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LETTER TO THE EDITOR

Mutational analysis of BCORL1 in the leukemic transformation of chronic myeloproliferative neoplasms

Giada Rotunno · Paola Guglielmelli · Flavia Biamonte · Elisa Rumi · Mario Cazzola · Alessandro M. Vannucchi

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Dear Editor,
The chronic myeloproliferative neoplasms (MPN) are clonal hematopoietic stem cell disorders characterized by dysregulated proliferation and expansion of one or more of the myeloid lineages and include polycythemia vera, essential thrombocythemia and primary myelofibrosis [1]. All can transform, with variable frequencies and up to 15–20 % of patients with myelofibrosis, to acute myeloid leukemia (AML) [2, 3]. Several molecular abnormalities have been described in MPN, particularly in myelofibrosis [4], but information about their prognostic relevance and the role in the leukemic transformation are scanty [5]. Leukemia after MPN is characterized by a greater molecular complexity compared with the chronic phase, and also appears to involve a different mutational profile compared with de novo leukemia [6]. Milosevic et al. reported mutations in TP53, del7q, and 9pUPD as the most recurrent aberrations in post-MPN leukemia [7] and Puda et al. suggested the role of PRC2 complex in the leukemic transformation [8]. Recently, novel somatic mutations in the trascriptional corepressor gene BCORL1 have been reported in 5.8 % of patients with de novo AML, AML with myelodysplastic changes, and treatment related-AML, pointing to BCORL1 as a novel candidate tumor suppressor gene recurrently mutated in AML [9]. BCORL1 is located on the chromosome Xq25-q26.1 and encodes a protein of 1711 amino acids containing a nuclear localization signal, tandem ankyrin repeats, and an LxxLL nuclear receptor recruitment motifs found in coregulator proteins [10]. The majority of BCORL1 mutations reported by Li et al. resulted in a shortened protein lacking the LxxLL motif and the C-terminus, suggesting that loss of function of BCORL1 may be important in the leukemogenic process [9].

The aim of this study was to determine whether BCORL1 mutations are also expressed in AML developing from MPN. We studied 35 post-MPN AML patients diagnosed according to the 2008 World Health Organization criteria. Patients were recruited from the database of the hematology units of Florence and Pavia, and provided an informed consent according to institutional review board-approved protocols. Mutational analysis was performed on mononuclear cells purified from peripheral blood at the time of leukemia diagnosis. Genomic DNA was amplified by Whole Genome Amplification (GE-Healthcare); direct bidirectional sequencing of all coding exons of BCORL1 was performed using Sanger technique. Traces were analyzed with Mutational Surveyor® (Softgenetics®); all nucleotide variants were confirmed on unamplified DNA.

We detected minimal variations in the coding region of BCORL1 (Table 1). We identified four known polymorphisms listed in NCBI dbSNP and three additional exon 4 variants representing previously not described silent mutations. The exon 11 p.L1600I variant is a novel missense amino acid substitution; however, according to Polyphen-2 score it is predicted to be “benign”. The Q1039X variant, located in exon 4 is a nonsense, previously not described, mutation; however, lack of germline material did not allow us to confirm its somatic nature.

In conclusion, BCORL1 mutations do not seem to be commonly associated with leukemic transformation of MPN, further substantiating the different molecular profile compared with denovo leukemias. Although the small

G. Rotunno · P. Guglielmelli · F. Biamonte · A. M. Vannucchi (✉)
Dipartimento di Medicina Sperimentale e Clinica, University of Florence, Largo Brambilla 3, 50134 Florence, Italy
e-mail: amvannucchi@unifi.it

E. Rumi · M. Cazzola
Department of Hematology Oncology, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy

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Table 1 BCORL1 variants detected in post-MPN leukemia patients

	Amino acid shift	SNP variants	BCORL1 exon
rs5932715, 8210G>A	G209S	SNP	4
rs36043572, 8101 T>C	N172N	SNP	4
rs61752973, 8368G>GA	A261A	SNP	4
rs112032085, 9031G>A	P482P	SNP	4
10354C>CT	L923L	Silent	4
10981C>CT	L1132L	Silent	4
20067G>GA	E1318E	Silent	6
46773C>CA	L1600I	Missense	11
10700C>CT	Q1039X	Nonsense	4

number of cases does not allow us to exclude that BCORL1 mutations can be found also in post-MPN AML, their occurrence is, at least, very infrequent and their detection does not appear to deserve clinical relevance.

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