Allogeneic haematopoietic stem cell transplantation for metastatic renal carcinoma in Europe

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Background: An allogeneic antitumour effect has been reported for various cancers. We evaluated the experience of allogeneic haematopoietic stem cell transplantation (HSCT) for renal cell carcinoma (RCC) in 124 patients from 21 European centres.

Patients and methods: Reduced intensity conditioning and peripheral blood stem cells from an HLA-identical sibling (n = 106), a mismatched related (n = 5), or an unrelated (n = 13) donor were used. Immunosuppression was cyclosporine alone, or combined with methotrexate or mycophenolate mofetil. Donor lymphocyte infusions (DLI) were given to 42 patients. The median follow-up was 15 (range 3–41) months.

Results: All but three patients engrafted. The cumulative incidence of moderate to severe, grades II–IV acute GVHD was 40% and for chronic GVHD it was 33%. Transplant-related mortality was 16% at one year. Complete (n = 4) or partial (n = 24) responses, median 150 (range 42–600) days post-transplant, were associated with time from diagnosis to HSCT, mismatched donor and acute GVHD II-IV. Factors associated with survival included chronic GVHD (hazards ratio, HR 4.12, P < 0.001), DLI (HR 3.39, P < 0.001), <3 metastatic sites (HR 2.61, P = 0.002) and a Karnofsky score >70 (HR 2.33, P = 0.03). Patients (n = 17) with chronic GVHD and given DLI had a 2-year survival of 70%.

Conclusion: Patients with metastatic RCC, less than three metastatic locations and a Karnofsky score >70% can be considered for HSCT. Posttransplant DLI and limited chronic GVHD improved the patient survival.

Key words: allogeneic stem cell transplantation, antitumour effect, reduced intensity conditioning, renal cell carcinoma

Introduction

The fact that the immune system may control cancer is evident by both experimental and clinical studies [1–4]. In clinical allogeneic haematopoietic stem cell transplantation (HSCT), graft-versus-host disease (GVHD) was found to contribute to an antileukaemic effect. Such an antileukaemic effect is most probably induced by donor T-lymphocytes and is seen both for the acute and the chronic form of GVHD. The graft-versus-leukaemia effect may be induced or enhanced by post-transplant addition of donor lymphocyte infusions (DLI) [5]. The effect of DLI has been especially pronounced in patients with chronic myeloid leukaemia (CML). An allogeneic graft-versus-tumour (GVT) effect has also been reported for breast cancer, renal cell carcinoma (RCC), colon carcinoma and ovarian carcinoma [6–13]. Although responses have been reported in some patients, many patients have died of progressive disease [8–16]. Childs and co-workers reported responses in 10 out of 19 patients who underwent HSCT for RCC, which was associated with acute GVHD with no apparent effect of DLI [9]. Because of the variability in the outcome, there has been uncertainty regarding the indications for HSCT in RCC. Furthermore, which patients should be selected and what is the optimal protocol? We here report the European experience in 124 patients who underwent HSCT for RCC. Since metastatic RCC is resistant to chemoradiotherapy, all patients were treated...
with reduced intensity conditioning (RIC) to induce marked immunosuppression and pave the way for the donor immuno-haematopoietic system [17–19]. Based on analyses of two European prospective studies, we suggest which patients are more likely to have an immune mediated response, and which parameters are associated with tumour response and survival.

