Clinical evidence of a graft-versus-lymphoma effect against relapsed diffuse large B-cell lymphoma after allogeneic hematopoietic stem-cell transplantation

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Background: A graft-versus-lymphoma effect against diffuse large B-cell lymphoma (DLBCL) is inferred by sustained relapse-free survival after allogeneic stem-cell transplantation; however, there are limited data on a direct graft-versus-lymphoma effect against DLBCL following immunotherapeutic intervention by either withdrawal of immunosuppression or donor lymphocyte infusion (DLI).

Materials and methods: An analysis was carried out to determine whether a direct graft-versus-lymphoma effect exists against DLBCL. The analysis was restricted to patients with DLBCL, who were either not in complete remission at day +100 after allogeneic stem-cell transplantation or subsequently relapsed beyond this time point.

Results: Fifteen patients were identified as either not in complete remission (n = 13) at their day +100 evaluation or subsequently relapsed (n = 2) and were assessed for subsequent responses after withdrawal of immunosuppression or DLI. Eleven patients were treated with either withdrawal of immunosuppression (n = 10) or a DLI (n = 1) alone; four patients received chemotherapy with DLI to reduce tumor bulk. Nine (60%) patients subsequently responded (complete = 8, partial = 1). Six responses occurred after withdrawal of immunosuppression alone. Six patients are alive (range 42–83+ months) in complete remission without further treatment.

Conclusion: The demonstration of sustained complete remission following immunotherapeutic intervention provides direct evidence of a graft-versus-lymphoma effect against DLBCL.

Key words: allogeneic, diffuse large B-cell lymphoma, graft-versus-lymphoma

introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common histology among the non-Hodgkin’s lymphomas and the most common lymphoid malignancy in adults [1]. Conventional chemotherapeutic regimens can result in high response rates and cure a significant percentage of adult patients with DLBCL [2]. For patients with DLBCL who either does not enter into a complete remission or recurs after conventional treatments, high-dose therapy and autologous hematopoietic stem-cell transplantation can result in prolonged disease-free survival, provided that the disease is chemotherapy sensitive [3, 4]. However, for patients with DLBCL that is chemotherapy refractory or recurs after autologous hematopoietic stem-cell transplantation, available therapeutic options are relatively limited and rarely result in long-term survival. Allogeneic hematopoietic stem-cell transplantation has been successfully used to treat a variety of hematologic malignances [5]. The efficacy of allogeneic hematopoietic stem-cell transplantation is attributed both to the antitumor cytotoxic effects of the conditioning regimen given before the transplant and in part to an immune-mediated graft-versus-tumor effect provided by components of the allogeneic stem-cell graft [6]. The existence of a graft-versus-tumor effect is supported by observations that withdrawal of immune suppression or the infusion of donor lymphocytes distant from the time of transplant can result in sustained, molecular remissions in patients with recurrent hematologic malignancy after allogeneic hematopoietic stem-cell transplantation, most notably in patients with chronic myelogenous leukemia [7, 8].

Although allogeneic hematopoietic stem-cell transplantation can result in long-term disease-free survival for patients with relapsed and refractory non-Hodgkin’s lymphoma, including DLBCL, evidence for a graft-versus-lymphoma effect is
relatively limited as compared with its use in leukemias. The greatest support for a graft-versus-lymphoma effect comes from the observation of decreased relapsed rates as compared with results with autologous hematopoietic stem-cell transplantation [9–11]. However, a large analysis by The Lymphoma Working Committee of the International Bone Marrow Transplant Registry and the European Group for Blood and Marrow Transplantation failed to find evidence of a significant graft-versus-lymphoma effect when allogeneic was compared with syngeneic hematopoietic stem-cell transplantation [12]. These data indicated that tumor contamination of the graft, rather than an immunologic graft-versus-lymphoma mechanism, may explain the differences in relapse rates between autologous and allogeneic hematopoietic stem-cell transplantation [13].

