Brief report

Imatinib mesylate as salvage therapy for refractory sclerotic chronic graft-versus-host disease

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Imatinib is a promising candidate for the treatment of fibrotic diseases. This retrospective study evaluated the use of imatinib for the treatment of refractory sclerotic chronic graft-versus-host disease in 14 patients with different hematologic malignancies. Imatinib was started at a median of 44 months after transplantation (range, 16-119 months after transplantation) and was administered for a median of 5.9 months from time of initiation (range, 2.1-74 months from time of initiation). With a median overall follow-up of 11.6 months from time of initiation (range, 4.1-74 months from time of initiation) of imatinib, 4 patients (29%) had to stop imatinib because of drug intolerance. All other adverse reactions were of mild-to-moderate grade and could be managed symptomatically. Overall, 7 patients responded to imatinib (50%; 95% confidence interval, 24%-76%) with 4 patients improving their Rodman score more than or equal to 90%. In addition, imatinib therapy allowed for a significant reduction of corticosteroid dosage. Despite its limited size, this cohort suggests some beneficial activity of imatinib in sclerotic chronic graft-versus-host disease, warranting further prospective investigations. (Blood. 2009;114:719-722)

Introduction

Chronic graft-versus-host disease (cGVHD) remains a major cause of morbidity and mortality after allogeneic stem cell transplantation (allo-SCT). Standard primary treatment of cGVHD is a combination of corticosteroids (CSs) and calcineurin inhibitors. There is no standard therapy for those who fail to respond to CS, and CS-resistant cGVHD is associated with high morbidity.1 From the clinical standpoint, many cGVHD patients present with features of autoimmune collagen vascular disease, with clinical manifestations similar to those of autoimmune scleroderma and systemic lupus erythematosus.2 Likewise, sclerotic cGVHD (ScGVHD) is one of the most severe forms of the disease and is frequently refractory to standard treatment approaches.3,5 Thus, therapeutic options are usually limited for those patients with severe ScGVHD. Imatinib mesylate (IM), a clinically well-tolerated tyrosine kinase inhibitor, has been shown to be effective in patients with chronic myeloid leukemia and those with stromal gastrointestinal tumors.6,7 IM exerts selective, dual inhibition of the transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF) pathways.8 On the other hand, blockade of TGF-β or PDGF signaling has been shown to reduces the development of fibrosis in various experimental models.9-11 Therefore, IM is a promising candidate for the treatment of fibrotic diseases, such as ScGVHD. This retrospective analysis describes the outcome of 14 patients experiencing severe or refractory ScGVHD and who received oral IM as salvage therapy.

Methods

Study design

This was a retrospective study performed in 2 allo-SCT centers in France (Lille, n = 12; and Nantes, n = 2), which examined the safety and efficacy of IM therapy for refractory ScGVHD. Informed consent was obtained according to institutional guidelines in accordance with the Declaration of Helsinki. The off-label use of imatinib in the setting of ScGVHD was authorized by the Institutional Review Board of Centre Hospitalier Regional Universitaire, according to French laws in a compassionate setting for those patients presenting with advanced and refractory ScGVHD clinical features.

Study evaluations and therapy

Patient and transplantation characteristics are summarized in Table 1. Acute and cGVHD grading was performed according to classic criteria. A detailed history and physical examination were performed and documented before IM initiation. Physical examination included skin score and measurement of range of motion. The modified Rodman skin score was used to assess cutaneous sclerosis changes.12 The Rodman skin score measured thickness, graded from 0 to 3 as follows: 0 indicates uninvolved skin; 1, skin involvement with ability to pinch; 2, inability to pinch; and 3, inability to move. The pinch was done in one movement of moderate intensity, and using only fingertips. All affected areas were assessed, and the results of all areas were added up to give a final overall score. Responses in cutaneous sclerosis were always measured in the areas with the most severe involvement. All 14 patients analyzed in this retrospective study (of whom 2 were previously reported13) had refractory cGHVD with significant

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cutaneous sclerosis manifestations, and who failed at least 2 lines of prior systemic immunosuppressive therapy. IM (Glivec/Gleevec, Novartis France) was started in oral doses, usually of 400 mg/day (patient 12, a child, received 100 mg/day). IM treatment duration was at the discretion of the attending physician. Patients who had received myeloablative or reduced-intensity conditioning were examined in this analysis, as were recipients of related and unrelated stem cell grafts. All recipients underwent transplantation at least 6 months before IM initiation, none had received donor lymphocyte infusions in the preceding 100 days, none had signs of late onset aGVHD, and none was currently undergoing extracorporeal photopheresis. All patients continued to receive standard prophylaxis against Pneumocystis carinii, Toxoplasma gondii, fungal, and herpesvirus infection during study therapy. First response to IM was assessed 2 months after the start of therapy, and then on a monthly basis. At each evaluation, the attending physician usually collected the subjective feelings of the patient and the macroscopically visible changes of the skin before treatment and during follow-up, and evaluated their respective organ system as well as their RS. All concomitant medications and adverse events were captured from the patients’ medical source files. For the purpose of this analysis, complete response was defined as resolution of all manifestations in involved organs, whereas partial response was defined as an improvement more than 50% in at least one cGVHD manifestation, and minor response was defined as an improvement less than 50% without any new organ involvement or progression in a previously involved organ. Failure was defined as the absence of response after 2 months. Patients who progressed after an initial response to IM were recorded as in flair of their cGVHD. The benefit could be also evaluated in terms of CS taper. The CS dose received was assessed at last follow-up and compared with the previous CS dose received at time of initiation of IM therapy.