patients and methods

Between July 1999 and September 2003, 124 patients with metastatic RCC underwent HSCT at 21 European centres. Patient and donor characteristics are given in Table 1. All but six patients underwent tumour reducing nephrectomy before HSCT. Second to fourth line therapy, often including immunotherapy with interferon-α or interleukin-2, was given to 66 patients. At the time of HSCT, 108 patients had progressive disease, nine had stable disease, four partial remission and three were not reported. The locations of the metastases were the following: lungs 85 patients, lymph nodes 48, bone 41, liver 30, brain five, other in 33 patients. The five patients with brain metastases were included when in partial remission (n = 2), stable disease (n = 1) or progressive disease (n = 2). Four of them had more than two sites of metastases. In the total study group, three of the four patients with partial remission had metastases in lungs and liver, one of them in addition had bone metastases. A Karnofsky score pretransplant was 90–100% in 81%, 80% in 23, and 60–70% in 20 patients. Karnofsky score for the patients with brain metastases was 70% (n = 3) and 90% (n = 2). Most donors were HLA-identical siblings (n = 106, Table 1). A few mismatched related and HLA A, B and DR subtype antigen matched unrelated donors were used. HLA-typing was initially serologic for class I and high-resolution polymerase chain reaction-single-stranded polymorphism (PCR-SSP) for HLA class II. In some centres, PCR-SSP was also used for HLA class I, especially when selecting unrelated donors. All patients received peripheral blood stem cells (PBSC) from donors treated with granulocyte colony-stimulating factor (G-CSF) of 10 μg/kg/day given for 5–7 consecutive days. A median of 5.5 (range 0.78–20.5) ×10⁸ CD34+ cells/kg of recipient’s body weight (BW) was infused following 2 to 4 aphereses.

This study collects the data from two prospective protocols, the phase I study of the European Group for Blood and Marrow Transplantation Solid Tumour Working Party (EBMT STWP) and the French ITAC group on RCC patients [16]. The protocols were approved by the respective ethics committee at each centre and informed consent was given.

preparative regimens

Mainly four RIC regimens were used: (1) fludarabine (FLU, 125 mg/m²) and cyclophosphamide (CY, 120 mg/kg) in 53 patients, (2) thiopeta (5–10 mg/ kg/day) for 2 days, FLU 30 mg/m² days –4 and –3 in one patient and combined with CY 30 mg/kg days –4 and –3 in 29 patients, (3) FLU 125 mg/ m², busulphan (8 mg/kg) and anti-T-cell globulin (ATG) (SangStat, Lyon, France) in 18 patients [16], or (4) FLU 30 mg/m² days –4 to –2 and 2 Gy of total body irradiation (TBI) in 23 patients. The dose of chemotherapy, especially FLU, was reduced by 25–30% in patients with decreased renal function due to nephrectomy. In addition, ATG (SangStat, Lyon, France or Fresenius AG, Bad Homburg, Germany) was given to 25 patients and alemtuzumab (Schering AG, Berlin, Germany) was given to two patients due to HLA mismatch.

Prophylaxis against GVHD consisted of cyclosporine alone, cyclosporine combined with three or four doses of methotrexate or with prednisolone or with mycophenolate mofetil (Table 1) [9–16, 19].

Donor lymphocyte infusions were given monthly or every second month [16] in escalating doses to patients with progressive status, usually starting with 1–10 × 10⁶ CD3+ cells/kg of the recipient’s BW (n = 42). In the absence of GVHD, this was followed by escalation of the CD3+ cell dose with 0.5-log (n = 25). Twelve patients received a third dose of 3–10 × 10⁶ CD3+ cells/kg. Five patients received four to five DLI doses.

chimerism and graft-versus-host disease

Chimerism was analysed using the local PCR amplification method by variable number of tandem repeats on CD34+ cells separated with immunomagnetic beads [20]. In some centres, PCR was applied on total DNA extracted from lymphoid peripheral blood cells after gradient centrifugation. Complete donor chimerism (DC) was defined as ≥95% of the separated cell populations being of donor origin. Acute GVHD was diagnosed from clinical symptoms and/or biopsies from skin, oral mucosal membranes, liver and gut. Acute GVHD was graded from 0 to IV, grade 0 referring to limited, grade I mild, grade II moderate, grade III-IV severe with grade IV being life-threatening [2–4]. In limited to mild acute GVHD, less than 50% of the body surface showed signs of reddish inflammation, and in grade II it was more than 50%. Acute GVHD grade III consisted of more severe skin inflammation and/or inflammatory bowel and/or liver dysfunction. Chronic GVHD occurring after 90 days post-HSCT was classified as limited or extensive [2–4].