It has been indicated that the strongest evidence supporting the existence of a clinically relevant graft-versus-lymphoma effect would be the demonstration of tumor regression after withdrawal of immune suppression or the infusion of donor lymphocytes after transplantation [14]. There is relatively good evidence of graft-versus-lymphoma effect, using these criteria, against follicular non-Hodgkin’s lymphoma [14–18]. However, there have been relatively few reports of clinical responses in patients with DLBCL following either withdrawal of immune suppression or a donor lymphocyte infusion (DLI), which have included registry results [15, 19–21]. These reports have generally cited responses in a single patient, often describe patients as having ‘high-grade’ non-Hodgkin’s lymphoma, and the responses have rarely been sustained. van Besien et al. [15] described one partial and one complete response to withdrawal of immune suppression among five patients, who were distinctly identified as having DLBCL. In this series, only one response was sustained (60+ months), and although the patient was described as having a complete response, there was concurrent marrow involvement with small, cleaved cell lymphoma. Despite lower relapse rates following allogeneic hematopoietic stem-cell transplantation [22], the relative paucity of specific data demonstrating clinical response to either withdrawal of immune suppression or the infusion of donor lymphocytes to treat relapse have led reviewers of this subject to question whether a clinically meaningful graft-versus-lymphoma effect exists against DLBCL [14, 23].

The use of non-myeloablative and reduced-intensity conditioning regimens before allogeneic hematopoietic stem-cell transplantation has increased the reliance upon graft-versus-lymphoma effects to achieve durable remissions in the treatment of malignant lymphomas [20, 21, 24–26]. At the same time, reduced-intensity conditioning regimens also provide a unique opportunity to assess graft-versus-lymphoma effects against specific histologies [14]. Prompted by the report of Bierman et al. [12] and the review of this subject by Grigg and Ritchie [14], we designed a retrospective analysis to determine whether a graft-versus-lymphoma effect exists against DLBCL. In this analysis, we evaluated patients with refractory DLBCL, who were uniformly treated with reduced-intensity allogeneic hematopoietic stem-cell transplantation. In order to detect a specific graft-versus-lymphoma effect against DLBCL, distinct from the effects of the conditioning chemotherapy, the analysis was restricted to patients who had disease that was either initially refractory to or that subsequently relapsed at a time point distant from their transplant conditioning regimen. The results of this analysis provide direct clinical evidence of a graft-versus-lymphoma effect against DLBCL.

### materials and methods

#### patients

The study population was derived from a database of 63 patients with relapsed and refractory non-Hodgkin’s lymphomas who underwent reduced-intensity allogeneic hematopoietic stem-cell transplantation from a human leukocyte antigen (HLA)-matched sibling, as part of two sequential National Cancer Institute protocols. Patients were not required to have chemotherapy-sensitive disease to participate on either of these protocols; as such, patients were only excluded from trial participation if they did not meet minimal requirements for major organ functions. Eighteen patients with relapsed and refractory DLBCL were identified from the available database for use in the analysis. Diagnosis of DLBCL was confirmed by the National Cancer Institute Laboratory of Pathology using the World Health Organization classification [27]. Patients with transformed DLBCL and patients with mixed histology were excluded from the analysis. The protocols on which these patients participated, NCT00019851 and NCT00055744 (http://clinicaltrials.gov/ct2/home), were both approved by the National Cancer Institute Institutional Review Board, and informed written consent was obtained from each patient and his or her respective donor.

#### study design and statistical analysis

All patients received an identical conditioning regimen consisting of fludarabine (30 mg/m²/day) and cyclophosphamide (1200 mg/m²/day) administered i.v. from day −6 to day −3 before transplantation [28]. All patients received T-cell replete peripheral blood stem-cell grafts mobilized with filgrastim from an HLA-matched sibling donor.

Cyclosporine was started on the day before transplantation for prevention of graft-versus-host disease (GVHD); it was administered at therapeutic level until 100 days after transplant and then tapered between days 100 and 180 after transplant depending on the presence or absence of GVHD. For patients participating on NCT00019851, cyclosporine was administered with or without donor-derived Th2 cells [29]. For patients participating on NCT00055744, cyclosporine was administered in conjunction with methotrexate on days 1, 3, 6, and 11 after transplant to prevent GVHD.

