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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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Keywords

Allogeneic hematopoietic stem cell transplantation; Bortezomib; Donor lymphocytes; Durable remission Mantle cell lymphoma; PEG-interferon

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-cellemediated 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.

Case Report

A 34-year-old Hispanic man had a history of stage IV MCL disease in 2001. Despite multiple treatment regimens of chemotherapy, including Rituximab, Cyclophosphamide, Hydroxydaunorubicin (doxorubicin), Oncovin (vincristine), and Prednisone $\times$ cycles, dose-intensive cyclophosphamide and etoposide (+R) 1 cycle, and ifosfamide, carboplatin, etoposide $\times$ 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 (+), γ -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/m²/d given on days -5 to -1. He received cyclosporine A and intravenous methotrexate (5 mg/m²/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 splenomegaly. An inguinal node biopsy revealed relapse of his MCL. He again achieved a CR after treatment with rituximab (375 mg/m²), a fifth DLI on May 9, 2005 (5×10^7 CD3+ cells/kg), involved field external beam radiation to the inguinal node, and monthly rituximab from May to December 2005. By September 2005, CT scans confirmed he had achieved a second CR. To enhance his lymphoma's sensitivity to a GVT

effect to prevent disease relapse, he was treated with IFN, 1×10^6 units 3 times per week followed by a sixth DLI (5×10^7 CD3+cells/kg) in October 2005. Because of the patient's side effects, IFN 3 times per week was switched to PEG-IFN (180 mg/wk) in February 2006. The patient developed severe fatigue associated with PEG-IFN treatment that he self-discontinued in August 2006.

Six months later (~4 years post-transplant), the patient experienced a second relapse with imaging studies revealing new left axillary, supraclavicular, and subclavicular lymph nodes. He was treated with rituximab, and on April 13, 2007, he received a seventh DLI (5×10^7 CD3+cells/kg). He was also reinitiated on PEG-IFN (180 µg/wk, 3 weeks on and 1 week off), but this later was discontinued because of thrombocytopenia with repeat CT scans showing persistent disease. He subsequently was treated with a salvage regimen consisting of 2 cycles of bortezomib 1.3 mg/m²/dose (given on days 1, 5, 8, and 11) and rituximab 375 mg/m² (day 1), followed by an eighth DLI (1×10^7 CD3+cells/kg). CT scans performed in October 2007 revealed no evidence of disease, consistent with a third CR.

The patient did well until June 2009 when he relapsed for the third time, with a restaging positron emission tomography CT scan revealing evidence of recurrent disease in his right inguinal region. A biopsy of his right inguinal node confirmed MCL recurrence (Fig. 2A, B), and he was subsequently treated with 3 cycles of salvage bortezomib and rituximab, achieving a fourth CR by August 2009. To prevent disease relapse, he received a ninth DLI (1×10^7 CD3+cells/kg) in September 2009 followed by weekly treatment with PEG-IFN (180 µg/wk). Because of thrombocytopenia and poor tolerance, his weekly PEG-IFN dosage was reduced first to 144 mg/wk (May 2010) and then to 108 µg/wk (September 2010). The patient continues to do well with only mild oral chronic GVHD (Fig. 3) approximately 10 years post-transplant with restaging CT scans (November 2012) showing that he remains in remission more than 3 years since his third relapse.

Discussion

MCL is a rare and aggressive subtype of B-cell non-Hodgkin lymphoma that represents 6% to 8% of all non-Hodgkin lymphoma. Despite significant improvements in therapy for MCL over the past decade, more than 50% of patients will relapse after conventional chemotherapy or autologous stem cell transplantation.²⁻⁴ Allogeneic stem cell transplantation can result in durable remission for patients with relapsed MCL, with approximately 50% of patients achieving long-term disease-free survival.^{2,3} Given the lower risk of causing transplant-related mortality, most centers prefer to use a reduced-intensity conditioning approach because cures after allogeneic transplantation occur not as a consequence of dose-intensive conditioning but rather are mediated by engrafting donor T cells that induce powerful and curative GVT effects.^{3,5,9} Investigators recently reported excellent results after reduced-intensity transplants for relapsed MCL. By using a novel reduced-intensity regimen, Khouri et al¹⁰ reported a 100-day mortality of 0%, a CR rate of 94%, a 3-year progression-free survival of 82%, and a median overall survival of 85% in patients with advanced/ recurrent MCL.

