

Case Report

Chronic Myeloid Leukemia Relapsing 25 Years after Allogenic Stem Cell Transplantation

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Received 6 July 2018; Revised 15 August 2018; Accepted 28 August 2018; Published 23 September 2018

Academic Editor: Kazunori Nakase

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Chronic myeloid leukemia (CML) is a myeloproliferative disorder in which neoplastic cells exhibit the Philadelphia chromosome and the related oncoprotein *BCR-ABL1*. Allogenic stem cell transplantation (allo-SCT) was considered the first-line treatment for CML, before the introduction of tyrosine kinase inhibitors (TKIs). However, patients are at risk for relapse years after transplantation. We present a patient who relapsed 25 years after allo-SCT for chronic phase CML. Polymerase chain reaction (PCR) detected gradually evaluated levels of *BCR-ABL1* transcripts, eventually leading to the diagnosis of relapsed disease. Additional mutational analyses did not reveal mutations in the *BCR-ABL1* gene, or other cooperating mutations. The patient was successfully treated with imatinib 400 mg daily, leading to new molecular remission. The case presentation emphasizes the need for long-term follow-up of such patients and the potential benefit of initiating TKI treatment with early signs of relapse.

1. Introduction

Nearly 1.5 million people worldwide suffer from chronic myeloid leukemia (CML), which is morphologically characterized by an accumulation of myeloid precursor cells in the peripheral blood and bone marrow. Philadelphia chromosome-positive CML is identified by the genetic translocation t(9;22)(q34;q11.2) [1], with the fusion of the Abelson (*ABL1*) oncogene with the breakpoint cluster region (*BCR*) gene. The malignant transformation is hence caused by the acquisition of the constitutively active tyrosine kinase *BCR-ABL1* in a hematopoietic stem cell, transforming it into a leukemic stem cell (LSC) that self-renews, proliferates, and differentiates to give rise to a myeloproliferative neoplastic disease [2, 3]. CML LSCs are believed to evolve as a result of both epigenetic and genetic events and to divide less

frequently, representing a reservoir for relapsed and resistant disease [2, 3].

Since the introduction of tyrosine kinase inhibitors (TKIs), targeting the kinase activity of *BCR-ABL1*, CML has transformed from a once fatal to a manageable disease for the vast majority of patients [4]. However, before the introduction of TKIs, the only potential curative treatment offering hope of long-time survival was allogenic stem-cell transplantation (allo-SCT) [5], although associated with high rates of treatment-related mortality and morbidity. Most patients who relapsed after allo-SCT would do so within the first year after transplant, although later relapses have also been described [6–9]. Here, we present a patient relapsing 25 years after initial allo-SCT of CML, emphasizing the importance of long-time follow-up for allo-transplanted patients.

2. Case Presentation

A previously healthy 41-year-old woman was diagnosed with CML, after presentation of symptoms caused by hypersplenism with gravity sensation under the right costal margin. Initial blood tests demonstrated severe leukocytosis $227 \times 10^9/L$ (normal range $4\text{--}11 \times 10^9/L$) together with increased serum concentration of lactate dehydrogenase (LDH) 969 U/L (200–450 U/l) and cobalamin 2834 pmol/L (150–840 pmol/L). A blood smear demonstrated dominance of myeloid precursor with increased metamyelocytes and rods. CML was confirmed by identification of the Philadelphia chromosome $t(9; 22)$ by using conventional G-banding analyses.

Treatment was initiated with hydroxyurea combined with interferon, and the patient reached morphological remission, then proceeded to allo-SCT for consolidation treatment. The transplantation was performed by a myeloablative condition (MAC) regime with busulphan 1 mg/kg for four days followed by cyclophosphamide 60 mg/kg for two days, followed by bone marrow-derived stem cell from her human leukocyte antigen- (HLA-) matched sister. Standard graft versus host disease (GVHD) prophylaxis by using cyclosporine A and methotrexate on day 1, 3, 6, and 11 after transplant was given [10]. No severe complications were observed after transplant, and especially, she did not develop any signs of acute or chronic GVHD.

