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AML with BCR-ABL1 Fusion treated with Imatinib, a Hypomethylating Agent and Venetoclax

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ABSTRACT

A patient with history of myelodysplastic syndrome (MDS) presented with multifocal pneumonia and was found to have Philadelphia chromosomepositive (Ph+) acute myeloid leukemia (AML). A tyrosine kinase inhibitor (TKI) was added to decitabine and venetoclax combination, providing a molecular and cytogenetic complete response despite additional cytogenetic and molecular abnormalities. She remains in remission after eleven cycles of treatment. Our report describes the tolerability and success of a triplet regimen that incorporates a TKI to a backbone of decitabine and venetoclax in a patient with high-risk disease and with significant comorbidities.

1. Introduction

The Philadelphia chromosome (Ph+) represents a reciprocal translocation between chromosome 9q34 (Abelson murine leukemia gene, *ABL1*) and 22q11 (breakpoint cluster gene, *BCR*) resulting in the formation of the *BCR-ABL1* fusion gene and development of the constitutively active BCR-ABL tyrosine kinase. Depending on the breakpoints in the BCR gene, three different *BCR-ABL1* oncogenic proteins are typically produced, p190 (e1a2), p210 (e13a2 or e14a2), and p230 (e19a2) [1]; the numerical value represents the size of the hybrid protein in kDa. The *BCR-ABL1* fusion is classically associated with chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), and mixed-phenotype acute leukemia (MPAL) [2,3]. In most patients diagnosed with CML, the e13a2 or e14a2 *BCR-ABL1* fusion products are identified. Less frequently, atypical BCR-ABL transcripts with e1a2 or e19a2 junctions are identified. The presence of a *BCR-ABL1* fusion in *de novo* acute myeloid leukemia (AML) is rare, with an incidence of 0.5%−3% of newly diagnosed cases [4–6].

AML with *BCR-ABL1* has been introduced as a provisional entity in the 2016 revised World Health Organization (WHO) classification [2], and is considered an aggressive disease. It is associated with an adverse prognosis [7], and typically poorly responds to conventional AML therapy or single agent *ABL* tyrosine kinase inhibitor (TKI).

We herein report, to our knowledge, the first case of AML carrying a *BCR-ABL1* transcript p190 (e1a2) who was successfully treated with a triplet regimen consisting of decitabine, venetoclax, and imatinib, followed by a brief literature review.

2. Case report

A 71-year-old woman with history of breast cancer diagnosed at age 45, was initially treated with lumpectomy and axillary lymph node dissection and declined undergoing adjuvant chemotherapy, agreeing to adjuvant radiotherapy and to five-year course of tamoxifen. At age 67 she was found to have bilateral disease recurrence, ER/PR positive and HER2 negative, low risk score (Oncotype Dx score 12), and underwent bilateral total mastectomy followed by reconstruction and anastrozole therapy. At age 70, while still on anastrozole, she was diagnosed with high-grade myelodysplastic syndrome with excessive blasts (MDS-EB2) and declined chemotherapy management. Three months later she presented to the emergency department with fever and dyspnea. On admission, her white blood cell (WBC) count was 8000/μL, absolute neutrophil count (ANC) 5200/μL, and no evidence of basophilia. Chest imaging showed bilateral lung infiltrates prompting treatment for a suspected multifocal pneumonia. On physical exam, there was no evidence of splenomegaly.

Her most recent bone marrow aspirate and biopsy (BM bx), six weeks prior to admission, had revealed a MDS-EB2, with 15% blasts (Fig. 1)

