Successful re-treatment with azacitidine in a patient with low blast count AML transformed from MDS after suspension of this agent

TO THE EDITOR: The treatment approach to acute myeloid leukemia (AML) transformed from high-risk myelodysplastic syndrome (MDS) after azacitidine failure is not standardized and the clinical results achievable in this setting are generally disappointing [1-3]. Similarly, poor outcomes have also been reported in the setting of AML transformation following azacitidine discontinuation due to reasons other than hematologic progression in MDS patients initially responding to hypomethylating therapy [4]. Little is known of azacitidine-responsive MDS patients who progressed to AML with 20–30% bone marrow (BM) blasts after suspension of this agent, nor of the possibility to re-induce hematological control after the resumption of hypomethylating therapy.

Herein, we report the case of a 63-year-old woman diagnosed in April 2007 with refractory anemia with excess blasts subtype 2 (RAEB-2) who presented with trilinear symptomatic pancytopenia, a 15% BM blast infiltration, a normal karyotype, and a significant transfusion requirement of red blood cells (RBC) units. The International Prognostic Scoring System (IPSS) [5] score was 2, qualifying the patient’s MDS as intermediate-2 risk. The World Health Organization (WHO)-adapted Prognostic Scoring System (WPSS) [6] score was 4 (high risk). The patient presented with cardiac, pulmonary, and gastrointestinal comorbidities indicating a MDS-Comorbidity Index (CI) score [7] as high as 3 (high risk). Therefore, the patient was qualified as unsuitable for AML intensive chemotherapy (IC). So that, in July 2007, she was started on azacitidine (75 mg/m², schedule 5+2+2) with good compliance and without significant adverse effects. After 8 cycles (May 2008), a complete remission (CR) was documented. The patient then continued the same treatment (28 cycles) in CR with normal blood counts and without significant toxicity until March 2011, when febrile diverticulitis, an infected perianal fistula and, soon after, pneumonia were consecutively observed. Because of the normal neutrophil count, these clinical complications were considered to be related to the pre-existing comorbidities rather than associated with the azacitidine therapy. However, given the severity of the complications, requiring surgery and long term antibiotic therapy, azacitidine was stopped. A progressive pancytopenia was observed after the discontinuation of azacitidine to the point of disease progression to AML that was diagnosed 4 months later (July 2011). The BM was characterized by multilineage dysplasia with 25% of myeloblast cells positive for HLA-DR, CD13, CD15, CD64, CD34, and CD117. The karyotype was normal by standard cytogenetic and fluorescence in situ hybridization (FISH) analysis. Molecular studies for the most frequent AML-related alterations (CBFβ/MYH11, DEK/CAN, NPM1, FLT3, and RUNX1/ETO) showed no abnormalities. The hemogram revealed a trilinear pancytopenia and a low white blood cell (WBC) count with 3% peripheral blood blasts. Therefore, the patient, once again, was qualified as unsuitable for IC. In view of the previous response to treatment and the lack of effective therapeutic alternative measures, upon the resolution of the clinical complications (September 2011), azacitidine was resumed. The response to hypomethylating therapy was suboptimal during the first 4 cycles, until a significant improvement in peripheral blood counts, a reduction of transfusion requirement and, finally, the achievement of a partial response (8% blasts) after 6 cycles of treatment were observed. At present, 3.2 and 7.5 years from the AML and RAEB-2 diagnoses and 22 and 50 cycles of azacitidine therapy, respectively, the patient is in fair general condition with a moderate transfusion requirement (2 RBC units/month) and controlled, although persistent, disease (10% BM blasts).

Oligoblastic AML includes heterogeneous diseases with outcomes and responsiveness to treatment ranging from high-risk MDS to AML with >30% BM blasts, emphasizing the importance of the disease-related biological features and the patient’s clinical status and comorbidities rather than the percentage of BM blasts itself. Hypomethylating agents have shown efficacy with reduced toxicity when administered to elderly patients with 20–30% BM blasts, not eligible for IC [8]. Therefore, these agents have the potential...
to substitute for IC in elderly patients or in patients who are younger but are unsuitable for IC because of severe comorbidities, as was the case for our patient, who presented with relatively indolent AML, displaying a normal karyotype and a low peripheral WBC count, the latter being an identified favorable prognostic factor to achieve a therapeutic response in AML patients treated with azacitidine [8]. In the context of a relatively non-aggressive disease which had shown a previous response to azacitidine, re-treatment with the same agent resulted in long-lasting disease control with a reduced BM blast count and significant hematological improvement, such that our patient presented the clinical features of a relatively indolent MDS rather than an aggressive myeloproliferative disorder, such as AML.

In conclusion, our case is indicative of the possibility of re-treatment with azacitidine in AML if the evolution to AML from high-risk MDS was related to a treatment interruption for reasons other than hematologic progression in patients who initially responded very well to hypomethylating therapy.

Pasquale Niscola1, Andrea Tendas1, Laura Scaramucci1, Marco Giovannini1, Stefano Fratoni2, Paolo de Fabritiis1

1Hematology Division and 2Pathology Department, Sant’Eugenio Hospital, Rome, Italy

Correspondence to: Pasquale Niscola
Hematology Division, S. Eugenio Hospital, Piazzale dell’Umanesimo 10, 00144, Rome, Italy
E-mail: pniscola@gmail.com

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