A 21-Year-Old Woman With Blastic NK Cell Leukemia/Lymphoma Who Achieved Durable Remission With HyperCVAD and Unrelated Umbilical Cord Blood Transplant

Jennifer M. Duff, MD[1]
Michelle L. Rossi, MD[1,2]
Jason Fromm, MD[1,2]
Jack W. Hsu, MD[1,2]

[1]Department of Medicine; [2]Division of Hematology and Oncology, University of Florida, Gainesville Florida

Background

Blastic natural killer (NK) cell neoplasms are rare, highly aggressive malignancies with a poor prognosis. They have a predilection for the skin, and disseminate rapidly into the blood, bone marrow, lymph nodes, and extranodal organs.[1] Because of their rarity, there is no standard treatment. Chemotherapy alone does not result in long-term remissions[2]; therefore, stem cell transplantation is essential to achieving a durable remission.[3] Umbilical cord blood stem cells have emerged as an alternative source of stem cells for patients without suitable donors.[4] Here we report a 21-year-old woman diagnosed with blastic NK cell leukemia/lymphoma who is in complete remission 14 months after hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyperCVAD) chemotherapy followed by a myeloablative unrelated single umbilical cord blood transplant.

Case Presentation

In May 2008, a previously healthy 21-year-old woman of Pacific Islander descent experienced progressive fatigue; bruising on her chest, arms, cheeks, and abdomen; and mucosal bleeding. She developed bulky lymphadenopathy in the neck and diffuse abdominal pain, leading to her evaluation in July 2008. On presentation, she had raised violaceous patches on her cheeks and ecchymoses scattered across her body (Figure 1).

Address correspondence to:
Jack W. Hsu, MD, Division of Hematology Oncology, Department of Medicine, University of Florida, 1600 SW Archer Rd, P.O. Box 100277, Gainesville, FL 32610-0277; Phone: 352-273-7832; Fax: 352-273-5006; E-mail: jack.hsu@medicine.ufl.edu.

A complete blood count showed a white blood cell count of 45,000/μL with 86% peripheral blasts, platelets of 6,000/μL, and hematocrit of 22.7%. Flow cytometry of the peripheral blood showed that the neoplastic cells expressed CD4, CD56, CD123, CD45RA, HLA-DR, and weak terminal deoxynucleotidyl transferase, and were negative for myeloperoxidase, CD34, CD117, CD13, CD33, CD64, CD15, CD14, and T or B cell antigens. A bone marrow biopsy revealed a markedly hypercellular marrow with extensive involvement by blastic NK cells. Cytogenetics demonstrated multiple abnormalities of chromosomes 6, 8, 9, 10, 11, and 12. Computed

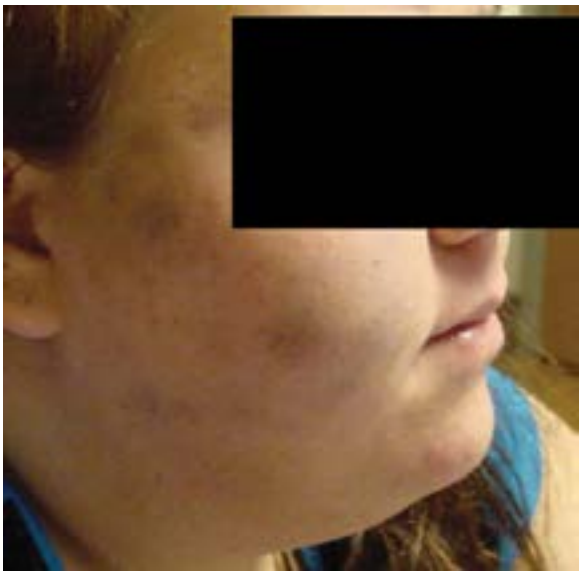

Figure 1. Cutaneous manifestation of blastic natural killer cell.

tomography imaging revealed splenomegaly and diffuse enlargement of most lymph node regions in the head and neck, chest, abdomen, and pelvis. Magnetic resonance imaging of the head did not show parenchymal or meningeal involvement. These findings were consistent with a diagnosis of blastic NK cell leukemia/lymphoma.

The patient started induction chemotherapy with hyperCVAD part B on July 26, 2008. Cerebrospinal fluid (CSF) analysis prior to intrathecal methotrexate on day 12 of induction revealed no involvement with leukemia. She was in first partial remission after induction with residual cervical and retroperitoneal adenopathy and a negative bone marrow biopsy. The patient received 3 additional cycles of hyperCVAD part B, with her clinical course complicated by a cutaneous *Aspergillus flavum* infection that was successfully treated with posiconazole. CSF samples were persistently negative for disease. She was found to be in complete remission after chemotherapy.

