chemotherapy. After chemotherapy, bilirubin levels returned to normal, and the patient was diagnosed with liver involvement of AML. **Conclusion:** The clinical presentation of extramedullary involvement varies depending on the affected organ and region. A definitive diagnosis is made through biopsy. In patients with AML, as in our case, a biopsy may not always be feasible due to the risk of bleeding. Therefore, in cases where hepatomegaly, abnormalities in liver function tests, and elevated bilirubin levels cannot be explained by other diseases, liver involvement should be considered.

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PP 06

## IS ALL-TRANS RETINOIC ACID EFFECTIVE IN PULMONARY HAEMORRHAGE IN PATIENTS WITH ACUTE PROMYELOBLASTIC LEUKAEMIA?

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**Objective:** Acute myeloid leukaemia (AML) develops from myeloid precursor cells in the bone marrow. Acute promyelocytic leukaemia (APL) is an aggressive subtype (5-10%) of AML with the t(15;17) translocation. It is sensitive to all-trans retinoic acid (ATRA). The aim of this article is to emphasise the efficacy of ATRA treatment in pulmonary haemorrhage associated with APL and to contribute to the literature. **Case Report:** A 14-year-old girl presented with malaise, pallor and bruises since 1 month. On examination, she was pale and had bruises on the trunk and extremities, but no organomegaly. Investigations revealed pancytopenia and atypical mononuclear cells in peripheral blood smear. Bone marrow aspirate showed promyeloblasts (80%) and AML-M3 surface markers were positive in flow cytometry. Cytogenetic analysis revealed t(15;17) translocation. AML-BFM 2012 chemotherapy protocol was initiated. During induction chemotherapy, the patient developed dyspnoea and pulmonary haemorrhage. The child was transferred to intensive care unit and ATRA was added to the chemotherapy at a dose of 25 mg/m2/day. Coagulation tests improved 2 days after ATRA treatment and clinical findings improved 4 days later. On the 9th day of intensive care unit admission, the patient was transferred to inpatient ward and there was no bleeding during follow-up. **Discussion:** Haemorrhagic complications are frequent in APL patients and are one of the main causes of early death (5-9%) (1,2). Increased plasmin production (60-fold) due to excessive annexin-II receptor expression in promyeloblasts has been shown to cause fibrinolysis. It is thought that patients develop increased hyperfibrinolysis rather than consumption coagulopathy (2). ATRA is highly effective in bleeding control (3). **Conclusion:** Patients should be monitored with coagulation tests at regular intervals due to the high risk of bleeding. Undesirable haemorrhagic conditions may develop before and during treatment. ATRA can provide effective control in treatment.

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### Adult Hematology Abstract Categories

