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Case Report

Tyrosine Kinase Inhibitor-Associated Aplastic Anemia- A Lethal Adverse Effect and its Management Difficulties

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Abstract:

In the pre-tyrosine kinase inhibitors era, allogenic bone marrow transplant was the treatment of choice for chronic myeloid leukemia-chronic phase (CML-CP). In the tyrosine kinase inhibitor (TKI) era life expectancy of CML-CP patients has matched the general population making it the treatment of choice. TKI is associated with hematological and non-hematological side effects. TKI-associated bone marrow hypoplasia is a rare complication and can be lethal if the patient presents with severe sepsis. Here we describe two fatal cases of TKI-associated bone marrow hypoplasia. The first patient was a 50-year-old newly diagnosed CML-CP patient who had a complete hematological response with BCR ABL quantitative 10.6% at 3 months of Dasatinib therapy. After four and half month's patient presented with severe sepsis, grade-4 pancytopenia, and hypoplastic marrow and succumbed despite the best supportive care, growth factors, and stoppage of TKI. The second patient was a 50-year-old case of CML-CP refractory to 3 lines of TKI therapy. After 2 months of 4th-line Bosutinib therapy, the patient presented with sepsis, grade 4 pancytopenia, and hypoplastic marrow. This patient also succumbed despite the best supportive care, growth factors, and stoppage of TKI therapy. So TKI-associated bone marrow hypoplasia is a fatal side effect. It should be suspected in patients presenting with grade-4 pancytopenia either after 3 months of 1 st line TKI therapy or before 3 months of TKI therapy in patients on 2 nd or more lines of TKI therapy due to refractory disease.

Key words: lethal; hypoplastic marrow; febrile neutropenia; pancytopenia; dasatinib; tyrosine kinase receptor inhibitors; chronic myeloid leukemia (cml)

Introduction

Chronic myeloid leukemia- Chronic phase (CML-CP) is the most common myeloproliferative neoplasm, representing 15-20% of newly diagnosed leukemia [1]. With the approval of tyrosine kinase inhibitor (TKI) and subsequent introduction of second and third-generation TKI, the life expectancy of CML patients has reached age-matched individuals in the general population [2]. As these TKI need to be continued lifelong till the progression of the disease so drugs drug-associated side effect is an important concern. TKI is also associated with various hematological and non-hematological side effects. Hematological side effects are more common during the first 4-6 weeks of treatment [3]. Hematological toxicity is the major cause of treatment discontinuation or dose reduction [3]. Grade 3-4 neutropenia was seen in 12%, 21%,11%, and 20% cases of CML treated with nilotinib, dasatinib, bosutinib, and imatinib, respectively [4-6]. Grade 3-4 thrombocytopenia was seen in 10%, 19%,14%, and 10% cases of CML were treated with nilotinib, dasatinib, bosutinib, and imatinib, respectively [4-6]. Grade 3-4 anemia was seen in 3%, 10%,6%, and 7% cases of CML treated with nilotinib, dasatinib, bosutinib, and imatinib, respectively [4-6]. Aplasia of bone marrow due to TKI is very rare, with few cases reported, and associated with a very high mortality risk. Here we are reporting two cases of bone marrow

aplasia due to TKI therapy who presented with sepsis, grade 4 cytopenia, and hypoplastic marrow. Both patients' cytopenia did not recover with the stoppage of TKI therapy, administration of G-CSF, and thrombopoietin analog, so ultimately both patients died due to sepsis.