A donor search identified only cord blood units as suitable donors. The patient consented to undergo a single umbilical cord blood transplant on a Clinical Trials Network protocol. Her conditioning regimen consisted of fludarabine 25 mg/m^2 once daily for 2 days (total dose 50 mg/m^2), total body irradiation at 1,320 cGy, and cyclophosphamide 60 mg/kg daily for 2 days (total dose 120 mg/kg). She received her unrelated single umbilical cord blood graft on January 5, 2009, with a total nucleated cell dose of 3.2×10^7/kg. Graft-versus-host disease (GVHD) prophylaxis consisted of mycophenolate mofetil and cyclosporine. On day 11 posttransplant, she developed a rash, and a skin biopsy confirmed grade II acute GVHD, which was treated with prednisone. Sorted chimerism analysis on days 30 and 60 confirmed 100% donor in all cell lines. A bone marrow biopsy on day 100 revealed a 50% cellular marrow with multilineage hematopoiesis, no cells expressing CD56 or CD4, and no cytogenetic abnormalities. She was released to her local oncologist on a slow prednisone taper, and remains disease-free 14 months after transplant.

Discussion

Blastic NK cell leukemia/lymphomas are rare malignancies that are thought to be derived from the plasmacytoid dendritic cell.[1] There is no standard therapy, and they are associated with a poor prognosis. The median survival time when treated with chemotherapy alone is 12–20 months[2]; therefore, bone marrow transplantation is the only option for long-term remission.[3] A retrospective analysis by Suzuki and colleagues comparing stem cell transplantation to chemotherapy alone in patients with a variety of NK neoplasms revealed a significant increase in long-term survival in the transplant arm versus the chemotherapy alone arm (40% at median follow-up of 51 months vs 25% at median follow-up 32 months).[2] Patients who underwent an allogeneic transplant had higher transplant-related mortality (TRM), but a lower relapse rate compared to autologous transplant patients, suggesting a graft-versus-leukemia effect.

For patients without a suitable matched donor, umbilical cord blood (UCB) has emerged as a viable alternative source of hematopoietic progenitor cells. In comparison to matched unrelated donor (MUD) bone marrow allografts, UCB demonstrates a greater degree of tolerance to human leukocyte antigen (HLA) mismatches with similar rates of severe acute GVHD. Additionally, cord blood has a high concentration of donor-derived NK cells that exhibit functional cytotoxic properties, which may confer protection through a graft-versus-leukemia effect.[4-6] There are, however, several recognized disadvantages to using UCB transplants. A major limitation is that they have a fraction of the total nucleated cells compared to an adult donor, which results in prolonged neutrophil and platelet engraftment.[4] There is also a delay in immune recovery and narrowing of the T-cell repertoire, leading to an increase in the susceptibility to infections. Stanevsky and associates discusses several approaches to improve the time to engraftment and reduce graft failure rates.[6] One of these methods include transplanting 2 cord blood units to increase the total transplanted cell dose, which may contribute to earlier neutrophil recovery, thus improving the success of engraftment. They emphasize 2 variables—cell dose and degree of HLA disparity—as the significant factors for successful engraftment, with the total cell dose having the most influence on engraftment and patient survival. Cohen and coworkers reported a day 100 TRM approaching 50% in myeloablative UCB transplants for advanced hematologic malignancies and nonmalignant conditions, with death mainly from toxicities, infection, and disease relapse.[4] Grafts with higher CD34-positive cell doses have been associated with substantially less TRM. Stanevsky and colleagues discussed that using reduced intensity conditioning may contribute to substantially less day-100 TRM.[6] A meta-analysis of 6 comparative studies by Hwang and associates evaluating unrelated bone marrow transplant (UBMT) versus unrelated cord blood transplant (UCBT) in pediatric and adult patients showed a slight increase in early TRM in the UBMT group, no significant difference in 2- and 3-year overall survival or the risk of developing acute GVHD, and a decreased risk of developing chronic GVHD with UCBT compared with UBMT.[7] Both groups had similar risks of relapse, and there was no difference in disease-free survival. Only 1 study revealed a statistically significant increase in overall survival favoring the UCBT group.