Chronic Leukemias
PP 07

## MULTI-TYROSINE KINASE INHIBITOR-ASSOCIATED APLASTIC ANEMIA AND A BRIEF LITERATURE REVIEW

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**Objective:** Chronic myeloid leukemia (CML) is a malignancy classified under the group of chronic myeloproliferative neoplasms. It is characterized by uncontrolled leukocytosis, bleeding, thrombosis, recurrent infections, and hepatosplenomegaly. With the introduction of imatinib in 2001, followed by the second- and third-generation tyrosine kinase inhibitors (TKIs), a new era in the treatment of CML began, as overall survival rates have since reached levels comparable to normal life expectancy. In this article, we review the first case of aplastic anemia that developed after bosutinib treatment, along with other cases of aplastic anemia reported in the literature following the use of TKIs. **Case Report:** A 57-year-old female was referred for leukocytosis identified during evaluation for fatigue, weakness, and early satiety. Initial lab results showed a WBC of $384 \times 10^9$/L, NEU of $246 \times 10^9$/L, Hb of 7.2 g/dL, and Plt of $281 \times 10^9$/L. Abdominal ultrasound revealed splenomegaly (23 cm), and peripheral blood smear suggested chronic myeloid leukemia (CML), leading to BCR-ABL transcript testing. Hydroxyurea was initiated while awaiting results. Two weeks later, the BCR-ABL transcript level was 49%, and imatinib 400 mg/day was started on December 15, 2022. The February 2023 earthquake disrupted the patient's imatinib use for three months. Upon return in May 2023, labs showed a WBC of $17 \times 10^9$/L, NEU of $14 \times 10^9$/L, Hb of 14.1 g/dL, Plt of $424 \times 10^9$/L, and BCR-ABL remained at 49%. Imatinib was resumed. In August 2023, BCR-ABL decreased to 41%. However, in October 2023, pancytopenia emerged, leading to imatinib discontinuation (WBC: $2.98 \times 10^9$/L, NEU: $0.5 \times 10^9$/L, Hb: 4.1 g/dL, Plt: $2 \times 10^9$/L). ABL mutation analysis showed no resistance mutations (Hemogram values at diagnosis and after treatment are shown in Figure 1). After two weeks without medication and no improvement in pancytopenia, bone marrow biopsy confirmed aplastic anemia (Figure 2A). Following ten weeks of recovery, normocellular marrow was observed (Figure 2B), and dasatinib 50 mg/day was started on February 1, 2024, later increased to 100 mg/day. Due to worsening cytopenias in late February, dasatinib was reduced and eventually discontinued in March. Bosutinib 500 mg/day was initiated in May, with BCR-ABL at 27.9%. As cytopenias progressed, bosutinib was reduced to 300 mg/day. Despite a BCR-ABL decrease to 8.63% in August, cytopenias persisted, and bosutinib was further

reduced 100 mg/day. The patient is currently being evaluated for allogeneic stem cell transplantation. **Methodology:** Until the 2000s, chronic myeloid leukemia (CML) was a fatal malignancy within the group of chronic myeloproliferative neoplasms. However, a significant breakthrough occurred following the approval of imatinib mesylate, the first tyrosine kinase inhibitor (TKI) for CML treatment, by the FDA in 2001 and the EMA in 2003. This was followed by the development of second-generation (dasatinib, nilotinib, bosutinib) and third-generation (ponatinib) TKIs, which greatly improved disease outcomes and significantly reduced TKI resistance. Common side effects of TKIs include pleural/pericardial effusion, pretibial edema, hyperglycemia, hyperlipidemia, liver dysfunction, diarrhea, and thrombosis, most of which can be managed by temporarily discontinuing the drug or reducing the dosage. Transient myelosuppression is also a frequently observed side effect of TKI therapy. However, prolonged aplastic anemia (AA) is a rare adverse effect secondary to TKIs. To date, cases of bone marrow aplasia associated with imatinib, dasatinib, and nilotinib have been reported in the literature, and the approaches to managing these cases are summarized in Table 1. Common management strategies include discontinuation of the drug, observation without medication, switching to another TKI, or performing allogeneic stem cell transplantation. Additional treatments such as cyclosporine, antithymocyte globulin (ATG), and filgrastim have also been employed. Unfortunately, despite various interventions, some patients have succumbed to septic mortality associated with prolonged neutropenia and intracranial hemorrhage linked to thrombocytopenia. The small number of cases makes it challenging to establish a standardized treatment approach. The mechanism of TKI-induced aplastic anemia (AA) remains unclear, but four potential pathophysiologies are considered: 1) acellularity in the hematopoietic system due to bone marrow infiltration by the CML clone [19], 2) blastic evolution during treatment [13], 3) suppression of hematopoietic stem cell proliferation through inhibition of kinases like c-kit, PDGFR, and SRY [8], and 4) toxic drug levels due to genetic polymorphisms in drug metabolism [20] **Results:** Studies have shown that higher doses of TKIs are associated with increased rates of myelosuppression [21]. Since routine monitoring of drug levels is not available in many healthcare facilities, using lower-than-standard TKI doses may be a viable alternative in cases of prolonged, severe cytopenias. In our patient, the progressive decline in BCR-ABL transcript levels suggests that the cause of AA is more likely due to nonspecific suppression of hematopoietic stem cells by TKIs rather than blastic evolution. Due to the unavailability of drug level testing at our center, we could not rule out bone marrow suppression related to drug toxicity. However, our patient tolerated bosutinib better, with the BCR-ABL transcript level dropping below 10% for the first time, distinguishing bosutinib from other TKIs. The milder cytopenic profile observed may be related to bosutinib's weaker inhibition of PDGFR and c-kit [22]. **Conclusion:** In cases of aplastic anemia following TKI therapy, various case-based treatment approaches exist, but no standardized method has been widely accepted. During the TKI era, allogeneic stem cell transplantation remains a necessary option for CML patients with AA. Asciminib, with its distinct mechanism of action, could be considered a treatment option in such cases, though no data currently exist in the literature. While the patient's BCR-ABL transcript level after bosutinib 100 mg/day is eagerly awaited, lower-dose bosutinib may present a viable alternative for this patient group.

