

sentation of symptomatic PCM and MDS RCMD unrelated to prior chemotherapy or radiotherapy. A more extensive study would be required to investigate the clinical characteristics and outcomes in patients with such a condition.

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REFERENCES

1. Gertz MA, Terpos E, Dispenzieri A, et al. Therapy-related myelodysplastic syndrome/acute leukemia after multiple myeloma in the era of novel agents. *Leuk Lymphoma* 2015;56:1723-6.
2. Pemmaraju N, Shah D, Kantarjian H, et al. Characteristics and outcomes of patients with multiple myeloma who develop therapy-related myelodysplastic syndrome, chronic myelomonocytic leukemia, or acute myeloid leukemia. *Clin Lymphoma Myeloma Leuk* 2015;15:110-4.
3. Reddi DM, Lu CM, Fedoriw G, et al. Myeloid neoplasms secondary to plasma cell myeloma: an intrinsic predisposition or therapy-related phenomenon? A clinicopathologic study of 41 cases and correlation of cytogenetic features with treatment regimens. *Am J Clin Pathol* 2012;138:855-66.
4. Malhotra J, Kremyanskaya M, Schorr E, Hoffman R, Mascarenhas J. Coexistence of myeloproliferative neoplasm and plasma-cell dyscrasia. *Clin Lymphoma Myeloma Leuk* 2014;14:31-6.
5. Várkonyi J, Jánosy J, Gopcsa L, et al. Myelodysplasia and multiple myeloma or monoclonal gammopathy. A non-fortuitous coexistence. *Hungarian Med J* 2007;1:107-12.
6. Tsiara S, Economou G, Panteli A, Isaakidis P, Kapsali E, Bourantas KL. Coexistence of myelodysplastic syndrome and multiple myeloma. *J Exp Clin Cancer Res* 1999;18:565-6.
7. Yoshida Y, Oguma S, Ohno H, et al. Co-occurrence of monoclonal gammopathy and myelodysplasia: a retrospective study of fourteen cases. *Int J Hematol* 2014;99:721-5.

Regaining the response to erythropoietin following azacitidine in chronic myelomonocytic leukemia previously evolved from refractory anemia

TO THE EDITOR: In a previously published issue of the Journal, we reported an unusual case of chronic myelomonocytic leukemia (CMML) type 2 (CMML-2) that evolved from refractory anemia (RA) [1]. The complete development of CMML was preceded by the loss of response to epoetin alpha (EPO). EPO had allowed the patient to maintain the transfusion independence (TI) for 7 years until then. The patient received azacitidine, achieving complete remission (CR) of CMML-2 after 6 treatment courses. However, the TI was observed after 2 cycles of hypomethylating therapy despite the persistence of myelodysplastic features. The optimal response to azacitidine in this patient was in line with that reported by our group earlier [2]. Moreover, the limited clinical efficacy of azacitidine in transfusion-dependent and erythropoiesis-stimulating agent (ESA)-resistant, low and intermediate-1 risk myelodysplastic syndrome (MDS) has been recently outlined [3]. Therefore, we could speculate that several and different biological components and pathogenic mechanisms, stemming from different patterns of response to distinct therapeutic agents, may be responsible for the myelodysplasia and the resulting clinical phenotype. These findings might be observed more easily during treatment with hypomethylating agents as these agents induce downstaging of high-risk MDS to low-risk MDS.

Here, we report the updated follow-up of the clinical course of our patient, wherein we observed a dynamic evolution of MDS clones that showed different responses to azacitidine and EPO. The response to EPO was likely related to the persistence of RA clones that re-emerged despite azacitidine. After the achievement of the TI and the CR following the second and the sixth azacitidine courses, respectively, the patient continued to receive hypomethylating therapy as maintenance. However, after the fourteenth course, preceded by several weeks in which the patient complained of profound weakness and fatigue [4], progressive anemia (hemoglobin ~7.0 g/dL) requiring red blood cell (RBC) transfusions was noted. Therefore, the patient was reevaluated in the light of the suspicion of a loss of response to azacitidine and evolution to acute myeloid leukemia. However, examination of the bone marrow (BM) showed the disappearance of blast cells and a marked reduction of monocytes in a MDS framework, which was characterized by trilineage dysplasia and erythroid predominance with the features of ineffective erythropoiesis, as observed at the onset of MDS when the patient was diagnosed with RA [1]. According to its disease-modifying effects in MDS,

