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Myelodysplastic Phase During a Complete Course of Polycythemia Vera: Confirming Azacytidine Effectiveness on Myelodysplastic but not on Myeloproliferative Clone

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Abstract

This report describes a patient with polycythemia vera harboring JAK2^{V617F} mutation, whose condition progressed to myelodysplastic syndrome after 15 years. Several months after initiation of the hypomethylating agent azacytidine, the bone marrow was reset in a polycythemia vera pattern, thus displaying the re-occurrence of neoplastic stem cell with JAK2^{V617F}. Interestingly, a subsequent bone marrow reassessment showed an evolution to myelofibrosis: this evidence could be explained through the ability of azacytidine to manage the myelodysplastic clone in the bone marrow, thereby allowing the natural course of the myeloproliferative disorder.

Keywords: Polycythemia vera; Azacytidine; Myelodysplastic syndrome; MDS-EB-2; Myelofibrosis; JAK2^{V617F}

Introduction

Polycythemia Vera (PV) is a Philadelphia-negative chronic myeloproliferative neoplasm (Plh- MPN), characterized by erythrocytosis, often leukocytosis and/or thrombocytosis and low Erythropoietin (EPO) serum levels.

The incidence rate is 0.7-2.6 cases per 100,000 people, mainly affecting subjects older than 60 years. Diagnostic criteria were revised in 2016 according to the WHO classification: a combination of clinical, morphological, laboratory and molecular features have since been required to fulfil all criteria [1,2]. The Bone Marrow (BM) typically exhibits trilinear hyperplasia. The hallmark mutation $JAK2^{V617F}$ is detectable in 95% of cases [3].

Myelodysplastic Syndromes (MDS) comprise a group of myeloid neoplasms occurring *de novo* or after exposure to DNA-damaging agents. Moreover, aside from therapy, they can arise as a result of MPN progression [4]. The median age at diagnosis is 70 years and there are approximately 20-50 cases per 100,000 individuals. BM dysplasia plays a key role in the diagnosis, while cytogenetic abnormalities are crucial for risk stratification, according to the revised International Prognostic Scoring System (IPSS-R) [5]. Peripheral blood usually shows cytopenia. The classification of MDSs was updated by the WHO in 2016 [6,7].

Myelofibrosis (MF) is a rare Plh- MPN. It can arise *de novo* (primary myelofibrosis, PMF) or as fibrotic evolution in patients with previous diagnosis of polycythemia vera (post-PV MF – PPV MF) or essential thrombocythemia (post-ET MF – PET MF) [4,8]. Genetic mutations are detected in 90% of MF patients: these can be driver mutations ($JAK2^{V617F}$, CALR or MPL), disease-initiating mutations (e.g. TET-2, DNMT3A) or disease-progression mutations (ASXL2, SRSF2) [9,10].

Symptoms are often unclear and not specific: fatigue is the most common report from patients; pruritus, weight loss, fever and night sweats (last three known as “B symptoms”) can be present. Anemia and massive splenomegaly are typical in the advanced stages [11]. Diagnostic criteria for MF are reported in the 2016 WHO classification for myeloproliferative neoplasms [4].
This report describes the story of a patient who experienced an entire course of PV, with a MDS interlude and final evolution to PPV-MF.