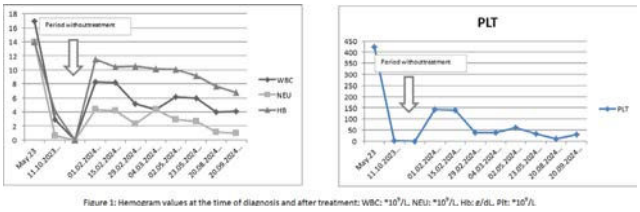


Figure 1: Hemogram values at the time of diagnosis and after treatment: WBC: *10³/L. NEU: *10³/L. Hb: g/dL. Plt: *10³/L

Figure 1

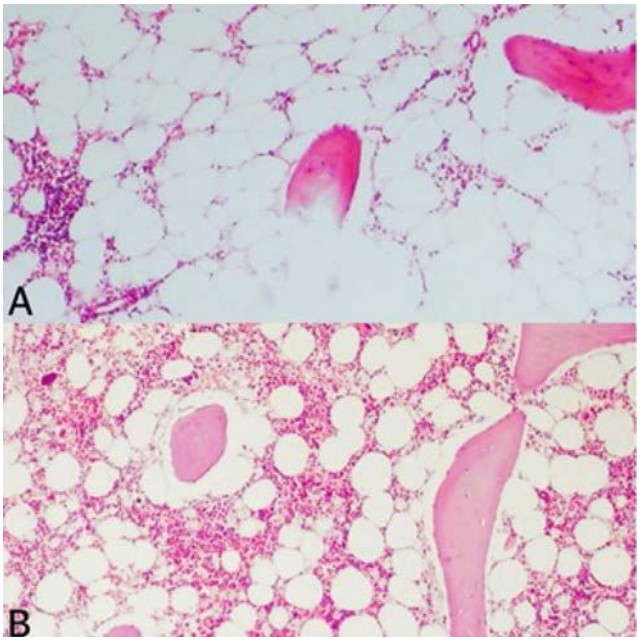


Figure 2: A) Bone marrow biopsiy demonstrating loss of cellularity following imatinib-associated pancytopenia. B) Bone marrow biopsy showing increased cellularity performed 10 weeks after discontinuation of imatinib.