Statistical analysis

Descriptive statistical methodology was used for all analyses.

Results and discussion

cGVHD features, responses to IM, and outcomes are summarized in Table 2. IM was started at a median time of 44 months (range, 16-119 months) after allo-SCT. Patients who did not develop drug-related intolerance received IM for a median of 5.9 months (range, 2.1-74 months) from time of initiation. With a median overall follow-up of 11.6 months (range, 4.1-74 months) from time of initiation of IM, 4 patients (29%) had to stop IM because of drug intolerance directly related to IM according to the investigator’s assessment (patients 6, 8, 9, and 10). In the latter 4 patients, side effects (especially cramps) could not be managed using a lower dose of IM. Six other patients experienced some adverse reactions of mild to moderate grade that could be managed symptomatically and did not require IM discontinuation. IM dosage had to be reduced from 400 to 300 mg/day in one patient (patient 14) because of side effects. Overall, 7 patients responded to IM (50%; 95% confidence interval, 24%-76%) with 4 patients improving their Rodman score more than or equal to 90%. At last follow-up, 2 patients were in complete response and 5 were in partial responses of their cGVHD. In those responding patients, the patient felt improvement as soon as one month after the initiation of IM. In addition, IM therapy allowed for a significant reduction of CS dosage to those assessable patients. With an overall median follow-up of 56 months (range, 25-147 months) from transplantation, only one patient (patient 8) in this series of very advanced cGVHD patients died of refractory ScGVHD (infection).

Currently, there is no standard “second-line” therapy for CS-resistant cGVHD. Several candidate drugs were already tested with variable results, and the response of ScGVHD is usually disappointing. In our study, the global response rate to IM was high if considered in terms of salvage therapy and cutaneous sclerosis manifestation improvement. On the other hand, the incidence of IM-related adverse reactions reflected the usual rate observed in chronic myelogenous leukemia treatment.

In animal models, IM has been shown to prevent fibrosis through inhibition of PDGF signaling and fibroblast proliferation mediated by TGF-β. ScGVHD is a recalcitrant disease featuring multiorgan fibrosis and dysfunction. The ability of IM to abrogate...
<table>
<thead>
<tr>
<th>Case no.</th>
<th>Maximal tolerated daily dose of IM, mg</th>
<th>IM therapy discontinuation at last follow-up, mo</th>
<th>Side effects/IM discontinuation at last follow-up</th>
<th>RS before IM initiation</th>
<th>RS after 2 mo of IM initiation</th>
<th>cGVHD status at 2 mo of IM</th>
<th>RS at last follow-up</th>
<th>cGVHD response in other organs at last follow-up*</th>
<th>cGVHD status at last follow-up</th>
<th>Percentage CS reduction (last dosage mg/d)</th>
<th>Overall follow-up, mo</th>
<th>Follow-up since IM initiation, mo</th>
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<td>600</td>
<td>74.1</td>
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<td>Mouth</td>
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<td>—</td>
<td>failure</td>
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<td>NE</td>
<td>—</td>
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<td>MR</td>
<td>7</td>
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<td>MR</td>
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<td>Eyes, joints contracture</td>
<td>MR</td>
<td>0 (30)</td>
<td>67.2</td>
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</tbody>
</table>

IM indicates imatinib; RS, Rodman score; cGVHD, chronic graft-versus-host disease; CS, corticosteroids; PR, partial response; CR, complete response; NE, not evaluable; and MR, minor response.

*Only patients showing at least PR are mentioned.
†Patient 1 had simultaneous disease recurrence (CML) at time of IM initiation.
‡Patient 12 did not have assessable sclerotic skin lesions.
the activation of the PDGF receptor entails its use in the treatment of ScGVHD. Indeed, IM at clinically relevant concentrations has potent antifibrotic effects in vitro and in vivo and can prevent the development of inflammation-driven experimental fibrosis when treatment was initiated before administration of the profibrotic stimulus. In addition, IM might be effective for the treatment of established fibrosis. At present, several trials aiming to examine the use of IM in the treatment of systemic sclerosis are currently underway. Despite its limited size, this cohort (and other case reports) demonstrates evidence of beneficial activity of IM in ScGVHD. Hence, given its oral administration, efficacy, and safety profile, evaluation of the role of IM in refractory ScGVHD warrants further investigation in sufficiently powered, well-controlled multicenter prospective trials using the robust National Institutes of Health consensus staging and response criteria.

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References


Authorship

Contribution: L.M. provided clinical care, recorded and collected clinical data, and commented on the manuscript; M.M provided clinical care, collected patient data, analyzed data, and wrote and revised the report; B.C., V.C., P.C., L.T., and J.-P.J. provided clinical care and recorded clinical data; and I.Y.-A conceived and designed the study, provided clinical care, collected patient data, analyzed data, and revised the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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