Case Presentation

The patient is a 77-year-old Caucasian female with a history of headaches and weight loss, when she had been diagnosed with PV in 2003. Laboratory data revealed Hb: 17,3 g/dl; Hct: 54%; RBC: 6.58 X 10^{12}/L; WBC: 11.5 X 10^9/L with N: 7.92 X 10^9/L; PLT 476 X 10^9/L. She was a smoker, reported on-treatment-hypertension and no drug allergies. The following data were recorded: hypercellular BM (erythroblasts 45%, myeloblasts 50%, plasma cells 2%, lymphocytes 3%); extremely low serum Erythropoietin (EPO) levels (0.9 mUI/mL - reference value 3,3-16,6 mUI/mL); BCR-ABL rearrangement was absent and cytogenetic profile was normal; there was evidence of spontaneous erythroid colony formation (EEC) and a high red cell mass (RCM) (39 mL/Kg - reference value 25-30 mL/Kg). These data were consistent with a PV diagnosis. After six months of phlebotomy approach, a regimen of daily aspirin (100 mg) and subcutaneous interferon α-2b (IFNα-2b - 1.5 M UI, three times a week) was instituted.
In 2007, she was hospitalized with acute coronary syndrome. Following admission, IFNα-2b therapy was switched to hydroxyurea (HU - 2 tablets per day, five days a week). In 2009, a $JAK2^{V617F}$ mutation was detected with an allele burden of 32,6%.

The patient's hematological condition was stable until February 2018, when a complete blood count (CBC) showed Hb: 7.2 g/dL, WBC: 2.02 X 10^9/L, PLT:192 X 10^9/L and serum LDH levels of 836 UI/L. The patient was hospitalized with suspect leukemic transformation. She underwent a single-unit blood transfusion. Molecular analysis of FLT3-ITD, FLT3-D835, NPM1 mutations, BCR-ABL and MLL rearrangement, inv(16) CBFB-MYH11, t(15;17) (q24;q21) PML-RARα fusion genes and t(8;21), did not show any abnormalities. Importantly, BM aspiration revealed hypocellularity with trilinear dysplasia (17% myeloid blast cells) and myeloid immunophenotype (CD3: 2%; CD19: 2%; HLA-Dr: 75%; CD56: 2%; CD38: 77%; CD7: 1%;

CD45: 89%; CD14: 1%; CD33: 34%; CD13: 72%; CD34: 73%; CD117: 35%). A BM biopsy was not performed. A diagnosis of intermediate to high risk (IPSS-R score of 4.5) refractory anemia with excess blasts type 2 (MDS-RAEB-2), was made [7]. It was worth noting that the IPSS-R score was estimated without the cytogenetic profile, due to a lack of metaphases in the BM aspirate. She was discharged with an aspirin (100 mg od) and epoetin alfa (40.000 UI sc, twice a week) therapy.

In April 2018, the Food and Drug Administration and European Agency for the Evaluation of Medicinal Products Azacytidine (AZA) schedule was started (75 mg/m^2/d for seven days, every 28 days), since the patient was not eligible for Hematopoietic Stem Cell Transplantation (HSCT). Six months later (between VII-VIII AZA cycles), she was readmitted to the emergency department with a hypertensive crisis (220/110 mmHg), vomiting, dizziness and a mild headache. Laboratory analysis was normal, apart from a significant increase of LDH serum levels (1813 UI/L) and severe thrombocytosis (1067 X 10^9/L). Remarkably, CT imaging showed a mild splenomegaly, which had never emerged before.

The latter event and the CBC curve after AZA therapy (Figure 1), raised a suspicion of MPN recurrence. In March 2019, the patient was reassessed by studying cytogenetic and the molecular markers of acute myeloid leukemia (AML), BM aspiration, BM biopsy, Prussian blue Perls'staining and the $JAK2^{V617F}$ mutation allele burden. AML markers showed a normal profile; $JAK2^{V617F}$ mutation was confirmed with a 34,2% allele burden; surprisingly, the BM biopsy revealed a 40% cellularity, trilineage hyperplasia with enhanced megakaryopoiesis and grade 1 reticulin fibrosis; no ring sideroblasts were detected. Cytogenetic profile was inconclusive due to the lack of metaphases. These findings confirmed PV recurrence [4].

