All-trans-retinoic-acid and arsenic trioxide induced remission in promyelocytic blast crisis

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20% constituting acute lymphoid leukemia (ALL) [2]. CML-BC is characterized by acute leukemic transformation of BCR-ABL mutant cells. The majority of cases (80%) are acute myeloid leukemia (AML) with blast crisis (BC). Since the development of tyrosine kinase inhibitors (TKIs), the progression from CML-CP to AP or BC has been markedly reduced from 20% per year to 1.5% per year [1]. CML-BC is defined by karyotyping, fluorescence in situ hybridization, and quantitative real-time polymerase chain reaction. Promyelocytic blast crisis of CML is a rare event with historically poor outcomes. Treatment of our patient with all-trans-retinoic acid (ATRA) and arsenic trioxide (ATO) resulted in complete morphologic remission. We review here the relevant literature of promyelocytic blast crisis and highlight the potential of ATRA/ATO as first line management.

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ABSTRACT

A 78-year-old male with chronic myeloid leukemia (CML) treated for seven years with dasatinib developed an acute promyelocytic leukemia complicated by disseminated intravascular coagulopathy. A promyelocytic blast crisis was diagnosed by demonstrating co-expression of chimeric BCL/ABL and PML/RARA translocations by karyotyping, fluorescence in situ hybridization, and quantitative real-time polymerase chain reaction. Promyelocytic blast crisis of CML is a rare event with historically poor outcomes. Treatment of our patient with ATRA-ATO in our patient and review the current literature.

1. Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm originating from a balanced translocation of t(9;22)(q34;q11.2) that results in BCR-ABL fusion gene. CML classically evolves through three phases: chronic phase (CP), accelerated phase (AP), and the terminal blast crisis (BC). Since the development of tyrosine kinase inhibitors (TKIs), the progression from CML-CP to AP or BC has been markedly reduced from 20% per year to 1−1.5% per year [1]. CML-BC is characterized by acute leukemic transformation of BCR-ABL mutant cells. The majority of cases (80%) are acute myeloid leukemia (AML) with 20% constituting acute lymphoid leukemia (ALL) [2]. CML-BC management is based on the blast lineage (AML vs ALL) and prior therapy [2]. Generally, a TKI is given in combination with intensive chemotherapy for treatment of AML or ALL CML-BC followed by allogeneic stem-cell transplant if possible in complete remission (CR).

An acute promyelocytic CML-BC is exceedingly rare with no consensus on treatment. Similar to de novo acute promyelocytic leukemia (APL), promyelocytic blast crisis is distinguished by a balanced translocation between chromosomes 15 and 17, t(15;17)(q22;q21), resulting in the PML-RARA fusion gene. This aberrant retinoid receptor blocks myeloid differentiation and leads to accumulation of immature promyelocytes [3]. Upfront treatment of de novo APL with all-trans-retinoic-acid (ATRA) induces differentiation of leukemic promyelocytes into mature granulocytes, and when combined with arsenic trioxide (ATO), results in complete remission rates over 90% [4]. ATRA-ATO has less hematologic toxicities and significantly improved survival and relapse risk when compared to ATRA with chemotherapy in low-intermediate risk patients (defined by WBC less than 10 × 10⁹/L on presentation) [5,6]. The combination of ATRA-ATO acts synergistically with more pronounced reductions of PML-RARA transcripts, expedited achievement of CR, and decreased relapse rates compared to ATRA or ATO alone [7]. Here, we describe the treatment of promyelocytic BC with ATRA-ATO in our patient and review the current literature.

2. Case presentation

A 78-year-old Hispanic man with history of Alzheimer’s disease, chronic obstructive pulmonary disease, type 2 diabetes mellitus, and hypertension was diagnosed with CML in 2010 with Sokal score of 0.88 (intermediate-risk). He began treatment with imatinib 400 mg daily but approximately six months later it was switched to dasatinib 100 mg daily due to development of dizziness and fatigue. He was intermittently nonadherent with medication and clinic appointments and was lost to follow-up on multiple occasions. In mid-2016, due to development of anemia with hemoglobin (Hb) of 8.9 mg/dL, dasatinib was held and then restarted at a lower dose of 80 mg daily. Six months later, the hemoglobin had improved to 11.9 mg/dL along with hyperesthesia with CML-BC followed by allogeneic stem-cell transplant if possible in complete remission (CR).
an otherwise normal complete blood count (CBC) and differential.

