BFR (bendamustine, fludarabine, and rituximab) allogeneic conditioning for chronic lymphocytic leukemia/lymphoma: reduced myelosuppression and GVHD

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Key Points
- BFR is an effective allogeneic conditioning for chronic lymphocytic leukemia/lymphoma.
- Remarkably, this BFR regimen resulted in a low incidence of myelosuppression and severe acute GVHD.

Myelosuppression, graft-versus-host disease (GVHD), and relapse remain major causes of morbidity after stem cell transplantation for relapsed lymphoma. In this phase 1/2 study, we tested the safety and efficacy of escalating doses of bendamustine (70, 90, 110, and 130 mg/m² per day for 3 days), coupled with our historical fixed doses of fludarabine and rituximab (BFR), as a nonmyeloablative allogeneic conditioning regimen for patients with relapsed lymphoma (n = 41) and chronic lymphocytic leukemia (CLL) (n = 15). Ten patients entered the phase 1 study; none experienced a dose-limiting toxicity. Forty-six additional patients were then treated in the phase 2 study at the maximum dose of 130 mg/m² per day for 3 days. The proportions of transplants from matched siblings or unrelated donors were 54% and 46%. Remarkably, 55% of patients did not experience severe neutropenia. Forty-nine patients (88%) did not require platelet transfusion. The incidence of acute grade II-IV GVHD was 11%. The 2-year rate of extensive chronic GVHD was 26%. After a median follow-up duration of 26 months (range, 6-50 months), the 2-year overall and progression-free survival rates were 90% and 75%. In conclusion, our new BFR regimen is safe and effective for relapsed CLL and lymphoma patients. This trial was registered at www.clinicaltrials.gov as #NCT00880815. (Blood. 2014;124(14):2306-2312)

Introduction

Conventional chemoimmunotherapy and recently developed targeted therapies for advanced, relapsed non-Hodgkin lymphoma (NHL) have led to improved patient outcomes, but a significant proportion of patients will eventually experience relapse and require a succession of therapies.1,2 Moreover, the long-term disease-free survival results of autologous stem cell transplantation (SCT) have been suboptimal in patients with relapsed indolent lymphoid malignancies and relapsed mantle cell lymphoma.3-5 A significant proportion of potentially curable diffuse large B-cell lymphoma cases are refractory to or ineligible for autologous SCT.

The outlook for patients with NHL has improved with the use of allogeneic SCT (allo-SCT).6 The past 15 years have witnessed a dramatic shift in how this procedure is performed, with increasing numbers of patients receiving less toxic, nonmyeloablative, or reduced-intensity conditioning regimens that promote the engraftment of donor cells and rely primarily on graft-versus-lymphoma (GVL) induction.7-10 Numerous regimens of various intensities continue to be developed to minimize the toxicity of transplantation while maximizing GVL activity. However, graft-versus-host disease (GVHD) remains a serious concern, with a risk of acute II-IV GVHD of 20% to 50% and chronic GVHD of up to 70%.11 An ideal regimen would allow donor cell engraftment with the shortest period of neutropenia, least toxicity, and lowest incidence of GVHD while allowing early disease control via the GVL effect. However, in the absence of randomized trials, it has been difficult to demonstrate the superiority of one regimen over another.

Bendamustine was first synthesized in the early 1960s.12 Structurally, it is a nitrogen mustard that consists of chloroethylamine, an alkylating group that is attached to a benzimidazole ring, a purine analog, and a butyric acid side chain that imparts water solubility.12 Functionally, it is only partially cross-resistant with other DNA-binding anticancer agents, such as cisplatin and doxorubicin, and it is not cross-resistant with other alkylating agents, which are the major drugs used in the first- and second-line treatment of NHL.13 Bendamustine has proven to be effective in the treatment of several hematologic malignancies.14-18 Its efficacy and safety profile were evident from the results of a randomized trial of it plus rituximab vs R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone): patients with indolent and mantle cell lymphomas had higher survival rates; fewer toxicities, including a hematologic toxicity rate of 30% vs 68% (P < .0001); and a lower rate of infections (36% vs 50%; P = .0025).18 Favorable outcomes


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were also reported with intense doses of bendamustine as an autologous SCT conditioning regimen. These findings encourage the use of bendamustine in allo-SCT.