Chimerism analysis was carried out by the variable number of tandem repeats-PCR method in a Clinical Laboratory Improvement Amendments-certified laboratory at the Blood Center of Southeastern Wisconsin. Chimerism was determined at days +14, +28, +56, +100, and +365 after transplant on total peripheral blood mononuclear cells. In most cases, chimerism was additionally determined on post-transplant samples enriched for myeloid (CD15+ or CD33+) or T lymphoid (CD3+) subsets. All patients underwent computed axial tomography of the chest, abdomen, and pelvis and a bone marrow examination before study entry, and at days +28, +100, +6 months, +9 months, +12 months, and thereafter annually unless otherwise clinically indicated. 18F-fluorodeoxyglucose–positron emission tomography (FDG–PET) was used to assess questionable abnormalities and after demonstration of complete remission by computerized axial tomography.

To assess for a clinical graft-versus-lymphoma effect, an analysis was carried out on patients who either had not achieved a complete remission at 100 days after transplant or had recurrent disease after having been determined to be in a complete remission at day +100. The 100-day time point was selected to distinguish between any potential antitumor effects of...
the chemotherapy within the transplant conditioning regimen from immune-mediated graft-versus-lymphoma effects. Patients who were not in a complete remission at day +100 or who experienced relapse after transplant were treated in a consistent manner with removal of immune suppression and/or DLI, depending on the presence or absence of GVHD. In a minority of instances, where there was clinician concern over rapidly growing tumor, chemotherapy was administered before a DLI. Disease response was assessed according to the recommendations of the National Cancer Institute Sponsored International Working Group for the standardization of response criteria for non-Hodgkin’s lymphoma [30]. Overall survival duration was calculated from the day of transplant until date of death or last follow-up. The probability of survival as a function of time was calculated using the Kaplan–Meier method [31].

**results**

Of 18 patients with either refractory and/or relapsed DLBCL enrolled on to the two studies from July 1999 to September 2004, 15 were identified as having persistent disease at or relapsed beyond day +100 after transplantation. For this cohort of 15 patients, the median follow-up time after allogeneic hematopoietic stem-cell transplantation until date of analysis was 58.8 months. Five patients were identified as having a complete remission at day +100, but two of these patients were subsequently documented to have disease relapse at 157 and 169 days after transplantation, respectively. Five patients either remained in or had achieved a partial remission at day +100, as compared with their day +28 evaluation. The other eight patients had documented disease progression, as compared with their day +28 evaluation, including one patient (#3) who died of progressive disease at day +76 after transplant (Table 1).

Evaluation of the 15 patient’s pre-transplantation characteristics (Table 1) demonstrated that 11 patients had disease that was refractory to the last chemotherapy regimen administered before the transplantation conditioning regimen, including eight patients with primary refractory disease. The median number of therapies before transplantation was three (range 2–9). Eight patients (53%) had received prior autologous hematopoietic stem-cell transplantation; the remaining seven patients did not receive autologous hematopoietic stem-cell transplantation, as their disease was not chemotherapy sensitive. All 15 patients demonstrated evidence of complete (>95%) donor lymphoid and myeloid chimerism at 28 days after transplantation. All 15 patients were assessable for acute GVHD before day +100, and five (33%) patients developed grades II–IV acute GVHD. Seven of 14 (50%) assessable patients developed extensive chronic GVHD.

The two patients (#5 and #7) who were determined to be in complete remissions at day +100 subsequently had disease relapse at day +157 and day +169, respectively (Table 2). These two patients received a DLI alone and a DLI with concomitant chemotherapy, respectively. Both patients achieved second complete remissions, which have been sustained without further treatment. All 13 patients who had not achieved a complete remission at 100 days after transplantation were initially treated by withdrawal of cyclosporine immune suppression alone. Five of these patients subsequently received additional treatments with a DLI (1–10 x 10^7 CD+ cells/kg), including three patients who received one to two cycles of conventional chemotherapy to reduce tumor bulk immediately before DLI (Table 2). Responses to these interventions were analyzed relative to the patient’s respective disease status at their day +100 evaluation. Among the five patients who were determined to have partial remissions at day +100, three achieved sustained complete remissions by withdrawal of immune suppression alone. Among the eight patients who were determined to have progressive disease at day +100, one achieved a partial remission and three achieved complete remissions, of which two have been sustained without further therapy. The overall

