

LETTER TO THE EDITOR

Successful matched unrelated BMT for secondary AML which developed simultaneously with relapsed Hodgkin's lymphoma

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Although most patients with Hodgkin's lymphoma (HL) can be cured with first-line therapy, long-term survivors are at risk for secondary malignancy as well as for relapse of the primary disease. Myelodysplasia (MDS) and acute myeloid leukemia (AML) are the most frequently observed secondary malignancies, and outcomes are poor.¹ Management for relapsed HL also remains a challenge. To date, there have been no case reports of relapsed HL with a concurrent secondary malignancy. Here, we report a patient with relapsed HL who simultaneously developed secondary AML, was successfully treated with a matched unrelated BMT, and who then became disease-free.

A 29-year-old Japanese woman with widespread cervical lymphadenopathy was diagnosed with HL (mixed cellularity, CS IIB) in August 1999. She underwent six courses of standard ABVD chemotherapy, and achieved complete remission (CR) after receiving an additional 40 Gy irradiation to the remaining cervical lesions in March 2001. She remained in CR for 3 years, but developed generalized lymphadenopathy in June 2004. Biopsy revealed a relapse of the primary HL. She also presented with pancytopenia and a small amount of blastic cells in her peripheral blood. Her BM specimen was hypercellular with a 70% increase in myeloperoxidase-positive myeloblasts and no evidence of HL cells. The blasts were positive for CD13, CD33, CD34 and HLA-DR. A chromosome analysis revealed complex abnormalities including a partial deletion of chromosome 11q, thus indicating relapsed HL and secondary AML (M2).

She underwent induction chemotherapy consisting of idarubicin and cytarabine in August 2004. Her lymphadenopathy completely disappeared after the first course, but additional induction chemotherapy with mitoxantrone and cytarabine was required to achieve CR for AML. However, she experienced a relapse of the AML during consolidation therapy, and a regimen of high-dose cytarabine led to second CR in February 2005. Computed tomography (CT) scan and FDG-PET showed the HL to remain in second CR throughout the treatment courses. An unrelated BMT was planned due to the lack of a suitable related donor.

The conditioning regimen consisted of orally administered BU, given in four equally divided doses daily on days –7 to –4 to achieve a steady plasma concentration between 800 and 900 mg/cm³ (total dose 14.0 mg/kg), and 60 mg/kg intravenous cyclophosphamide (CY), given once daily on

days –3 to –2 (total dose 120 mg/kg). She received an HLA full-matched unrelated BM containing 2.4×10^8 nucleated cells/kg in March 2005. Cyclosporine A (CsA) and short-term methotrexate (MTX) were administered for prophylaxis against graft-versus-host disease (GVHD). The granulocyte number recovered to more than 500/mm³ on day 24. The bone marrow (BM) sample on day 31 revealed hematological CR with complete donor chimerism. A CT scan and FDG-PET on day 40 revealed no residual HL lesions. She developed acute GVHD within her upper intestine on day 45 and was successfully treated with prednisolone. She went on to develop *quiescent*-type extensive chronic GVHD on day 120, which caused mild liver damage, dysphagia, and sicca syndrome. She was again treated with CsA and prednisolone for 11 months, and finally discontinued medication 14 months after bone marrow transplantation (BMT). She has remained in CR for both diseases for 20 months to date.

The cumulative risk of developing secondary AML in patients with HL ranges between 1.0 and 3.3%.^{1,2} Factors related to the development of secondary AML include a higher age at primary diagnosis, a more advanced disease stage, being within the first year after the completion of initial therapy, number of treatment regimens, and a regimen containing nitrogen mustard and alkylating agents.^{3,4} The role of irradiation with regard to the risk of secondary AML is not clear, but a role in increasing the risk for developing a solid tumor has been shown.^{2,4}

The advantage of allogeneic transplantation for secondary AML is still controversial. Josting *et al.*¹ reported an 8% 2-year overall survival in patients with secondary AML/MDS after HL treatment, a rate that was similar among patients receiving allogeneic transplantation or conventional chemotherapy. Anderson *et al.*⁵ reported on the outcomes of stem cell transplantation (SCT) as an initial treatment for secondary AML. The 5-year disease-free survival (DFS) was 24.4%, thus suggesting an advantage in prompt transplantation for secondary AML. Witherspoon *et al.*⁶ described the impact of allogeneic SCT on secondary MDS and AML. The 5-year DFS was 16%, and the authors pointed out that earlier transplantation reduced the risk of relapse and use of targeted BU improved outcome. Recently, reduced-intensity conditioned transplantation has been shown to be useful in treating secondary AML.⁷

Our patient developed secondary AML simultaneously with a relapse of primary HL. This very rare case occurred 3 years after the end of initial therapy, a relatively long time when compared with previous studies.¹ Her cumulative intensity of cytotoxic drugs was smaller than the average

intensity measured in previously reported cases,⁸ but the previous irradiation might have increased the risk of developing secondary AML. Because her AML was more aggressive than the relapsed HL, we decided to give treatment for the secondary AML precedence over HL, and the patient successfully achieved CR in regard to both diseases. However, the treatment for secondary AML was insufficient to treat the HL, thus leaving her at high risk for a second relapse of HL. We therefore considered this to be the best time to undertake an allogeneic SCT. Regarding the poor prognosis of both relapsed HL and secondary AML, we theorized that standard myeloablative therapy would be crucial in eliminating any residual disease. Because of the prior irradiation, we avoided total body irradiation (TBI) and instead chose a BU + CY regimen. Although the impact of allogeneic transplantation on relapsed HL is not yet clear, several authors have recently demonstrated a graft-versus-Hodgkin's lymphoma effect associated with allogeneic transplantation.^{9,10} Our patient developed extensive chronic GVHD, which might have potentially augmented the graft-versus-Hodgkin's lymphoma effect as well as the GVL effect and could have consequently contributed to her CR. To the best of our knowledge, this is the first case of secondary AML occurring simultaneously with a relapse of primary HL. The results are encouraging, suggesting that allogeneic BMT may be an effective method for eliminating secondary AML and relapsed HL.

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