After the development of polymerase chain reaction (PCR) analysis for *BCR-ABL1* transcripts [11], this test has been regarded as mandatory in the follow-up of CML patients [11]. Six years after the allo-SCT, an *e13a2* transcript of *BCR-ABL1* was detected by nested PCR. She was therefore controlled twice yearly, without signs of progression judged from karyotyping and interphase fluorescence in situ hybridization (FISH) of 200 interphases with probes against *BCR* and *ABL1* in the bone marrow. By standardization of quantitative real-time (RT) PCR, yearly analyses were performed [11], and low but detectable transcript levels were still observed, although molecular remission (MR) levels were below MR3.

Her transcript levels then suddenly increased rapidly, and she lost her MR (Figure 1). This was confirmed by analysis at two different laboratories. The patient proceeded to bone marrow examination showing normal metaphases by G-banding and only one cell with *BCR-ABL1* of 245 interphases by FISH using dual fusion probes, and this was regarded as insignificant. The bone marrow smear was hypercellular with increased myeloid precursors and megakaryocytes, although without evidence of increased myeloblasts. Hence, we maintained the diagnosis of CML with molecular relapse appearing 25 years after initial allo-SCT. The patient was screened for other mutations commonly occurring in myeloid malignancies, including mutations in *BCR-ABL1*, but no additional mutations were detected. Donor chimerism status revealed that the majority of myeloid cells (99%) were of donor origin. We thought that her relapsed disease was likely to be sensitive to treatment with first-generation TKI, and she was given imatinib 400 mg daily. She tolerated the treatment well without major

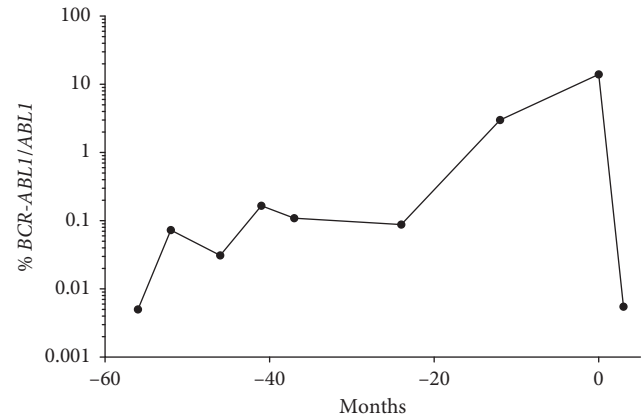


FIGURE 1: Development in *BCR-ABL1/ABL1* transcript levels in the setting of relapsed CML. The figure shows the *BCR-ABL1/ABL1* transcript levels in peripheral blood for the patient. Time point 0 represents the diagnosis of CML relapse and initiating of imatinib therapy.

side effects; after three months, she obtained MR4 status (Figure 1), and imatinib treatment was continued with regular monitoring of *BCR-ABL1* quantitative RT-PCR.

3. Discussion

Allo-SCT played a central role in CML treatment before the TKIs era because it was the only treatment with proven curative potential [5]. For this reason, CML was the most common indication for allo-SCT until the beginning of the new millennium. The susceptibility of CML to the graft-versus-leukemia (GVL) effect, the documented effect of donor lymphocyte infusion (DLI) in CML relapse, and the possibility to monitor minimal residual disease (MRD) were features placing this disease at the forefront of allo-SCT research. However, the introduction of imatinib, and the clearly therapeutic benefits of this treatment approach, led to a rapid decline of the transplantation rates in CML. However, several patients successfully transplanted for CML are still under follow-up worldwide. Most CML relapses after allo-SCT occurred during the first year after transplant, although late relapses, including extramedullary relapses can also be detected [6–9,12–15].

The present patient was allografted before the introduction of TKIs. She was given induction therapy with hydroxyurea and interferon, considered as the standard treatment at that time [16]. After receiving a complete morphological remission, she was allografted with an HLA-matched sibling donor. During the posttransplant follow-up, she had persistent detection of *BCR-ABL1* transfusion transcripts. The method of detecting *BCR-ABL1* transcripts has been standardized more recently [11]; hence, an accurate quantitative measurement of *BCR-ABL1* transcripts has been available only the last years before the relapse (Figure 1). However, the patient had proven detection of *BCR-ABL1* transcript for >5 years before the posttransplant relapse. The detection of such minimal residual disease (MRD) is not uncommon neither for allografted patients nor for

patients treated with TKIs [17]. The detection of *BCR-ABL1* transcripts is believed to be caused by the persistence of an LSC pool in CML patients [2]. However, the clinical importance or therapeutic implications of such MRD detection is controversial, although a rapid increase in transcript levels or loosing of previous MR should wake the attention from the treating physician.

