Limited efficacy of imatinib in severe pulmonary chronic graft-versus-host disease

We read with interest that Olivieri et al.1 observed complete or partial responses to imatinib 100 or 200 mg daily with improvement of lung function in 7 of 11 patients (64%) with pulmonary chronic graft-versus-host disease (cGVHD) of mild severity (lung function score [LFS] of responders, 2-5; percent predicted forced expiratory volume [FEV1], 44-78).2

We have conducted a single-center, prospective, open-label, nonrandomized pilot study of imatinib at 100 to 400 mg daily as antifibrotic treatment targeting the platelet-derived growth factor receptor (PDGFR) and transforming growth factor β (TGFβ) pathways3,4 in patients with refractory cGVHD of the lung. Since November 1995, 9 patients with moderate to severe pulmonary cGVHD have been included (see Table 1). Median age was 45 years (range, 24-50 years); 3 patients were female and 6 male. Peripheral blood stem cell transplantation from sibling (n = 7) or unrelated (n = 2) donors had been performed after myeloablative (n = 7) or reduced-intensity (n = 2) conditioning for acute or chronic myeloid leukemias or lymphomas. All patients had skin, mucosal, visceral, and/or fasciitic manifestations in addition to pulmonary cGVHD; the median duration of pulmonary cGVHD was 6 months (range, 1-28 months). All patients had already received extensive combination therapies with steroids, calcineurin inhibitors, mycophenolate, and/or extracorporeal photopheresis. Additional imatinib was started generally at 100 mg per day and increased monthly up to 400 mg per day, as tolerated. All patients were evaluated monthly for toxicity and response (pulmonary function tests).

Imatinib toxicity (hematologic, nausea, or fluid retention) was mostly mild, except in 2 patients who discontinued the drug due to reversible dyspnea. Dose increase was not possible in a substantial fraction of patients (as has been noted by others5,6): only 3 of 9 reached the target dose of 400 mg. After a median duration of 4 months (range, 1-17+ months) of imatinib treatment, pulmonary function recovered only in 1 patient from severe to moderate. Applying the same response criteria as Olivieri et al, partial responses (ie, possibility of tapering steroids) were found only in

<table>
<thead>
<tr>
<th>UPN</th>
<th>FEV1 before imatinib (%)</th>
<th>Maximum daily dose of imatinib (mg)</th>
<th>Duration of imatinib treatment (mo)</th>
<th>Side effects</th>
<th>FEV1 after imatinib (%)</th>
<th>Response*</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>763</td>
<td>24%</td>
<td>200</td>
<td>16</td>
<td>–</td>
<td>20%</td>
<td>partial</td>
<td>alive</td>
</tr>
<tr>
<td>824</td>
<td>36%</td>
<td>200</td>
<td>10</td>
<td>–</td>
<td>45%</td>
<td>partial</td>
<td>alive</td>
</tr>
<tr>
<td>1093</td>
<td>29%</td>
<td>200</td>
<td>2</td>
<td>–</td>
<td>26%</td>
<td>none</td>
<td>died</td>
</tr>
<tr>
<td>1307</td>
<td>32%</td>
<td>100</td>
<td>1</td>
<td>Dyspnea → withdrawal</td>
<td>35%</td>
<td>none</td>
<td>alive</td>
</tr>
<tr>
<td>1371</td>
<td>18%</td>
<td>100</td>
<td>1</td>
<td>–</td>
<td>25%</td>
<td>none</td>
<td>died</td>
</tr>
<tr>
<td>1466</td>
<td>25%</td>
<td>400</td>
<td>17+</td>
<td>–</td>
<td>21%</td>
<td>none</td>
<td>alive</td>
</tr>
<tr>
<td>1068</td>
<td>24%</td>
<td>200</td>
<td>4</td>
<td>–</td>
<td>29%</td>
<td>none</td>
<td>alive</td>
</tr>
<tr>
<td>736</td>
<td>41%</td>
<td>400</td>
<td>4</td>
<td>Dyspnea → withdrawal</td>
<td>42%</td>
<td>none</td>
<td>alive</td>
</tr>
<tr>
<td>1730</td>
<td>33%</td>
<td>400</td>
<td>1+</td>
<td>–</td>
<td>21%</td>
<td>none</td>
<td>alive</td>
</tr>
</tbody>
</table>

