Durable Remission of Mantle Cell Lymphoma Relapsing a Third Time After Allogeneic Hematopoietic Stem Cell Transplantation Treated With Rituximab, Bortezomib, Donor Lymphocytes, and Pegylated Interferon

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Clinical Practice Points

- There is currently no gold-standard rescue therapy for mantle cell lymphoma (MCL) relapsing multiple times after allogeneic hematopoietic stem cell transplantation (allo-HCT) and donor lymphocyte infusions (DLIs).
- To the best of our knowledge, we report the first case report of a patient achieving long-term disease control (> 3 years) after a third relapse of MCL after allo-HCT by treatment with a combination of rituximab/bortezomib, pegylated interferon, and a ninth DLI.
- This report emphasizes the role of rituximab and bortezomib in combination with donor lymphocytes as salvage therapy of MCL in patients with multiply relapsed disease after allo-HCT.
- This case also suggests that graft-versus-tumor effects can still be bolstered years after an allogeneic transplant, even in patients who have relapsed multiple times, by DLIs whose efficacy may be enhanced by combination with interferon-based cytokine treatment.

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Introduction

Although there has been noteworthy progress in the treatment of mantle cell lymphoma (MCL) over the past decade,[1] disease relapse after dose-intensive chemotherapy or autologous stem cell transplantation remains problematic.[2-4] Allogeneic hematopoietic stem cell transplantation (allo-HCT) is capable of curing patients with relapsed MCL, including those with disease progression after autologous stem cell transplantation.[3] Disease remission after allo-HCT is attributable to the cytoreductive effects of dose-intensive conditioning and to donor T-cell–mediated graft-versus-tumor effects.[3-8] Even when patients relapse after an allo-HCT, donor lymphocyte infusions (DLIs) leading to graft-versus-MCL effects can still induce long-term disease remission in a subset of patients. However, for patients relapsing after DLI, long-term disease control is rare because tumors frequently develop mechanisms to evade donor immunity. We report a patient with MCL with multiple relapses after reduced-intensity conditioning (RIC) allo-HCT and DLIs who achieved a fourth disease remission that is ongoing more than 3 years after the last relapse after treatment with a combination of rituximab/bortezomib, pegylated interferon (PEG-IFN), and a ninth DLI. This case suggests that graft-versus-tumor (GVT) effects can still be bolstered years after an allogeneic transplant, even in patients who have relapsed multiple times, by DLIs whose efficacy may be enhanced by combination with interferon (IFN)-based cytokine treatment.

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Case Report

A 34-year-old Hispanic man had a history of stage IV MCL disease in 2001. Despite multiple treatment regimens of chemotherapy,

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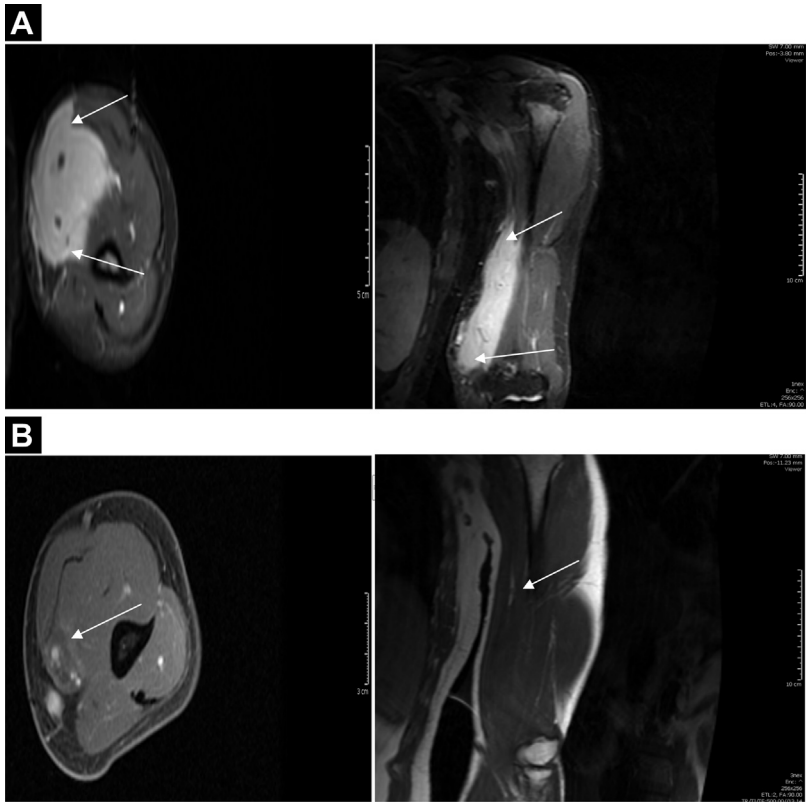
Figure 1 Magnetic Resonance Imaging of Left Arm. (A) May 2003: MCL Involving the Biceps Muscle (Arrows) 3 Months After Undergoing an Allo-HCT Before DLIs. (B) August 2003: Disappearance of MCL 6 Months After Allo-HCT After Multiple DLIs and Radiation Therapy (Arrows Show Normal Biceps Muscle Formally Infiltrated With MCL)