Three months later (seven years after initial diagnosis) he presented to clinic for a routine follow-up. His white blood cell count (WBC) was 1.03 × 10^9/L, Hb 7.8 g/dL, and platelets (Plt) 6 × 10^9/L with 2% blasts and 18% promyelocytes. He was found to have a prothrombin time (PT) of 3.4 s [9.4–12.5 s], activated partial thromboplastin time (aPTT) of 30.5 s [25.1–36.5 s], D-dimer of 10,107 ng/mL [0–232 ng/mL], fibrinogen of 189 mg/dL [200–393 mg/dL], and fibrin monomers and > 80 mg/L fibrin split products were detected. Peripheral blood smear showed abnormal promyelocytes that were strongly positive for myeloperoxidase. Bone marrow biopsy and aspirate revealed 80% cellularity, 88% promyelocytes, 2% blasts, and was notable for replacement of normal marrow elements with sheets of promyelocytes (Fig. 1a). Unstimulated peripheral blood culture revealed a male karyotype with a reciprocal translocation between the long arms of chromosomes 9 and 22–t(9;22)(q34;q11.2) and a reciprocal translocation between the long arms of chromosomes 15 and 17–t(15;17)(q24;q21) in all cells analyzed (Fig. 1b). BCR-ABL1 gene fusions, which detect the t(9;22)(q34;q11.2) were observed in 165 of 200 interphase nuclei using all cells analyzed (Fig. 1b). Conventional cytogenetics demonstrated an abnormal karyotype of 46, XY, t(9;22)(q34;11.2), t(15;17)(q24;q21). Fluorescent in situ hybridization (FISH) confirmed the presence of (C) t(9;22)(q34;q11.2)/BCR-ABL, and (D) t(15;17)(q24;q21)/PML-RARA fusions.

3. Discussion

Promyelocytic BC is a rare entity with only 24 cases reported in the English literature since 1980 (see supplement). Based on our patient’s presenting counts (WBC 1.03 × 10^9/L and Plt 6 × 10^9/L), his promyelocytic CML-BC would be categorized as an intermediate-risk APL as per Sanz scoring system [8]. He was therefore treated with ATRA-ATO which constitutes our institute’s standard-of-care management for this APL subset. Dasatinib was held secondary to pancytopenia. He tolerated ATRA-ATO therapy well with clearing of peripheral blood blasts and promyelocytes within 20 days (Fig. 2c).

Although there was concern for DIC given the consumptive coagulopathy seen on admission labs, the patient did not experience significant bleeding or signs of organ failure. ATRA-ATO therapy improved the coagulopathy panel within one week (Fig. 2a). A restaging bone marrow biopsy and aspirate on day 28 showed that the patient achieved a morphological CR with incomplete blood count recovery (CRi). The aspirate continued to show trilineage hypoplasia, and less than 1% blasts. Molecular analysis revealed reduced BCR-ABL p210 and PML-RARA transcript levels to 17.225 IS-NCN and 1.28 IS-NCN respectively (Fig. 2c). FISH analysis from marrow aspirate showed PML-RARA and BCR-ABL fusion genes in 18/200 and 21/200 cells respectively. Karyotyping showed 1/20 cells with 46,XY,t(9;22)(q34;q11.2). Shortly thereafter, the patient’s family decided against pursuing additional treatment due to advanced dementia and all active therapy was withdrawn after 35 days of therapy. The patient was discharged to a long-term care facility and died two months after initiating treatment for BC.
daunorubicin, cytarabine, and thioguanine (DAT) chemotherapy in the early 1980s, to ATRA monotherapy or mitoxantrone in combination with etoposide or cytarabine in the 1990s, to ATRA with different chemotherapy regimens with or without a TKI in the 2000s (Supplemental Information). In general, the outcomes of promyelocytic BC reported in the literature are far inferior to those with de novo APL patients [5]. Most reported cases were categorized as high-risk by Sanz scoring system. Of the 24 cases in the literature, 16 (67%) died of their disease, with 14 dying within 6 months of BC diagnosis. Because ATRA was introduced for APL in the late 1980s, merely 8 of 19 cases included ATRA as part of the treatment regimen, with all of them achieving CR. Of those 19 cases, only two would have been considered intermediate- and one low-risk per Sanz scoring [9–11]. The cases presented by Oku et al. and Chung et al. were treated with ATRA in combination with induction chemotherapy or TKI inhibitor respectively. The low-risk patient presented by Oku et al. did well with survival reported up to two years after the blast crisis. The intermediate-risk patient presented by Chung et al. survived for only two months, possibly due to lack of ATO as part of the therapy that is now standard for de novo intermediate-risk APL patients. The third intermediate risk patient reported by Cai et al. was one of only three patients (including our patient) to have received ATRA-ATO for promyelocytic blast crisis. This patient did not achieve CR and had ATRA-ATO discontinued due to development of an arrhythmia [9]. The other patient who was treated with ATRA-ATO achieved CR but died of multisystem organ failure within two months of BC diagnosis [12]. Closer investigation revealed that this second patient presented with an initial WBC of $17 \times 10^9/L$, and per the Sanz system, would have been considered a high-risk APL. Triple therapy with ATRA-ATO-anthracycline chemotherapy for high-risk patients is currently under investigation and preliminary studies have been encouraging [4,13]. Given our success in inducing remission with ATRA-ATO in our patient with minimal side effects, there is hope that ATRA-ATO combination therapies will continue to gain traction in managing these challenging cases.

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Conflict of interest

The authors have no relevant conflicts of interest to report.

Supplementary materials

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