Table 1: Cases of aplastic anemia secondary to tyrosine kinase inhibitors reported in the literature to date

| | Age/sex | Hematological parameters at starting treatment with TKI or diasnosis | BCR-ABL FISH levels | Type of TKI | Aplaziye kadar geçen tedavi süresi | Hematological parameters at aplasia | Duration of treatment before aplasia2 | Management of aplasia | Clinical situation when recovery from aplasia | References |
|---|---|---|---|---|---|---|---|---|---|---|
| Patient 1 | 46/m | N/A | BCR-ABL FISH: + Transcript levels: N/A | Imatinib | 128 days | Hb: 5-6 gr/dL, NEU 400*$10^9$ /L, Plt: 10-20000*$10^9$ /L | 222 days and ongoing | cessation of drug | optimal response | Chng WJ et al. (2) |
| Patient 2 | 72/m | N/A | BCR-ABL FISH: + Transcript levels: N/A | Imatinib | 3 years | WBC: 0.2 × 109 L, Hb: N/A, Plt: N/A | 1 month | cessation of drug, sisklosporin +ATG ve GCSF treatments were given | major molecular response | Hernández-Boluda JC et al (3) |
| Patient 3 | 47/f | WBC: 123*$10^9$/L (tanı anı) | BCR-ABL FISH: + Transcript levels: N/A | Imatinib | 3 years | WBC: 0.2 × $10^9$ L, Hb: 4,6 g/dl, Plt: 34*$10^9$/L | 1 month | IVIG and prednisolon treatments were given | recovery from aplasia, but BCR-ABL FISH: +41,4 postivei | LeMarbre G et al (4) |
| Patient 4 | 46/f | Hb: 10,2 gr/dL, WBC: 73*$10^9$/L Plt: 533*$10^9$/L (tanı anı, TKI başlangıç değeri belirtilmemiş | BCR-ABL FISH: + Transcript levels: N/A | Imatinib | 53 days | WBC: 0,2*$10^9$/L, Hb: 5 gr/dl, Plt: 17*$10^9$/L | 2 weeks, then died | cessation of drug, GCSF was given | died | Lokeshwar N et al (5) |
| Patient 5 | 51/m | WBC:56*$10^9$/L, Hb: N/A, plt: N/A | BCR-ABL FISH: + Transcript levels: N/A | Imatinib | 19 months | WBC: 1900*$10^9$/L, Hb: 7,3 gr/dl, Plt: 42*$10^9$/L | 35 days, then died | cessation of drug, GCSF was given | died | Khan KA (6) |
| Patient 6 | 54/f | WBC:130*$10^9$/L, Hb: 10,6 g/dl; Plt:212*$10^9$/L | BCR-ABL FISH: + Transcript levels: N/A | Imatinib | 6 months | WBC: 2.2*$10^9$ /dl, Hb: 5,4 g/dl, Plt: 32*$10^9$ /L | N/A | cessation of drug | BCR-ABL FISH: Positive | Srinivas U et al (7) |
| Patient 7 | 38/f | WBC: 122*$10^9$/L, Hb: 7,2 g/dl, Plt: 100*$10^9$/L | BCR-ABL FISH: + Transcript levels: N/A | Imatinib | 6 months | WBC: 1.9*$10^9$ /L, Hb: 5,3 g/dl, Plt: 17*$10^9$ | N/A | cessation of drug | BCR-ABL FISH: Positive | Srinivas U et al (7) |
| Patient 8 | 28/m | WBC: 135*$10^9$/L, Hb: 6,4 g/dl, Plt: 222*$10^9$/L | BCR-ABL FISH: + Transcript levels: N/A | Imatinib | 6 months | WBC: 1.58*$10^9$ /L, Hb: 4,8 g/dl, Plt: 12*$10^9$ /L | N/A | cessation of drug | BCR-ABL FISH: Positive | Srinivas U et al (7) |
| Patient 9 | 15/m | WBC: 157*$10^9$ /L, Hb: 6,6 g/dl, Plt: 268*$10^9$ /L | BCR-ABL FISH: + Transcript levels: N/A | Imatinib | 3 months | WBC: 1.3*$10^9$ /L, Hb: 5,5 g/dl, Plt: 23*$10^9$ /L | N/A | cessation of drug | BCR-ABL FISH: Positive | Srinivas U et al (7) |
