Imatinib mesylate therapy for relapse after allogeneic stem cell transplantation for chronic myelogenous leukemia

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Twenty-eight adults with chronic myelogenous leukemia (CML) that had relapsed after allogeneic stem cell transplantation (SCT) received imatinib mesylate (400-1000 mg/d). Disease was in chronic phase in 5 patients, accelerated in 15, and blastic in 8 (7 medullary, 1 extramedullary); median time from transplantation to relapse was 9 months (range, 1-137 months). Thirteen patients had undergone salvage donor lymphocyte infusion (DLI) (median time from DLI to imatinib mesylate therapy, 4 months [range, 2-39 months]). The overall response rate was 79% (22 of 28 patients); the complete hematologic response (CHR) rate was 74% (17 of 23 patients), and the cytogenetic response rate was 58% (15 of 26 patients; complete response in 9 [35%] patients). CHR rates were 100% for chronic phase, 83% for accelerated phase, and 43% for blastic phase. The patient with extramedullary blastic disease achieved complete response. Cytogenetic response rates were 63% (12 of 19 patients) for chronic or accelerated phases (complete cytogenetic response in 8) and 43% for blastic phase (3 of 7 patients). At median follow-up of 15 months, 19 patients were alive, 9 with no evidence of disease. The 1-year estimated survival rate was 74%. Five patients had recurrence of grade 3 (3 patients) or grades 1 to 2 (2 patients) graft-versus-host disease (GVHD). Severe granulocytopenia developed in 43% of patients and thrombocytopenia in 27%; both conditions reversed with dose adjustments of imatinib mesylate. We conclude that imatinib mesylate effectively controlled CML that recurred after allogeneic SCT, but it was associated with side effects including myelosuppression and recurrence of severe GVHD. (Blood. 2002; 100:1590-1595)

Introduction

Recent advances in the understanding of Philadelphia chromosome (Ph)–positive chronic myelogenous leukemia (CML) and progress in therapy have improved the prognosis for patients with this disease.1-7 The 2 primary types of first-line therapy for CML involve interferon-α (IFN-α) and allogeneic stem cell transplantation (SCT). IFN-α–based therapy produces a median survival time of 7 years and a major cytogenetic response rate (ie, reduction of the proportion of Ph-positive cells to less than 35%) of 30% to 50%; among patients who achieve a major cytogenetic response, the 10-year survival rate is 70% or more.5-7 Allogeneic SCT produces excellent long-term event-free survival rates of 40% to 80%, but the 1-year mortality rate can vary from 5% to 50% depending on factors such as patient age, source of stem cells (related versus unrelated donor), degree of mismatch, cytomegalovirus status, and use of prophylactic antibiotics or prophylaxis for graft-versus-host disease (GVHD). Disease phase at SCT also affects the success of SCT for CML; relapse rates among patients who undergo transplantation during the chronic phase of the disease range from 5% to 20%; those for patients who undergo transplantation during the accelerated or blastic phase are as high as 30% to 60%.

Relapse after allogeneic SCT has been treated with donor lymphocyte infusion (DLI), IFN-α therapy, or additional transplantation,8-13 but each treatment has its drawbacks. Although DLI can produce complete molecular-level response (ie, abolishment of the Bcr-Abl oncoprotein) rates of 60% to 70% in chronic phase CML, it can also cause recurrence of GVHD, myelosuppression–associated complications, and death.8-9 IFN-α–based therapy is only moderately successful, inducing responses in 40% to 50% of selected patients.10,11 A second allogeneic SCT can be offered if relapse occurs 12 months or more after the first transplantation, but second transplantation is usually reserved for patients whose disease does not respond to DLI.12,13 In general, DLI has become the favored front-line approach in patients with CML relapse after allogeneic SCT.

A new form of therapy for CML involves the tyrosine kinase inhibitor imatinib mesylate (Gleevec, STI571), which specifically inhibits the function of the Bcr-Abl oncoprotein associated with Ph-positive disease.14,15 Phase I and II studies of imatinib mesylate for patients with CML in the chronic, accelerated, and blastic phases have produced impressive results.16-21 In one such study of patients with chronic phase CML whose disease did not respond to IFN-α, imatinib mesylate produced a complete hematologic response (CHR) rate of 95%, a major cytogenetic response rate of 60%, and an estimated 1.5-year survival rate of 95%.18 The purpose of the present study was to determine whether imatinib mesylate is effective against CML that relapses after allogeneic SCT.
Patients, materials, and methods

