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Case Report

A Possible Association between Deep Molecular Response and Combination of Tyrosine Kinase Inhibitor and Immunochemotherapy in a Patient with Coexisting Chronic Myeloid Leukemia and Follicular Lymphoma: A Case Report

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Abstract

Tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of chronic myeloid leukemia (CML) and improved survival rates, however, concerns about TKI-related secondary malignancies persist. We report the case of a 55-year-old male with chronic phase CML who achieved a minimal molecular response (MR3.0) under nilotinib treatment. The patient subsequently developed multiple lymphadenopathies and was diagnosed with follicular lymphoma. After receiving bendamustine and rituximab (BR) with rituximab maintenance therapy, he not only achieved complete remission of follicular lymphoma but also an unexpected improvement in CML molecular response from MR3.0 to MR4.5. This case highlights both the potential risk of TKI-related secondary malignancies and the unexpected improvement in molecular response following immunochemotherapy. The improved molecular response after BR therapy suggests possible synergistic effects between TKIs and immunochemotherapy. Although the definite mechanism remains unknown, immunomodulatory mechanisms similar to those observed with interferon-alpha in CML treatment may be a potential explanation. Further investigations into the role of immunochemotherapy in achieving a deeper molecular response in CML patients are warranted.

Keywords: Bendamustine, chronic myeloid leukemia, follicular lymphoma, rituximab, tyrosine kinase inhibitor

Introduction

Chronic myeloid leukemia (CML) is a clonal stem cell disorder caused by t (9; 22) (q34; q11) translocation, which leads to abnormal BCR::ABL fusion gene rearrangement.[1] Tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of CML and become the current standard of care. Five-year

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overall survival rates have dramatically improved from below 50% in the pre-TKI era to higher than 80% in the contemporary TKI era.[2] However, this improved survival has raised concerns about the potentially increased risk of secondary malignancies. Current literature presents conflicting evidence regarding this issue.[3-5] In the long-term observation of CML Study IV, 4.2% of patients developed secondary malignancies after a median follow-up of 67.5 months, with the most common types being prostate cancer, lung cancer, colorectal cancer, and non-Hodgkin lymphoma. After population-adjusted analysis, non-Hodgkin lymphoma was associated with the most significantly increased risk.[6]

In this case report, we present a patient with CML who received nilotinib treatment and achieved a minimal molecular response (MR, 3.0-log reduction), which was below that required to achieve the goal of treatment-free remission (TFR). After 4 years of nilotinib treatment, second primary follicular lymphoma was diagnosed, and the patient underwent treatment with bendamustine and rituximab (BR). He achieved both complete remission of the follicular lymphoma and a deeper MR (MR4.5) after BR treatment and during maintenance rituximab therapy. The long-term MR4.5-log reduction provided an opportunity to achieve TFR. We report this case to emphasize the possibility of TKI-related secondary malignancies and the association of a deeper MR with the combination of TKIs and immunochemotherapy, although the mechanism remains unclear.

Case Report

A 55-year-old man presented with periumbilical pain, nausea, diarrhea, and low-grade fever for 3 days, without tarry stool, cough, or dysuria. A physical examination revealed splenomegaly (6 cm below the costal margin), and laboratory examination showed leukocytosis (white blood cell count 300,100/uL) with left shift (blast 1%, promyelocyte 3.4%, myelocyte 34.6%, meta-myelocyte 4.4%, band 7.4%, segment 44.6%, and lymphocyte 2.8%) but without excess basophils. Bone marrow aspiration and biopsy showed hypercellularity (95%), with an extremely high myeloid/erythroid ratio of 16:1 and normal myeloid maturation [Figure 1]. No increase in blasts was noted (3%). Real-time polymerase chain reaction showed positive results for b2a2 BCR::ABL1 fusion transcripts. The final diagnosis was CML, chronic phase, with a Sokal score of 0.98 (intermediate risk). Nilotinib 300 mg was given orally twice daily. The minimal required MR of 3.0-log reduction was achieved 4 years after initiating nilotinib treatment, and the BCR::ABL1 kinase mutation test was negative.