Table 1. Patient demographics of 124 haematopoietic stem cell transplanted patients with metastatic renal cell carcinoma (RCC)

| Sex (M/F) | 92/32 |
| Age, median (range), years | 52 (18–68) |
| Donor sex (M/F) | 65/57* |
| Donor age, median (range), years | 47 (21–73) |
| RCC type | |
| Clear cell | 111 |
| Papillary | 7 |
| Unknown | 6 |
| Karnofsky score pretransplant (%) | |
| 60–70/80/90–100 | 20/23/81 |
| Number of previous therapies | 6/1/2/3/4 |
| CMV prophylaxis | |
| CsA/Prednisolone 1 | 36 |
| CsA/Thiostepa | 1 |
| CsA/Methotrexate | 62 |
| CsA/Prednisolone | 1 |
| CsA/MMF | 25 |

CMV, cytomegalovirus; *some patient data is missing.
metastatic responses
Complete response (CR) was defined as disappearance of all measurable lesions. Partial response (PR) was defined as a more than 50% decrease of the sum of all metastatic lesions for at least 30 days. A patient had a stable disease (SD) when he/she did not qualify as partial or complete responder or progressive disease. This required at least 1 month of duration but usually a 3-monthly follow-up was reported. Progressive disease (PD) was defined as increase in size of more than 25% in one or more lesions and/or appearance of new metastases. All patients underwent computer tomography (CT) scanning before HSCT and at least at 3, 6 and 12 months during the first year and then at least yearly. In some centres, CT was performed every month.

statistics
Survival was analysed on 10 February 2004 with the Kaplan-Meier product limit method and using the log-rank (Mantel-Cox test), taking censored data into account. Time to TRM, response, acute and chronic GVHD was estimated using a non-parametric estimator of cumulative incidence curves. Competing events for TRM were death or progressive disease, for response death without response, and for GVHD death without GVHD. A patient was defined as evaluable concerning tumour response and chronic GVHD if she/he had survived more than 90 days [21, 22]. The Cox’ regression model was used for survival and tumour response in uni- and multivariate analysis. In the multivariate analysis, factors with a cumulative incidence of response was 32% (95% CI; 18–46%) (Figure 2). Complete response (n = 4) was seen at median 265 (range 180–315) days after HSCT, while partial response (n = 24) was seen median 135 (range 42–600) days. Eleven of the 45 patients (24%) given ATG showed CR (n = 1) or PR (n = 10) and 17 of 74 patients (23%) not given this treatment presented with CR (n = 3) or PR (n = 14) (ns).

tumour responses
A complete tumour response was seen in four of 98 evaluable patients. Partial response was seen in 24 patients. During the study, 24 patients had a stable disease. Sixty-seven patients had progressive disease with a fatal outcome in 54 cases. Five patients died early in HSCT related complications. A tumour response was seen in 28 of 98 evaluable patients. The cumulative incidence of response was 32% (95% CI; 18–46%) (Figure 2).

results
engraftment, donor lymphocyte infusions and transplant-related complications
All but three patients engrafted (98%). An absolute neutrophil count (ANC) of more than 0.5 × 10^9/l for three consecutive days was reached at a median of 12 days (range 0–28 days) after HSCT. A platelet count of more than 20 × 10^9/l in the absence of transfusions was reached on a median of 9 days (range 0–43 days) in 110 patients with available data. Complete donor CD3+ cell engraftment was seen in 32 of 96 (33%) patients at one month, 48 of 80 (60%) at three months, and in 45 of 51 (88%) of the patients analysed at six months post-HSCT. At 30 days post-HSCT, patients given fludarabine, busulphan and ATG based RIC showed the earliest DC (Figure 1).

The first DLI was given at median 124 (range 42–620) days after SCT. The response to DLI was reported as PR (n = 9), SD (n = 10) and PD (n = 15).

Reactivation of cytomegalovirus (CMV) was diagnosed in 33/106 (31%) of the patients. One patient developed a fatal CMV pneumonitis (Table 2).

Acute GVHD grades II–IV developed in 47 of 119 patients at median 55 days (range 9–196 days) after HSCT with a cumulative incidence of 40% (95% CI; 30.2–49.8%). Acute GVHD grades I, II, III and IV were reported in 17, 26, 13 and eight patients, respectively. In many patients, this occurred soon after cyclosporine withdrawal, or following DLI. Chronic GVHD was diagnosed as limited in 21 and extensive in 18 of 98 evaluable patients at median 122 days (range 69–485 days) after HSCT.

