

Role of hematopoietic stem cell transplantation in Philadelphia chromosome-positive acute lymphoblastic leukemia: a report of 2 unique cases

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Abstract

We report, to our knowledge, the first reported case of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) developing 26 years after allogeneic stem cell transplantation for chronic myeloid leukemia (CML). The second case involved de novo Ph+ALL that developed 16 years post-autologous stem cell transplantation in sustained molecular remission. These cases illustrate and raise some key issues in the management of patients with Ph+ leukemias, including the role of hematopoietic stem cell transplantation, tyrosine kinase inhibitors, and long-term post-transplantation follow-up.

Key words: acute lymphoblastic leukemia, tyrosine kinase inhibitor, chronic myeloid leukemia, hematopoietic stem cell transplantation.

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Introduction

Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL) (Ph+ALL) is a biologically and clinically distinct type of ALL associated with poor prognosis¹. Ph+ALL can result from disease transformation or blast crisis of chronic myeloid leukemia (CML). CML relapse more than 15 years after allogeneic (allo) hematopoietic stem cell transplantation (HSCT) is rare, and the development of Ph+ALL following allo-HSCT for CML is also uncommon². Our first case involved the development of Ph+ALL 26 years post-allo-HSCT for CML. Our second case was one of de novo Ph+ALL in molecular remission for 16 years after autologous (auto)-HSCT, even after cessation of tyrosine kinase inhibitors (TKIs).

Case Presentation

Case 1

A 37-year-old man was originally diagnosed with chronic-phase CML following investigations for right eye retinal vein thrombosis in September 1990. After initial leukapheresis and hydroxycarbamide, he underwent allo-

HSCT from his 41-year-old human leukocyte antigen (HLA)-identical brother in August 1991. A myeloablative conditioning regimen comprised busulfan and cyclophosphamide, and he received graft-versus-host disease (GVHD) prophylaxis with methotrexate and cyclosporine. His post-transplant course was uneventful except for bacterial sepsis before engraftment, grade I acute GVHD and limited chronic GVHD of the skin. In August 2017, he was found to lose molecular response with a bcr-abl p210 transcript of 59%. The patient was asymptomatic; blood counts were normal except for occasional circulating blasts. Bone marrow biopsy revealed a markedly hypercellular marrow with blasts of 90%. The blasts were positive for cluster of differentiation (CD) 19, CD20, CD22, CD34, and HLA-DR. Cytogenetics showed 47,XY, t (9; 22) (q34; q11.2), +der (22) t (9; 22) (q34; q11.2), and RT-PCR demonstrated BCR/ABL mRNA of b2a2 type. Cerebrospinal fluid analysis did not show central nervous system involvement. The patient received reinduction with GRAALL regimen³ and imatinib and achieved cytogenetic and molecular remission. In February 2018, he underwent second allo-HSCT with peripheral blood stem cells from his original sibling donor. He received reduced-intensity conditioning with

fludarabine and melphalan, and GVHD prophylaxis consisted of methotrexate and cyclosporine. Imatinib was reinitiated on day 28 post-transplant. His post-transplant course was complicated by bacterial line sepsis and grade I acute skin GVHD. He achieved full donor chimerism post-transplant and remains in complete molecular remission to date.

Case 2

A 52-year-old man was diagnosed to have de novo Ph + ALL in November 2001. He presented with a 6-week history of dyspnea, bruising, gum bleeding, and retroperitoneal bleeding. A full blood count revealed a white blood cell count of $118 \times 10^9/L$ with 91% blasts, a hemoglobin level of 117 g/L, and a platelet count of $9 \times 10^9/L$. Bone marrow biopsy showed a markedly hypercellular marrow with 96% blasts expressing CD10, CD19, CD20, CD22, CD34, and HLA-DR. Cytogenetics showed t(9; 22). He initially received imatinib, followed by multimodality chemotherapy (LALA-94 protocol)⁴. Morphologic and cytogenetic remission was achieved in February 2002, and he underwent auto-HSCT due to the unavailability of a suitable donor in May 2002. The conditioning regimen consisted of cyclophosphamide and busulfan. Apart from bacterial sepsis, his post-transplant course was uneventful; imatinib was recommenced 1 month post-transplant. He sustained cytogenetic remission post-transplant, and the bcr-abl transcript has remained undetectable since 2003. In September 2010, maintenance therapy containing imatinib was switched to dasatinib because of progressive sensory peripheral neuropathy, which was thought to be imatinib-related after comprehensive neurological assessment. The neuropathy subsequently resolved and remained quiescent for 6 years. In June 2016, dasatinib was discontinued after extensive investigations for progressive motor and sensory peripheral neuropathy. Subsequently, the symptoms improved, which was also supported by nerve conduction study findings. He is currently well and remains in complete molecular remission 17 years after diagnosis and 2 years after discontinuing TKIs.

Discussion

Although TKIs have replaced allo-HSCT as frontline therapy for CML, allo-HSCT remains an effective therapeutic option to produce durable remissions in patients resistant to TKIs and in those with advanced disease⁵. Disease phase at transplantation, absence of GVHD, and the use of T-cell-depleted grafts are the major risk factors of relapse⁶, but our first case lacked these factors. The majority of relapses after allo-HSCT for CML occur within the first 3 years, and so far, only one case of relapse with myeloid transformation (accelerated phase)

24 years after allografting has been reported². Thus, our case highlights the risk of very late relapse of CML after allo-HSCT and a need for indefinite monitoring as effective salvage treatment is available.

An unusual feature of the second case was peripheral neuropathy, which developed in a clear temporal association with TKI use. Peripheral neuropathy is an extremely uncommon side effect of TKIs, and the underlying mechanism is unclear^{7,8}. It may be due to direct toxic effects or off-target immune attacks on nerve myelin sheaths. One case report suggested drug interactions as a potential cause and recommended therapeutic monitoring of plasma imatinib levels⁷. In our case, no concomitant medication was administered.

The other uniqueness of our second case was the long-term disease-free survival after auto-HSCT, demonstrating auto-HSCT with TKIs as a suitable consolidation modality for Ph + ALL. Historically, Ph + ALL was considered a high-risk subtype and allo-HSCT was considered the standard of care for eligible patients despite significant treatment-related risks¹. As the incorporation of TKIs in treatment regimens has resulted in improved clinical outcomes, frontline auto-HSCT plus TKIs has become a potential alternative option^{1,3,9}. Long-term follow-up of de novo Ph + ALL patients in the GRAAPH-2003 study reported a 4-year overall survival of up to 80% and 4-year disease-free survival of 50% after auto-HSCT³. A recent registry-based, retrospective analysis showed comparable outcomes of auto-HSCT and allo-HSCT in patients with Ph + ALL in first molecular remission in the TKI era⁹.

In summary, both cases clearly emphasize the role of TKIs in the management of de novo or secondary Ph + ALL. However, there are no commonly accepted standards or strong evidence regarding the choice of TKI, dosage, time of initiation, or treatment duration¹⁰. Considering the associated adverse events, the effects on quality of life and economic impact of long-term TKI use, it is particularly important to investigate the possibility of safe treatment cessation. Further randomized control trials are warranted.

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Author's contribution

Design, manuscript writing and approval of manuscript: YL and DM.

Conflicts of Interest

The authors declare no conflict of interest. Disclosure forms provided by the authors are available here.

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