Rapid and robust reversion to essential thrombocythemia on treatment with Decitabine in a case of hydroxyurea-induced t-MDS/AML

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Introduction

Essential Thrombocythemia (ET) is one of the traditional BCR/ABL(−) myeloproliferative neoplasms (MPN) characterized by conspicuously elevated circulating platelets as a result of autonomous megakaryocyte proliferation. Patients with ET have a propensity to develop thrombotic complications and chronic treatment with the cytoductive agent hydroxyurea is preferred to mitigate this risk. Ultimately, 2–7% percent of ET cases will progress to myelodysplastic syndrome (MDS) and/or acute myelogenous leukemia (AML) [1], and a controversial association between treatment with hydroxyurea and leukemic transformation (t-MDS/AML) has been proposed [2].

Regardless of its genesis, MDS/AML arising in ET patients has typically required myeloablative treatment, which is often toxic and plagued with poor and unpredictable responses. Notably, the hypomethylating chemotherapeutic agent Decitabine recently demonstrated improved response rates and overall survival in older patients with newly diagnosed AML in a phase III, multicenter trial [3].

Herein, we report a case of t-MDS/AML arising in a patient with a 13-year history of ET on hydroxyurea maintenance. Treatment with Decitabine rapidly ablated the leukemic clone, but the patient subsequently presented with neutropenic fever, severe thrombocytosis and virtual replacement of bone marrow elements with megakaryocytes.

Case Report

In 2001, a then 61-year-old Caucasian man diagnosed with ET was referred to our institution with platelets of $1300 \times 10^9/L$. Bone-marrow sampling showed moderate expansion of maturing myeloid precursors and megakaryocytes in a minimally fibrotic stroma (Fig. 1, top). Cytogenetic analysis showed a 46,XY normal karyotype; molecular screening a later date resulted positive for calreticulin exon 9 insertion of five base-pairs and negative for JAK2 V617F. Due to his age and cardiac comorbidities, he was considered high-risk for thrombosis and was started on hydroxyurea. At 7.5–8.5 g per week, platelets fluctuated around $\sim 450 \times 10^9/L$ for several years.
Then, in April 2013 during a routine follow-up he was noted to be pancytopenic with a white blood cell (WBC) count of $1.7 \times 10^9/\mu L$. With an impression of hydroxyurea-related myelosuppression, dosage was decreased initially to 1000 mg/day and then to 500 mg/day. Not surprisingly, the platelets increased to $996 \times 10^9/\mu L$ in June 2013 and subsequently to $1500 \times 10^9/\mu L$ in July 2013 (Fig. 2). However, the WBC count remained low at $2.8 \times 10^9/\mu L$ with persistent anemia. New bone marrow sampling revealed $>90\%$ cellularity with myelodysplastic changes, including 53% ringed sideroblasts (RS) and 11% myeloblasts. Cytogenetic analysis revealed a new abnormal karyotype in 30/41 cells: 45,XY,r(5)(q15.2q13~15),add(9)(q34),dic(12;17)(p10;p10),del(13)(q13q22),der(16)t(12;16)(q13;q22). The complex karyotype coupled with pancytopenia and high blast count prompted a diagnosis of therapy-related myelodysplasia (t-MDS) and stratified the patient into the intermediate-2 prognostic category. He was started on lenalidomide 5 mg/day, ultimately increased to 10 mg/day.

By late September 2013, no response could be appreciated and a new bone marrow sampling was performed (Fig. 1, middle). At this time, aspirate smears demonstrated increased myeloblasts to 26% on a 300-cell count differential and cytogenetic analysis revealed that 100% of cells harbored the abnormal karyotype, overall consistent with progression to t-MDS/AML. Decitabine was begun at 20 mg/m$^2$ for 5 days out of a 28-day cycle with a plan for six cycles based on a recent study showing the benefit of Decitabine over other options for elderly patients with leukemia [3]. Compared to a nadir of $60 \times 10^9/\mu L$ on lenalidomide, the platelet count increased to $450 \times 10^9/\mu L$ after the first cycle of Decitabine. One week after the second cycle of Decitabine, in November 2013, the patient was admitted with a fever of 102°F. At this time, the platelets were $3700 \times 10^9/\mu L$ and the WBC count was $0.4 \times 10^9/\mu L$ with 75% neutrophils and few metamyelocytes and myelocytes. Astonishingly, bone marrow biopsy revealed $>90\%$ infiltration by megakaryocytes and only 4.3% CD34(+) myeloblasts (Fig. 1, bottom). Anagrelide (3 mg/day) and plateletpheresis were initiated to control rising platelets. Following commencement of the third cycle of Decitabine in late November 2013 and with continuance of Anagrelide, platelets dropped to $\sim 500 \times 10^9/\mu L$ and remained stable. Further, WBC counts increased to $4.5 \times 10^9/\mu L$ with a normal differential, bone marrow demonstrated

Figure 1. Chronology of Bone Marrow Studies. Top Row: Initial BM sampling from 2001 shows a hypercellular marrow with expansion of maturing myeloid elements and abundant large polylobated megakaryocytes in a minimally fibrotic stroma, as demonstrated with a reticulin stain depicted on the right. Middle Row: After 12 years of initial presentation, there is evidence of histologic progression to MDS/AML characterized by further increase in cellularity, noticeable increase in left-shifted dyspoietic myeloid precursors, erythroid precursors with 53% ringed sideroblasts (see iron stain on aspirate smear, middle picture inset), and dyspoietic megakaryocytes. Myeloblasts accounted for 26% of cells (300-cell count differential) as illustrated by flow cytometric analysis and CD34 immunostain of biopsy section (right image and inset; color code for inset: Red: Myeloblasts, Blue: Monocytes, Green: Maturing myeloid precursors). Bottom Row: After 6 months of initial therapy with Decitabine and maintenance with Anagrelide, aberrant myeloid, and erythroid precursors have greatly decreased with cellularity consisting mostly of large polylobated megakaryocytes, compatible with blossoming ET. There is a persistent population of aberrant CD34(+) myeloblasts (4.3%; right picture and inset) with similar karyotypic abnormalities seen in the t-MDS/AML clone.

