

LETTER TO THE EDITOR



Double remission of simultaneously occurring secondary AML and CLL by venetoclax monotherapy

Pasquale Niscola^a , Nélida Inés Noguera^b, Gianfranco Catalano^a, Luca Cupelli^a, Stefano Fratonì^c, Marco Giovannini^a, Carla Mazzone^a, Benedetta Neri^a, Laura Scaramucci^a, Malgorzata Monika Trawinska^a, Paolo de Fabritiis^a and Elisabetta Abruzzese^a

^aHematology Unit, Saint' Eugenio Hospital, Tor Vergata University of Rome, Rome, Italy; ^bNeuro Oncohematology Unit, Santa Lucia Foundation and Department of Biomedicine and Prevention, Tor Vergata University of Rome, Rome, Italy; ^cDepartment of Pathology, Saint' Eugenio Hospital, Rome, Italy

To the Editor,

Philadelphia chromosome (Ph)-negative (Ph-) chronic myeloproliferative neoplasms (MPN) represent a group of heterogeneous clonal blood stem cell disorders which include polycythemia Vera (PV), essential thrombocytemia (ET), and myelofibrosis (MF) [1]. Approximately 5–10% of patients with Ph-negative MPN may progress into acute myeloid leukemia (AML) portraying a very dismal outcome because treatment options for such patients are very limited [2,3] and only a minority of them are suitable for intensive chemotherapy and allogeneic stem cell transplantation (SCT) [2,3]. Notwithstanding this traditional and discouraging scenario, the development of new diagnostic methods and innovative therapies is progressively changing the treatment paradigm of transformed MPNs allowing for an effective management for an ever-growing number of affected patients [3] compared to the traditional standard care, as illustrated by the clinical case, which we report herein. On April 2015, a 75-year-old woman was diagnosed with refractory anemia with excess blasts (RAEB)-2 after an about 17-years history of PV. The Janus kinase 2, studied when available (December 2007), turned out to be positive for V617F point mutation. The bone marrow (BM) trephine biopsy was notable for a hypercellular BM, abundant megakaryocytes, and focally moderate reticulum and collagen fibrosis as well as a percentage of CD34⁺ blasts of 15% of the overall cellularity. Cytogenetic analysis revealed a normal karyotype and no molecular abnormality typically associated with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) was found. A secondary MDS, in the form of a RAEB-2 was diagnosed. On the basis of the patient's overall fitness level and her ineligibility to SCT, we recommended therapy with azacitidine (75 mg/m², schedule 5 + 2 + 2) with palliative and life-prolonging intents. Therapy was started on June 2015 and was well-tolerated without significant adverse effects. After 6 cycles (December 2015), a complete remission (CR) was documented. The patient then continued the same treatment for another 22 cycles maintaining a CR without any significant toxicity until September 2017, when a progressive

pancytopenia unveiled the progression to secondary AML. Meanwhile, a mild clonal B-cell lymphocytosis appeared leading to the diagnosis of chronic lymphocytic leukemia (CLL). At that time, other than the slight splenomegaly, the patient's physical examination and the radiological work-up were unremarkable; in particular, neither superficial nor deep adenomegalies were found. The BM trephine biopsy, the BM smears and the immunophenotype revealed a diagnosis of AML concomitant to CLL (CD38 negative, mutated status of Ig-K and ZAP-20 negative clonal B-cells), without any cytogenetic and molecular abnormalities other than the presence of the Jak2 V617F point mutation (*ASXL1*, *IDH1*, *IDH2*, *EZH2*, and *TET2* negative). The patient was suffering and highly transfusion-dependent. Therefore, after the approval of Institutional Board of our Hospital, on November 2017, she consented to therapy with venetoclax (off label use) as a single agent up to a dosage of 400 mg after an appropriate run-up and the adoption of recommended measures for preventing tumor lysis syndrome. A normalization of peripheral blood count and the clearance of the clonal lymphocytosis were observed within two weeks, along with a brief and transient disappearance of transfusion needs. The patient reached morphological complete remission with persistence of Jak2 (V617F) mutation, a less than 1% percentage of clonal small lymphocytes was still present. Indeed the benefits provided by venetoclax were transitory (just over two months) and were followed shortly by a progression of her AML up to the irreversible evolution of the disease until the patient's death (May 2018). PV and other Ph-MPNs concomitantly associated with other blood-related disorders have been sporadically described [4–6], but the simultaneous occurrence of a secondary (AML), diagnosed at the failure of a long-term hypomethylating treatment of a high-risk MDS transformed from a long-lasting Ph-MPN, with a concomitant CLL is extremely rare. Our case posed the traditional therapeutic challenges that daily the practical hematologist encounters in the setting of transformed Ph- MPNs. The beneficial role of hypomethylating agents, such as azacitidine [7,8] and decitabine [9–11], as salvage treatment of