Case Presentation

Case 1

A woman in her 50s presented to the hematology outpatient department with weakness, arthralgia, and early satiety for 2 months. On examination, the patient had massive splenomegaly (10 cm below the left costal margin) and mild hepatomegaly (2 cm below the right costal margin). There was no lymphadenopathy. Routine investigation showed hyperleukocytosis with left shift and basophilia. BCR ABL qualitative was positive for major transcript (p210). Peripheral smear and bone marrow aspirate were consistent with CMLCP. Karyotying showed 46 XX, t (9;22) (q34; q11). The patient was diagnosed with chronic myeloid leukemiachronic phase with Sokal high risk and ELTS -intermediate risk group. The patient was started on Tab Dasatinib 100 mg once a day and was regularly followed up. After 3 months of TKI therapy, the patient had a complete hematologic response and BCR ABL quantitative was 10.6% on an international scale. So, patient continued on the same treatment. After four and half months of therapy patient presented to the emergency with complaints of weakness, oral ulcers, and pedal edema for 7 days. On examination, the patient had oral candidiasis, pedal edema, and hypotension. Complete blood count showed grade-4 cytopenia (Hemoglobin 60gm/L, WBC - 0.15 ×109/L, and platelet 10 × 109/L). So patient was diagnosed with TKI-induced severe myelosuppression and was managed conservatively with antibiotics, antifungal, growth factor, vasopressor, and blood products and TKI was withheld. The patient recovered from septic shock but given persistent grade-4 cytopenia even after stopping TKI and 12 days of growth factors, bone marrow aspiration, and biopsy were done which were suggestive of severely hypoplastic-marrow with few areas showing small clusters of blast-like cells but were CD34 negative. So, the impression was drug-induced aplastic marrow (Figures 1 and 2). The patient was started on thrombopoietin analogue and danazol. Patient cytopenia persisted with continuous requirement of blood product support. On day 25 of admission, patient again developed septic shock, required mechanical ventilator support, and later succumbed to illness.

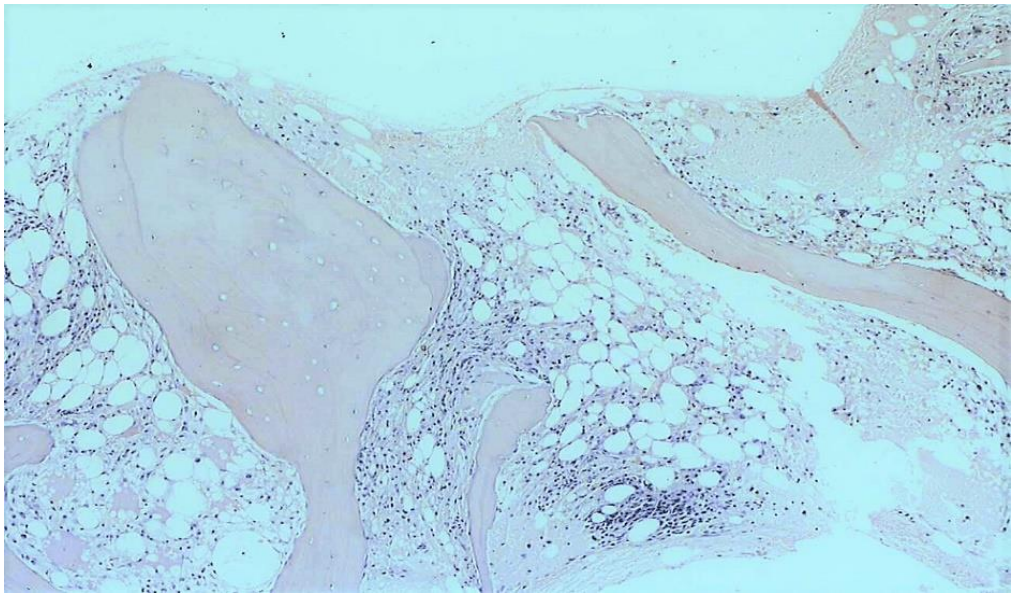

Figure 1: Scanner view showing hypocellular marrow spaces with a predominance of lymphocytes (H&E stain, x40)