Patients

Adults with Ph-positive CML that had relapsed after allogeneic SCT were eligible to participate in several ongoing protocols (all sponsored by Novartis Pharmaceuticals Corporation, East Hanover, NJ). Informed consent was obtained for all studies according to institutional guidelines. Eligibility criteria included having disease in the chronic phase with molecular, cytogenetic, or hematologic evidence of relapse; or disease in the accelerated or blastic phase (definitions are provided below). Additional eligibility criteria were performance status of level of 0 to 2 on the Eastern Cooperative Oncology Group scale, adequate renal function (creatinine level less than 2 mg/100 mL), adequate hepatic function (bilirubin, aspartate aminotransferase, and alanine aminotransferase levels less than twice the upper limits of normal), and adequate cardiac function.

Therapy

Imatinib mesylate was given in oral doses ranging from 400 to 1000 mg daily, with doses adjusted according to previously published guidelines. Of the 28 participating patients, 6 received 400 mg daily, 1 received 500 mg daily, 13 received 600 mg daily, and 2 received 750 mg daily; the remaining 6 patients received 400 mg or 500 mg twice daily. Treatment was continued until the disease was considered unresponsive to imatinib mesylate, death, a change to more definitive therapy (eg, second SCT), or the appearance of unacceptable toxic effects that did not respond to dose modifications.

Definitions of response and CML phases

CHR was defined as the normalization of peripheral blood cell counts and differential counts and the disappearance of all signs and symptoms of CML. Cytogenetic responses were categorized as complete (no Ph-positive metaphase cells in bone marrow or blood samples), partial (1%-34% Ph-positive cells), or minor (35%-90% Ph-positive cells). Samples from patients with a complete cytogenetic response were subjected to quantitative competitive reverse transcription–polymerase chain reaction (RT-PCR) for BCR-ABL transcripts as evidence of molecular response.

Blastic phase CML was defined as the presence of 30% or more blasts in the peripheral blood or marrow or of extramedullary disease. Accelerated phase disease was characterized as the presence of 15% or more blasts, 20% or more basophils, 30% or more blasts ± promyelocytes, thrombocytopenia (less than 100 x 10^9/L) unrelated to therapy, or clinical cytogenetic clonal evolution.

Imatinib mesylate

Survival time from the initiation of imatinib mesylate therapy and survival as a function of disease phase at therapy were calculated using the Kaplan-Meier method.

Results

Patients

Characteristics of the 28 patients who underwent imatinib mesylate therapy are shown in Table 1. Median patient age was 43 years (range, 25-64 years); 16 (57%) patients were men. Twelve of the 17 patients who underwent SCT from related donors were 6/6 matches; of the 11 patients with unrelated SCT donors, HLA-matching data were available for 9, and 7 of those 9 were 6/6 matches. Median time from allogeneic SCT to evidence of relapse was 9 months (range, 1-137 months). Six patients underwent T-cell–depleted allogeneic SCT. With regard to previous salvage therapy after relapse, 13 patients underwent DLI—6 underwent it once, and 7 underwent it 2 or more times. Median time from the last DLI to imatinib mesylate therapy was 4 months (range, 2-39 months). Fifteen patients had been off immunosuppressive therapy for a median of 11 months (range, 1-125 months). When imatinib mesylate therapy was begun, 4 patients had chronic phase active disease, 1 had chronic phase disease with CHR and 0% Ph-positive cells (complete cytogenetic response) and Bcr-Abl transcripts positive by PCR, 15 had accelerated phase disease, and 8 had blastic phase disease.

Treatment responses

Imatinib mesylate therapy produced responses in 22 (79%) of the 28 patients (Table 2). Responses according to disease phase at the initiation of therapy are summarized in Table 3. The sole patient with chronic phase, Bcr-Abl–positive disease (Table 2, patient 20) had no molecular evidence of disease after imatinib mesylate therapy. All 4 patients in active chronic phase CML achieved CHR, and 1 of these patients also had a partial cytogenetic response (24% Ph-positive cells). Of the 15 patients in accelerated phase CML, 1 of the 3 who had been in CHR (normal white blood cell [WBC] count but clonal evolution) achieved a complete cytogenetic response and a complete molecular response (PCR-negative). Twelve patients had active accelerated phase disease: 10 (83%) achieved CHR, 7 had complete cytogenetic response including 1 with complete molecular response; 3 had partial cytogenetic response. Of these 12 patients, one patient was categorized as having accelerated phase CML based on thrombocytopenia alone; he achieved a complete cytogenetic response. Six patients had clonal evolution as the only accelerated phase criterion: all 6 achieved CHR.
with complete cytogenetic response and 3 with partial cytogenetic response. The remaining 5 patients had multiple accelerated phase features; 3 achieved CHR and complete cytogenetic response.