In this phase 1/2 study, we determined the tolerance and efficacy of an escalating dose of bendamustine (70, 90, 110, and 130 mg/m² per day for 3 days), coupled with historical fixed doses of fludarabine and rituximab, as an allo-SCT conditioning regimen for patients with resistant or relapsed chronic lymphocytic leukemia (CLL) and lymphoma.

Patients and methods
Study oversight and conduct
This investigator-initiated trial (#NCT00880815) was performed at The University of Texas MD Anderson Cancer Center (Houston, TX) in accordance with the Declaration of Helsinki and the International Conference on Harmonized Guidelines for Good Clinical Practice. The study protocol was approved by the center’s institutional review board and was in compliance with institutional guidelines. The study drug, bendamustine, was provided free of charge by Cephalon, who provided no other financial or logistical support for the study.

Patients
Patients were recruited consecutively between April 2009 and February 2013 and signed informed consent. The eligibility criteria were age 18 to 70 years and a diagnosis of resistant or relapsed CD20+ CLL or NHL. With the advent of publications demonstrating efficacy of bendamustine in T-cell lymphoma, the protocol was amended to also include these histologies; these T-cell lymphoma patients did not receive rituximab with the conditioning. The other inclusion criteria were an Eastern Cooperative Oncology Group performance status score of 0 to 2 and adequate liver function (bilirubin and liver enzyme concentrations up to 3 times the upper limit of normal), renal function (creatinine <1.6 mg/dL), cardiac function (ejection fraction >40%), and pulmonary function (>40% of predictive value). In addition, patients were required to have a 6/6 HLA-compatible sibling donor or HLA-A, -B, -C, and -DRB1 identical unrelated donor if no sibling donors were available, according to our department’s standard practice guidelines. The exclusion criteria included active central nervous system involvement with disease, prior refractoriness to bendamustine, a prior allo-SCT, pregnancy, breastfeeding, or known infection with HIV, human T-lymphotropic virus, or hepatitis B or C virus. Additional exclusion criteria were the concurrent presence of other malignancies (with the exception of squamous cell or basal cell carcinoma), uncontrolled infection, stroke or myocardial infarction within 6 months of study entry, a prior allogeneic transplant, the use of other investigational drugs, and hypersensitivity to bendamustine.

Procedure and study design
Escalating doses of bendamustine (70, 90, 110, and 130 mg/m² per day for 3 days), coupled with fixed standard doses of fludarabine and rituximab, were administered in an inpatient setting as a preparative regimen. Bendamustine doses of 70 and 90 mg/m² were infused over 30 minutes, and doses of 110 and 130 mg/m² were infused over 60 minutes. Patients received the bendamustine and 30 mg/m² per day fludarabine IV over 30 minutes for 3 days (–5 to –3 days before allo-SCT); those with B-cell disease were given 375 mg/m² rituximab on day –13 and 1000 mg/m² on days –6, +1, and +8.7 Allo-SCT was performed on day 0 (Figure 1).

The dose levels of bendamustine were studied using the continual reassessment method described by O’Quigley et al. with a target toxicity probability of 30%. To determine the maximum tolerated dose, we defined a dose-limiting toxicity (DLT) as death, any grade IV nonhematologic toxicity within 30 days after SCT, and failure to experience engraftment of at least 50% of donor T cells by days 25 to 30 after transplantation. A maximum of 26 patients were to be treated in cohorts of 2, for a maximum of 13 cohorts.

Transplantation and GVHD
Donor chimerism and engraftment were assessed using polymerase chain reaction–based methods, as described in detail elsewhere. GVHD prophylaxis consisted of tacrolimus 0.015 to 0.03 mg/kg (starting on day 0) and methotrexate of 5 mg/m² on days 1, 3, and 6. Patients who received transplantations from matched unrelated donors received an additional dose of methotrexate of 5 mg/m² on day 11 and 1 mg/kg of rabbit antithymocyte globulin IV on days –2 and –1 before allo-SCT. Tacrolimus taper was initiated at 6 months after allo-SCT in patients with no active GVHD. Acute and chronic GVHD were graded according to consensus criteria that were reported previously. Patients received supportive care with antibiotics, antifungals, and antivirals, as per institutional guidelines.