Pulmonary scoring according to FEV1 (% predicted) or lung function score (LFS): mild, FEV1 60%-79% or LFS 3-5; moderate, FEV1 40%-59% or LFS 6-9; and severe, FEV1 < 40% or LFS 10-12.

CTC > 2 indicates toxicities graded as greater than 2 according to the international Common Toxicity Criteria.

*Response to imatinib treatment, as defined by Olivieri et al.1
2 patients (22%), whereas 5 patients showed no change, and 2 patients died due to progression of pulmonary GVHD and/or the underlying malignancy.

The patients in our study were older, had all received peripheral blood stem cells, and had much more severe pulmonary cGVHD according to FEV₁,² which may account for the differences observed, whereas imatinib dosage and duration of exposure were comparable.

Taking together both studies, it appears that imatinib shows best results in mild pulmonary cGVHD, but has limited efficacy in patients with severe, refractory pulmonary cGVHD. Conceivably, a stronger effect might be seen with more potent tyrosine kinase inhibitors. However, it remains unknown to what extent the fibrosis, once established, can be reversed. Further prospective studies are warranted to establish the suggested role of early PDGFR/TGFβ pathway inhibition as antifibrotic treatment in pulmonary cGVHD.

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Acknowledgment: This work was supported by a grant from the German Federal Ministry of Education and Research (01EO0802). The contents of this manuscript are the sole responsibility of the authors.

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

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References


Response

Imatinib in lung cGVHD of mild to moderate severity

We appreciated the letter written by Stadler and colleagues reporting their experience with imatinib for treating patients with severe chronic graft-versus-host disease (GVHD) involving lungs. They had results that were less satisfactory than ours, only 2 of their 9 patients benefiting from partial response (PR). We treated with imatinib 19 patients with cGVHD, 11 of them with lung involvement; the study approval was obtained from the institutional review board of Potenza (Italy). Informed consent was provided according to the Declaration of Helsinki. Clearly, our experience was more encouraging, as 6 of our 11 patients markedly improved (reduction by 2 or more points) their lung function score (LFS), and 2 of them were able to discontinue steroid therapy.¹ As also suggested by Stadler et al, several factors may easily explain this apparent discrepancy of efficacy. Indeed, in the 9 patients treated by Stadler and colleagues, lung deterioration was much more severe, as shown by the values of forced expiratory volume (FEV₁). It is reasonable to conceive that when lung tissue damage is too severe, even an antifibrotic effect²,³ will not be able to restore respiratory function. Support for this interpretation is provided by the observation that also our 2 patients with the worst lung deterioration (namely, those with LFS ≥ 5) did not respond to treatment. Moreover, patients treated by Stadler et al were older than ours, and it is possible that young patients have a better capacity to repair tissue damage. Finally, we found that most patients converted from no response to PR or from PR to complete response in 3 to 6 months of treatment, suggesting that the prolongation of treatment can increase both the response rate and the quality of response at lung level. Six of the 9 patients treated by Stadler et al were given imatinib mesylate for only 1 to 4 months, which possibly contributed to the unsatisfactory results they reported. In view of all these findings, we confirm our recommendation that, in the absence of an early response (ie, within 1-3 months), imatinib should not be discontinued before reaching at least 6 months of treatment. Earlier discontinuation may be premature or even detrimental.

In conclusion, available evidence suggests that imatinib mesylate may be effective in a relevant proportion of patients with lung involvement by chronic GVHD, especially in those with mild to
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graft-versus-host disease

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