azacitidine had “down-staged” the patient's malignancy from the transformed form of CMML-2 to refractory cytopenia with multilineage dysplasia (RCMD), resulting in a clinical phenotype similar to primary RA. On the basis of these findings, the patient continued to receive azacitidine as maintenance hypomethylating therapy and EPO was re-introduced. A rapid response with the achievement of TI was soon recorded. Therefore, the patient displaying near normal peripheral blood counts, continued to receive azacitidine concomitant with EPO, in order to maintain CR and TI. Our case presents some interesting observations. Initially, our patient was responsive to EPO for many years until the occurrence of an important transfusion requirement corresponding to transformation towards CMML-2. The treatment with azacitidine resulted in the clearance of this transformed, aggressive leukemic component probably by restoring a previous framework consistent with a low MDS risk, such as RCMD, as observed at the onset of primary MDS diagnosis. Therefore, it is likely that the clinical picture of the patient reflected maintained response to azacitidine, with good control of the CMML-2 and re-emergence of ineffective erythropoiesis typically associated with RA/RCMD MDS, which was again responsive to EPO. The patient was 83 years old and had a MDS history for 9 years; he was well after 21 courses of azacitidine and 6 months of TI with EPO. Although both the use of ESA [5] (to reduce the high burden of transfusion requirement in MDS patients [6]) and azacitidine [7, 8] (to contain or reverse the natural progression of disease) are well established, very few studies have explored the therapeutic role exerted by the association of azacitidine with EPO in the setting of higher-risk MDS. A retrospective French study that included 32 higher-risk MDS patients, who concomitantly received ESA and azacitidine found that the addition of ESA to the hypomethylating therapy significantly improved overall survival independent of azacitidine schedule and duration [9]. These findings may reflect synergistic effects exerted by two agents or their separate actions on distinct mechanisms and/or components of MDS. However, no prospective studies have confirmed these findings and there is a need for prospective studies for confirmation [10]. However, we have not been able to thoroughly investigate this case with molecular techniques, owing to which we cannot clarify the biological and pathogenic bases for what we observed. Our case showed that MDS over its course can display different clinical manifestations, combining aspects associated with both high- and low-risk MDS forms. These different manifestations could correspond to underlying biological heterogeneity of different neoplastic clones or their transformation over time in the context of a continuum clonal evolution that may be influenced by the pattern of response to disease-modifying treatments.

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REFERENCES

1. Niscola P, Tendas A, Scaramucci L, Giovannini M, Fratoni S, de Fabritiis P. Evolution of chronic myelomonocytic leukemia from refractory anemia: the unusual course of a myelodysplastic syndrome. *Blood Res* 2013;48:152-3.
2. Tendas A, Cupelli L, Siniscalchi A, et al. Azacitidine in chronic myelomonocytic leukemia: an effective and manageable approach. *Mediterr J Hematol Infect Dis* 2014;6:e2014020.
3. Tobiasson M, Dybedahl I, Holm MS, et al. Limited clinical efficacy of azacitidine in transfusion-dependent, growth factor-resistant, low- and Int-1-risk MDS: Results from the nordic NMDSG08A phase II trial. *Blood Cancer J* 2014;4:e189.
4. Efficace F, Gaidano G, Breccia M, et al. Prevalence, severity and correlates of fatigue in newly diagnosed patients with myelodysplastic syndromes. *Br J Haematol* 2015;168:361-70.
5. Spiriti MA, Latagliata R, Niscola P, et al. Impact of a new dosing regimen of epoetin alfa on quality of life and anemia in patients with low-risk myelodysplastic syndrome. *Ann Hematol* 2005; 84:167-76.
6. Niscola P, Tendas A, Giovannini M, et al. Transfusions at home in patients with myelodysplastic syndromes. *Leuk Res* 2012;36: 684-8.
7. Santini V, Alessandrino PE, Angelucci E, et al. Clinical management of myelodysplastic syndromes: update of SIE, SIES, GITMO practice guidelines. *Leuk Res* 2010;34:1576-88.
8. Breccia M, Voso MT, Maurillo L, et al. Real-life experience with azacitidine in myelodysplastic syndromes according to IPSS cytogenetic profile. *Am J Hematol* 2014;89:565.
9. Itzykson R, Thépot S, Beyne-Rauzy O, et al. Does addition of erythropoiesis stimulating agents improve the outcome of higher-risk myelodysplastic syndromes treated with azacitidine? *Leuk Res* 2012;36:397-400.
10. Breccia M, Loglisci G, Salaroli A, et al. Combination of azacitidine and ESA in myelodysplastic patients: the need for prospective studies. *Leuk Res* 2012;36:682-3.