Donor lymphocyte infusions (DLIs) were administered, in combination with rituximab (in cases of B-cell lymphoma), to patients with persistent or progressive disease after allo-SCT and no GVHD. Tacrolimus doses were rapidly tapered. Rituximab was then given at a dose of 375 mg/m² IV, followed by 3 weekly doses of 1000 mg/m². A DLI of 1 × 10⁷ CD3-positive lymphocytes/kg was administered.
T cells/kg was given after the first 2 doses of rituximab if no GVHD occurred. An escalated DLI dose was given at 6-week intervals if there was persistent active disease and no GVHD. DLIs were not routinely administered in patients with stable mixed chimerism if their disease remained in remission. Patents who experienced a rapid decrease of donor cells received DLIs with the goal of achieving complete donor chimerism.

Statistical analysis

Summary statistics of patients’ demographic and clinical characteristics were obtained from patients’ electronic medical records provided. Patient survival end points (overall survival [OS] and progression-free survival [PFS]) were estimated using the Kaplan-Meier method. Survival end points between patient groups were compared using the log-rank test. The cumulative incidence rates of nonrelapse mortality and acute and chronic GVHD were estimated and compared using Gray’s method with the R software package “cmpsk”. All tests were 2 sided, and P values of .05 or less were considered statistically significant. The statistical analysis was carried out using SAS software version 9 (SAS Institute, Cary, NC). Statistical plotting was performed using R software version 2.15.1 (R Foundation, Vienna, Austria).

Results

Patient characteristics

Sixty eligible patients were considered for allo-SCT during the study period. Three patients did not undergo conditioning or SCT (2 with rapidly progressive disease [1 with central nervous system involvement] while waiting to start the conditioning regimen and 1 with progressive liver toxicity from salvage conventional chemotherapy). One patient experienced pulmonary distress and hypoxemia to the first dose of bendamustine. This patient had a history of obstructive sleep apnea. He recovered with steroid therapy, but the transplantation was aborted. Thus, 56 patients were evaluated in this study.

Ten (18%) of these patients entered the phase 1 study: 2 were treated at a bendamustine dose of 70 mg/m² per day, 3 at 90 mg/m² per day, 3 at 110 mg/m² per day, and 2 at 130 mg/m² per day for 3 days. The monitoring team accepted to treat 3 patients at levels 2 and 3, as patients number 2 and 3 within each cohort were considered for a transplant at the same time. None of these patients experienced DLTs. The remaining 46 (82%) patients entered the phase 2 part of the study at the maximum dose of 130 mg/m² per day for 3 days.

Patients’ characteristics are shown in Table 1. Eleven (20%) patients had bone marrow involvement, and 14 (25%) had >1 extranodal site of involvement with disease. β-2 microglobulin of ≥3 mg/L was present in 23% of patients.

Both the lymphoma and CLL patients had received a median of 3 previous therapies. Seven (17%) of 41 lymphoma patients who had experienced recurrence of their disease after a prior autologous SCT were enrolled in this study at a median time of 48 months (range, 10-108 months) from their first transplant.

The CLL patients were generally considered to have high-risk disease (Table 1). Two patients had Richter transformation. Ten (91%) of 11 patients with data that could be evaluated had unmutated immunoglobulin variable heavy-chain gene. A total of 33% of the patients had 17p13.1 deletions, and 20% had 11q22.3 deletions. All patients received prior therapies with nucleoside analogs (47% were resistant), rituximab, and an alkylator. In addition, 20% of patients were also resistant to lenalidomide and 13% to ofatumumab, and 1 patient progressed while receiving ibrutinib.