Eight patients had blastic phase disease (7 in the bone marrow); 1 had extramedullary (EMD) blastic phase but with marrow

morpologic and cytogenetic complete remission and PCR positivity (Table 2, patient 17). Of the 7 patients with medullary blastic phase, 3 had CHR; 1 had a complete cytogenetic response, and 2 had a partial cytogenetic response. The patient with blastic EMD achieved tumor complete response (CR) and PCR negativity in the bone marrow.

All 11 patients with a complete cytogenetic response (the 9 listed above plus the patient with molecular-only disease and the patient with blastic EMD) had PCR analysis of samples after treatment; 4 achieved complete molecular response (detailed above). Clonal analysis of marrow samples from 4 patients who showed diploid hematopoiesis after treatment revealed that clones in all 4 originated from the donor rather than the host.

Thirteen patients had undergone prior DLI salvage therapy. Nine of 11 (85%) patients with active disease (including the patient with blastic EMD) had CHR or tumor CR, and 8 of 12 (66%) evaluable patients for cytogenetic response had a major cytogenetic response. Fifteen patients did not receive DLI salvage therapy; 9 of 13 (69%) patients with active disease achieved CHR, and 7 of 14 (50%) evaluable patients for cytogenetic response had a major cytogenetic response.

Survival analyses

At a median follow-up of 16 months (range, 9-24 months), 20 (68%) patients were alive, and 9 of them had no evidence of disease. Hence, the estimated 1-year survival rates were 74% for the group as a whole and 100% for patients treated while the disease was in chronic phase (Figures 1 and 2). Nine patients have died so far, including 6 with progression to blast phase, 1 with cardiopulmonary failure from viral pneumonia, and 2 whose deaths
occurred outside the institution (probably from disease progression; no definite documentation). There were no deaths related to imatinib mesylate therapy.

**Side effects**

The incidence and type of side effects from imatinib mesylate therapy were similar to those in previous reports. Skin rashes occurred in 11 patients; they were mild to moderate in 8 and severe in 3. Skin biopsy specimens were consistent with GVHD in 4 of the 5 patients tested for skin rashes. Three had grade 3 GVHD, 1 had grade 2 GVHD, and 1 was clinically evaluated as having grade 1 GVHD. The other 6 occurrences of mild to moderate skin rashes were attributed to imatinib mesylate and resolved with symptomatic therapy (topical steroids). Other severe toxic effects are listed in Table 4. Only 1 of 5 patients with liver toxicity required permanent discontinuation of therapy; liver function in the other 4 improved after dose adjustments. Myelosuppression was observed in 6 of 14 patients who had had normal granulocyte counts at the beginning of therapy, and thrombocytopenia was noted in 4 of 15 patients with previously normal platelet counts. These, too, resolved with dose adjustments.

**Discussion**

In our study, imatinib mesylate showed encouraging efficacy against CML that relapsed after allogeneic SCT. The overall response rate was 79% (22 of 28 patients). The CHR rate was 74%, the major cytogenetic response rate was 58%, and the complete cytogenetic response rate was 35%. Myelosuppression was noted in 27% to 43% of patients but was reversible with dose adjustments; 3 (11%) patients experienced reactivation of severe skin GVHD. Significantly, 13 (46%) patients had already been given DLI, and 11 of those patients responded to imatinib mesylate.

The results of our study were similar to those reported by other investigators. Chambon-Pautas et al25 reported on 15 patients whose CML relapsed after allogeneic SCT—12 in chronic phase, 2 in accelerated phase, and 1 in second chronic phase. Twelve patients had received IFN-α, and 9 had received DLI for CML relapse. CML relapse developed 9 months to 11 years after allogeneic SCT. Five complete cytogenetic responses and 3 partial cytogenetic responses occurred among 10 evaluable patients.25 There were no recurrences of GVHD, but granulocytopenia (4 of 15 patients, 27%) and edema were noted as side effects of therapy. Wassmann et al26 treated 13 such patients (9 blastic, 3 accelerated, 1 chronic). Median duration from transplantation to relapse was 6.5 months (range, 2 to 50 months). CHR was obtained in 7 patients (54%; 4 of 9 in blastic phase, 2 of 3 in accelerated phase, and 1 of 1 in chronic phase). CHR is ongoing in 6 of 7 patients for a median of 9 months (range, 5 to 17 months), with all 6 patients in complete cytogenetic response and 3 of them in complete molecular response. No patient experienced GVHD recurrence; other side effects were mild to moderate gastrointestinal discomfort and edema. Soiffer et al27 reviewed their experience in 12 patients with CML and 4 patients with Ph-positive acute lymphoid leukemia following allogeneic SCT relapse who received imatinib mesylate. The median interval from SCT to relapse was 12 months (range, 2 to 24 months); 5 patients received DLI; 7 patients were classified in accelerated phase based on clonal evolution and 5 in blastic phase. Six CHRs were observed among the 7 patients in accelerated phase, including 3 complete cytogenetic responses and 1 partial cytogenetic response. Among the 9 patients with CML blastic or Ph-positive ALL, 2 achieved complete cytogenetic response. In a report by Ullmann et al,28 17 patients with CML relapse after allogeneic SCT were treated with imatinib mesylate—10 in chronic phase and 7 in more advanced phases. Median time from SCT to relapse was 17