Studies have demonstrated that patients with *BCR-ABL1* expression in the hematopoietic stem cell compartment seem to have inferior survival irrespective of the disease status [18]. The quantitative RT-PCR has become widely used for monitoring minimal residual disease after allo-SCT for CML. However, most of these studies were performed using qualitative RT-PCR, and the interpretation of the results obtained has been conflicting. By the use of quantitative RT-PCR performed early within three to five years after allo-SCT, a clear relationship between *BCR-ABL1* transcript level and probability of relapse seem apparent [19].

In the 1990s, donor lymphocyte infusion (DLI) was the mainstay of treatment for posttransplant CML relapse [20, 21]. DLI induced durable responses in 60–70% of patients relapsing with chronic phase CML [21], whereas durable remissions in patients relapsing into accelerated or blast phase are less frequent [21]. The main obstacle in allografted patients is GVHD that can be a very severe complication. On the other hand, GVHD seems to be highly correlated to response rates [21, 22]. TKIs are now accepted as the preferred alternative for treating CML relapse after allo-SCT [23–25]. TKIs can induce complete cytogenetic responses (CCRs) and deep molecular response (MR), even in patients failing DLI, and the treatment is without risk of GVHD [26–28]. Early identification of altered intracellular signaling may be a predictor of response to TKI therapy [29], although whether this is evident also in patients relapsing after allo-SCT remains elusive.

BCR-ABL1 kinase domain point mutations are detectable in approximately 50% of patients with treatment failure and progression on TKIs, although the incidence of *BCR-ABL1* mutations in patients relapsing after allo-SCT remains uncertain. Although our patient had not been exposed to TKIs previously, we considered this as a relapsed disease. We therefore investigated her for *BCR-ABL1* mutations, but this could not be detected. Hence, treatment with imatinib was initiated. No clinical studies comparing different TKIs in CML relapse after allo-SCT exist, and the choice of TKI should in our opinion be based on risk for potential side effects, patient age, previous exposure to TKI, and potential *BCR-ABL1* mutations.

The use of maintenance TKI treatment after allo-SCT has also been investigated [30–33] and seems to be well-tolerated with a low risk for GVHD [30–33]. TKIs have the potential for changing the kinetics of the disease and should probably be recommended for CML patients allo-grafted [33, 34], also in the advanced phase of the disease [33, 34]. Maintenance therapy may not be required for patients that achieve full donor chimerism and deep MR [25].

To conclude, our case report emphasizes the need for long-time follow-up for allo-transplanted CML patients.

Despite stable levels of *BCR-ABL1* transcripts over years, relapse can still occur. Early diagnostics and introduction of TKI therapy are crucial to avoid transformation to more advanced stage of CML.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

The study was supported by Øyvinn Mølbach-Pedersen's foundation, Helse Vest, and the Norwegian Cancer Society.