including Rituximab, Cyclophosphamide, Hydroxydaunorubicin (doxorubicin), Oncovin (vincristine), and Prednisone × 8 cycles, dose-intensive cyclophosphamide and etoposide (+R) × 1 cycle, and ifosfamide, carboplatin, etoposide × 1 cycle, the patient achieved a partial response with a partial regression of his left arm mass. He was subsequently referred to the National Heart, Lung, and Blood Institute (National Institutes of Health) in February 2003 to undergo treatment with RIC allo-HCT.

Pre-transplant staging studies showed no evidence of disease in the blood or bone marrow by flow cytometry and no adenopathy in the neck, chest, abdomen, or pelvis; however, there was a mass in the left biceps region suspicious of lymphoma. Biopsy of the left arm mass revealed D20 (+), CD 19(+), CD 5(+), κ-light chain (+), λ-light chain (-), and CD 23(-) lymphoma cells. Fluorescence in situ hybridization of the tumor revealed chromosomal translocation t,[11,14] and molecular studies were positive for an immunoglobulin heavy chain locus and T-cell receptor gamma rearrangement—all consistent with MCL. On February 20, 2003, the patient underwent an RIC allo-HCT using granulocyte colony stimulating factor mobilized peripheral blood stem cells collected from his human leukocyte antigen (HLA)-identical brother. His transplant-reduced conditioning regimen consisted of cyclophosphamide 60 mg/kg/d given on days −7 and −6 and fludarabine 25 mg/m^2/d given on days −5 to −1. He received cyclosporine A and intravenous methotrexate (5 mg/m^2/dose days +1, +3, and +6) for graft-versus-host disease (GVHD) prophylaxis. Restaging studies performed 3 months post-transplant showed no evidence of new disease with persistence of the left humerus (Fig. 1A) mass, which magnetic resonance imaging showed had increased in size compared with pretransplant images, consistent with disease progression. He subsequently received involved-field external beam radiation to the left arm mass from June 2003 to July 2003 (total radiation dose of 36 gray given as 200 cGy fractions), followed by 4 escalating doses of DLI (5×10^6, 1×10^7, 5×10^7, 1×10^8 CD3+cells/kg/dose) given from June 3 to September 17, 2003. Approximately 1 month after his fourth DLI, the patient achieved 100% donor chimerism in both myeloid and T-cell lineages. In August 2003, repeat staging studies, including magnetic resonance imaging of the arm, showed no residual measurable disease (Fig. 1B), consistent with the patient achieving a complete remission (CR). His post-transplant course was complicated by mild chronic GVHD of the mouth that was responsive to topical steroids.

The patient did well and remained in remission for 20 months until April 18, 2005, when a repeat staging computed tomography (CT) scan revealed an enlarged right inguinal node with evidence of