MCL seems to be exquisitely sensitive to the GVT effects mediated by engrafting donor T cells. However, little data exist on an optimal treatment strategy to manage patients who have disease relapse after an allogeneic transplant. In a recent series describing the outcome of patients with a variety of lymphomas relapsing after allogeneic transplant, all 4 patients with MCL achieved a CR after treatment with DLIs, with three quarters of patients achieving long-term disease control.¹¹ However, for patients with lymphoma who achieved a CR after a DLI who subsequently proceed to relapse, prognosis is poor with subsequent treatments being given with the goal of achieving disease palliation rather than cure. In particular, little information exists as to whether patients with MCL who relapse after a DLI can achieve a durable remission with subsequent DLIs. A number of escape mechanisms have been described through which tumors evade donor immunity by loss or downregulation of HLA expression leading to disease relapse.¹²⁻¹⁵ In the context of haploidentical stem cell transplants, leukemia cells can escape donor anti-leukemic T cells through the loss of the mismatched HLA haplotype leading to disease relapse.¹⁴ The patient described in the current report is remarkable for a number of reasons:

First, the patient was able to be induced into a remission after a reduced-intensity allogeneic transplant despite having primary treatment refractory MCL that failed to respond to multiple different combinational chemotherapy regimens, including dose-intensive chemotherapy. External beam radiation was obviously critical to the patient achieving his first CR post-transplant. It is unclear whether DLIs given early after transplant mediated a GVT effect, because these DLIs were primarily given in an effort to break donor immune tolerance to the recipient by converting chimerism from mixed to full donor.

Second, after relapsing a third time, treatment with a combination of rituximab/bortezomib, PEG-IFN, and a DLI led to a fourth disease remission. Third, the synergistic effect of combining rituximab with bortezomib that helped the patient achieve a third remission was reinducible, allowing the patient to achieve a fourth remission that has proven to be durable and ongoing. Furthermore, the third CR lasted 2 years without the use of PEG-IFN, highlighting the powerful synergistic anti-MCL effect of combining rituximab with bortezomib, with disease durability occurring perhaps as a consequence of the DLI. Finally, despite multiple relapses, the donor immune-mediated anti-tumor effect achieved after a ninth DLI proved to be durable when combined with PEG-IFN, with the patient remaining disease-free 10 years post-transplant with no evidence of disease recurrence more than 3 years since his last DLI (Fig. 4).

In vitro studies have shown that IFN- α and γ can upregulate major histocompatibility complex class I molecules and tumor antigens sensitizing to T-cellebased immunotherapy.^{16,17} In addition, Brouwer et al¹⁸ recently showed that loss or downregulation of HLA class I expression at the allelic level in acute leukemia can be restored by IFN. By virtue of this mechanism, we added IFN- α to the patient's treatment regimen after his second and third relapses to increase the potential of subsequent DLIs to achieve a durable GVT against the patient's MCL.^{19,20}

Conclusion

Despite receiving a total 9 DLIs, this patient developed only mild chronic oral GVHD that was treated successfully with topical steroid therapy. Even more remarkable, these DLIs successfully converted the patient from mixed to full donor chimerism, and after a third disease relapse, induced a fourth disease remission of his MCL, which is ongoing more than 3 years. Data from this case suggest that 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 IFN-based cytokine treatment.