References

- [1] J. D. Rowley, "Letter: a new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining," *Nature*, vol. 243, no. 5405, pp. 290–293, 1973.
- [2] T. L. Holyoake and D. Vetrie, "The chronic myeloid leukemia stem cell: stemming the tide of persistence," *Blood*, vol. 129, no. 12, pp. 1595–1606, 2017.
- [3] A. Tarafdar, L. E. Hopcroft, P. Gallipoli et al., "CML cells actively evade host immune surveillance through cytokine-mediated downregulation of MHC-II expression," *Blood*, vol. 129, no. 2, pp. 199–208, 2017.
- [4] B. J. Druker, M. Talpaz, D. J. Resta et al., "Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia," *New England Journal of Medicine*, vol. 344, no. 14, pp. 1031–1037, 2001.
- [5] J. M. Goldman, J. F. Apperley, L. Jones et al., "Bone marrow transplantation for patients with chronic myeloid leukemia," *New England Journal of Medicine*, vol. 314, no. 4, pp. 202–207, 1986.
- [6] A. S. Yong and J. M. Goldman, "Relapse of chronic myeloid leukaemia 14 years after allogeneic bone marrow transplantation," *Bone Marrow Transplantation*, vol. 23, no. 8, pp. 827–828, 1999.
- [7] A. Sekhri, D. Liu, M. Rasul, N. Ahmed, T. Ahmed, and K. Seiter, "Very late relapse of chronic myelogenous leukemia after allogeneic bone marrow transplantation," *Leukemia Research*, vol. 33, no. 9, pp. 1291–1293, 2009.
- [8] M. Richards and J. Gajewski, "Very late relapse of chronic myelogenous leukemia following stem cell transplant," *Hematology and Transfusion International Journal*, vol. 1, no. 1, article 00005, 2015.
- [9] K. Hirschbuehl, A. Rank, T. Pfeiffer et al., "Ponatinib given for advanced leukemia relapse after allo-SCT," *Bone Marrow Transplantation*, vol. 50, no. 4, pp. 599–600, 2015.
- [10] T. Ruutu, A. Gratwohl, T. De Witte et al., "Prophylaxis and treatment of GVHD: EBMT-ELN working group recommendations for a standardized practice," *Bone Marrow Transplantation*, vol. 49, no. 2, pp. 168–173, 2014.
- [11] C. C. Yeung, D. Egan, and J. P. Radich, "Molecular monitoring of chronic myeloid leukemia: present and future," *Expert Review of Molecular Diagnostics*, vol. 16, no. 10, pp. 1083–1091, 2016.
- [12] A. F. Yilmaz, N. Soyer, N. Ozsan et al., "Extramedullary relapse in a CML patient after allogeneic stem cell transplantation," *Case Reports in Hematology*, vol. 2017, Article ID 6350267, 3 pages, 2017.