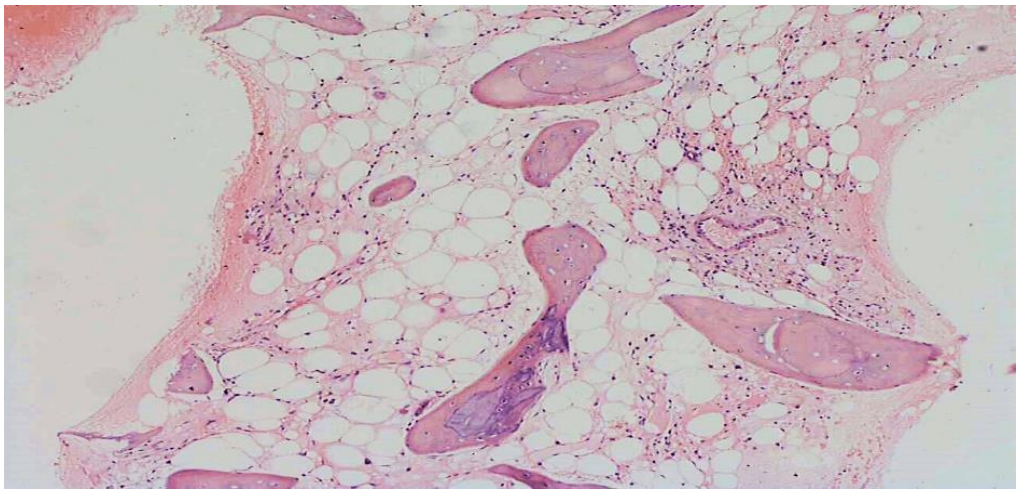

Figure 2: Hypocellular marrow showing predominantly fat and increased number of lymphocytes and plasma cells. No hematopoietic elements are seen. (H&E stain, x100)

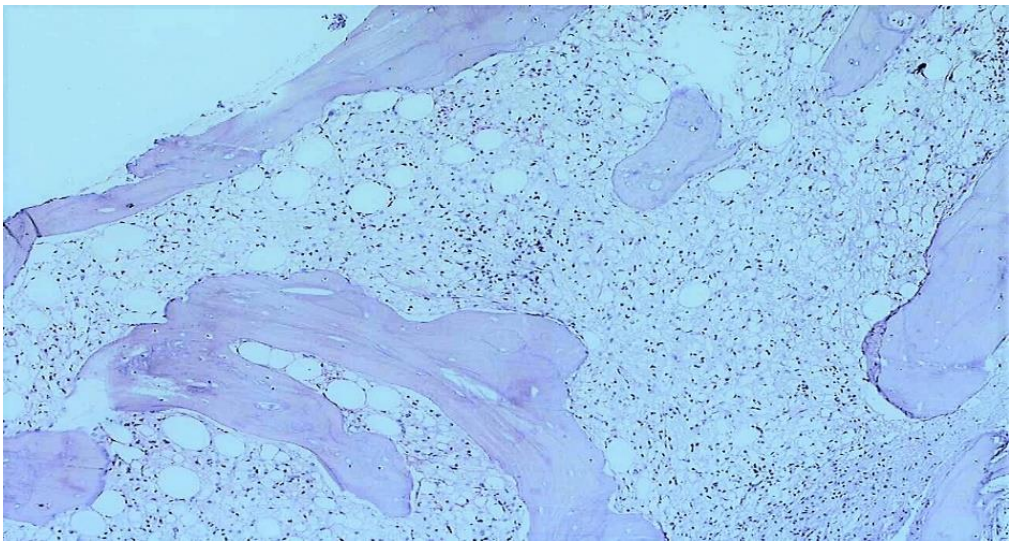

Figure 3: Hypocellular marrow spaces with stromal edema and predominance of lymphocytes (H&E stain, x100)

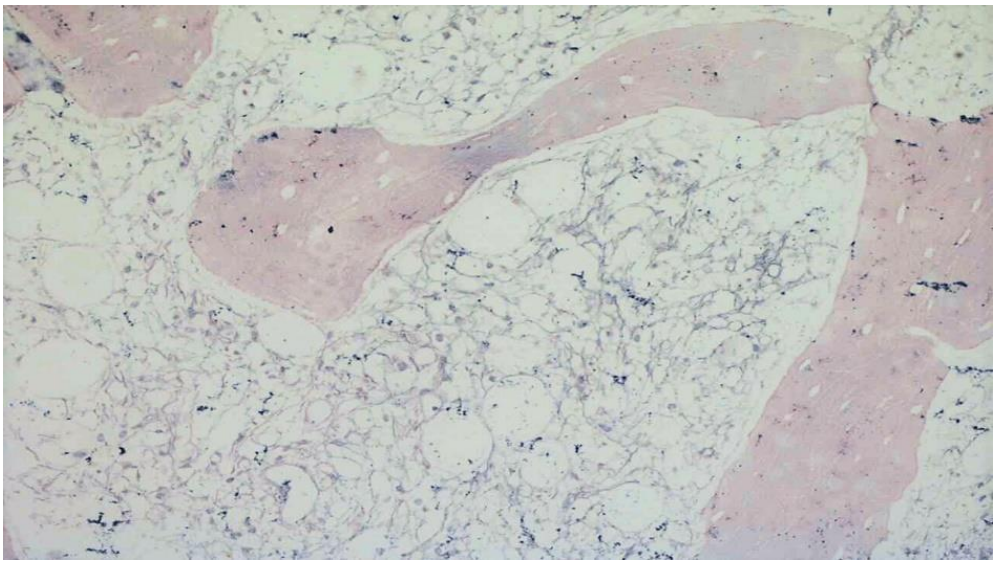

Figure 4: Same case as Figure 3, showing diffusely increased reticulin fibres with extensive intersection – WHO Grade 2 fibrosis (Reticulin stain, x400)