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age</th>
<th>Sex</th>
<th>Time from Dx to RIST (months)</th>
<th>Number of prior Tx</th>
<th>Prior auto HSCT</th>
<th>Disease status at study entry</th>
<th>IPI score at study entry</th>
<th>CMV serology (donor/recipient)</th>
<th>Donor sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>F</td>
<td>10</td>
<td>2</td>
<td>No</td>
<td>Primary refractory</td>
<td>2</td>
<td>Neg/Neg</td>
<td>M</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>F</td>
<td>11</td>
<td>3</td>
<td>No</td>
<td>Primary refractory</td>
<td>0</td>
<td>Neg/Neg</td>
<td>M</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>F</td>
<td>16</td>
<td>3</td>
<td>Yes</td>
<td>Refractory relapse</td>
<td>2</td>
<td>Pos/Neg</td>
<td>M</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>F</td>
<td>9</td>
<td>3</td>
<td>No</td>
<td>Primary refractory</td>
<td>1</td>
<td>Pos/Pos</td>
<td>F</td>
</tr>
<tr>
<td>5</td>
<td>43</td>
<td>F</td>
<td>18</td>
<td>2</td>
<td>No</td>
<td>Sensitive relapse</td>
<td>1</td>
<td>Pos/Neg</td>
<td>F</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
<td>M</td>
<td>18</td>
<td>3</td>
<td>Yes</td>
<td>Refractory relapse</td>
<td>2</td>
<td>Neg/Pos</td>
<td>F</td>
</tr>
<tr>
<td>7</td>
<td>31</td>
<td>F</td>
<td>16</td>
<td>3</td>
<td>Yes</td>
<td>Sensitive relapse</td>
<td>1</td>
<td>Neg/Neg</td>
<td>M</td>
</tr>
<tr>
<td>8</td>
<td>54</td>
<td>F</td>
<td>126</td>
<td>2</td>
<td>No</td>
<td>Sensitive relapse</td>
<td>1</td>
<td>Neg/Pos</td>
<td>F</td>
</tr>
<tr>
<td>9</td>
<td>32</td>
<td>M</td>
<td>14</td>
<td>4</td>
<td>Yes</td>
<td>Primary refractory</td>
<td>2</td>
<td>Pos/Pos</td>
<td>F</td>
</tr>
<tr>
<td>10</td>
<td>58</td>
<td>F</td>
<td>10</td>
<td>6</td>
<td>Yes</td>
<td>Primary refractory</td>
<td>2</td>
<td>Pos/Pos</td>
<td>M</td>
</tr>
<tr>
<td>11</td>
<td>39</td>
<td>M</td>
<td>10</td>
<td>2</td>
<td>No</td>
<td>Primary refractory</td>
<td>2</td>
<td>Neg/Neg</td>
<td>M</td>
</tr>
<tr>
<td>12</td>
<td>50</td>
<td>M</td>
<td>60</td>
<td>6</td>
<td>Yes</td>
<td>Refractory relapse</td>
<td>0</td>
<td>Neg/Neg</td>
<td>M</td>
</tr>
<tr>
<td>13</td>
<td>43</td>
<td>M</td>
<td>15</td>
<td>3</td>
<td>Yes</td>
<td>Sensitive relapse</td>
<td>3</td>
<td>Neg/Neg</td>
<td>F</td>
</tr>
<tr>
<td>14</td>
<td>49</td>
<td>M</td>
<td>43</td>
<td>5</td>
<td>No</td>
<td>Refractory relapse</td>
<td>2</td>
<td>Pos/Pos</td>
<td>F</td>
</tr>
<tr>
<td>15</td>
<td>41</td>
<td>M</td>
<td>71</td>
<td>9</td>
<td>Yes</td>
<td>Refractory relapse</td>
<td>4</td>
<td>Pos/Pos</td>
<td>F</td>
</tr>
</tbody>
</table>

Pt, patient; Dx, diagnosis; Tx, Treatments before; RIST, reduced-intensity stem transplantation; CMV, cytomegalovirus; Auto HSCT, autologous hematopoietic stem-cell transplant; IPI, international prognostic index; M, male; F, female; Pos, positive serology; Neg, negative serology; NA, not available.
Table 2. Interventions and response in DLBCL patients who relapsed or were not in CR at or beyond day +100 after transplant