**Table 4. Incidence of severe (grades 3-4) side effects from imatinib mesylate therapy**

<table>
<thead>
<tr>
<th>Side effect</th>
<th>No. patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, vomiting</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
</tr>
<tr>
<td>Skin rashes</td>
<td>—</td>
</tr>
<tr>
<td>Drug-related</td>
<td>0</td>
</tr>
<tr>
<td>GVHD-related</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Bone or joint aches</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Periorbital</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Lower extremities</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Weight gain greater than 10%</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>5 (18)</td>
</tr>
<tr>
<td>Other effects</td>
<td>—</td>
</tr>
<tr>
<td>Drug fever</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Infection</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Granulocytopenia lower than 0.5 × 10^9/L</td>
<td>6 of 14 (43)</td>
</tr>
<tr>
<td>Thrombocytopenia lower than 50 × 10^9/L</td>
<td>4 of 15 (27)</td>
</tr>
</tbody>
</table>

**Figure 1. Survival of patients after allogeneic SCT from the time imatinib mesylate therapy was initiated.**

**Figure 2. Survival by CML phase.**
months (range, 2 to 234 months). Among the 7 patients in advanced CML phases, 5 (71%) achieved CHR and 4 had major cytogenetic responses (2 complete, 2 partial). Among the 10 patients in chronic phase, 8 (80%) achieved major cytogenetic responses (2 complete, 6 partial). Treatment-related side effects were mild gastrointestinal discomfort; severe myelosuppression was observed in 6 of 15 (40%) evaluable patients but was reversed with dose reductions of imatinib mesylate. No GVHD recurrences were reported, but there was one myelosuppression-associated infectious death. Moreira et al treated 13 patients with CML relapse after allogeneic SCT (n = 10) or autologous SCT (n = 3). Median time from SCT to relapse was 15 months (range, 5 to 68 months); CML phase was chronic in 5 patients, accelerated in 6, and blastic in 2. Five patients received DLI concomitant with imatinib mesylate therapy: one patient acquired skin and liver GVHD and achieved a complete cytogenetic response. All 13 (100%) patients achieved CHR; 3 (23%) patients achieved complete cytogenetic response, 7 patients (53%) acquired severe myelosuppression, and 3 (23%) patients had severe nonhematologic toxicities (arthralgias, edema, weight gain, diarrhea).

Several of the imatinib mesylate toxicities overlapped with those of recurrent GVHD (diarrhea, skin rashes, liver dysfunction), making it difficult at times to attribute causality to one or the other. This is important in assessing the relative efficacy and toxicity of imatinib mesylate versus DLI. Generally, DLI is associated with 20% to 40% rates of recurrent grades 3-4 GVHD, 30% to 40% significant myelosuppression, and 20% treatment-related deaths. The cumulative data from this and 5 other series suggest that imatinib mesylate therapy was associated with severe myelosuppression in 10% to 50% (reversible in most with dose reductions), recurrence of GVHD in 0% to 11%, and rare imatinib mesylate–associated mortality (Table 5).

In summary, the results of imatinib mesylate therapy in patients who have CML relapse following allogeneic SCT appear encouraging. However, treatment with imatinib mesylate in these patients is not without side effects, and the long-term outcome of such therapy is unknown. Future studies will help clarify the role of imatinib mesylate for CML relapse following allogeneic SCT. Imatinib mesylate therapy alone may be most reasonable in patients who still have persistent GVHD at the time of CML recurrence, to avoid potential worsening of GVHD. Combined-modality approaches of imatinib mesylate with DLI (simultaneous or sequential), IFN-α, or cytarabine should be explored further.

References


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