Transplant-related mortality (TRM), i.e. death from all causes but cancer, occurred at a cumulative incidence of 16% (95% CI; 8.4–23.6%) including GVHD (n = 8), multi-organ failure (n = 4), infections (n = 5) and other causes (n = 2) (Table 2).

Table 2. Fatal outcome in toxicity of reduced intensity conditioning and allogeneic stem cell transplantation in 124 renal cell carcinoma patients

<table>
<thead>
<tr>
<th>Type of toxicity</th>
<th>No. of patients</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft-versus-host disease (grade III-IV)</td>
<td>8</td>
<td>(6.5)</td>
</tr>
<tr>
<td>Infections</td>
<td>5</td>
<td>(4.0)</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Bacterial septicaemia</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus pneumonitis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Multi-organ failure</td>
<td>4</td>
<td>(3.2)</td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>(1.6)</td>
</tr>
<tr>
<td>Hemorrhagic cystitis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Type not reported</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>(15.3)</td>
</tr>
</tbody>
</table>
In multivariate analyses, tumour response was associated with a time period of less than one year from the diagnosis of RCC to HSCT, HLA mismatched donor and acute GVHD II-IV (Table 3). The various RIC protocols, the different immunosuppressive regimens used and donor CD3+ cell engraftment had no significant impact on tumour response or survival. Localisation or number of the metastatic sites did not influence the response, neither of the patients had SD or PD pre-HSCT. The four patients with complete response had the following common features: few metastatic localisations, a high Karnofsky score, shorter time to reach a full donor chimerism, and three of them developed chronic GVHD before response.

**survival**

Overall patient survival was 30% at two years after HSCT. Sixty-three patients died of progressive disease. All five patients with brain metastases died of progressive disease median 5 (range 1–21) months after SCT. Among the four patients undergoing HSCT while in partial remission, two died of progressive disease. When chronic GVHD was included in the multivariate analysis of survival, a landmark analysis on patients surviving more than 90 days post HSCT was performed. In univariate analysis, poor survival was associated with the following factors: a Karnofsky score <80% \( (P < 0.001) \), lymph node metastases \( (P = 0.016) \), liver metastases \( (P = 0.08) \), bone metastases \( (P = 0.02) \), no DLI \( (P < 0.001) \), no chronic GVHD \( (P < 0.001) \) or number of metastases \( (P < 0.001) \). Patients with a Karnofsky score of >70% had a better survival, compared to those between 60 and 70% (Figure 3, \( P < 0.001 \)). Patients with two or fewer sites of metastases \( (n = 88) \) had a better survival, compared to those with 3–5 locations of metastases \( (n = 35) \) (Figure 4, \( P < 0.001 \)). Patients with chronic GVHD who also received DLI \( (n = 17) \) had a 2-year survival of 70% (Figure 5). In contrast, patients without chronic GVHD and not given DLI \( (n = 34) \) had a 2-year survival of 18% \( (P < 0.001) \). Patients with chronic GVHD and not given DLI \( (n = 22) \) or patients given DLI without development of chronic GVHD \( (n = 24) \) showed in both groups a similar survival between these two extremes. The probability of survival was significantly better for patients given DLI compared to patients not given DLI, 62% versus 39% at 1 year \( (P = 0.003) \); a landmark analysis from day 90. In multivariate analysis of overall patient survival, chronic GVHD, DLI, a Karnofsky score 280% and less than three sites of metastases, were associated with improved survival after HSCT (Table 3).

**discussion**

A report by Childs and co-workers with a tumour response rate of 10 of 19 in patients undergoing HSCT for RCC encouraged the present European trials [9]. In addition, the trials were justified due to the extremely poor prognosis in metastatic RCC with a median survival usually of less than 1 year [23, 24]. Systemic chemotherapy is ineffective, but some responses have been seen with interleukin-2 and interferon-\( \alpha \), with response rates below 20% [22–26].