Table 1. Reports of Umbilical Cord Blood Transplant for Natural Killer (NK) Cell Neoplasms

Case	Age/Sex	NK Cell Tumor Classification	Status at Time of Transplant	Stem Cell Source	Outcome
Current case	21 y/F	Blastic NK cell	1st CR	Unrelated UCB	CR >14 mo
Yoshimasu et al[9]	15 y/M	Blastic NK cell	2nd CR after allo-PBSCT	Unrelated UCB	CR >18 mo
Tezuka et al[10]	2 y/M	Myeloid/NK cell	1st CR	Unrelated UCB	CR >24 mo
Suminoe et al[11]	7 mo/M	Precursor NK cell	1st CR	Unrelated UCB	CR 14 mo
Yokoyama et al[12]	36 y/F	Nasal NK/T cell	2nd CR	Unrelated UCB	CR 33 mo
Mori et al[13]	52 y/F	Nasal NK/T cell	PR	Unrelated UCB	CR 18 mo

allo-PBSCT=allogeneic peripheral blood stem cell transplant; CR=complete remission; NK=natural killer; PR=partial remission; UCB=umbilical cord blood.

A meta-analysis by Wang and coauthors of 10 studies evaluated the survival benefit of UCBT versus UBMT among adults and children with malignant and non-malignant hematologic disorders.[8] Secondary outcomes included GVHD, TRM, and relapse. Approximately 600 adults received UCBT and 1,500 underwent UBMT; the majority of those who received cord blood had 1–3 HLA loci mismatches. The study showed a statistically significant increase in overall survival favoring UBMT patients. In adults, the risk of developing grade II–IV acute GVHD was significantly less in those who underwent UCBT; however, the incidence of chronic GVHD, disease relapse, and TRM did not differ significantly between the 2 groups. Cumulatively, these meta-analyses support that UCBT has a similar to lower risk of acute GVHD despite antigen mismatches at multiple loci, similar or decreased risk of chronic GVHD, and no difference in TRM or relapse when compared to UBMT. More trials are needed to determine whether UBMT offers a survival advantage over UCBT.

A review of the literature identified 5 published cases of using UCB for NK cell neoplasms (Table 1). The first case was described by Yoshimasu and associates in 2002.[9] A 15-year-old boy underwent autologous stem cell transplant in first complete remission, then relapsed 6 months later. He underwent reinduction therapy followed by a UCB transplant in second complete remission, and has remained in remission 18 months later. To our knowledge, the case we have reported is the first to describe an adult patient receiving UCB transplant for blastic NK cell leukemia/lymphoma. We demonstrate that a durable remission is possible in this disease with high-dose, multi-agent chemotherapy followed by an unrelated UCB transplant.

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We thank our patients for their relentless courage against fighting their disease and their trust in the science that guides our treatment decisions.

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Review

Treatment of Blastic Plasmacytoid Dendritic Cell Neoplasms With Cord Blood Transplants

Sathish Krishnan, MBBS, FRCP,
Daryl Tan, MBBS, MRCP,
and William Y. K. Hwang, MBBS, FRCP

Department of Haematology,
Singapore General Hospital
Singapore

Blastic plasmacytoid dendritic cell neoplasms (BPDCN) are a newly recognized entity in the current World Health Organization (WHO) classification system.[1,2] They were grouped as blastoid/blastic natural killer (NK) cell leukemia/lymphoma in the previous WHO classification. These tumors are rare and must be differentiated from aggressive NK cell leukemia and nasal NK/T-cell leukemia.[3] The disease is characterized by a good response (complete remission [CR] in 70% and partial remission [PR] in 10% of patients) to multiagent chemotherapy but also with rapid relapses. A total of 10–20% of BPDCN are associated with myelomonocytic leukemia. This might represent a direct progression of the BPDCN or an underlying coexisting myelodysplastic syndrome (MDS).

There is evidence to suggest that myeloid cells and dendritic cells exhibit developmental "plasticity". For example, CD56 positivity is seen in acute myeloid leukemia (AML) and CD4 positivity is associated with monocytic and myelomonocytic differentiation. This would explain the association between myelomonocytic leukemia and BPDCN.[3,4]

Duff and colleagues describe durable remission of BPDCN with the use of umbilical cord blood transplantation (UCBT) using fludarabine, cyclophosphamide and 1,350 cGy total body irradiation (TBI) after initial chemotherapy with the hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyperCVAD) regimen.[5] The patient had mild graft-versus-host disease that responded to steroids, but remained in tumor-free remission at 14 months posttransplant. Yoshimasu and colleagues have also reported the successful use of cord blood stem cells in treating relapsed NK blastic cell leukemia/lymphoma, which would be classified as BPDCN in the current WHO nomenclature.[6]

Address correspondance to:
William YK Hwang, MBBS, FRCP, Department of Haematology, Singapore General Hospital, Outram Road, Singapore 169608, Republic of Singapore
E-mail: william.hwang.y.k@sgh.com.sg.

