5-azacytidine for the treatment of massive hepatosplenomegaly in a case of myelodysplastic/myeloproliferative neoplasm-unclassifiable

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Abstract

Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN) represent a distinct category of myeloid diseases in the World Health Organization classification, defined at diagnosis by clinical, morphologic and laboratory features which overlap both those of MDS and MPN.

Within the “Overlap” MDS/MPN syndromes, MDS/MPN-Unclassifiable (MDS/MPN-U) is the least well characterized. MDS/MPN-U is a rare diagnosis, making up less than 5% of all myeloid disorders with no standard prognostic or treatment algorithms.

5-azacytidine is a standard treatment for MDS, but controversial results are available about its role for MDS/MPN-U and its effectiveness on extramedullary disease and hepatosplenomegaly.

We reported the clinical management of a MDS/MPN-U patient characterized by massive hepatosplenomegaly with optimal response to 5-azacytidine.

Keywords: myelodysplastic/myeloproliferative syndrome; hepatosplenomegaly; 5-azacytidine.

Case report

Myelodysplastic/Myeloproliferative neoplasm-unclassifiable (MDS/MPN-U) is a heterogeneous group of hematologic diseases inside of MDS/MPN category with limited data about clinicopathologic characteristics, natural history and therapeutic management [1-3].

MDS/MPN-U account for <5% of all myeloid disorders [1-3]; the 2016 World Health Organization (WHO) defined as diagnostic criteria occurrence of dysplastic features in ≥1 hematopoietic cell line, <20% of blast count in the bone marrow and peripheral blood, and the absence of Philadelphia chromosome, PDGFRα/β rearrangements, isolated del(5q), t(3;3)(q21;q26) or inv(3) (q21q26). A prominent myeloproliferative feature should also be present, such as platelet count ≥450 x 10^9/L, White Blood Count (WBC) ≥13 x10^9/L or splenomegaly. Moreover, a preceding history of MPN or MDS and recent use of cytotoxic therapy or growth factor should be excluded [4].

Genomically, MDS/MPN-U has a similar frequency of epigenetic and splicing gene mutations of adult-onset MDS/MPN syndromes like Chronic Myelomonocytic Leukemia (CMML), with predominant activation of JAK-STAT pathway. Somatic mutations in ASXL1, TET2, JAK2 and SRSF2 are described in more than 20% patients with a MDS/MPN-U diagnosis [5].

Due to the absence of specific-risk stratification system and lack of treatment modalities, MDS/MPN-U clinical management is usually extrapolated from MDS or MPN. Prognostication is generally carried out using International Prognostic Scoring System (IPSS), revised-IPSS (IPSS-R) or MD Anderson prognostic scoring (MDAS) [6-8]. Therapeutic management could be very heterogeneous and focused on individualized symptomatology. In patients with symptomatic cytopenia, Hypomethylating Agents (HMA) were the most frequently utilized treatment strategy, while the best therapeutic approach to splenomegaly is not known [1].

Herein, we describe the clinical features and therapeutic management of a MDS/MPN-U patient characterized by massive hepatosplenomegaly responsive to 5-azacytidine.

The followed procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 1983.

In May 2017 a 70-year-old Caucasian woman presented with mild isolated thrombocytopenia.

She suffered from arterial hypertension and atrial fibrillation. On initial presentation the Hemoglobin concentration (Hb) was 13.3 g/dl, WBC was 5.7x10^9/L, absolute neutrophil count 3.9x10^9/L, absolute lymphocytes 1.2 x10^9/L, absolute monocytes 0.36 x10^9/L and platelet count was 71x10^9/L, common liver and renal function tests (albumin, bilirubin, alanine transaminase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, creatinine) were in a normal range. Serum Lactate Dehydrogenase (LDH) was 138 U/L. Screening tests for hepatitis B and C virus and antiphospholipid antibodies were negative; immune thrombocytopenia and pseudothrombocytopenia were excluded.

