



UPDATE ON MOLECULAR GENETICS IN ACUTE MYELOID LEUKEMIA POST MYELOPROLIFERATIVE NEOPLASMS

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Abstract. Myeloproliferative neoplasms (MPN) are indolent hematologic cancers that are characterized by excessive production of mature blood cells. Acute myeloid leukemia (AML) is an uncommon, but often deadly complication of these chronic disorders. In the last years significant progress has been made in the diagnostic algorithm and therapeutic management of AML postMPN.

Keywords: molecular genetics, mutations, myeloproliferative neoplasms, leukemic transformation, acute myeloid leukemia

Introduction

Myeloproliferative neoplasms (MPN) are a spectrum of clonal disorders of hematopoiesis characterized by proliferation of mature-appearing myeloid cells and accumulation of bone marrow fibrosis [1]. MPN initiation and progression can not be explained by a single pattern of clonal changes, but rather by the acquisition of a wide panel of genetic anomalies.

The molecular biology of the BCR-ABL1-negative chronic myeloproliferative neoplasms (MPNs) has witnessed unprecedented progress since the discovery of the acquired JAK2 V617F mutation in 2005, which was a turning point in the molecular diagnostic of these hematopoietic disorders [2].

But despite the high prevalence of JAK2V617F in polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), and the common finding of dysregulated JAK-STAT signaling in these disorders, it is now appreciated that MPN pathogenesis can reflect the acquisition of multiple genetic mutations that alter several biologic pathways, including epigenetic control of gene expression (2). Genetic studies have identified recurrent somatic alterations in the majority of MPN patients, including acquired mutations in JAK2 (JAK2V617F) in 90% of polycythemia vera (PV) patients and ~50% to 60% of patients with essential thrombocytosis (ET) and primary myelofibrosis [3-6].

It has been long recognized that patients with myeloproliferative neoplasms (MPNs) are at significant, cumulative risk of leukemic transformation to acute myeloid leukemia (AML), which is associated with adverse clinical outcome and resistance to standard

AML therapies [7]. Leukemic transformation occurs in 8% to 23% of MF patients in the first 10 years after diagnosis and in 4% to 8% of PV and ET patients within 18 years of diagnosis and is associated with a universally poor prognosis [8-10].

Post-MPN AML is characterized by acquired somatic gene mutations, but, interestingly, mutations such as JAK2V617F, who appear to have a major etiologic role in the MPN, are sometimes absent in the AML clone, which means that a substantial proportion of patients with AML derived from a JAK2-mutant MPN are negative for JAK2 [11,12,13].

Studies showed that somatic tumor protein 53 (TP53) mutations are common in JAK2V617F-mutant, post-MPN AML, but not in chronic phase MPN and lead to clonal dominance of JAK2V617F/TP53-mutant leukemic cells [7].

Certain gene anomalies are identified at higher frequencies with disease evolution to the blast phase. The most frequent mutations involved in AML derived from a preexisting MPN were identified in TET2, ASXL1, IDH1, and JAK2 [14-17].

In the majority of patients with JAK2-mutated MPN who progress to AML, the mutant clone is lost and TET2 mutations may be present in a clone distinct from that harboring a JAK2 wild-type cell. We could certainly affirm that in the pathogenesis of transformation to AML at least two different malignant clones are involved [18].

In contrast, ASXL1 mutations seemed to be detected in all phases of disease, and, most important, may precede the acquisition of JAK2 or even TET2 mutations in myeloblastic transformation [14,16].

Alterations in TET2 and ASXL1 can in some cases occur at an early stage of myeloid neoplasia, before the patient acquired a JAK2 mutation or even developed clinical evidence of MPN, which means that the acquisition of additional mutations leads to the development of clinically manifest disease phenotypes

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[14,15,16]. But although TET2/ASXL1 mutations may precede acquisition of JAK2 mutations by the MPN clone, mutations in TET2 and IDH1, but not ASXL1, are commonly acquired at the time of leukemic transformation [14,16,17].

Conclusion

Although TET2, ASXL1, and IDH1 mutations have been identified in patients with a spectrum of myeloid malignancies, the timing of acquisition of TET2/ASXL1/IDH1 mutations and the role of TET2/ASXL1/IDH1 mutations in progression from MPN to AML are not well known so far [14].

It seems that TET2 mutations are acquired after JAK2V617F or other myeloproliferative disorder disease alleles at the time of leukemic transformation of a JAK2V617F-positive or JAK2V617F-negative MPN clone. The mutational order of events in MPN and secondary AML varies in different patients, and TET2 and ASXL1 mutations have distinct roles in MPN pathogenesis and leukemic transformation, which maybe requires further research.

The presence of secondary AML that have no preexisting JAK2/TET2/ASXL1/IDH1 mutations, indicates the existence of other oncogenic alleles yet to be identified that are necessary for leukemic transformation [14].

All this progress made by genomic analysis of leukemic transformation occurred in MPN may have therapeutic implications who could improve the prognosis and outcome of these complex hematologic malignancies.

Conventional AML-style treatment appears to have limited efficacy in secondary AML emerging from MPN, although when coupled to allogeneic stem cell transplantation, some patients have long-term survival and prolonged DFS and OS (11). More likely, combinations of drugs that target different pathways will be required to develop successful therapeutic approaches in this disease. Less-intensive therapies/regimens such as hypomethylating agents appear to have significant clinical benefits in this group of patients. Combination of these agents with JAK1/ JAK 2 inhibitors, such as ruxolitinib, may add significant clinical benefits in some patients [19]. Also, both of these drugs seem to be well tolerated, with an acceptable toxicity profile, an important issue in the older age group [19].

More studies are needed in the future in order to emphasize the impact of genetic features on outcome and thus to optimize the therapeutic responses.

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