The putative cell of origin of the BPDCN is the plasmacytoid dentritic cell, which is characterized by CD4, CD56, CD123, and TCL1 positivity. Other NK cell–related disorders and AML also show CD56 positivity with or without CD4 positivity, but BPDCN are consistently negative for Epstein-Barr virus infection as well as for CD3, CD5, CD13, and CD16 expression. They are characterized by skin involvement in the form of nodules and patches in more than 90% of cases followed by bone marrow and blood abnormalities and lymph node involvement. The median age of presentation is older than 60 years, with a female predilection; however, approximately 20–30% of patients are younger than 60 years at presentation. Patients younger than 18 years of age have better outcomes compared to adults. Patients without cutaneous manifestations at presentation who were treated with acute lymphoblastic leukemia-type chemotherapy had 100% overall survival at 60 months versus 60% overall survival for patients with cutaneous manifestations who received AML-type chemotherapy. It is not clear whether the intrinsic biology of the disease varies between the phenotype with cutaneous manifestation and without cutaneous manifestation, or the different induction regimens these patients received resulted in different survival results. Recently, the proteasome inhibitor bortezomib (Velcade, Millennium Pharmaceuticals) has been shown to suppress function and survival of plasmacytoid dendritic cells, thus suggesting a possible therapeutic role for this drug for BPDCN.[7] However, this was only an in vitro study on normal plasmacytoid dendritic cells and not on a malignant clone.

A review of 97 published cases showed a median survival of 13 months. Many patients treated with lymphoma-like regimens showed CR rates of approximately 60%, whereas treatment on acute leukemia–like protocols in adults attained more CR rates of 90% or higher. Both modalities, however, have demonstrated a short median survival of approximately 13 months.[8] Myeloablative therapy followed by autologous (n=4) or allogeneic (n=6) hematopoietic stem cell transplantation (HSCT) in 10 patients resulted in an improved median survival of 31 months. Three of 4 patients who underwent autologous HSCT had disease relapse; those who underwent allogeneic HSCT experienced fewer relapses (2 of 6 patients), with some long-term tumor-free survivors. This appeared to suggest that allogeneic transplantation is the only potentially curative option for this otherwise fatal disease.[9] However, transplants need to be performed for chemoresponsive disease in first remission. Patients with various hematologic malignancies treated

with 1–2 antigen mismatched UCBT had equivalent survival to patients treated with fully matched unrelated bone marrow transplants.[10] Hence, if no matched sibling or unrelated donor is readily available, UCBT should be performed if a suitable cord blood unit is found. The myeloablative regimens used above precluded the use of HSCT in older patients. However, Dietrich and colleagues reported on the outcome of 6 patients who were transplanted using reduced intensity conditioning (RIC) regimens (median age, 67 years) comprising fludarabine, busulfan, cyclophosphamide, fludarabine, and treosulplan, as well as antithymocyte globulin (for those receiving transplants from unrelated donors).[11] Patients received standard induction chemotherapy regimens for AML and acute lymphoblastic leukemia (ALL). Although the numbers are small, this retrospective analysis showed that RIC regimens can result in long-term disease control. Chronic GVHD was associated with long-term disease control in 1 of the 6 patients. Chemoresponsive disease and the attainment of maximum response to chemotherapy was related to better outcomes in both studies by Reimer and Dietrich.[8,11] Although it appears that transplanting at first complete remission improved outcome in the small number of patients reported, no definite conclusions can yet be drawn.

Conclusions

BPDCN remain an aggressive disease in adults, and better treatment options are still lacking. Induction chemotherapy with AML- or ALL-type chemotherapy seems to confer better response rates compared to lymphoma-type induction. Allogeneic BMT seems to prolong survival compared to chemotherapy-only regimens. However, prompt and adequate initial treatment is needed, as chemoresponsive disease and attainment of CR are associated with better outcome. Although a graft-versus-leukemia effect appears to be seen in the few reported cases, there is a need for more data. It is vital to recognize those patients requiring transplant as soon as possible, as the ideal time to transplant a patient is in first complete remission. Given the successful treatment with UCBT in this case report, if a matched sibling or a fully matched unrelated donor cannot be found, a suitably matched unrelated donor UCBT should be identified as soon as possible.

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