Table 1. Demographic and clinical characteristics of allogeneic SCT patients who were given bendamustine, fludarabine, and rituximab

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>56</td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>59 (30-70)</td>
</tr>
<tr>
<td>Age ≥60 y</td>
<td>24 (43)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 35 (63), Female 21 (38)</td>
</tr>
<tr>
<td>LDH above normal</td>
<td>13 (23)</td>
</tr>
<tr>
<td>ZAP70 positive</td>
<td>7/11 (64)</td>
</tr>
<tr>
<td>Complex cytogenetic</td>
<td>5 (33)</td>
</tr>
<tr>
<td>Median no. of prior chemotherapies (range)</td>
<td>3 (1-7)</td>
</tr>
<tr>
<td>Prior autologous transplantation</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Histologic types</td>
<td>Follicular lymphoma 13 (23), Mantle cell lymphoma 16 (29), Diffuse large B-cell lymphoma 9 (16), Peripheral T-cell lymphoma 3 (5), CLL/Richter 13/2 (23/4)</td>
</tr>
<tr>
<td>IgHV unmutated</td>
<td>10/11 (91)</td>
</tr>
<tr>
<td>Median time from diagnosis to transplantation, y (range)</td>
<td>4.3 (0.4-19.2)</td>
</tr>
<tr>
<td>Disease status at transplantation</td>
<td>CR 25 (45), PR 25 (45), Chemorefractory 6 (10)</td>
</tr>
<tr>
<td>Donor</td>
<td>Matched related 30 (54), Matched unrelated 26 (46)</td>
</tr>
<tr>
<td>Stem cell source</td>
<td>Peripheral blood/marrow 52/4 (93/7), ABO-mismatched recipient/donor 27 (48)</td>
</tr>
<tr>
<td>Cytomegalovirus status</td>
<td>Data are n (%) unless otherwise indicated.</td>
</tr>
</tbody>
</table>

Transplantation and engraftment

All patients received unmanipulated grafts from the peripheral blood (52 patients) or bone marrow (4 patients). The median number of CD34-positive cells infused was 5.58 × 10⁶/kg. Thirty-one patients (55%) never experienced an absolute neutrophil count (ANC) <0.5 × 10⁹/L (Figure 2A). Patients recovered an ANC >0.5 × 10⁹/L at a median of 0 days after allo-SCT (range, 0-16 days). The median number of days of granulocyte-colony stimulating factor treatment was 1.5 days (range, 0-8 days), as 23% of patients recovered with no growth factor support. Forty-nine patients (86%) did not require platelet transfusions (Figure 2B). Platelet counts recovered to >20 × 10⁹/L in the remaining 7 patients after a median of 11 days (range, 10-19 days). Patients who required transfusions had thrombocytopenia prior to study entry.

Donor chimerism

All patients who underwent allo-SCT, both from sibling or unrelated donors, experienced donor cell engraftment. By day 30 after SCT, the median values of donor myeloid and T cells were both 97%.
These increased to 100% by day 90. Donor cell recovery was similar in both sibling and unrelated transplantations. In 2 patients who were tested for engraftment on day 8, the percentages of donor cells were 0% and 8%, respectively. These both increased to 90% by day 30 without intervention.

Two patients experienced secondary graft rejection. One was a patient with CLL in Richter transformation who experienced rejection of sibling donor cells 17 months after allo-SCT. He remained alive, in molecular complete response (CR), 29 months after transplantation. Another patient experienced a secondary graft failure after receiving a suboptimal number of unrelated donor marrow cells (CD34 count, $1.3 \times 10^6$/kg). He recovered with autologous cells.

**Clinical response**

Fifty patients (89%) experienced a CR, 3 (5%) experienced a partial response (PR), and 2 (10%) had stable disease. One patient was not evaluable because of early death. With a median follow-up duration of 26 months (range, 6-50 months), the estimated 2-year OS and PFS rates were 90% (95% confidence interval [CI], 82% to 99%) and 75% (95% CI, 63% to 89%) (Figure 3A), respectively.

In patients with indolent disease (CLL and follicular lymphoma), mantle cell lymphoma, and aggressive lymphoma (diffuse large B-cell and peripheral T-cell lymphoma), the 2-year OS rates were 91% (95% CI, 80% to 100%), 94% (95% CI, 83% to 100%), and 83% (95% CI, 65% to 100%), respectively ($P = .63$) (Figure 3B); the 2-year PFS rates were 77% (95% CI, 61% to 97%), 68% (95% CI, 48% to 96%), and 83% (95% CI, 65% to 100%) ($P = .75$). A similar outcome was observed in patients who underwent a sibling (n = 30) or unrelated donor transplantation (n = 26). The 2-year OS rates were 89% (95% CI, 77% to 100%) and 92% (95% CI, 83% to 100%), respectively ($P = .61$) (Figure 3C); the 2-year PFS rates were 69% (95% CI, 54% to 90%) and 83% (95% CI, 69% to 100%) ($P = .50$)