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positive for HLA-DR, CD45 (dim), CD117, CD34, CD11b, CD56 (partial), cMPO, and a complex karyotype with autosomal monosomies and structural abnormalities (47–53,XX,add(2)(q33),-3,del(5)(q22q35),der(6)t(6;13)(p23;q12),add(7)(q22),+8,-13,der(14)t(3;14)(q21;q22),-18,+21,+21,+22,+0–2r,+2–3mar[*cp*16]/46,XX [4]). A repeat BM bx showed AML with myelodysplastic changes, and immunophenotypic characterization of the blast population revealed co-expression of CD34, CD33, CD11b, CD13, and CD38, and negative for CD117 and HLA-DR. In addition, a significant population of monocytes (CD45 moderate region) with atypical immunophenotype including co-expression of CD64 (weak), CD14 (partial), CD15, CD11b, CD33, and CD16, and negative for CD4 and CD56 was identified. In view of her good performance status (ECOG PS 0–1), significant co-morbidities (coronary artery disease, diabetes mellitus, hypertension) and recently diagnosed pneumonia, she was started on decitabine 20 mg/m^2 for five days and venetoclax 100 mg daily (reduced dose due to concomitant posaconazole treatment for invasive fungal infection prophylaxis). Subsequently, fluorescence in-situ hybridization (FISH) study identified a *BCR-ABL1* fusion (35.8% of nuclei). The reverse transcriptase-polymerase chain reaction (RT-PCR) analysis showed a minor (p190, e1a2) *BCR-ABL1* fusion mRNA transcript (Fig. 2). Karyotyping revealed a complex clone with monosomies and multiple structural abnormalities including 5q deletion and 7q deletion in 16 of 20 metaphases analyzed. The next-generation sequencing (NGS) revealed mutations in TP53 (variant allele 35%) and ASXL1 (variant allele 49%) genes. On day 20 of induction chemotherapy, venetoclax was held due to febrile neutropenia complicated by acute renal insufficiency due to interstitial nephritis secondary to AML infiltration, evidenced on renal biopsy, and successfully treated with high-dose corticosteroids.

The second cycle of decitabine and venetoclax was started with a ten-day delay due to the complications developed during the first cycle, despite persistent circulating blasts. Imatinib 100 mg daily (dose adjusted to her renal function) was added but temporarily held after 24 days due to worsening renal function attributed to a rapid taper of the corticosteroid therapy, attempted in view of her diagnosis of diabetes, and successfully resumed and with a subsequent slow tapering. On day 35 of cycle 2, a BM bx showed molecular complete remission (mCR) with undetectable *BCR-ABL1* fusion and a normal karyotype. Imatinib was restarted on day 4 of cycle 3. A repeat BM bx at the end of cycle 7 showed persistent mCR. She has currently completed eleven cycles of decitabine 20 mg/m^2 for five days in a 35-day cycle, venetoclax 50 mg daily 21 out of 28-day cycle (dose adjusted due to drug interaction with posaconazole and severe neutropenia), and imatinib 100 mg daily continuously.

3. Discussion

Ph+ AML is a rare subtype of *de novo* AML that was introduced in the 2016 revised WHO classification [2], and the 2017 European LeukemiaNet risk stratification allocates Ph+ AML to the adverse risk group [7]. Different breakpoints in the *BCR* or *ABL1* genes, produce *BCR-ABL1* fusion proteins with different molecular weight including p190 and p210, which in AML are the most commonly observed *BCR-ABL* proteins, with nearly equal distribution. In view of the rarity of the disease, a standard treatment plan for *de novo* Ph+ AML has not been established, especially in elderly patients with significant co-morbidities.

The differentiation between *de novo* Ph+ AML and CML with myeloid blast phase (CML-BP) is an important diagnostic consideration that carries therapeutic implications. CML-BP usually presents with splenomegaly and basophilia in the blood and/or bone marrow, both uncommon in *de novo* Ph+ AML [6]. The Philadelphia chromosome is usually identified in 100% of the clone metaphases, however not observed in our patient. Moreover, the presence of additional cytogenetic abnormalities, including the MDS related changes identified in our patient, supports the