References

1. Campo E, Swerdlow SH, Harris NL, et al. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical application. *Blood*. 2011; 117:5019–32. [PubMed: 21300984]
2. Karl, BS. [November 15, 2012] FS4 mantle cell lymphoma facts. Jul 1–8. 2012 Available at: <http://www.lls.org/content/nationalcontent/resourcecenter/freeeducationmaterials/lymphoma/pdf/mantlecelllymphoma.pdf>.
3. Humala K, Younes A. Current and emerging new treatment strategies for mantle cell lymphoma. *Leuk Lymphoma*. 2013; 54:912–21. [PubMed: 23113685]
4. Dietrich S, Tiesch B, Rieger M, et al. Patterns and outcome of relapse after autologous stem cell transplantation for mantle cell lymphoma. *Cancer*. 2011; 117:1901–10. [PubMed: 21509767]
5. Le Gouill S, Kröger N, Dhedin N, et al. Reduced-intensity conditioning allogeneic stem cell transplantation for relapsed/refractory mantle cell lymphoma: a multi-center experience. *Ann Oncol*. 2012; 23:2695–703. [PubMed: 22440229]
6. Porter D. Allogeneic immunotherapy to optimize the graft-versus-tumor effect: concepts and controversies. *Hematology Am Soc Hematol Educ Program*. 2011; 2011:292–8. [PubMed: 22160048]
7. Le Gouill S, Mohty M, Guillaume T, et al. Allogeneic stem cell transplantation in mantle cell lymphoma: where are we now and which way should we go? *Semin Hematol*. 2011; 48:227–39. [PubMed: 21782065]
8. Shanbhag S, Smith MR, Emmons RV. Tackling mantle cell lymphoma (MCL): potential benefits of allogeneic stem cell transplantation. *Stem Cells Cloning*. 2010; 3:93–102. [PubMed: 24198514]
9. Deng C, Lee S, O'Connor OA. New strategies in the treatment of mantle cell lymphoma. *Clin Cancer Res*. 2012; 18:3499–508. [PubMed: 22700864]
10. Khouri IF, Lee MS, Saliba RM, et al. Nonablative allogeneic stem-cell transplantation for advanced/recurrent mantle-cell lymphoma. *J Clin Oncol*. 2003; 21:4407–12. [PubMed: 14645431]
11. Russell NH, Byrne JL, Faulkner RD, et al. Graft-versus-tumor effects donor lymphocyte infusions can result in sustained remissions in patients with residual or relapsed lymphoid malignancy following allogeneic haemopoietic stem cell transplantation. *Bone Marrow Transplant*. 2005; 36:437–41. [PubMed: 15980879]
12. Masuda K, Hiraki A, Fujii N, et al. Loss or down-regulation of HLA class I at the allelic level in freshly isolated leukemic blasts. *Cancer Sci*. 2007; 98:102–8. [PubMed: 17083564]
13. Weigert O, Weinstock D. The evolving contribution of hematopoietic progenitor cells to lymphomagenesis. *Blood*. 2012; 120:2553–61. [PubMed: 22869790]
14. Villalobos IB, Takahashi Y, Akatsuka Y, et al. Relapsed of leukemia with loss of mismatched HLA resulting from uniparental disomy after haploidentical hematopoietic stem cell transplantation. *Blood*. 2010; 115:3158–61. [PubMed: 20124217]
15. Vago L, Perna SK, Zanussi M, et al. Loss of mismatched HLA in leukemia after stem-cell transplantation. *N Engl J Med*. 2009; 361:478–88. [PubMed: 19641204]
16. George PM, Badiger R, Alazawi W, et al. Pharmacology and therapeutic potential of interferons. *Pharmacol Ther*. 2012; 135:44–53. [PubMed: 22484806]

17. Rossi E, Goldenberg D, Cardillo T, et al. CD20-targeted tetrameric interferon- α , a novel and potent immunocytokine for the therapy of B-cell lymphomas. *Blood*. 2009; 114:3864–71. [PubMed: 19710501]
18. Brouwer RE, Heiden P, Gezeina M, et al. Loss or down-regulation of HLA class I expression at the allelic level in acute leukemia is infrequent but functionally irrelevant, and can be restored by interferon. *Hum Immunol*. 2002; 63:200–10. [PubMed: 11872238]
19. Fishburn CS. The pharmacology of PEGylation: balancing PD with PK to generate novel therapeutics. *J Pharm Sci*. 2008; 97:4167–83. [PubMed: 18200508]
20. Baron S, Tyring SK, Fleischmann WR, et al. The interferon mechanism of action and clinical applications. *JAMA*. 1991; 266:1375–83. [PubMed: 1715409]

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.

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 Formerly Infiltrated With MCL)

Figure 2.
Inguinal Lymph Node Biopsies. Relapse of MCL in 2009 (A) (Original Magnification, x1000), With Stain for Cyclin D1 (B) (Original Magnification, x400)

Figure 3.
Oral Chronic GVHD. Arrow Shows Buccal Mucosa With Lichenoid Changes Consistent With Mild Chronic GVHD

Abbreviations: DLI = donor lymphocyte infusion; PEG-IFN = pegylated interferon.

Figure 4.
Clinical Outcome and Treatment of Patient With MCL Relapsing Multiple Times After
Reduced-Intensity Allo-HCT