- [13] A. Thomas, C. K. Stein, T. C. Gentile, and C. M. Shah, "Isolated CNS relapse of CML after bone marrow transplantation," *Leukemia Research*, vol. 34, no. 4, pp. e113–e114, 2010.
- [14] S. Hosseini, S. Ansari, P. Vosough et al., "Bilateral maxillary, sphenoid sinuses and lumbosacral spinal cord extramedullary relapse of CML following allogeneic stem cell transplant," *International Journal of Hematology-Oncology and Stem Cell Research*, vol. 10, no. 2, pp. 106–110, 2016.
- [15] Q. Huang, Y. Wu, D. S. Snyder et al., "Clinical and pathologic analysis of 16 cases of relapsed chronic myeloid leukemia after stem cell transplantation," *American Journal of Clinical Pathology*, vol. 128, no. 4, pp. 565–570, 2007.
- [16] Italian Cooperative Study Group on Chronic Myeloid Leukemia, S. Tura, M. Bacarani et al., "Interferon alfa-2a as compared with conventional chemotherapy for the treatment of chronic myeloid leukemia," *New England Journal of Medicine*, vol. 330, no. 12, pp. 820–825, 1994.
- [17] J. Kaeda, D. O'Shea, R. M. Szydlo et al., "Serial measurement of BCR-ABL transcripts in the peripheral blood after allogeneic stem cell transplantation for chronic myeloid leukemia: an attempt to define patients who may not require further therapy," *Blood*, vol. 107, no. 10, pp. 4171–4176, 2006.
- [18] N. A. Jain, S. Ito, X. Tian et al., "Clinical and biological predictors of outcome following relapse of CML post-allo-SCT," *Bone Marrow Transplantation*, vol. 50, no. 2, pp. 189–196, 2015.
- [19] E. Olavarria, E. Kanfer, R. Szydlo et al., "Early detection of BCR-ABL transcripts by quantitative reverse transcriptase-polymerase chain reaction predicts outcome after allogeneic stem cell transplantation for chronic myeloid leukemia," *Blood*, vol. 97, no. 6, pp. 1560–1565, 2001.
- [20] D. L. Porter, M. S. Roth, C. McGarigle, J. L. Ferrara, and J. H. Antin, "Induction of graft-versus-host disease as immunotherapy for relapsed chronic myeloid leukemia," *New England Journal of Medicine*, vol. 330, no. 2, pp. 100–106, 1994.
- [21] R. H. Collins Jr., O. Shpilberg, W. R. Drobyski et al., "Donor leukocyte infusions in 140 patients with relapsed malignancy after allogeneic bone marrow transplantation," *Journal of Clinical Oncology*, vol. 15, no. 2, pp. 433–444, 1997.
- [22] M. Boyiadzis, M. Arora, J. P. Klein et al., "Impact of chronic graft-versus-host disease on late relapse and survival on 7,489 patients after myeloablative allogeneic hematopoietic cell transplantation for leukemia," *Clinical Cancer Research*, vol. 21, no. 9, pp. 2020–2028, 2015.
- [23] E. Olavarria, O. G. Ottmann, M. Deininger et al., "Response to imatinib in patients who relapse after allogeneic stem cell transplantation for chronic myeloid leukemia," *Leukemia*, vol. 17, no. 9, pp. 1707–1712, 2003.
- [24] D. J. DeAngelo, E. P. Hochberg, E. P. Alyea et al., "Extended follow-up of patients treated with imatinib mesylate (gleevec) for chronic myelogenous leukemia relapse after allogeneic transplantation: durable cytogenetic remission and conversion to complete donor chimerism without graft-versus-host disease," *Clinical Cancer Research*, vol. 10, no. 15, pp. 5065–5071, 2004.
- [25] H. Jin, Y. Xiong, J. Sun et al., "Is imatinib maintenance required for patients with relapse chronic myeloid leukemia post-transplantation obtaining CMR? a pilot retrospective investigation," *PLoS One*, vol. 8, no. 6, Article ID e65981, 2013.
- [26] H. M. Kantarjian, S. O'Brien, J. E. Cortes et al., "Imatinib mesylate therapy for relapse after allogeneic stem cell transplantation for chronic myelogenous leukemia," *Blood*, vol. 100, no. 5, pp. 1590–1595, 2002.
- [27] M. Shanavas, H. A. Messner, S. Kamel-Reid et al., "A comparison of long-term outcomes of donor lymphocyte infusions and tyrosine kinase inhibitors in patients with relapsed CML after allogeneic hematopoietic cell transplantation," *Clinical Lymphoma Myeloma and Leukemia*, vol. 14, no. 1, pp. 87–92, 2014.
- [28] J. F. Zeidner, M. Zahurak, G. L. Rosner, C. D. Gocke, R. J. Jones, and B. D. Smith, "The evolution of treatment strategies for patients with chronic myeloid leukemia relapsing after allogeneic bone marrow transplant: can tyrosine kinase inhibitors replace donor lymphocyte infusions?," *Leukemia and Lymphoma*, vol. 56, no. 1, pp. 128–134, 2015.
- [29] S. E. Gullaksen, J. Skavland, S. Gavasso et al., "Single cell immune profiling by mass cytometry of newly diagnosed chronic phase chronic myeloid leukemia treated with nilotinib," *Haematologica*, vol. 102, no. 8, pp. 1361–1367, 2017.
- [30] Z. DeFilipp, A. A. Langston, Z. Chen et al., "Does post-transplant maintenance therapy with tyrosine kinase inhibitors improve outcomes of patients with high-risk Philadelphia chromosome-positive leukemia?," *Clinical Lymphoma Myeloma and Leukemia*, vol. 16, no. 8, pp. 466–471 e1, 2016.
- [31] Y. Luo, X. Y. Lai, Y. M. Tan et al., "Reduced-intensity allogeneic transplantation combined with imatinib mesylate for chronic myeloid leukemia in first chronic phase," *Leukemia*, vol. 23, no. 6, pp. 1171–1174, 2009.
- [32] Y. Luo, Y. Zhao, Y. Tan et al., "Imatinib combined with myeloablative allogeneic hematopoietic stem cell transplantation for advanced phases of chronic myeloid leukemia," *Leukemia Research*, vol. 35, no. 10, pp. 1307–1311, 2011.
- [33] M. Bar and J. Radich, "Maintenance therapy with tyrosine kinase inhibitors after transplant in patients with chronic myeloid leukemia," *Journal of the National Comprehensive Cancer Network*, vol. 11, no. 3, pp. 308–315, 2013.
- [34] M. Bacarani, M. W. Deininger, G. Rosti et al., "European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013," *Blood*, vol. 122, no. 6, pp. 872–884, 2013.