SOHO Supplement 2016

A Concise Update on Risk Factors, Therapy, and Outcome of Leukemic Transformation of Myeloproliferative Neoplasms

John Mascarenhas

Abstract

Myeloproliferative neoplasms (MPN) in chronic phase that evolve into blast phase (BP) hold a dismal prognosis and represent an urgent unmet clinical need. The mutational landscape of MPN-BP is distinct from de novo acute myeloid leukemia and offers insight into molecular mechanisms contributing to clonal evolution providing potential novel drug targets. A number of retrospective studies have identified patient- and disease-specific variables associated with increased risk of leukemic transformation (LT) of an underlying MPN. Several prognostic models have been developed to identify those MPN patients at highest risk for LT that may warrant early aggressive therapeutic intervention. Acute myeloid leukemia–type induction chemotherapy does not offer a significant survival benefit for MPN-BP unless followed by hematopoietic stem-cell transplantation. Unfortunately, most patients with MPN-BP are not candidates for hematopoietic stem-cell transplantation as a result of advanced age, competing comorbid conditions, or lack of an acceptable donor graft option. *JAK2* inhibitor monotherapy is effective in reducing splenomegaly and symptom burden in the majority of treated patients with myelofibrosis, but LT can still occur. High-dose *JAK2* inhibitor monotherapy appears tolerable but only modestly active in the treatment of MPN-BP. Current *JAK2* inhibitor–based combination therapy approaches are supported by preclinical investigation and are currently being tested in multicenter clinical trials.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 16, No. S1, S124-9 © 2016 Elsevier Inc. All rights reserved.
Keywords: Blast phase, Decitabine, *JAK2*, Leukemic transformation, Myeloproliferative neoplasm, Ruxolitinib

Introduction

Essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF) are Philadelphia chromosome–negative chronic myeloproliferative neoplasms (MPN) that are heterogeneous both in clinical course and outcome. MPN are recognized as clonal hematopoietic stem-cell malignancies characterized by bone marrow findings (myeloproliferation, megakaryocyte atypia, and varying degrees of reticulin and collagen fibrosis); abnormal hematologic profile; progressive organomegaly attributed to extramedullary hematopoiesis; and constitutional symptoms mediated by elevated inflammatory cytokines.[1,2] Thrombotic sequelae, bleeding diatheses, infectious complications, and evolution to acute leukemia can all affect morbidity and mortality in an MPN patient.[3,4]

Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

Submitted: Feb 9, 2016; Accepted: Feb 9, 2016

Address for correspondence: John Mascarenhas, MD, Icahn School of Medicine at Mount Sinai, One Gustave L Levy Place, Box 1079, New York, NY 10029
Fax: (212) 876-5276; e-mail contact: john.mascarenhas@mssm.edu

Hyperactivity of the JAK-STAT signaling pathway is now recognized as the cornerstone of MPN pathogenesis and has been linked to many facets of the disease: erythrocytosis in PV, thrombocytosis in ET, and systemic symptoms in PMF.[5] Driver mutations in *JAK2*, *MPL,* and *CALR* are identified in approximately 98% of patients with PV (*JAK2V617F*, *JAK2* exon 12) and 90% of patients with ET and myelofibrosis (MF) (*JAK2V617F*, *MPL515L/K*, *CALR* exon 9), and they appear to influence clinical phenotype.[6] Recently reports have demonstrated an association between triple-negative status (lack of mutation in *JAK2*, *MPL,* and *CALR*) and reduced overall survival (OS) and leukemia-free survival in patients with MF.[7] The acquisition of additional somatic mutations that are important for epigenetic regulation, cell signaling, and RNA splicing further contribute to disease progression and clonal evolution.[8,9] The molecular pathogenesis of MPN–blast phase (BP) remains an area of active research and is expertly addressed elsewhere.[10,11]

According to the World Health Organization, a patient with an underlying MPN and the presence of 10% to 19% blasts documented in either peripheral blood or bone marrow has MPN–accelerated phase disease and a minimum of 20% blasts in either blood or bone marrow has MPN-BP.[12] Although typically a peripheral blood blast

2152-2650/$ - see frontmatter © 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.clml.2016.02.016

percentage of at least 20% is seen in the case of MPN-BP, it is not uncommon to have discordance between the bone marrow blast percentage and the peripheral blood. This may be a result of clonal evolution from a site of extramedullary hematopoiesis such as the spleen.[13] Cases of MPN-related extramedullary leukemia have also been reported, and its unusual occurrence may be influenced by type of therapy.[14] Leukemic transformation (LT) of ET, PV, and PMF occurs at rates of approximately 1%, 4%, and 20%, respectively, over the first decade from time of MPN chronic phase diagnosis.[3,15]

Although MPN-BP is synonymous with acute myeloid leukemia (AML), it is increasingly appreciated that there are distinct differences at the molecular and clinical level.[11] Mutations involving *JAK2*, *IDH1/2*, *TP53*, *ASXL-1*, and *TET2* are more common in MPN-BP, whereas mutations in *N/KRAS*, *DNMT3a*, *NPM1*, and *FLT3* are more frequently observed in de novo AML.[8,10] A higher frequency of M6 and M7 morphologic subtypes by the French–American–British (FAB) classification are seen in MPN-BP compared to de novo AML.[16,17] The blast phenotype is most often myeloid, and distinct morphologic features of bone marrow megakaryocytes have been reported.[15,17,18] Favorable AML karyotype is infrequently seen in MPN-BP compared to de novo AML.[8] Unlike de novo AML, the median survival for MPN patients with LT is < 6 months, and induction chemotherapy (IC) response rates and overall outcome remain dismal.[15-17,19-23] Therefore, the laboratory and clinical investigation of MPN-BP should be separated from that of de novo AML.