Case 2

A woman in her 50's was diagnosed with CML-CP with a low sokal score in 2014. She was started on Imatinib therapy. She achieved all the milestones and achieved MMR at 12 months of therapy and maintained MMR till May 2018. In 2018 she relapsed so bone marrow aspirate, karyotyping, and tyrosine kinase mutation studies were done which showed disease in the chronic phase with no additional cytogenetic abnormality and no evidence of TKI resistant mutation respectively. The patient was started on Dasatinib therapy. She again achieved MMR. In October 2020 she relapsed again and on repeat evaluation showed disease in the chronic phase with no additional cytogenetic abnormality and no evidence of TKI-resistant mutation. So, she was started on Nilotinib but failed to achieve a haematological response at 3 months so was counseled regarding Ponatinib and bone marrow transplant but due to financial constraints was started on generic Bosutinib in August 2021. In October 2021 the patient was admitted with complaints of fever and breathing difficulty. CECT chest showed consolidation in right upper lobe and complete blood count showed grade 4 cytopenia (Hemoglobin 72 g/L, Total leukocyte count -0.2 × 109/L, and platelet 20 × 109/L). Due to breathing difficulty patient was put on a mechanical ventilator and started on IV empirical antibiotics, antifungal, growth factors, and other supportive care with blood products. TKI was withheld considering drug-induced cytopenia. In view of persistent cytopenia, on Day 7 of admission, the patient was started on subcutaneous Injection romiplostim(weekly). The patient clinical condition progressively worsened and continued to have persistent grade 4 pancytopenia requiring daily support with platelets. So, on day 12 of admission, bone marrow aspiration and biopsy was done which was suggestive of severely hypoplastic marrow with grade 2 fibrosis on reticulin stain. So, impression was Hypocellular marrow with grade 2 fibrosis (Figure 3 and 4). Patient clinical condition further worsened in spite of escalation of antibiotics and antifungal and she developed refractory septic shock and on day 16 succumbed to her illness.

Discussion

In CML patients tyrosine kinase-associated bone marrow hypoplasia can occur for two reasons. Firstly, delayed recovery of normal hemopoietic cells during the first 3 months of the start of therapy: In patients with CML, myelosuppression occurs after 4-6 weeks of the beginning of TKI therapy due to reduction of BCR-ABL positive leukemic stem cells and delayed recovery of prolonged suppressed normal hemopoietic stem cells

[3]. So early myelosuppression during the first 3 months is an indicator of the efficacy of TKI therapy. However, this myelosuppression can be grade 3-4 and can even lead to prolonged bone marrow hypoplasia in patients who are receiving TKI as 2nd line or 3rd line therapy due to resistant disease [3,7-11]. Secondly, True therapy-related hypoplasia, occurs after 3 months of TKI therapy in responding patients due to drug-associated myelosuppression.

All TKI are associated with myelosuppression; however, dasatinib is associated with the greatest hematologic toxicity, which also depends on dose and schedule [3]. In patients on dasatinib, grade 2 to 4 neutropenia or thrombocytopenia occurs in 87% of patients in 1st 90 days and is also associated with recurrence of cytopenia after 90 days in 88% of patients [12]. It is also known that dasatinib inhibits the proinflammatory function of mature neutrophils [13]. So, myelosuppression and anti-inflammatory action of dasatinib can cause severe infections in CML patients.

So, case 1, had true therapy-related bone marrow hypoplasia as it occurred at 4 and 1/2 months after optimal response with the normal count at 3 months of dasatinib therapy. Secondly, due to myelosuppression and anti-inflammatory action of dasatinib, our patient presented with severe sepsis. In case 2, prolonged pancytopenia with hypoplastic marrow occurred after 8 weeks of starting bosutinib as 4th line therapy in imatinib, dasatinib, and nilotinib-resistant disease. So prolonged cytopenia could be due to prolonged suppression of normal hemopoietic stem cells due to resistant disease.