In patients with CR, PR, and refractory disease at study entry, the 2-year OS rates were 86% (95% CI, 72% to 100%), 91% (95% CI, 80% to 100%), and 100%, respectively ($P = .69$); the 2-year PFS rates were 91% (95% CI, 80% to 100%), 94% (95% CI, 83% to 100%), and 83% (95% CI, 65% to 100%), respectively ($P = .63$) (Figure 3B); the 2-year PFS rates were 77% (95% CI, 61% to 97%), 68% (95% CI, 48% to 96%), and 83% (95% CI, 65% to 100%) ($P = .75$). A similar outcome was observed in patients who underwent a sibling (n = 30) or unrelated donor transplantation (n = 26). The 2-year OS rates were 89% (95% CI, 77% to 100%) and 92% (95% CI, 83% to 100%), respectively ($P = .61$) (Figure 3C); the 2-year PFS rates were 69% (95% CI, 54% to 90%) and 83% (95% CI, 69% to 100%) ($P = .50$).
rates were 77% (95% CI, 61% to 97%), 80% (95% CI, 63% to 100%),
and 40% (95% CI, 14% to 100%) (P = .12).
A total of 5 (71%) of the 7 lymphoma patients who experienced
recurrence of their disease after a prior autologous SCT remained
alive at a median follow-up of 30 months (range, 12-40 months) after
allo-SCT.
Five patients with CLL had a 17p13.1 deletion. Three had
undergone 3 prior lines of therapy, 1 had undergone 4, and 1 with de
novo disease received 1 line of therapy prior to allo-SCT. Three had
received transplantation from a matched unrelated donor and 2
from a sibling donor. One patient experienced a response to DLI
18 months after transplantation. All patients were alive, with 4 being
in CR, at 24, 24, 29, and 56 months.

DLI
Overall, 9 patients experienced disease progression after allo-SCT.
One patient with refractory mantle cell lymphoma received a level 1
dose of bendamustine; of the other 8, 1 with refractory CLL/Richter
received a level 2 dose and 7 received level 4. Two cases of disease
progression occurred in the central nervous system, with remission
elsewhere. One of these 2 patients had a history of central nervous
system involvement by peripheral-T-cell lymphoma and did not
experience a response to a prior autologous SCT. Five patients
received a DLI and rituximab, 1 because of graft failure (with no
response) and 4 because of progressive disease (1 with follicular
lymphoma, 2 with CLL, and 1 with mantle cell lymphoma). Two
patients (follicular lymphoma and CLL [described above]) experi-
enced a CR.

GVHD and toxicity
Patients had at least 6 months of follow-up after transplantation and
were therefore evaluable for GVHD. The incidence rate of grade
II-IV acute GVHD was 11% (Figure 4A). This rate did not statistically
significantly differ after adjusting for matched siblings and unrelated
donors (7% and 15%, respectively [P = .27]). Four patients had grade
III acute GVHD (1 sibling and 3 matched unrelated donors). Grade IV
acute GVHD was observed in only 1 patient. The 2-year cumulative
incidence rate of extensive chronic GVHD was 26% (Figure 4B); in
siblings and matched unrelated donors, the rates were 20% and 34%,
respectively (P = .23).
Nonhematologic toxicity was not dose limiting at any bend-
amustine dose with the conditioning. None experienced alopecia.
Only 1 patient (2%) experienced a grade III oral mucositis; none
had a grade IV. Nausea and vomiting were mild in all patients. No
grade III-IV nephrotoxicity was observed. No grade III-IV cardiotox-
icity was observed. No episode of veno-occlusive disease was
reported.
Seven patients died. Two deaths were related to disease pro-
gression, 1 to acute GVHD, and 1 to chronic GVHD. One patient (2%)
developed a grade IV gastrointestinal bleeding; she had a history of
exposure to involved field radiation to the stomach and scleroderma
with involvement of the esophagus, with 26 prior endoscopies. She
later died of sepsis. Two additional patients died because of infection
(1 fungal and 1 West Nile virus infection). The latter patient had
undergone autologous SCT 4 years earlier because of transformed
lymphoma; she had a history of traveling to endemic areas and being
exposed to ticks. She developed symptoms of fever and headache on
day 3 after her transplantation and died on day 26 after allo-SCT. Thus,
the treatment-related mortality (TRM) rates at 100 days and 2 years
were 1.8% and 9%, respectively (Figure 4C).