Figure 2. Platelet Count Through Disease Progression and Treatment. Circulating platelet levels at different time-points during the progression of this patient’s ET, first to MDS and eventually to AML, and in response to various treatments. D1, D2, D3, D4 correspond to the Decitabine cycles; An, anagrelide; RS, ringed sideroblasts; BM, bone marrow; MK, megakaryocytes. X-axis labels are month-year.
<5% blasts, and his hemoglobin rose to 11.5 without the need for further transfusions. The patient remained in remission for 20 cycles of Decitabine before relapsing with AML.

Discussion

We present a case of hydroxyurea-managed ET progressive to t-MDS/AML in which treatment with Decitabine not only incited rapid remission but also seems to have stimulated bone marrow hyper replacement with megakaryocytes. On treatment with Decitabine, bone marrow biopsy demonstrated <5% of the leukemic clone, a clone that constituted 26% of cellularity 6 weeks prior. Moreover, the platelet count rose and circulating blasts disappeared.

t-MDS/AML occurs in patients exposed to cytotoxic chemotherapy and/or radiation and is associated with distinct karyotypic abnormalities. Whilst the role of alkylating agents and DNA topoisomerase-II inhibitors is recognized, the long-term leukemogenic risk of agents such as hydroxyurea, a nonalkylating cytoreductive agent that inhibits DNA synthesis through inhibition of the ribonucleotide reductase, is less well established. A distinct t-MDS with associated 17p deletion has been recognized specifically in patients treated with hydroxyurea [4].

Although complete response of AML to treatment with Decitabine is not uncommon (17.8% in the phase III trial), the rapidity with which it occurred is surprising. In the aforementioned trial, median time to response was 4.3 months (95% CI 3.8–5.1 months) [3]. Further, the degree to which the bone marrow was infiltrated with megakaryocytes and the observed thrombocytosis following treatment with Decitabine seems not to be replicated within the literature. It is well known that ET is associated with expansion of megakaryocytes in the bone marrow, but >90% megakaryocytes is unprecedented in this setting. Treatment with Decitabine (as well as its sister compound azacitidine) is known to induce significant thrombocytosis [5, 6]. While, the precise mechanism of action of Decitabine is yet to be verified, it is known that these drugs can reactivate tumor-suppressor gene expression thus promoting maturation and/or apoptosis of deregulated hematopoietic cells [7]. It is, therefore, conceivable that epigenetic regulation of the drivers of this patient’s underlying ET clone by Decitabine is responsible for the recidivism to the MPN state with megakaryocyte and platelet proliferation.

Mutation of Janus 2 kinase (JAK2) was the first precipitating genetic lesion identified in ET and is present in about half of these patients [8]. Rare mutations in the gene coding for the thrombopoietin receptor MPL and a recently identified mutation in the calreticulin gene CALR [9, 10] have since been described as the cause in ~90% of the remainder. The commonality between these mutants (and all MPNs for that matter) is their tendency to exhibit enhanced JAK/STAT signaling [11]. An interaction between hypomethylating agents and the JAK/STAT pathway could provide a mechanistic explanation for our patient’s unique presentation.

Negative regulators of the JAK/STAT pathway appear to be subject to hypermethylation in MPN, an event implicated in blastic progression to MDS/AML [12–15]. If so, it seems plausible that “undoing” this epigenetic event with hypomethylating agents would revert the disease to the benign MPN state rather than selectively repressing the ET clone. Return to the MPN state would explain the profound thrombocytosis observed in the above patient on treatment with Decitabine. This mechanism is supported by an analogous paradigm in primary myelofibrosis (PMF), in which many patients with PMF progressive to MDS/AML treated with azacitidine demonstrate reversal to a chronic phase of PMF, rather than clonal suppression [16, 17]. In a mouse model of PMF, azacitidine was shown to reverse CXCR4 promoter hypermethylation at the epigenetic level [18], similar to the interaction between JAK2 and the nucleic chromatin assembly in hematopoietic cells [19]. Decitabine also enhances both megakaryocyte maturation and platelet release in the mouse [20]. Importantly, hypomethylating agents have been shown to perturb JAK signaling in other hematologic malignancies [21].

In conclusion, although the association between hydroxyurea and t-MDS/AML remains controversial, the chromosomal characteristics of this patient (complex karyotype including deletion 5q) are consistent with those of therapy-related myeloid neoplasms. Upon rapid Decitabine-induced remission, his bone marrow showed >90% megakaryocytes and his platelet count rose to greater than 3000 × 10^9/L. Though hardly proven, we posit that this dramatic presentation resulted from Decitabine-mediated reversion of the MDS to benign ET via hypomethylation of JAK/STAT pathway repressors.

Conflict of Interest

The authors report no conflicts of interest.

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