Successful allogeneic engraftment of mismatched unrelated cord blood following a nonmyeloablative preparative regimen

David A. Rizzieri, Gwynn D. Long, James J. Vredenburgh, Christina Gasparetto, Ashley Morris, Timothy T. Stenzel, Patti Davis, and Nelson J. Chao

Reduction in the toxicity of allogeneic transplantation with nonmyeloablative induction regimens has expanded the scope of practice to older and more debilitated patients. However, the limited availability of matched sibling donors requires that alternative donor sources be investigated. Reported here are 2 cases of patients with advanced hematologic malignancies without matched siblings, partially matched family members, or matched unrelated donors who successfully underwent nonmyeloablative conditioning therapy followed by infusion of partially matched, unrelated-donor cord blood cells. The patients are in remission and remain 100% donor as assessed by short tandem repeat analysis of the marrow 6 and 12 months following transplantation. (Blood. 2001;98:3486-3488)

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Introduction

The significant toxicity associated with myeloablative allogeneic stem cell transplantation (SCT) has limited this approach to younger, healthier patients with severe disorders. The lack of matched sibling donors has further limited the application of this therapy. Cord blood may serve as an effective source of stem cells, thereby broadening the scope of patients who may benefit from allogeneic SCT. Recently, less toxic nonmyeloablative regimens using peripheral blood stem cells or marrow from matched donors have allowed the expansion of allogeneic SCT to older, more debilitated patients. The approach is still limited by the lack of matched sibling donors, and alternative donor sources must be sought. We report the cases of 2 patients without matched siblings or other alternative donors who consented to participate in a Duke University institutional review board–approved trial investigating nonmyeloablative allogeneic therapy using cord blood as the stem cell source.

Study design

Case report no. 1

A 62-year-old white American man presented complaining of anorexia, weight loss, and night sweats. Evaluation revealed bilateral axillary adenopathy and pancytopenia. Computed tomography scans revealed axillary, mediastinal, and abdominal lymphadenopathy, and hepatosplenomegaly. Lymph node examination was consistent with mantle cell lymphoma (CD5, CD20, and FMC7 positive and CD23 negative; t(11;14) positive). Lactate dehydrogenase and bone marrow examinations were not initially performed. He was entered on a high-intensity, brief-duration induction protocol of induction therapy followed by autologous transplantation. He received cytarabine 3 g/m2 for 12 doses and mitoxantrone 12 mg/m2 daily for 4 days with an excellent partial response. He was given cyclophosphamide 500 mg/m2 daily for 4 days with resolution of all evidence of active disease. His performance status remained 60%. He proceeded to nonmyeloablative transplantation with unrelated-donor, 4/6 matched cord blood to consolidate his response (Table 1).

Nonmyeloablative cord blood transplantation

Unrelated-donor, mismatched cord blood was infused following fludarabine 30 mg/m2 and cyclophosphamide 500 mg/m2 daily for 4 days with antithymocyte globulin 30 mg/kg per day for 3 days. Acute graft-versushost disease (GVHD) prophylaxis consisted of cyclosporine and prednisone as previously described. Supportive care and anti-infective prophylaxis followed our standard practice. Patient no. 1 received G-CSF 5 μg/kg subcutaneously daily, beginning on day +1. Patient no. 2 received granulocyte-macrophage CSF (GM-CSF) 500 μg daily, not starting until day 21 due to prior reactions to growth factors. Growth factors were continued until the absolute neutrophil count (ANC) was greater than 1000/μL for at least 3 days.

Case report no. 2

A 39-year-old African American male presented with stage IB diffuse large-cell non-Hodgkin lymphoma. He received 4 cycles of cyclophosphamide, vincristine, prednisone, and adriamycin (CHOP) followed by 3600 cGy of radiation to the site of disease. He had a recurrence 2 years later in multiple nodal sites, with visceral involvement in the lungs, liver, kidneys, and bones. He responded well to salvage chemotherapy consisting of etoposide, solumedrol, cytarabine, and cisplatin (ESHAP) and so proceeded to high-dose therapy with autologous stem cell support. He relapsed 1 year later with disease in nodal areas and the kidneys. He did not respond to CHOP with rituximab and entered the phase 2 weekly paclitaxol trial as for the patient above. He had a partial response lasting 3 months and proceeded to nonmyeloablative transplantation with unrelated-donor, 4/6 matched cord blood at the time of early progression (Table 1).