<table>
<thead>
<tr>
<th>Day +28 response</th>
<th>Day +100 response</th>
<th>Intervention</th>
<th>Response to intervention</th>
<th>GVHD*</th>
<th>Current status (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 SD</td>
<td>PD</td>
<td>WOI</td>
<td>PD</td>
<td>Y (acute + chronic)</td>
<td>PD/died (4)</td>
</tr>
<tr>
<td>2 SD</td>
<td>PR</td>
<td>WOI</td>
<td>CR</td>
<td>Y (acute + chronic)</td>
<td>CR/died sepsis (80)</td>
</tr>
<tr>
<td>3 PR</td>
<td>PD (+40)b</td>
<td>WOI</td>
<td>PD</td>
<td>Y (acute)</td>
<td>PD/died (2.5)</td>
</tr>
<tr>
<td>4 PR</td>
<td>PD</td>
<td>WOI</td>
<td>PR</td>
<td>Y (acute)</td>
<td>PD/died (6)</td>
</tr>
<tr>
<td>5 CRu</td>
<td>CR → PD (+157)</td>
<td>DLI</td>
<td>CR</td>
<td>N</td>
<td>CR/alive (83+)</td>
</tr>
<tr>
<td>6 CRu</td>
<td>CRu → PD (+169)</td>
<td>Chemo + DLI</td>
<td>CR</td>
<td>Y (chronic)</td>
<td>CR/alive (74+)</td>
</tr>
<tr>
<td>7 PR</td>
<td>PR</td>
<td>WOI</td>
<td>PD</td>
<td>Y (chronic)</td>
<td>PD/died sepsis (11)</td>
</tr>
<tr>
<td>9 CR</td>
<td>PD</td>
<td>WOI, DLI, Chemo + DLI</td>
<td>SD</td>
<td>N</td>
<td>PD/died (21)</td>
</tr>
<tr>
<td>10 SD</td>
<td>PD</td>
<td>WOI</td>
<td>PD</td>
<td>N</td>
<td>PD/died (5.5)</td>
</tr>
<tr>
<td>11 PR</td>
<td>PR</td>
<td>WOI</td>
<td>CR</td>
<td>N</td>
<td>PD/died (26)</td>
</tr>
<tr>
<td>12 PR</td>
<td>PR</td>
<td>WOI</td>
<td>CR</td>
<td>N</td>
<td>CR/alive (63+)</td>
</tr>
<tr>
<td>13 PR</td>
<td>PR</td>
<td>WOI</td>
<td>CR</td>
<td>Y (chronic)</td>
<td>CR/alive (42+)</td>
</tr>
<tr>
<td>14 PR</td>
<td>PD</td>
<td>WOI</td>
<td>CR</td>
<td>Y (chronic)</td>
<td>CR/alive (44+)</td>
</tr>
<tr>
<td>15 SD</td>
<td>PR</td>
<td>WOI, DLI, Chemo + DLI</td>
<td>SD</td>
<td>Y (acute + chronic)</td>
<td>PD/died (12)</td>
</tr>
</tbody>
</table>

DLBCL, diffuse large B-cell lymphoma; GVHD, graft-versus-host disease; SD, stable disease; PD, progressive disease; CR, complete remission; CRu, complete remission undetermined; PR, partial remission; DLI, donor lymphocyte infusion; WOI, withdrawal of immunosuppression; Chemo, chemotherapy; Y, yes; N, No; m, months.

*All acute GVHD diagnosed before day +100.

bPD documented at day +40.

response rate to immunotherapeutic interventions was 60% (9 of 15) with eight complete remissions.