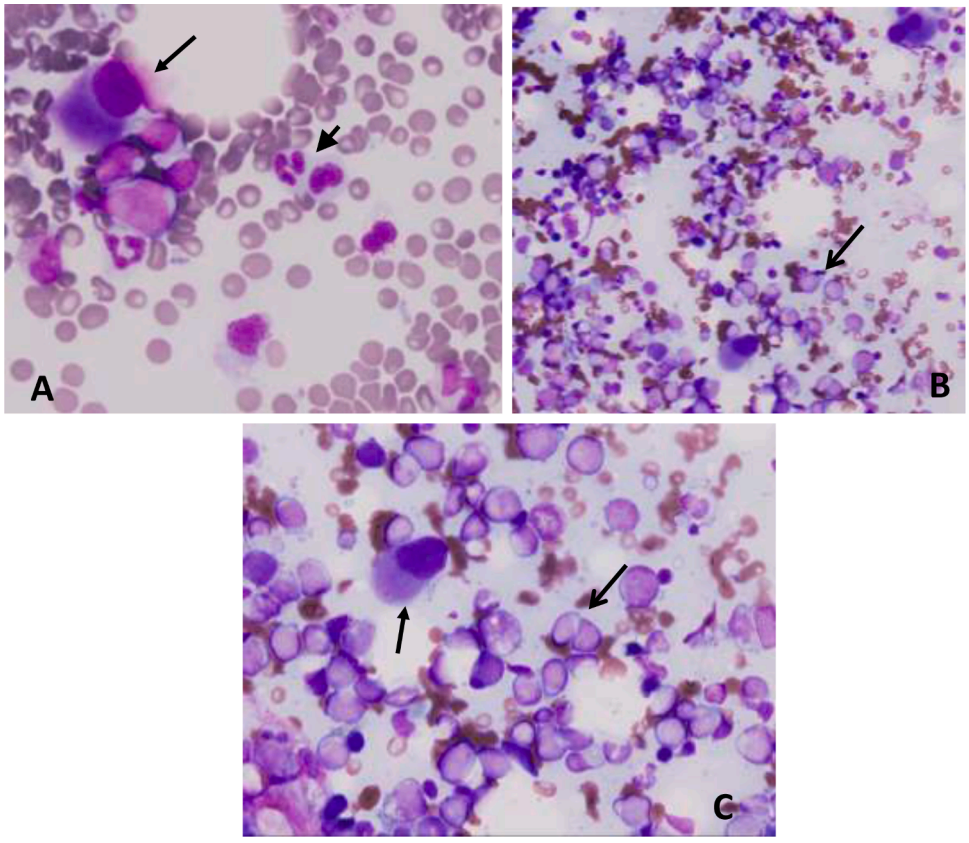

Fig. 1. Wright-Giemsa-stained bone marrow aspirate smears. Small hypolobate megakaryocyte (arrow), hypogranular neutrophils (arrowhead), and numerous immature mononuclear cells morphologically consistent with blasts (open arrow) (Panel A, 400x, B, 200x, and C, 400x).

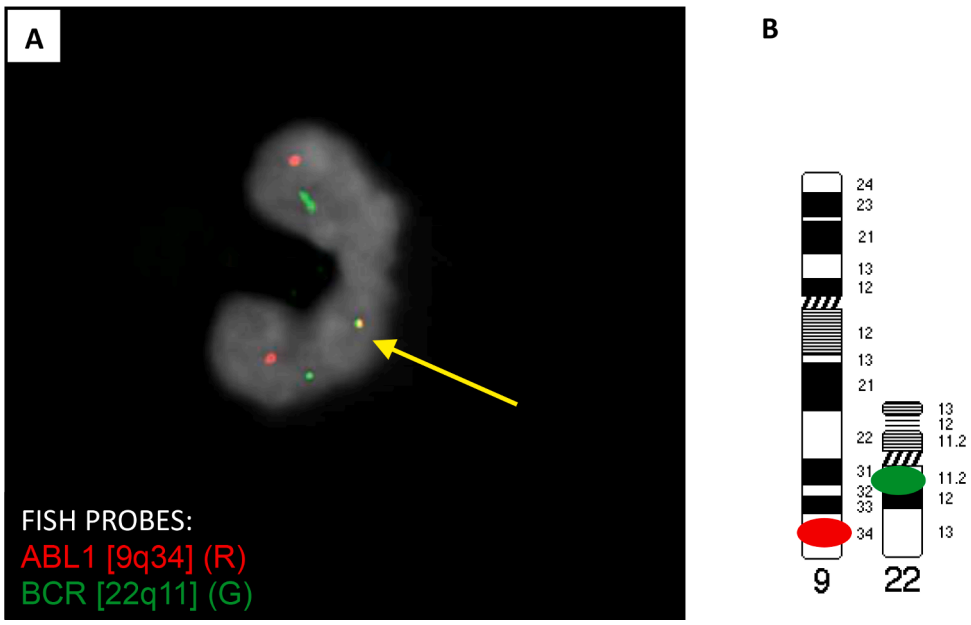

Fig. 2. A. Fluorescence in-situ hybridization shows *BCR/ABL1* fusion signal (arrow). **B**. Chromosomes 9 (ABL1) and 22 (BCR) with break-points depicted (9q34.1 and 22q11.2, respectively).

diagnosis of a *de novo* Ph+ AML rather than a CML-BP.