A recent study showed that neutralising antibody against vascular endothelial growth factor (VEGF) prolonged the time to progression of disease in patients with RCC, although survival was not significantly prolonged [27]. Furthermore, the first full report of a multitargeted tyrosine kinase inhibitor (TKI) of VEGF and platelet-derived growth factor receptors as a second-line treatment for patients of metastatic RCC demonstrated partial responses in 40% of patients with a median survival of 16.4 months [28]. These results are under evaluation in the light with preliminary reports on other TKIs [29]. The present European multicentre study confirms the previous encouraging effects using HSCT for patients with metastatic RCC [9, 12–16, 30].

Because of the TRM associated with HSCT, this procedure is in general only performed in patients with an otherwise dismal
outcome. To reduce TRM, reduced intensity conditionings have been introduced to treat haematological malignancy patients of high age or with organ impairment who would not be considered for full myeloablative chemoradiotherapy and HSCT [17–19]. Lately, RIC has also been used for metastatic solid tumours non-responsive to chemoradiotherapy [9–16]. In the present study, the cumulative probability of TRM was 16%, which may be improved with a better patient selection. Patients offered RIC and allogeneic HSCT should manage the treatment related potential toxicity of GVHD and infections counted into TRM. Although the maturation of the new immunity even after RIC may take over one year, in this study, infectious complications were rare (4%, Table 2).

Using RIC, there may be an increased risk of graft failure, compared to full myeloablative chemoradiotherapy. Graft failure rates of up to 20% have been reported using RIC by McSweeney et al. [31]. A graft failure rate of only 3% in the present series is therefore encouraging. However, McSweeney and co-workers only used 2 Gy of TBI as conditioning, combined with cyclosporine and mycophenolate mofetil as the post-transplant immunosuppression. This regimen has been reported to be associated with an increased risk of graft failure and also GVHD due to relatively long-lasting mixed chimerism allowing antigen presenting cells and T-cells of recipient origin to interfere as compared to the conditioning regimens used in most patients in the present study [32]. We found no significant effect of different RIC protocols or GVHD prophylaxis regarding tumour response or survival. The use of ATG did not influence tumour response. Interestingly, time to complete donor chimerism seemed faster using fludarabine, busulphan and ATG compared to the other RIC protocols (Figure 1). The role of ATG in this context needs to be evaluated. A correlation between donor chimerism and tumour response was earlier reported [9]. Therefore, more patients are needed to evaluate the optimal RIC protocol.

A complete and partial response rate of 29% of patients is similar to that seen by Artz et al. [12], but lower than 54% reported by Childs and colleagues [9]. This difference may be due to patient selection with more patients with advanced disease in the present report. Tumour response was associated with a short time from diagnosis to HSCT, HLA mismatched donors and GVHD (Table 3). Early transplantation seems beneficial, before the metastases are too widespread. In multivariate analysis, number of localisations of metastases, rather than the type of metastases, and a low Karnofsky score were significant factors also for survival. Furthermore, a previous study on HSCT for RCC showed that low performance status, increased CRP and LD were correlated to a poor prognosis [33].

The importance of HLA mismatch suggests an allogeneic anti-tumour effect directed against HLA antigens on the surface of the metastatic cells. This effect is further strengthened by the

| Table 3. Results from multivariate analysis for tumour response and survival among 124 haematopoietic stem cell transplanted patients with renal cell carcinoma |
|-----------------|--------|----------|-------------|-----------------|
| Response (CR + PR) | OR     | 95% CI   | P-value    |
| Time diagnose-HSCT | ≥1y/<1y | 2.94     | 1.29–6.71  | 0.009          |
| Mismatched donor   | No/Yes | 6.96     | 1.55–31.3  | 0.01           |
| Acute GVHD II-IV   | No/Yes | 2.43     | 1.13–5.19  | 0.02           |
| Survival           |        |          |            |                |
| Chronic GVHD       | No/Yes | 4.12     | 2.20–7.69  | <0.001         |
| DLI                | No/Yes | 3.39     | 1.86–6.18  | <0.001         |
| No. of metastatic sites | 3–5/0–2 | 2.61     | 1.44–4.74  | 0.002          |
| Karnofsky score (%)| 60–70/80–100 | 2.33     | 1.09–4.97  | 0.03           |
| CR, complete response; PR, partial response; OR, odds ratio; CI, confidence interval; HR, hazards ratio; DLI, donor lymphocyte infusion. 

