Brief report

Low-dose thalidomide and donor lymphocyte infusion as adoptive immunotherapy after allogeneic stem cell transplantation in patients with multiple myeloma

Nicolaus Kröger, Avichai Shimony, Maria Zagrivnaja, Francis Ayuk, Michael Liozov, Heike Schieder, Helmut Renges, Boris Fehse, Tatjana Zabelina, Amon Nagler, and Axel R. Zander

To improve the antimyeloma effect of donor lymphocyte infusion (DLI) after allogeneic stem cell transplantation in multiple myeloma, we investigated in a phase 1/2 study the effect of low-dose thalidomide (100 mg) followed by DLI in 18 patients with progressive disease or residual disease and prior ineffective DLI after allografting. The overall response rate was 67%, including 22% complete remission. Major toxicity of thalidomide was weakness grade I/II (68%) and peripheral neuropathy grade I/II (28%). Only 2 patients experienced mild grade I acute graft versus host disease (aGvHD) of the skin, while no grades II to IV aGvHD was seen. De novo limited chronic GvHD (cGvHD) was seen in 2 patients (11%). The 2-year estimated overall and progression-free survival were 100% and 84%, respectively. Adoptive immunotherapy with low-dose thalidomide and DLI induces a strong antimyeloma effect with low incidence of graft versus host disease. (Blood. 2004;104:3361-3363)

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Introduction

The relapse rate after dose-reduced conditioning followed by allogeneic stem cell transplantation from related and unrelated donors in patients with multiple myeloma is still considerable.1-3 Due to a well-documented graft versus myeloma effect, adoptive immunotherapy with donor lymphocyte infusion (DLI) has become a reasonable treatment option in patients with relapse after allogeneic stem cell transplantation.4-7 More recently, DLI has been integrated in dose-reduced allograft protocols for mixed chimerism or persistent disease.4,8 The response rate after DLI ranges between 30% and 50%, but only few achieve complete remission.4,6,7 Despite the efficacy of DLI there is a substantial risk of acute and chronic graft versus host disease (GvHD). The largest study reported 57% acute GvHD (aGvHD) and 47% chronic GvHD (cGvHD), resulting in a graft versus host disease–related mortality of 4%.7 Thalidomide induces remarkable response rates between 25% and 35% for relapsed and refractory patients.9,10 As a single agent in newly diagnosed patients, partial remission rates of 50% were observed,11 which can be enhanced to 60% to 70% by concomitant therapy with dexamethasone.12 Besides its inhibitory effect on tumor necrosis factor-α (TNF-α) production and angiogenesis, thalidomide has additional mechanisms of antilymphoma activity by modulation of myeloma cell binding to bone marrow stroma.13 The immunologic properties of thalidomide such as potentiation of natural killer (NK) cell activity, costimulation of CD8+ cells, and increase of interleukin-2 production make the drug a potential enhancer of immune-mediated antimyeloma response after allogeneic stem cell transplantation.13,14 In contrast, thalidomide has been shown to be active as an immunosuppressive drug in treatment of GvHD, especially cGvHD.15,16 The present phase 1/2 study was conducted to evaluate the antimyeloma effect, the toxicity, and the incidence of GvHD after low-dose thalidomide in combination with DLI.

Study design

Eighteen patients with a median age of 53 years (range, 31 to 64 years) were enrolled between December 2001 and December 2003. Twelve patients had received prior DLI and either relapsed again (n = 1) or showed no response (progressive disease [PD], n = 3; stable disease [SD], n = 8) (Table 1). Thalidomide was started at a dose of 100 mg once daily orally. After an interval of 14 days DLI was performed. Starting dose was 1 × 10⁶ CD3+ cells per kilogram of body weight (BW) for unrelated and 5 × 10⁶ CD3+ cells per kilogram of BW for related donors. If no response occurred within 6 weeks or progressive disease was noted, a dose escalation of thalidomide up to 300 mg and/or dose escalation (half log) of DLI was initiated. Exclusion criteria for DLI were active aGvHD or extensive cGvHD or severe infections. Toxicity was graded according to the Common Toxicity Criteria (http://ctep.info.nih.gov/reporting/index.html). Standard criteria were used for grading of acute and chronic GvHD.17 Response to treatment was defined according to the European Group for Blood and Marrow Transplant/International Bone Marrow Transplant Registry (EBMT/IBMTR) criteria.18 A written informed consent was obtained from each patient, and the local Ethics Committee of Hamburg, Germany, approved the study.