Ph+ AML is associated with limited response to standard chemotherapy and to single agent TKIs, and additional chromosomal alterations, for instance 5q deletion, predict a worse prognosis [6]. Elderly patients with co-morbidities are typically not eligible to standard intensive chemotherapy nor to allogeneic hematopoietic cellular transplantation (allo-HCT). On the other hand, TKIs are effectively used as salvage and bridging therapy to allo-HCT, as well as maintenance therapy post allo-HCT, improving outcomes in Ph+ AML [8].

The combination of venetoclax and a hypomethylating agent (HMA) has emerged as a new standard for elderly and/or unfit patients diagnosed with AML in view of improved response rates and comparable toxicity when compared to HMA alone [9]. Furthermore, BCL2 is upregulated by *BCR-ABL1* signaling, and venetoclax has shown pre-clinical activity against TKI-resistant CML cells as well as synergism with TKIs in eradicating leukemic stem cells in advanced CML. TKIs targeting the *BCR-ABL1* fusion gene are the standard of care as single agents in the management of CML, and in combination with chemotherapy in Ph+ ALL. Venetoclax plus TKI (ponatinib or dasatinib) -based regimens with decitabine or intensive chemotherapy showed favorable outcomes and hematologic responses in relapsed/refractory Ph+ AML in a retrospective study in which seven patients were treated [10], prompting its investigation in an ongoing phase II trial (NCT04188405). TKIs were also reported to provide molecular response in Ph+ AML carrying rare BCR-ABL1 transcripts, such as the e1a3 variant, and few cases of TKI monotherapy have provided durable molecular remissions [5,11].

In community-based practices it is common to obtain karyotyping, FISH studies, and NGS analyses as send-out testing to reference laboratories. Typical turnaround time for their results is 10 to 21 days, sometimes longer due to the negative impact of the COVID-19 pandemic, mainly due to limited staff availability. Currently, elderly patients with significant co-morbidities diagnosed with AML are preferably treated with minimal delays with venetoclax and an HMA. Once additional test results are available, therapy is adjusted accordingly, in our case by the addition of imatinib, its dose adjusted to patient's renal function at the time and to interactions with venetoclax. The decision to proceed with triplet therapy is supported by reports of different safe and effective combinations in the management of acute leukemias, including AML [10]. Additionally, there is evidence that the outcomes of Ph+ AML depend on a broad cytogenetic and/or molecular background control rather than limited to the *BCR-ABL* fusion itself. It further supports the use of a triplet therapy that does not solely targets the *BCR-ABL1* fusion. Our patient has achieved a mCR while receiving decitabine, venetoclax and imatinib. This observation, in addition to other published studies, adds to the evidence of the therapeutic potential of addition of a TKI to chemotherapy in AML with *BCR-ABL1* fusion.

4. Conclusion

AML with *BCR-ABL1* fusion is a rare entity associated with adverse prognosis given its suboptimal response to conventional AML therapy. Karyotyping, FISH analysis, and NGS studies, are important in characterizing the disease and to help guide therapeutic decisions. It is prudent to take into consideration not only the practice set-up (community-based versus academic centers) which frequently impacts the turn-around-time of various specialized tests that are needed for therapeutic decisions, but also drug interactions that might necessitate dosage adjustments. This is, to our knowledge, the first case of an AML carrying a *BCR-ABL1* transcript p190 (e1a2) who was successfully treated with a triple regimen consisting of decitabine, venetoclax, and imatinib. Less intense chemotherapy that allows the incorporation of additional targeted agents such as TKIs should be considered. In view of the uncertainty of optimal and standard treatment for this disease entity, further studies, particularly large cohort studies and well-designed prospective clinical trials, are warranted in order to demonstrate that venetoclax plus a HMA could serve as a mainstay therapy to which additional agents, such as TKIs, can be safely and effectively added.

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