Risk Factors for Development of LT

The identification of patient- and disease-specific risk factors for LT of an MPN has important implications within a risk-adapted treatment paradigm. A number of retrospective analyses have identified adverse prognostic factors associated with evolution to MPN-BP.[10] These include patient-specific factors (advanced age, prior exposure to certain MPN-directed therapies, splenectomy) and disease-specific factors (presence of circulating peripheral blood or bone marrow blasts, leukocytosis, anemia, thrombocytopenia, abnormal karyotype). It is unproven whether therapeutic modification of disease-specific variables will necessarily result in reduction in risk of LT. However, it is widely believed that a treatment approach that results in elimination of circulating blasts, karyotypic abnormalities, and molecular aberrations would imply arrest in LT and consequently improved survival.

Exposure to cytoreductive therapies such as chlorambucil, busulfan, and radioactive phosphorus (P32), erythropoietic agents such as erythropoiesis-stimulating agents and danazol, and surgical interventions such as splenectomy have all been linked to increased risk of LT. These have been reviewed extensively elsewhere.[10] Despite considerable controversy and concern, prospective data do not support hydroxyurea as a leukemogenic agent.[24-29] At present, there is no evidence to suggest leukemogenicity of ruxolitinib or any of the *JAK2* inhibitors in clinical testing. It is important to emphasize that evolution of an MPN to acute leukemia appears to be part of the natural history of the disease, which can occur independent of exposure to chemotherapeutic agents.

Prognostication and LT

MPN prognostication is an essential component of a personalized-medicine approach that applies a risk-based treatment plan for a given individual. This is particularly important when considering therapeutic goals and treatments in a patient with MF. Approximately a third of MF patients will die from direct consequences of LT.[3] Although several prognostication tools (Lille classification, International Prognostic Scoring System [IPSS], Dynamic IPSS [DIPSS], and DIPSS-Plus) have been developed in recent years to aid in this effort, the DIPSS-Plus specifically identified thrombocytopenia ($< 100 \times 10^9$/L) and unfavorable karyotype (8, 7/7q−, i(17q), 5/5q−, 12p−, inv(3), or 11q23 rearrangement) as independent predictors of leukemia-free survival.[3,30-32] Low risk (neither factor present) and high risk (at least 1 factor) were associated with 10-year risk of LT of 12% and 31%, respectively. Tefferi et al have also previously identified a cohort of PMF patients with $>$ 80% 2-year mortality.[33] This very high risk group is characterized by the presence of monosomal karyotype, inv(3)/i(17q) abnormalities, or any 2 of the following variables: circulating blasts $>$ 9%, leukocytes $\geq 40 \times 10^9$/L, or other unfavorable karyotype. The median survival of this very high risk group was only 9 months, with a significantly elevated risk of developing AML compared to the DIPSS high risk group of 31% versus 7%, respectively.

Karyotyping has proven to be a valuable tool in prognostication and prediction of risk for LT. Table 1 lists cytogenetic abnormalities associated with an increased risk of developing MPN-BP.[35,37] Molecular profiling of myeloid malignancies has become routine in many academic and community practices. Table 1 lists the genetic alterations associated with increased risk of LT in the setting of MPN. Rumi et al have demonstrated the prognostic influence of driver mutation (*JAK2*, *MPL*, *CALR*) status on survival and risk of LT.[7] In this retrospective analysis of 617 MF patients, the 10-year cumulative incidence of LT was 19.4%, 16.9%, 9.4%, and 34.4% in patients harboring a mutation in *JAK2*, *MPL*, or *CALR* and those lacking all 3 (triple negative), respectively. More recently, several groups have incorporated mutational profiling to further refine

Table 1 Karyotypic and Molecular Abnormalities Associated With Increased Risk of Leukemic Transformation of Underlying Myeloproliferative Neoplasm

Abnormality	Study
Cytogenetic Finding	
Abnormal karyotype	Dupriez 1996[31]
Chromosome 17 abnormality	Tam 2009[34]
Monosomy Karyotype	
1q, 7q, 5q, 6p, 7p, 19q, 22q, and 3q, del17p, −5, −7, and/or complex	Vaidya 2011[35]
+8, −7/7q−, i(17q), −5/5q−, 12p-, inv(3), 11q23 rearrangement, complex	Gangat 2011,[30] Caramazza 2011[36]
del17p, −5, −7, and/or complex	Quintas-Cardama 2013[37]
Genetic Finding	
Triple negative (*JAK2, CALR, MPL*)	Tefferi 2014,[38] Rumi 2014[7]
IDH1/2, SRSF2, ASXL1	Vannucchi 2013[39]
IDH1/2	Tefferi 2012[40]
SRSF2	Zhang 2012[41]
ASXL1, SRSF2	Vannucchi 2014,[39] Tefferi 2014[42]

Download English Version:

https://daneshyari.com/en/article/2754416

Download Persian Version:

https://daneshyari.com/article/2754416

Daneshyari.com