For a diagnostic suspect of MDS, a bone marrow evaluation was proposed. Bone marrow biopsy revealed 30% of cellularity with trilineage dysplasia, megakaryocytic hyperplasia, scattered linear reticulin with no intersections (MF-0), CD34+ precursor cells 2-3%. At morphological examination trilineage dysplasia and blast cells <5% were confirmed; cytogenetic analysis showed a normal female karyotype [46,XX(21)]. The conclusive diagnosis was myelodysplastic syndrome with multilineage dysplasia, risk score low according to IPSS and very low according to IPSS-R. A subsequent abdominal Ultrasound (US) documented a mild splenomegaly (spleen diameter 15 cm). A watch-and-wait strategy was applied and after one year we assisted to a progressive worsening of hematological laboratory values and liver/spleen enlargement. In September 2018 Hb was 10.5 g/dl, WBC 4.09x10^9/L (absolute neutrophil count 3.19x10^9/L, absolute monocytes 0.25x10^9/L) and platelet count 33x10^9/L. At US spleen diameter was 18 cm and a high liver volume was described. A new bone marrow evaluation confirmed the trilineage dysplasia and revealed an increased global cellularity (60%) and the appearance of del(11)(q13.3q23) at cytogenetic analysis. IPSS and MDS scores were intermediate-1, while IPSS-R score was low. JAK2 V617F mutation, BCR-ABL p210 transcript, MPL and calreticulin gene mutations were not identified. Hepatological investigations excluded other possible causes of hepatosplenomegaly than the hematological one. Transient elastography identified a score of liver stiffness of 4.8 kPa. In May 2019, when spleen diameter was 25 cm, a trans-jugular liver biopsy was performed and the hepatic venous pressure gradient was 5 mmHg. Histological examination showed centrilobular pattern reflecting sinusoidal congestion damage, minimal central perilisinusoidal fibrosis and aspect of extramedullary hematopoeisis. Echocardiography and esophagogastroduodenoscopy showed normal findings.

To complete the diagnostic pathway, a next-generation-sequencing analysis was conducted on peripheral blood using a Ion TorrentSS platform and ASXL1 p.Tyr591Ter mutation was identified (variant allele frequency 12.26%).

The prominent myeloproliferative clinical features associated to the last bone marrow description led us to a diagnosis of MDS/MPN-U.

Considering the hepatosplenomegaly and the peripheral blood cytopenia, despite little information available about the efficacy of HMA in this scenario, we decided to treat our patient with 5-azacytidine. Before therapy start, spleen diameter was 22 cm and liver/spleen margins were palpable at the umbilical line. A new bone marrow examination revealed 6-8% of CD34+ cells; Hb was 11.2 g/dl, absolute neutrophil count 4.11x10^9/L and platelet count 65x10^9/L. From November 2019 subcutaneous 5-azacytidine was obtained through an off-label access use and administered at dosage of 75 mg/m^2/day for 7 days in 28-day cycles. The treatment was well tolerated without serious adverse events and the patient progressively experienced a reduction of liver and spleen dimensions and a hematological improvement.

After 15 5-azacytidine cycles, at bone marrow CD34+ cells were 2-3%, cytogenetic alterations persisted, US spleen diameter was 13.8 cm and liver/spleen margins were just palpable. Hb was 13.9 g/dl and platelet count 87x10^9/L. The patient is still...
on 5-azacytidine and she has completed 19 cycles. The anatomicopathological data at diagnosis and at the main therapeutic time points are summarized in Figure 1.

MDS/MPN-U is a rare diagnosis and poor prognosis was suggested from the small available cohorts [1,9]. Median reported Overall Survival (OS) ranged between 12-24 months [1,9]. DiNardo et al. identified as favorable clinical parameters age<60 years, thrombocytosis, lack of circulating blasts and ≤5% bone marrow blasts. In a multivariate analysis only thrombocytosis was a significant predictor of survival [1]. A retrospective series [9] mentioned the absence of fibrosis among all three hematopoietic lines (d. hematoxylin eosin, 40x), accompanied by an increase in CD34+ blasts (e. CD34, 20x), with some clustering. Hepatic biopsy (f. hematoxylin eosin 20x) displays a picture of mild cholestasis and congestion of the sinusoids, with particular evidence of megakaryocytes (arrow).

Controversial results are available about the role of HMA for MDS/MPN-U patients [9,12]. A single-center retrospective review of 10 MDS/MPN-U patients treated with decitabine or 5-azacytidine demonstrated 20% of complete remission and 10% of partial remission with progressive disease observed in 30% of the cases [12]. A retrospective series reported by Mangaonkar et al. underlined a suboptimal response to HMA in 59 MDS/MPN-U patients treated with 5-azacytidine (80%) or decitabine (20%). Only 4 patients received a complete remission, while failure or disease progression was observed in 48% of the cases [9].

Until now little has been published about the effectiveness of 5-azacytidine on hepatosplenomegaly in MDS/MPN adult patients. In CMML a splenic response to HMA, considered as a shrinkage over 50% of baseline size, was found in 45% of the examined cases [13].

In conclusion, standard treatment of MDS/MPN-U needs further research; our experience suggests that 5-azacytidine might play a role for therapeutic management of massive hepatosplenomegaly in MDS/MPN-U scenario.

**Conflict of interest:** The authors declare that they have no conflict of interest.

**References**


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