient had received imatinib mesylate previously.

**Response to Treatment in Patients with SP-CML**

**Hematological Response.** All ten patients achieved a hematological response after 1 month of therapy with imatinib mesylate (Table 3). Nine of 10 patients had complete normalization of counts, and one has had stable mild pancytopenia.

**Cytogenetic Response.** After 3 months of imatinib mesylate therapy, 8 of the 10 patients (80%) with SP-CML achieved a major cytogenetic response. Five patients had a complete response, and 3 patients had a major response (<35% Ph+ metaphases). All three patients with a major cytogenetic

### Table 1: Patient characteristics with SP-CML

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Median age (yrs.)</td>
<td>47 (range, 30–62 year)</td>
</tr>
<tr>
<td>Gender</td>
<td>Female 4 Male 6</td>
</tr>
<tr>
<td>Disease status at time of BMT</td>
<td>SP-CML 10</td>
</tr>
<tr>
<td>Type of BMT</td>
<td>Fully matched related donor 9 Fully matched unrelated donor 1</td>
</tr>
<tr>
<td>GVHD prophylaxis</td>
<td>Cyclosporine/methotrexate 5</td>
</tr>
<tr>
<td>BMT-relapse to time of treatment interval (mos.)</td>
<td>21 (range, 28 days to 5 year)</td>
</tr>
<tr>
<td>Prior donor lymphocyte infusion</td>
<td>2</td>
</tr>
<tr>
<td>Disease status at time of imatinib initiation</td>
<td>SP-CML 10</td>
</tr>
<tr>
<td>Cytogenetic status at time of imatinib initiation</td>
<td>Ph+ - sole abnormality 4 Ph+ - with additional abnormalities 6</td>
</tr>
</tbody>
</table>

Abbreviations: SP-CML, stable phase chronic myelogenous leukemia; BMT, bone marrow transplantation; GVHD, graft-versus-host disease.

**Table 1** Patient characteristics with SP-CML
response and the one patient with a minor cytogenetic response (66 to 95% Ph+ metaphases) at 3 months achieved a complete cytogenetic remission after 6 months on therapy (Fig. 1). Only one patient failed to achieve a cytogenetic response. The cytogenetic responses have been durable in all nine patients with a median duration 19 months (range 13–26 months) since achieving complete cytogenetic response and 25 months since initiating imatinib (Fig. 1). Each one of these seven patients has remained PCR negative.

Donor Chimerism Studies. Donor chimerism studies were performed on seven patients with SP-CML who achieved a complete cytogenetic remission. Within 1 year on imatinib mesylate, six of seven patients had >99% donor-derived hematopoiesis in the bone marrow. Mixed donor/host chimerism was observed in all but one patient tested before initiation of treatment. All six of the patients who developed full donor chimerism achieved complete cytogenetic remission. The one patient who did not convert from mixed to full donor chimerism was the only patient in the cohort who did not achieve a cytogenetic response.

Toxicity. Imatinib mesylate has been extremely well tolerated in this group of patients, and no patient discontinued therapy because of side effects. There were no grade 3 or 4 nonhematological toxicities, and no patient developed any sign of acute or chronic GVHD. Only one patient required a dose reduction from 600 to 400 mg/day for hematological toxicity. This occurred in the patient who failed to achieve a cytogenetic remission.

Patient Outcome. Patients have now been followed for a median of 23 months (range, 15–30 months). The overall survival is 100% for the 10 patients treated with SP-CML. All of the nine patients who achieved a complete cytogenetic remission to imatinib mesylate therapy remain in remission. Imatinib therapy has been continued in all 10 patients.

Response to Treatment in Patients with Advanced Disease. Only one patient was treated with AP-CML. Although only a partial hematological response was achieved after 30 days of imatinib therapy, the patient entered a complete hematological response after 60 days of therapy (Table 4). Unfortunately, a cytogenetic response was never achieved, and the patient expired because of progressive disease after only 4 months of therapy.