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The importance of HLA mismatch suggests an allogeneic anti-tumour effect directed against HLA antigens on the surface of the metastatic cells. This effect is further strengthened by the
correlation between grades II–IV acute GVHD and response, which also confirms previous studies on allogeneic HSCT against solid tumors [9, 12, 14]. Harlin et al. demonstrated that the clinical tumour response in RCC patients after HSCT was associated with an expansion of interferon-α producing CD8+ T-cells [34]. Similarly, in patients treated using RIC and allogeneic HSCT for colorectal cancer, carcino-embryonal antigen (CEA) specific T-cells were detected concomitantly with GVHD and were associated with a decrease of serum CEA levels as well as clinical partial remission [35].

For survival, chronic GVHD and DLI were of utmost significance (Figure 5, Table 3). In patients with leukaemia, chronic GVHD has been found to have a more profound antileukaemic effect, compared to acute GVHD [2–4]. Obviously, chronic GVHD has an important effect on survival in metastatic RCC. This has not been reported previously. In the study of Childs and colleagues, the observation time was shorter and only four patients developed chronic GVHD. In that study, eight patients received up to three escalating doses of DLI with no effect on tumour responses or survival. In this European multicentre study, patients with chronic GVHD and receiving DLI had a survival of 70% two years after transplant (Figure 5, Table 3). Six patients got DLI after they had developed chronic GVHD. Based on these findings, patients with metastatic RCC should probably discontinue their immunosuppression early in the absence of GVHD to induce chronic GVHD. Indeed, in HLA-identical sibling transplants for leukaemia, those with low-dose cyclosporine of short duration had an increased probability of mild acute and chronic GVHD, resulting in a reduced probability of leukaemic relapse [36]. Such an approach may also be used in patients with metastatic RCC, because Childs and colleagues reported a correlation between acute GVHD and tumour response and the present study showed an anti-tumour effect of chronic GVHD [9]. In addition to chronic GVHD, RCC patients seem to need DLI. However, we still need to improve interventions of severe GVHD to decrease the TRM since severe GVHD is after relapse the second most common reason for fatal outcome in allogeneic HSCT.

At present, it is not possible to compare the outcome in HSCT patients with that using conventional therapy, or using interleukin-2, interferon-α, new inhibitors of the VEGF receptor or their combinations [23–29]. Using earlier cytokine-based immunotherapies, 3-year survival is reported around 20% [23–26]. Results of the first single-agent antibody against VEGF, bevacizumab, have improved in a trial combining it with another antibody, erlotinib, giving a median survival time of 23 months [27, 37]. In phase II/III trials for metastatic RCC, single agent antibodies against VEGF and TKIs have shown partial responses or stable disease and minor responses in approximately 20–50% and 40–80% of patients, respectively [29]. These impressive results are to be regarded as a step towards a reality of life-prolonging therapies with manageable but still treatment-limiting toxicity in elder patients. However, it is presently unknown if the patients with partial and complete responses with any therapy will be cured or not due to tendency of the development of tumor resistance. Longer observation times and additional studies on the precise clinical mechanisms of these drugs are required. As is the case in patients with leukaemia undergoing HSCT, it may be important to select patients at an earlier stage with a low tumour burden. It is probable that metastatic RCC requires several therapeutic strategies to significantly improve the long-term survival. It may be necessary to combine HSCT with other therapies, such as irradiation against metastases, anti-VEGF antibodies, TKIs, interferon-α, interleukin-2, etc. in order to prevent the risk for tumour escape mechanisms [38]. Combining the more direct tumour necrotising and inflammatory effect of the latter with the slowly developing allogeneic antitumour effect of HSCT using less toxic RIC offers a new platform in cancer therapy. Results on allogeneic HSCT in metastatic RCC may warrant further studies on patients with other metastatic solid tumours. Indeed, such studies are under way in the USA and within the EBMT.

To conclude, we observed tumour responses in a fraction of patients with metastatic RCC receiving allograft as salvage therapy. Based on the findings of this trial, patients with less than three metastatic sites and a Karnofsky score >70% can be considered for HSCT. Furthermore, it seems important to include DLI in the protocol and try to induce limited chronic GVHD.

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References