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Table 1. HLA typing and characteristics of the cord blood unit infused

<table>
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<tr>
<th>Patient no.</th>
<th>HLA-A</th>
<th>HLA-B</th>
<th>HLA-DRB1</th>
<th>Nucleated cells*</th>
<th>GM-CFU*</th>
<th>CD34+ cells*</th>
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<td>0404/0701</td>
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<td>0404/0701</td>
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<td>18/35</td>
<td>0701/1301</td>
<td>—</td>
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<td>1201/1301</td>
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</table>

*Per kilogram of patient weight.

Results and discussion

Patient no. 1

The patient maintained his initial performance status of 60% and remained neutropenic for 10 days from the time of infusion of cord cells. Two weeks after infusion he had a total white count of 3.5 × 10^9/L, a platelet count of 15 000/μL with biweekly transfusions, and a hemoglobin level of approximately 10 g/dL with weekly transfusion support. His bone marrow at day +14 revealed 30% cellularity, with interphase fluorescent in situ hybridization (FISH) examining 200 cells revealing 6.5% donor cells (Vysis). With no modifications in the patient’s therapy, his donor cells increased to 100% at 12 weeks as measured by FISH analysis of bone marrow (Table 2). Engraftment has persisted beyond 12 months with >99% donor cells in both the lymphoid and myeloid cellular fractions as measured by short tandem repeats (STRs). With a normocellular marrow. His clinical course and engraftment have been complicated by reactivation of cytomegalovirus (CMV). The patient also experienced Clostridium difficile colitis treated with metronidazole and vancomycin. With engraftment, he had grade 2 skin GVHD treated with the addition of topical steroids. Due in part to his pre-existing poor nutrition and performance status, he required parenteral nutrition during recovery. At 1 year from therapy, he is in remission, as measured by physical exam, radiographic scans, and marrow examination, and performance status is 70%.

Patient no. 2

The patient began therapy with a performance status of 80% and tolerated the induction period well. Due to prior reactions to growth factors, we did not institute growth factor support initially. He was initially neutropenic for only 3 days (days +7-10) and had a minimum platelet count of 62 000/μL. He developed progressive pancytopenia on day 16 and evaluation determined a CMV-positive DNA hybridization study from the blood. Ganciclovir therapy was added on day +21. During this neutropenic period, bone marrow analysis revealed that the few hematopoietic elements present were largely of cord blood donor origin, and the patient recovered granulocytes by day 30. Six months after transplantation his marrow has 40% cellularity and he continues to have >99% cord blood cells as measured by STR analysis of the marrow in both the lymphoid and myeloid cellular fractions (Table 2). He is in remission, as measured by physical exam, radiographic scans, and marrow examination, and performance status is 80%.

Nonmyeloablative allogeneic transplantation has provided an opportunity for immunotherapy for older, sicker patients who previously were not eligible for this potentially curative approach. The advent of alternative sources of donor cells for the majority of patients who do not have matched siblings is an important component of expanding the promise of nonablative therapy to a broader array of potential recipients. Typically, we increase the number of peripheral blood progenitor cells infused with nonablative therapy to enhance the chance for donor hematopoietic and immune recovery over autologous recovery. With cord blood transplantation, however, we usually have 10^7-10^8 fewer cells infused than would be considered standard for a matched sibling transplant. The unique cellular composition of cord blood cells, possibly due to more primitive stem cells or as-yet-unidentified characteristics of cord blood, may facilitate engraftment. With nonablative conditioning and unrelated, mismatched donors, the concern over rejection of the cord cells is increased. These cases suggest donor engraftment with mismatched unrelated cord blood cells is feasible, even with nonmyeloablative preparative regimens. Ongoing investigation of this approach includes the kinetics of cellular and immune recovery and broader experience with more patients and other disease states.

Acknowledgments

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References


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