| Patient 10 | 50/m | WBC: 123*$10^9$ /dL, Hb: 8,6 g/dl, Plt: 168*$10^9$ /L PB-blasts:32% | BCR-ABL FISH: + Transcript levels: N/A | Imatinib | 3 months | WBC: 2.5*$10^9$ /L, Hb: 6,8 g/dl, Plt: 40*$10^9$ /L | N/A | cessation of drug | BCR-ABL FISH: Positive | Srinivas U et al (7) |
| Patient 11 | 61/f | N/A | BCR-ABL FISH: + Transcript levels: N/A | Imatinib | 3,5 months | N/A | N/A | patient expired due to intracranial haemorrhage | N/A | Madabhavi I (8) |
| Patient 12 | 65/f | N/A | BCR-ABL FISH: + Transcript levels: N/A | Imatinib | 4 months | N/A | 10 months | cessation of drug, hydroxiurea was given | BCR-ABL FISH: Positive | Madabhavi I (8) |
| Patient 13 | 63/f | N/A | BCR-ABL FISH: + Transcript levels: N/A | Imatinib | 2 months | N/A | 14 months | cessation of drug, hydroxiurea was given | BCR-ABL FISH: Positive | Madabhavi I (8) |
| Patient 14 | 70/f | N/A | BCR-ABL FISH: + Transcript levels: N/A | Imatinib | 1,5 months | N/A | 9 months | cessation of drug, hydroxiurea was given | BCR-ABL FISH: Positive | Madabhavi I (8) |
| Patient 15 | 74/m | N/A | BCR-ABL FISH: + Transcript levels: N/A | Imatinib | 6 months | N/A | N/A | patient was succumbing due to septicemia | N/A | Madabhavi I (8) |
| Patient 16 | 68/f | N/A | BCR-ABL FISH: + Transcript levels: N/A | Imatinib | 6 months | N/A | 5 months | cessation of drug, hydroxiurea was given | BCR-ABL FISH: Positive | Madabhavi I (8) |
| Patient 17 | 76/f | N/A | BCR-ABL FISH: + Transcript levels: N/A | Imatinib | 4 months | N/A | 7 months | cessation of drug, hydroxiurea was given | BCR-ABL FISH: Positive | Madabhavi I (8) |
| Patient 18 | 34/m | N/A | BCR-ABL FISH: + Transcript levels: N/A | Imatinib | 2,5 months | N/A | 15 months | cessation of drug, hydroxiurea was given | BCR-ABL FISH: Positive | Madabhavi I (8) |
| Patient 19 | 42/m | N/A | BCR-ABL FISH: + Transcript levels: N/A | Imatinib | 2 months | N/A | 12 months | cessation of drug, hydroxiurea was given | BCR-ABL FISH: Positive | Madabhavi I (8) |
| Patient 20 | 55/f | N/A | BCR-ABL FISH: + Transcript levels: N/A | Imatinib | 3 months | N/A | 11 months | cessation of drug, hydroxiurea was given | BCR-ABL FISH: Positive | Madabhavi I (8) |
| Patient 21 | 32/m | N/A | BCR-ABL FISH: + Transcript levels: N/A | Imatinib | 2,5 months | N/A | 11 months | cessation of drug, hydroxiurea was given | BCR-ABL FISH: Positive | Madabhavi I (8) |
| Patient 22 | 49/m | WBC: 130*$10^9$ /L, Hb: 10,4 gr/dl, Plt: 781*$10^9$/L | BCR-ABL FISH: + Transcript levels: N/A | Nilotinib (switched from 7 months dasatinib treatment) | 19 months | WBC: 2,4*$10^9$ /L, Hb: 9,8 gr/dl Plt: 16*$10^9$ /L | 2 months | cessation of drug, 2 months later started nilotinib again due to BCR-ABL FISH postivity | FISH for BCR-ABL negative during aplasia, positive after 2 months later | Prodduturi P (9) |