The patient's conditions were stable until July 2020 (XXVII AZA cycle), when she was readmitted because of severe anemia (Hb: 7.4 g/dL) and leukopenia (WBC: 1.64 X 10^9/L). During the hospital stay, she was managed with blood transfusion (2 units) and supportive care. The AML transformation panel resulted negative. BM aspiration was not diagnostic because of inadequate material; the cytogenetic profile detected a 20q deletion. Unexpectedly, the BM biopsy (September 2020) showed a grade II/III fibrosis and 30% cellularity with reduced granulopoiesis, erythropoiesis on different maturation stages, diffused and dystrophic megakaryopoiesis and intravascular hematopoiesis. These findings, together with the occurrence of a new palpable splenomegaly, were consistent with post-PV myelofibrosis (PPV MF) [8].
CBC trend is illustrated in Figure 1.

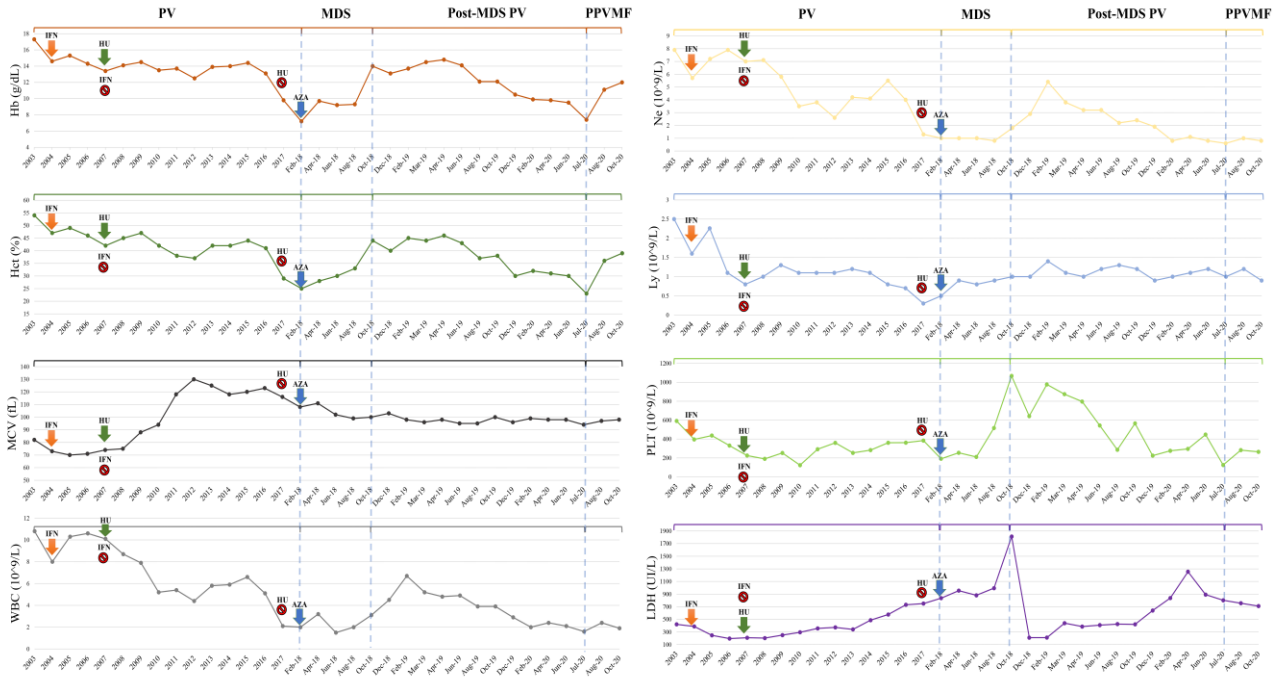

Figure 1: CBC trends and LDH values from the first diagnosis of PV, to the last cycle of AZA therapy.

Abbreviations: CBC (Complete Blood Count); LDH (Lactate Dehydrogenase); PV (Polycythemia Vera); AZA(5-Azacytidine).

The patient continued to receive AZA therapy (FDA-EMEA schedule) until October 2020 (total: XXXI cycles): she is currently in good health and under diagnostic and risk reassessment to start the therapy against the new phase of disease.