Management of TKI-associated myelosuppression requires withholding TKI in grade 3-4 cytopenias and starting at a lower dose when cytopenia improves to less than grade 3. Recurrent grade 3-4 cytopenia require a change of therapy but there is a chance of recurrence due to cross intolerance to hematological side effects [3].

Management of TKI-associated bone marrow hypoplasia is still not well defined and this condition can be lethal if not addressed on time. Below are the case reports of CML-CP which we could find from a literature search who developed TKI-associated bone marrow hypoplasia. In two cases reported by Ramdial et al., case 1 developed pancytopenia and bone marrow hypoplasia after 8 months of imatinib therapy, which required discontinuation of treatment for two months. The patient was later started on Dasatinib due to 95% BCRABL transcript and clonal cytogenetics abnormality after 12 months of imatinib therapy. However, the patient again developed pancytopenia and hypoplasia after four months of treatment. Given resistant disease even after six months of therapy, the patient was started on omacetaxine and later underwent an allogenic bone marrow transplant [11]. In case 2 of the same study, the patient was shifted to dasatinib after a suboptimal response to imatinib and later shifted to nilotinib due to intolerance. After 3 months of nilotinib, the patient developed hypoplastic marrow with clonal evolution (trisomy 8) but nilotinib was continued and counts gradually improved. The patient developed recurrent pancytopenia so the dose was reduced but again developed cytopenia with hypoplastic marrow. So patient was started on eltrombopag with planning for allogeneic BMT. But after 2 months of eltrombopag, a bone marrow biopsy showed 10-15% lymphoid blast and later on died due to hemorrhagic stroke due to severe thrombocytopenia [11].

In two cases reported by Feld et al, both developed dasatinib-induced hypocellular marrow with mild fibrosis and persistent BCR ABL positivity during 1st year of life. One case recovered with immunosuppressive therapy and the other required allogenic BMT [14]. In a case reported by Kausar et al, after a suboptimal response to imatinib after 3 months of therapy, dose was escalated to 600 mg. At 6th month developed pancytopenia with hypoplastic marrow with BCR ABL 0.1% so changed TKI to nilotinib and continued on the same dose even though the patient continued to have pancytopenia [15]. In a case report by lokeshwar et al, a patient who was initially treated with INFα, low dose Ara-c, and hydroxyurea developed pancytopenia with hypoplastic marrow after 6 weeks of starting imatinib and presented with E coli sepsis and later died due to pulmonary mucormycosis [9].

In a case report by Sumi et al., a patient who was initially treated with INFα, hydroxyurea, and busulfan developed pancytopenia with hypoplastic marrow after 12 weeks of starting imatinib and was managed conservatively with PRBC, platelet, and filgrastim [7]. In a case report by Khan et al, the patient developed pancytopenia with slightly decreased cellularity after 18 weeks of imatinib and later died due to pulmonary tuberculosis, liver failure, and worsening pancytopenia [16]. In a case report by Song et al., the patient achieved a complete cytogenetic response after 9 months of imatinib. Due to intolerance, it was shifted to nilotinib, but after 8 weeks of nilotinib, pancytopenia with hypoplastic marrow was developed. Nilotinib was discontinued, but even after 4 months of discontinuation, hematologic parameters did not improve even though the patient remained in complete cytogenetic response [8]. In a case report by Estephan et al., the patient developed pancytopenia with hypoplastic marrow after 10 weeks of nilotinib therapy, so it was discontinued and was started on Romiplostim. Cellularity improved after 2 months and the patient was started on Dasatinib 50 mg with good cytogenetics response [17]. In a case report by Prodduturi et al., the patient was shifted to dasatinib due to failure to achieve BCR ABL L<10% at the 7th month of imatinib therapy but developed anaphylaxis to dasatinib. After 6 months of nilotinib therapy, pancytopenia with hypoplastic marrow was developed but achieved a complete cytogenetic response. After discontinuation of nilotinib counts improved but the disease progressed. The patient was given a reduced dose of nilotinib 200mg twice a day but again developed pancytopenia with hypoplastic marrow after 1 month of therapy but again recovered after the stoppage of TKI [10].