Four years later, during hematology outpatient department follow-up, multiple lymphadenopathies were noted over the bilateral lower neck and bilateral axillary areas. Left axillary lymph node excisional biopsy was performed and the pathology showed follicular lymphoma, grade 2. Immunohistochemistry was positive for CD20, CD10, BCL-2, and BCL-6 and negative for CD3 and CD5, which was compatible with follicular lymphoma. Bone marrow showed no evidence of lymphomatous bone marrow involvement. Chest and abdominal computed tomography (CT) showed lymphadenopathies involving bilateral lower neck, bilateral axillary, mediastinum, para-aortic area, and bilateral pelvic region [Figure 2]. The final diagnosis was follicular lymphoma, grade 2, Ann Arbor stage III, with a FLIPI score of 2 (intermediate risk). According to the GELF criteria, treatment was required due to the presence of B symptoms. Therefore, six cycles of BR were given, which resulted in tumor regression in the interim CT. An end-of-treatment positron emission tomography/CT scan showed a 1.2 cm equivocal right paratracheal lymph node (Deauville 5PS score 3); otherwise, no residual lymphoma was present. The patient has continued to receive maintenance treatment with rituximab, and he remains in complete remission in follicular lymphoma according to follow-up studies. Surprisingly, he reached an MR more than 4.5-log reduction (MR4.5) after BR treatment and has maintained MR4.5 for 1 year until now [Figure 3].

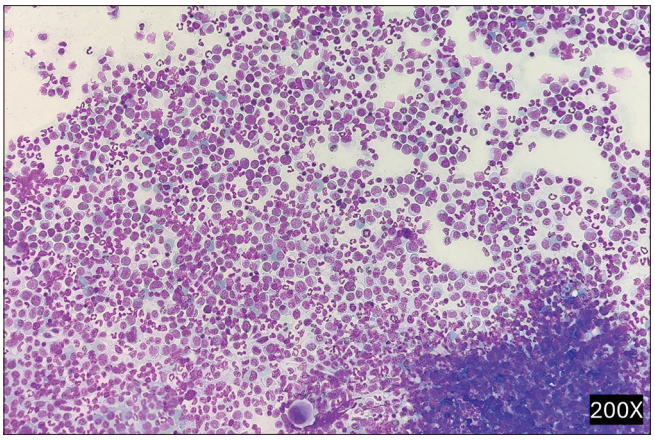

Figure 1: Bone marrow aspiration at the time of chronic myeloid leukemia (CML) diagnosis showed hypercellularity with high myeloid/erythroid ratio, eosinophilia, and left shift maturation without excess myeloblasts. It was compatible with the features of CML

Discussion

This case report describes a patient with CML who received nilotinib treatment and was diagnosed with follicular lymphoma 4 years later, raising concerns over TKI-related secondary malignancy. A notable finding is that the MR improved from a 3.0–4.5-log reduction after BR therapy and maintenance rituximab treatment and that it has remained MR4.5 until now. We present this valuable case with a detailed description of the CML and secondary follicular lymphoma clinical course to demonstrate the possible role of adding of immunochemotherapy to a TKI in the treatment of CML.

The risk of secondary malignancies related to TKI therapy remains uncertain. A study of 1445 patients with CML or myeloproliferative neoplasms revealed no significant increase in the risk of secondary malignancies compared to

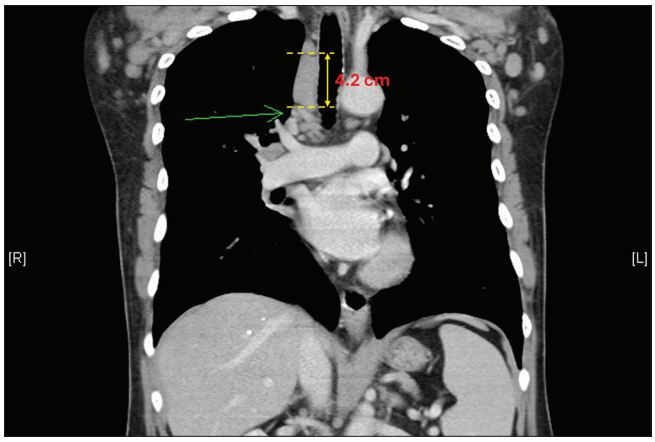

Figure 2: Computed tomography showed disseminated enlarged lymphadenopathies. This figure shows enlarged mediastinal lymph nodes (green arrow), with the largest node measuring 4.2 cm

the expected number from the surveillance, epidemiology, and end results database.[5] Conversely, some studies have reported a higher risk of secondary malignancies during TKI treatment. An analysis of 868 patients diagnosed with CML using the Swedish National CML Register showed a higher risk of second malignancies in the CML cohort.[3] Moreover, an analysis of 13,276 CML patients reported a 4.5% incidence of secondary malignancies in 69 month of follow-up, including 0.2% with secondary lymphoma.[4] These reports suggest that TKIs may slightly increase the risk of secondary malignancies, highlighting the importance of clinical surveillance in CML patients under TKI treatment.