Discussion
In this study of bendamustine-based conditioning for allo-SCT for
lymphoid malignancies, we found that higher doses of bendamustine
(up to 130 mg/m² per day for 3 days) could be administered safely in
combination with standard fludarabine and rituximab in the setting of
both related and unrelated donor nonmyeloablative hematopoietic
SCT. Recovery of neutrophils and platelets was prompt; 31 patients
(55%) never experienced an ANC ≤0.5 × 10⁹/L, and 87% required
no platelet transfusion. Furthermore, the incidence of grade II-IV
acute GVHD was 11%, which is lower than the 35% to 70% seen in
the scientific literature.26 Moreover, our findings showed a low
incidence of extensive chronic GVHD, despite a patient cohort that
was older than average; 46% of patients received a transplantation
from an unrelated donor. This outcome of immunosuppression with
no severe myelosuppression, together with a low incidence of GVHD, could also be due to bendamustine being an alkylator with a purine ring that has additional immunosuppressive properties.

Approximately 50% of patients with CLL and mantle cell lymphoma and more than 70% of patients with aggressive lymphoma experience relapsed disease after allo-SCT. Therefore, new conditioning regimens are required. In the search for the optimal conditioning regimen, we tested the safety and efficacy of bendamustine, fludarabine, and rituximab with escalating doses of bendamustine, a drug with more activity than in standard therapies for resistant and relapsed lymphoid malignancies.

We were surprised by the low level of myelosuppression in this study. We underestimated the number of patients who would not require growth factors, as all patients received granulocyte-colony stimulating factor by day 7 after SCT, as per our standard supportive care. Through the course of the trial, it was noted that many patients with normal ANC counts at study entry maintained an ANC of $>500$ cells/$\mu$L throughout and did not need growth factor support. This observation prompted us to modify our administration of growth factors, which led to the full recovery of counts in 23% of patients with no growth factor support.

Although our study was limited by its single-arm design, we were encouraged by the low incidence of grade II-IV acute and chronic extensive GVHD. One study evaluated low-dose total-body irradiation, with or without fludarabine and followed by mycophenolate mofetil and a calcineurin inhibitor, in 611 SCT patients with hematologic malignancies. The incidence of acute GVHD at day 120 was 43% for grade II-IV disease and 11% for grade III-IV, with a 2-year relapse rate of 51%.

Strategies that mitigate GVHD may be associated with increased relapse rates. In a phase 1/2 study of reduced-intensity conditioning hematopoietic SCT in which maraviroc was combined with standard GVHD prophylaxis, the incidence of grade II-IV acute GVHD was 29%, but the relapse rate was 56% at 1 year. We have previously found a 37% incidence rate of acute II-IV GVHD with the use of a fludarabine, cyclophosphamide, and rituximab conditioning regimen in CLL. The cumulative incidence of extensive chronic GVHD was 56% and the TRM rate at 1 year was 17%. The relapse rate in that fludarabine, cyclophosphamide, and rituximab study was 45%, with 37 of 39 (95%) relapses occurring within 18 months of transplantation.

In this current study, the BFR conditioning regimen showed a promising efficacy pattern. Despite the low acute GVHD rate, we did not note an increase in the relapse rate, suggesting that GVL was not altered substantially. Although this study was not powered to show differences in response between different histologic subtypes, the PFS rates among patients with indolent, mantle cell, and aggressive lymphoid histologic disease were similar.

In conclusion, in CLL/lymphoma patients undergoing related or unrelated donor nonmyeloablative conditioning for allo-SCT, a bendamustine dose of 130 mg/m² per day for 3 days combined with fludarabine and rituximab is safe and effective. This regimen resulted in a low incidence of myelosuppression and a low cumulative incidence of clinically significant GVHD, with no major adverse events. It may be considered as a platform for outpatient allogeneic transplantation.

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Authorship


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

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