Results and discussion

The median time from allograft to thalidomide was 12 months (range, 4 to 47 months). The major toxicity was constipation grade...
I in 12 patients and grade II in 1 patient; weakness grade I was seen in 10 patients while grade II was seen in 1 patient. Peripheral neuropathy grade I was seen in 3 patients and grade II in 2 patients. One patient stopped thalidomide after 12 months due to neuropathy, and he remains in complete molecular remission 8 months after withdrawal of the drug. In another patient with neuropathy thalidomide was discontinued 11 months after its start, and he remains in partial remission 4 months after withdrawal. In another patient thalidomide was reduced to 50 mg due to weakness. No venous thrombosis has been noted so far. Two patients developed aGVHD grade I of the skin (11%). No grade II–IV aGVHD was seen. Six of 16 patients (38%) had signs of limited cGVHD, but 4 of them already had signs of limited cGVHD prior to treatment. Therefore, only 2 patients (13%) developed de novo cGVHD after thalidomide and DLI. In comparison to prior DLI the incidence of acute and chronic GvHD was lower after thalidomide plus DLI (Table 2).

Four patients achieved a complete remission (22%), 5 had a partial remission (28%), and 3 patients showed minor response (17%), resulting in an overall response rate of 67%. Five patients showed stable disease (28%), and 1 patient experienced progression (5%). The median time to response was 108 days (range, 36 to 266 days). In 5 patients not responding to 100 mg, the dose of thalidomide was increased (200 mg, n = 4; 300 mg, n = 1), and subsequently 2 of them responded with partial remission. In 3 patients dose escalation of DLI was performed, resulting in 1 minor and 1 partial remission. No difference regarding response was observed between unrelated and related donors (66% each). Five of 6 patients with deletion 13 responded, while 5 of 9 patients without deletion 13 responded to thalidomide plus DLI. In patients who failed to respond to prior DLI, the disease status could be converted in 6 patients with SD after first DLI into complete remission (CR) (n = 2), partial remission (PR) (n = 3), and minor response (MR) (n = 1) while 2 with SD remained with SD after thalidomide plus DLI. In 3 patients with progressive disease after DLI the combination of thalidomide and DLI resulted in 1 CR, 1 PR, and 1 MR.

The response rate to low-dose thalidomide plus DLI was higher as reported in the literature if applied as single agents.6,7,10 In a retrospective analysis including 28 patients who relapsed after allogeneic stem cell transplantation (SCT) a response rate of 55% was observed after a median dose of 200 mg thalidomide (range, 50 to 600 mg), but none of the responders achieved CR with negative immunofixation.20 From the design of the present study it is unclear how much of the antimmunoma effect is attributed to DLI or thalidomide, but the high response rate of 67% with 22% complete remission indicates an additive or synergistic antimmunoma effect. The low incidence of acute and chronic GVHD is of importance because GVHD was observed in a substantial portion of patients after adoptive immunotherapy with DLI, and a close correlation between graft versus myeloma effect and GvHD after DLI has been described.4,6,7 Besides low-dose escalating DLI after allogeneic stem cell transplantation, a thalidomide-induced NK cell activation may contributed to the relatively low incidence rate of GVHD and the strong antimmunoma effect. The role of thalidomide in treatment of GVHD is controversial: While several studies suggested only minor, if any, effect on acute GVHD, for chronic GVHD thalidomide has been shown to be effective.16 In one randomized trial the addition of thalidomide to standard immunosuppression enhanced the rate of complete remission of cGVHD without improvement of survival,15 while in another trial thalidomide as prophylactic agent increased the rate of cGVHD and lowered overall survival.21 To reduce GVHD after DLI, either CD8+ T-cell clones or minor histocompatibility–restricted T cells could lead to a more specific antimmunoma T-cell response.22,23

After a median follow-up of 12 months (range, 4 to 28 months), the 2-year estimated overall and progression-free survival was 100% and 84% (95% confidence interval [CI], 62%-100%). At the this time this paper was accepted for publication, two patients progressed so far 33 and 322 days after treatment. These encouraging results of thalidomide and DLI should be further evaluated in a larger cohort as maintenance therapy or to enhance remission status after allogeneic stem cell transplantation, because it has been shown that achieving complete molecular remission after allografting is associated with long-term freedom from disease.24

Table 2. GvHD after allogeneic SCT, after prior DLI, and after thalidomide plus DLI

<table>
<thead>
<tr>
<th></th>
<th>GvHd after allotransplantation</th>
<th>GvHd after prior DLI</th>
<th>GvHd after thalidomide plus DLI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>18</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>aGvHd I–IV, %</td>
<td>61</td>
<td>42</td>
<td>11</td>
</tr>
<tr>
<td>aGvHd II–IV, %</td>
<td>28</td>
<td>25</td>
<td>None</td>
</tr>
<tr>
<td>Limited cGvHd, %</td>
<td>33</td>
<td>33</td>
<td>38*</td>
</tr>
<tr>
<td>Extensive cGvHd, %</td>
<td>6</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

*Four of 6 entered the trial with limited cGVHD without aggravation; 2 of 6 (13%) de novo limited cGVHD; of 18 patients included in the study, only 16 were evaluable for cGVHD.

HD indicates high dose; MUD, matched unrelated donor.

*Detected by fluorescence in situ hybridization (FISH).

**Acknowledgments**

We thank the staff of the BMT unit for providing excellent care of our patients and the medical technicians for their excellent work in the BMT laboratory.
References


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