Discussion

The frequency with which PV leads to MDS/AML is not well established (5-10% with a time-dependent increase of risk) [12]: there is a controversial association between the type of treatment and transformation. Furthermore, there is a lack of predictable variables and clear data concerning the distinctive risk of progressing to MDS alone. It is currently believed that the risk of its evolution is mainly related to the disease itself, whereas exposure to cytoreductive therapies is a secondary factor [12]. In contrast the relationship between 32P, chlorambucil, or pipobroman and the higher risk of developing AML as a blast-phase of PV is now well-investigated [13].

In this case report, we have presented a patient with IFN-HU managed PV, which progressed to MDS (MDS-EB-2, IPSS-R score of 4.5) [7]. The MDS developed 15 years after the diagnosis of PV, after 5 year IFNα-2b and 11 year HU treatment. Both drugs still play a key role in PV management, as well as in other MPNs, because of their efficacy and relatively safe profile [14,15]. In our case, AZA treatment proved effective in remission and seems to have re-set the BM back to trilineage hyperplasia (panmyelosis, a typical PV attribute) in March 2019. The BM biopsy performed on September 2020 confirmed an MF histopathologic pattern: this finding could be interpreted as a possible natural course of the previous PV.

AZA is an Hypomethylating Agent (HMA), recognized as a differentiation inducer, currently defined as a cornerstone of MDS treatment; in addition, it is effective and well tolerated in elderly patients (>75 years old), who cannot tolerate cytotoxic therapy. AZA is approved for low- and high- risk MDS, regardless of BM histology and fibrosis [16]. Nowadays HMA therapy (AZA or Decitabine based) is considered the most appropriate approach for patients who are not eligible for HSCT. AZA (FDA/EMEA approved schedule) showed superiority to intensive chemotherapy, low dose cytarabine, or the best supportive care in terms of median survival [16].

Our patient showed no cytogenetic abnormalities at the age of the PV diagnosis, in 2003. Acquisition of cytogenetic abnormalities seems to be part of the disease progression (14-20% in the chronic phase to 90% in the blast phase) and complex karyotype is a negative prognostic variable, similar to what is observed in AML and MDS [17]. Unfortunately, due to an absence of the cytogenetic profile when the MDS diagnosis was made, it is impossible to verify whether AZA had been able to limit the cluster harboring cytogenetic abnormalities. Only the 20q deletion was detected in the July 2020 cytogenetic study. AZA did not affect the $JAK2^{V617F}$ allele burden of the patient (from 38,4% in 2009 to 34,2% in 2019), confirming the observations of Quintàs-Cardama et al. [18].

The current features of the patient's BM biopsy and CBC could be explained by the ability of AZA to take the post-PV MDS back to the proliferative phase of the prior MPN, then to its spent phase. The same findings denote ineffectiveness of AZA in suppressing the MPN clone, as suggested in previous studies [19,20]. This is not the first example of MPN recurrence after AZA therapy in post-PV MDS [19], but it exhibits some distinctive traits: firstly, the allele burden was measured before and after AZA therapy, exhibiting its value as if frozen in time; secondly, the patient did not interrupt AZA even after MPN recurrence and progression (according to the current MDS treatment algorithm [5]); thirdly, this case is the first description of a 17 year follow up patient on XXXth AZA cycle: from the PV proliferative phase, to post-PV MDS, again to a proliferative phase, then finally to a PPV-MF diagnosis.

Conclusion

This case parallels other literature evidences [19,20] proving this little-known role of AZA: when used for treating MDS, it may enable the re-emergence of the $JAK2^{V617F}$ cluster, thus resetting the BM in a myeloproliferative status. This evidence may promote further investigations about the role of methylation in the PV progression to the AML/MDS phase, but not in determining the MPN itself [21]. Therefore, the AZA mechanism of action appears to be effective in delaying/reverting the progression, but not in dominating the MPN clone.

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