progressing MPNs have been reported, presenting these agents also a favorable manageable profile also in elderly and unfit patients [11,12]. The patient responded well to azacitidine with good quality of life and presented an optimal hematological control for over two years. The poor prognosis and the very dismal outcome [13,14] after azacitidine-failure are unfortunately currently unmet challenges for which no approved treatments as well as no standard therapeutic opportunities are available [14]. In our case, the coincidence of AML progression and CLL onset suggested the use of the BCL2 inhibitor venetoclax [15,16]. Highly selective, venetoclax binds specifically to BCL2 and displaces BH3 domain-only proteins to trigger BAX/BAK-mediated mitochondria-induced apoptosis in p53 deleted CLL and Myeloid leukemia stem cells [17–19]. The drug was approved by the US FDA for the treatment of CLL in 2016, and for the treatment of AML ineligible for intensive chemotherapy in 2018. In our case, the drug was effective, as envisaged, on both the B-CLL and the AML cellular clones. As a single agent, it allowed for hematological normalization, although transitory, in a patient with a very long history of multiple hematological malignancies and related treatments, meaning clonal evolution and selection of chemoresistant clones, with extremely unfavorable prognostic characteristics. Acquired resistance to venetoclax alone is commonly observed due to evolution and selection of subclones that leads to disease progression or relapse [20]. We could not associate, as in some ongoing experimental studies, hypomethylating agents because our patient had already received a long treatment with azacitidine, and association with other target drugs as MCL1 or BETP inhibitors are not yet available [21]. Thus, even if the final outcome was unfavorable, we feel that the experience indicates a possible role of BCL-2 inhibitors, of course in association with other agents with different mechanism of action (e.g. hypomethylating agents and targeted anti-cancer therapy with small-molecule inhibitors and antibodies, new apoptosis targeted drugs), in the treatment of clonal evolution of secondary AML. In conclusion, our report traces over 20 years of clinical history of patients suffering from PV through its clinical evolutions and diagnostics and therapeutic advances that have in time become available. The ongoing clinical and biological research is at the basis of advances for an ever more precise diagnosis and therapeutic developments aimed at offering an increasingly effective and personalized treatment [16,22]. In addition, our report emphasizes the shortcoming of our insight in the molecular mechanisms leading to myeloproliferative neoplasms onset and evolution: JAK2 (V617F), certainly present at the onset of PV, was the only anomaly we could ascertain in the long and eventful clinical history of the patient, suggesting this finding the necessity of the fundamental search for the original anomaly unleashing the primary tumor, more ancestral respect to the known, as indicated also by the existence of triple-negative MPNs. The concomitant onset of a lymphoproliferative cancer with secondary AML may be the effect of such a primal anomaly. Yet, novel agents such as venetoclax showed outstanding effects in the treatment of patients, often irrespective of their underlying genetic features, as it was for a short period in

our case. To be unveiled are still other additional anomalies leading to the clonal evolution of the disease. Those insights and the use of schemes comprehensive of different acting targeted molecules will undoubtedly revolutionize our management of this difficult to treat hematological malignancies.

Disclosure statement

The authors declare that they have no conflict of interest with regard to this paper.

ORCID

Pasquale Niscola  <http://orcid.org/0000-0002-2226-6518>

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