Among the nine patients with either a complete or partial remission, five developed GVHD after withdrawal of immunosuppression or DLI therapy alone. Four patients who achieved a complete remission had no clinical evidence of GVHD. An example of radiographic documentation of a response observed in the latter group is presented in Figure 1. The patient (#11) originally had achieved partial remission at his 28-day post-transplantation evaluation; there was extensive progression documented at his 100-day evaluation with marked increased uptake by FDG–PET imaging. It is of note that the patient had complete donor chimerism at his 28-day post-transplantation evaluation. At day +100 after transplant, however, donor chimerism had decreased to 80%. Cyclosporine was rapidly tapered over a 3-week period, and subsequent FDG–PET imaging 1 week after complete discontinuation of cyclosporine demonstrated significant decrease in extent and uptake. Chimerism at this point was 100% donor. An evaluation by FDG–PET imaging 1 month later demonstrated no abnormal uptake, which was sustained for 8 months without further therapy. In total, six of these nine patients are alive in a sustained complete remission without further therapy (Table 2). The median overall survival for the six patients who remain alive and in complete remission without further treatment is 68 months (range 42–83+ months).

discussion

An immune-mediated antitumor effect against malignant lymphomas, described as a ‘graft-versus-lymphoma effect’, was first reported in 1991 [9]. However, there have been relatively few specific reports providing evidence to support the presence of a clinically relevant graft-versus-lymphoma effect against DLBCL that has occurred after an immunotherapeutic measure, such as a DLI [14, 23]. This lack of data is attributable to several factors which are well outlined in a comprehensive review of this subject by Grigg and Ritchie [14]. These factors include the difficulty in interpreting the available literature due to the inclusion of DLBCL under a single heading of ‘aggressive’, ‘intermediate grade’, or ‘high-grade’ non-Hodgkin’s lymphoma, the lack of a centralized pathologic review, differences in pre-transplant patient characteristics, and inadequate follow-up relative to durability of responses to withdrawal of immune suppression or DLIs. In this context, our report provides additional evidence that patients with refractory and relapsed DLBCL can attain sustained, complete remissions directly attributable to a graft-versus-lymphoma effect, complementing observation made in prior analyses [15, 19–21].

The evidence for a graft-versus-lymphoma effect provided by the current analysis is on the basis of the characteristics of the study population and the methods of treatment. The selected patient population was documented to have the specific diagnosis of DLBCL, had relapsed, the majority of which was refractory to conventional chemotherapy, and was treated in a uniform manner with a reduced-intensity conditioning regimen. Still, relapsed and refractory DLBCL could have been relatively susceptible to the effects of cytotoxic chemotherapy in the reduced-intensity conditioning regimen. There were responses observed at the day +28 post-transplantation evaluation; however, the majority of these responses were transient. To further distinguish an immunological graft-versus-lymphoma effect from any antitumor effect of cytotoxic chemotherapy in the transplant conditioning regimen, we carried out an analysis only on patients who were not in...
complete remission beyond the first 100 days after transplant. It could be argued that the subsequent complete remissions observed in patients who were in a partial remission at this time point were a continued response to the effects of the conditioning regimen. However, the complete remissions observed in three patients with progressive disease at their 100-day post-transplant evaluation, as well as the complete responses in patients with late relapses, cannot be attributed to the effects of chemotherapy within the conditioning regimen. Further evidence of a graft-versus-lymphoma effect, using criteria indicated by Grigg and Ritchie, was the fact that the overwhelming majority of responses occurred with the withdrawal of immunosuppression alone and that they were documented to be sustained without additional therapy.

The data also demonstrate that responses can be observed in patients who fail to achieve a complete remission or who progress early after transplant. These patients, with highly advanced DLBCL, would typically be regarded as treatment failures. Further immunotherapy, alone or in combination with additional chemotherapy at conventional doses, however, resulted in long-term progression-free survival for a significant percentage of these patients. As such, the lack of initial response or early disease progression after transplant should not necessarily be perceived as treatment failure. Rather, we conclude that the actual transplant should be perceived as a component of therapy, and a successful clinical outcome may still be obtained through withdrawal of immune suppression or additional donor lymphocytes.

The clinical observations of sustained complete remissions after withdrawal of immune suppression and DLI beyond 100 days after transplant demonstrate that a clinically relevant graft-versus-lymphoma effect exists against DLBCL. These data, along with the observations cited above, complement the observations of decreased relapse rates and prolonged disease-free survival observed in patients undergoing allogeneic hematopoietic stem-cell transplantation as compared with autologous hematopoietic stem-cell transplantation. Taken together, they support the contention that a clinical relevant graft-versus-lymphoma effect can be generated against DLBCL. The data also provide the impetus to study the mechanisms that underlie these responses.

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**references**