Two patients with myeloid blast crisis cleared their circulating blasts after 1 month on imatinib mesylate (Table 4). One

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Patient characteristics with AP/BP-CML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (yrs.)</td>
<td>48.6 (range, 40–55 year)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 2, Female 3</td>
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<tr>
<td>Disease status at time of BMT</td>
<td>SP-CML 5</td>
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<tr>
<td>Type of BMT</td>
<td>Fully matched related donor 2, Fully matched unrelated donor 3</td>
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<td>GVHD prophylaxis</td>
<td>T-cell depletion 2, Cyclosporine/methotrexate 3</td>
</tr>
<tr>
<td>BMT-relapse to time of treatment interval (yrs.)</td>
<td>3.4 (range, 1 d to 7 year)</td>
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<tr>
<td>Prior donor lymphocyte infusion</td>
<td>2</td>
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<tr>
<td>Disease status at time of imatinib initiation</td>
<td>AP-CML 1, BP-CML 4, Myeloid blast crisis 3, Lymphoid blast crisis 1</td>
</tr>
<tr>
<td>Cytogenetic status at time of imatinib initiation</td>
<td>Ph+ - sole abnormality 0, Ph+ - with additional abnormalities 5</td>
</tr>
</tbody>
</table>

Abbreviations: AP, accelerated phase; BP, blast phase; CML, chronic myelogenous leukemia; BMT, bone marrow transplantation; GVHD, graft-versus-host disease; SP-CML, stable phase chronic myelogenous leukemia.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Patient disease status and clinical results for patients with SP-CML.</th>
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<tbody>
<tr>
<td>Patient no.</td>
<td>Disease status</td>
</tr>
<tr>
<td>1</td>
<td>SP-CML</td>
</tr>
<tr>
<td>2</td>
<td>SP-CML</td>
</tr>
<tr>
<td>3</td>
<td>SP-CML</td>
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<tr>
<td>4</td>
<td>SP-CML</td>
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<tr>
<td>5</td>
<td>SP-CML</td>
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<tr>
<td>6</td>
<td>SP-CML</td>
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<tr>
<td>7</td>
<td>SP-CML</td>
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<tr>
<td>8</td>
<td>SP-CML</td>
</tr>
<tr>
<td>9</td>
<td>SP-CML</td>
</tr>
<tr>
<td>10</td>
<td>SP-CML</td>
</tr>
</tbody>
</table>

NOTE. Percentages correspond to the percentage of Ph+ metaphases.

Abbreviations: SP-CML, stable phase chronic myelogenous leukemia; CR complete remission; Cyto, cytogenetic; Major, major cytogenetic remission (< 35%); Minor, minimal cytogenetic response (66–95%); NR, no cytogenetic response; pos or neg, RT-PCR status (not quantitative).
mesylate therapy, but she remained PCR positive for the cytogenetic remission after 3 months from the start of imatinib mesylate was eventually discontinued. She achieved a complete response for approximately 5 months before she developed progressive disease and died within 2 months from her discontinuation of imatinib mesylate. The second of these two patients cleared both her circulating and bone marrow myeloblasts after only 1 month on therapy. With continued imatinib therapy, she had persistent pancytopenia. Repeat bone marrow examinations showed the absence of any bone marrow blasts, but she had a markedly hypocellular bone marrow without any significant myeloid maturation. Her dose of imatinib mesylate was decreased from 600 to 300 mg/day without any improvement of her hematological indices. Repeat bone marrow examinations confirmed the absence of blast phase disease, and the imatinib mesylate was eventually discontinued. She achieved a complete cytogenetic remission after 3 months from the start of imatinib mesylate therapy, but she remained PCR positive for the BCR-ABL fusion gene product. Because of her persistent pancytopenia and marrow aplasia, she was treated with a stem cell infusion using a nonmyeloablative preparative regimen. She remains disease-free with normal peripheral blood counts in a complete cytogenetic remission 30 months after initiating imatinib mesylate. The third patient with myeloid blast crisis developed progressive disease within 30 days of initiating imatinib mesylate and died.

The patient with lymphoid blast crisis cleared his peripheral blood and marrow of blasts while on imatinib mesylate. This patient achieved a partial hematological remission based on the fact that his platelet count remained below 100,000. However, after 4 months on therapy, he developed severe GVHD of his skin and liver and ultimately died of secondary to progressive GVHD. It is not clear in this circumstance if disease response was attributable to imatinib mesylate or the presence of a graft-versus-leukemia effect induced by the withdrawal of immune suppression 3 months before the start of imatinib therapy.

**Toxicity.** Imatinib mesylate was generally well tolerated in this group of patients with advanced disease, although three patients developed grade 3 or 4 elevation of their liver function tests. In one of these cases the rise in abnormality of the liver function test was thought to be attributable to the development of GVHD concurrent with discontinuation of immune suppressive medications. Two patients had an elevation of their total bilirubin, and the other patient had a rise in his aspartate aminotransferase; the latter was thought to be secondary to GVHD. The elevation of the total bilirubin in both patients was thought to be secondary to leukemic infiltration because both of these patients developed rapidly progressive disease.