Conclusions

Bone marrow aplasia is a fatal rare adverse effect of TKI in CML-CP patients. It should be suspected in patients who develop prolonged pancytopenia on TKI as 2nd or 3rd line for resistant disease or in patients who develop prolonged pancytopenia on TKI after achieving optimal response at three months of therapy. Also, TKI-associated bone marrow hypoplasia is associated with prolonged and repeated discontinuation of TKI therapy, which is associated with either suboptimal response or disease progression. Hypoplasia can recur if the same TKI is continued or another TKI is started due to cross intolerance. Few cases can recover with growth factors and immunosuppressive agents but the ultimate treatment of TKI-associated bone marrow hypoplasia is an allogeneic bone marrow transplant due to the high incidence of recurrence or cross intolerance of hematological complications.

References

1. Hoffman R, Benz EJ, Silberstein LE, et al.: (2017). Hematology: Basic Principles and Practice. Hematology: Basic Principles and Practice.
2. Hochhaus A, Baccarani M, Silver RT, et al.: (2013). European LeukemiaNet recommendations for the management of chronic myeloid leukemia. Blood.,
3. Steegmann JL, Baccarani M, Breccia M, et al.: (2016). European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. Leukemia., 30:1648-1671.
4. Saglio G, Kim DW, Issaragrisil S, et al.: (2010). Nilotinib versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia. N Engl J Med., 362:2251-2259.
5. Kantarjian H, Shah NP, Hochhaus A, et al.: Dasatinib versus Imatinib in Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia. N Engl J Med. 2010, 362:2260-2270.
6. Cortes JE, Kim DW, Kantarjian HM, et al.: (2012). Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: results from the BELA trial. J Clin Oncol Off J Am Soc Clin Oncol., 30:3486- 3492.

7. Sumi M, Tauchi T, Shimamoto T, et al.: (2009). Chronic myeloid leukemia associated with sustained severe pancytopenia after imatinib mesylate therapy. Rinsho Ketsueki. 2002, 43:868-870.
8. Song MK, Choi YJ, Seol YM, et al.: Nilotinib-induced bone marrow aplasia. Eur J Haematol., 83:161-162.
9. Lokeshwar N, Kumar L, Kumari M: (2005). Severe bone marrow aplasia following imatinib mesylate in a patient with chronic myelogenous leukemia. Leuk Lymphoma., 46:781-784.
10. Prodduturi P, Perry AM, Aoun P, et al.: (2012). Recurrent bone marrow aplasia secondary to nilotinib in a patient with chronic myeloid leukemia: a case report. J Oncol Pharm Pract Off Publ Int Soc Oncol Pharm Pract., 18:440-444.
11. Ramdial JL, Aguirre LE, Ali RA, et al.: (2019). Aplasia in Chronic Phase CML Post-TKI Therapy: A Management Dilemma. Case Rep Hematol., 2019:1-7.
12. Quintás-Cardama A, De Souza Santos FP, Kantarjian H, et al.: (2009). Dynamics and Management of Cytopenias Associated with Dasatinib Therapy in Patients with Chronic Myeloid Leukemia in Chronic Phase After Imatinib Failure. Cancer., 115:3935-3943.
13. Futosi K, Németh T, Pick R, et al.: Dasatinib inhibits proinflammatory functions of mature human neutrophils. Blood. 2012, 119:4981-4991.
14. Feld J, Steinberg A, El Jamal SM, et al.: unexpected pancytopenia: Dasatinib induced aplastic anemia in chronic myeloid leukemia. J Oncol Pharm Pract Off Publ Int Soc Oncol Pharm Pract. 2022, 28:232-236.
15. Kausar M, Karpurmath SV, Nandennavar MI, et al.: (2019). Imatinib induced bone marrow hypoplasia in a case of chronic myelogenous leukemia. Int J Res Med Sci., 7:627-679.
16. Khan KA, Junaid A, Siddiqui NS, et al.: (2008). Imatinib-related bone marrow aplasia after complete cytogenetic response in chronic myeloid leukemia. J Coll Physicians Surg Pak., 18:176-178.
17. Estephan F, Rogers HJ, Visconte V, et al.: (2015). Spontaneous recovery of severe nilotinib-induced bone marrow aplasia and successful retreatment with dasatinib in a patient with Chronic Phase Chronic Myeloid Leukemia. Leuk Lymphoma., 56:811-813.

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