The risk of secondary malignancies related to TKI therapy has been discussed since the introduction of imatinib, and preclinical data have demonstrated an interaction of imatinib with DNA repair mechanisms.[7] Several possible mechanisms may contribute to secondary malignancies in CML patients. First, CML itself may increase the risk of cancer onset. The clinical course of CML includes the acquired BCR::ABL translocation and other chromosomal mutations, indicating the potential of genetic instability.[8] Second, TKIs have an immunosuppressive effect by inhibiting T-lymphocytes and macrophages.[9] Imatinib has been shown to affect the function and differentiation of antigen-presenting cells and inhibit the effector functions of T lymphocytes. Long-term immunosuppression may contribute to the development of secondary malignancies. Third, imatinib has been shown to induce centrosome and karyotype aberrations, leading to genetic instability. *In vitro* experiments with human dermal fibroblasts, Chinese hamster embryonal fibroblasts, and Indian muntjac fibroblasts have demonstrated significant dose-dependent centrosome and chromosome aberrations, which may contribute to the development of chromosomally unstable clones.[10] Furthermore, TKIs have been linked to follicular lymphoid hyperplasia in one case report,[11] possibly due to B cell proliferation through activation of the Akt/protein kinase B pathways during TKI treatment.[12]

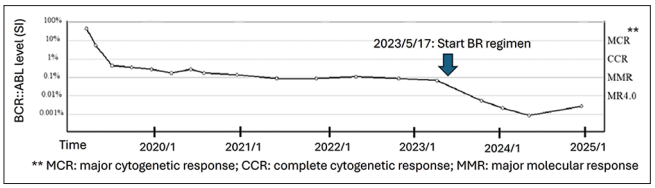

Figure 3: The molecular response of the BCR::ABL1 transcript over time. After nilotinib treatment, the greatest treatment response was a minimal required molecular response of MR3.0 until starting the BR regimen (arrow). Thereafter, a deeper response of more than MR4.5 was achieved

The overall survival and progression-free survival of CML patients with secondary malignancies during TKI treatment are significantly lower compared to those without secondary malignancies. In the long-term CML study IV, the 4-year survival rate of patients who developed secondary malignancies was 57%, which is significantly lower than the reported survival rate of 83%.[2] In case reports focusing on CML and secondary follicular lymphoma, the treatment response of follicular lymphoma was satisfactory.[13,14] In the present case, the patient had a good response to the initial BR regimen.

The effect of BR treatment on MR may be due to its immunomodulatory effect. Before the introduction of TKIs, interferon was the standard treatment for CML. Adding interferon to TKIs such as imatinib or nilotinib has been shown to improve the MR.[15,16] In the French SPIRIT phase III trial, the combination of imatinib 400 mg + Peg-IFN alfa-2a resulted in an improved major MR at 12 months and deep MR (MR4) over time.[15] The Australasian Leukaemia & Lymphoma Group (ALLG) CML 11 Pinnacle study reported that 50% of patients receiving nilotinib with Peg-IFN alfa-2b achieved molecular response (MR) 4.5 after 2 years, which was superior to nilotinib monotherapy.[16] The improvement in MR after the addition of interferon in recent studies has raised the hypothesis that immunomodulatory agents may have synergistic effects when used in combination with TKIs. The BR regimen combines chemotherapy (bendamustine) with target therapy (rituximab), however, the precise mechanism of action of the BR regimen is still under investigation. In a study of diffuse large B-cell lymphoma cell lines, the BR regimen was shown to have direct tumoricidal effects by promoting apoptosis and inducing cell cycle arrest. In addition, the BR regimen was also shown to trigger immune reactivity by activating the cGAS-STING pathway,[17] which is a key mediator of inflammation in the settings of infection, cellular stress, and tissue damage. It is possible that the BR combination led to the deeper MR in our case due to similar immunomodulatory effects as interferon. However, the detailed mechanism remains unknown.

In summary, we report a patient with CML who developed secondary follicular lymphoma after receiving 4 years of nilotinib. This case underscores the potentially elevated risk of secondary malignancies associated with TKI treatment, necessitating vigilant surveillance during long-term follow-up. Notably, the BR regimen unexpectedly enhances the MR.

Further studies are needed to investigate whether the mechanism of improved MR with the BR regimen is similar to that with a combination of interferon and TKI, or whether the mechanism is distinct.

Declaration of patient consent

This study was performed in accordance with and conforming to the Declaration of Helsinki. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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