**Patient Outcome.** Only one of the five patients with AP/BP-CML remains alive and free of disease. This patient received a nonmyeloablative transplant after achieving a complete cytogenetic remission while on therapy with imatinib mesylate.

**DISCUSSION**

Our results confirm that imatinib mesylate is safe and well tolerated in patients with CML who relapse after an allogeneic SCT. All 10 patients with SP-CML had a hematological response, and nine patients obtained a complete cytogenetic remission after 6 months on therapy. Seven of these patients also achieved a complete molecular remission. Our study confirms our initial observations and those reported in other case series: specifically that imatinib can induce hematological and cytogenetic remissions in patients with relapsed CML after allogeneic transplantation. Of note in our current series is the rapidity of cytogenetic responses, the durability of those responses, the association of response with conversion to full donor chimerism, and the absence of GVHD associated with that conversion. For patients with AP/BP-CML, combination therapy with imatinib and cytoreductive chemotherapy may lead to superior results than either approach alone.
The time to complete cytogenetic response (median, 3 months) appears faster than that reported in patients initiating imatinib in the absence of prior transplantation. Indeed, 9 of 10 stable phase patients achieved complete cytogenetic response by 6 months, a somewhat higher number than the 73.8% at 18 months that was reported in the recent International Randomized Study of Interferon and ST1571 trial of newly diagnosed patients with CML (10). Although additional studies would be needed to confirm this observation, it could be speculated that in the post-transplant relapse setting, the leukemic burden is less than in the *de novo* circumstance. More intriguingly, it is possible that the presence of allogeneic donor cells in the host may re-exert a graft-versus-leukemia effect after imatinib treatment, accelerating the time to response. Indeed, the time to cytogenetic and molecular response is similar to that reported after infusion of donor lymphocytes (4). All evaluable patients responding completely to imatinib developed full donor chimerism in contrast to the one patient who did not respond cytogenetically. Assessment of antileukemic activity from lymphocytes obtained before and after imatinib initiation is under way.

Our experience, as well as that from other centers, with imatinib treatment of patients with frank accelerated phase or blast crisis who relapse after an allogeneic SCT is less encouraging (11, 15–18, 23) when compared to the results for patients with SP-CML. However, in our series, of the six patients who might have been classified as accelerated phase based solely on clonal cytogenetic evolution, five developed a complete cytogenetic response. These data suggest that the presence of additional cytogenetic changes in relapsed patients who have previously undergone a bone marrow transplant may not predict for an adverse outcome.

Kantarjian et al. and others (11, 17, 18) have reported the development of apparent GVHD in patients treated with imatinib after transplantation. In contrast, we observed no acute or chronic GVHD with a median follow-up of 2 years despite conversion to full donor chimerism. One possible explanation for this difference is that in other series in which GVHD has been reported, many patients had been withdrawn from immune suppression shortly before starting imatinib. As well, in the series by Kantarjian et al., a number of patients had received DLI at a median of 4 months before treatment. It is possible that the withdrawal of immune suppression or recent DLI increased the likelihood of developing GVHD. In our series of stable phase patients, none had received immune suppressive medications or DLI for over a year before starting treatment.

Our response rate to imatinib is at least comparable with that expected from treatment with DLI alone. Moreover, responses occurred without the development of GVHD. Although the durability of the responses to imatinib post-transplant is unknown, it is encouraging that all responding patients continue in complete cytogenetic response with an average of 2 years after starting imatinib therapy. Reported data suggest that 10–20% of patients responding initially to DLI will subsequently develop recurrent disease. It is unclear if imatinib can replace DLI entirely or should be used as an adjunct to cell infusions. Because imatinib is well tolerated in this setting, it may be possible to combine imatinib with lower doses of DLI that are less likely to induce GVHD. Given the uniform conversion to full donor chimerism in those patients who achieve complete cytogenetic response, it is possible that imatinib will not need to be continued indefinitely. Because none of the patients in our study had been treated previously with imatinib, it remains unclear if these results can be duplicated in patients who receive imatinib therapy before SCT. Further exploratory and comparative studies will be crucial to establishing the role of imatinib mesylate for patients who have relapsed after transplantation.

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Clinical Cancer Research

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