Acta Haematologica Polonica 2021
Number 4, Volume 52, pages 278–283
DOI: 10.5603/AHP.2021.0054
ISSN 0001–5814
e-ISSN 2300–7117

REVIEW ARTICLE

Therapy of Philadelphia-negative myeloproliferative neoplasms in the blast phase

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Abstract

All four Philadelphia negative myeloproliferative neoplasms: essential thrombocythemia, polycythemia vera, pre-fibrotic myelofibrosis, and myelofibrosis, are at risk of transforming to blast phase disease. The risk is highest in the case of myelofibrosis and amounts to c.20%. In the case of essential thrombocythemia, the transformation rate is 1%, and in polycythemia vera it is 5–10%. The prognosis of patients during the blast crisis is poor, with a median survival time of a few months. For patients who qualify for intensive therapy, the basis of treatment are cycles analogous to those in acute myeloid leukemia and allotransplantation of hematopoietic stem cells. In the remaining patients, hypomethylating drugs such as azacitidine and decitabine can be used. Some hope has been raised by new drugs approved for the treatment of patients with acute myeloid leukemia such as venetoclax, IDH1 and IDH2 inhibitors ivosidenib and enasidenib. It is very important that patients with myeloproliferative neoplasms, especially those with myelofibrosis, properly assess the risk of blast transformation and qualify them early enough for allotransplantation of hematopoietic stem cells. New prognostic scales taking into account molecular factors can be very helpful in the assessment. This article discusses the risk factors of blast transformation, and prognostic scales as well as therapies that can be used during the blast crisis, including new drugs.

Key words: MPN blast phase, blast phase risk factors, treatment

Acta Haematologica Polonica 2021; 52, 4: 278–283

Introduction

The World Health Organization (WHO) classification system distinguishes four classic Philadelphia negative myeloproliferative neoplasms (MPN): primary myelofibrosis (PMF), pre-fibrotic PMF (pre-PMF), essential thrombocythemia (ET), and polycythemia vera (PV) [1]. In addition, 5–30% patients with ET or PV experience fibrotic progression of their disease over time, referred to as post-ET and post-PV myelofibrosis (MF), respectively [2]. All of these entities may evolve into blast phase disease (MPN-BP), defined by the presence of ≥20% blasts in the blood or bone marrow [2]. A second but closely related entity is accelerated phase (MPN-AP), defined as an elevation of peripheral or bone marrow blasts of between 10% and 20% [3].

The transformation frequency is the lowest for ET at roughly 1%, and highest for PMF and post ET/PV MF at about 20%. In the case of PV and pre-PMF about 5–10% of patients transform to the blast phase (BP) [4–6]. MPN-BP is associated with an aggressive course and very poor prognosis, with salvage chemotherapy and allogeneic stem cell transplant (allo-SCT) being the only curative treatment options [7, 8].

This paper discusses new prognostic scales that can facilitate the proper prognosis and selection of risk adapted therapy for patients with MPN, which may prevent at least some of them from progressing to the blast phase. The current possibilities of treating patients with MPN-BP are also discussed.

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Received: 03.05.2021 Accepted: 24.05.2021

Assessment of risk factors for blast transformation in patients with ET and PV

In PV and ET, leukemic transformation is a rare, usually late, complication. The interval between diagnosis and evolution to acute myeloid leukemia (AML) is highly variable, from a few years to 20 years [5, 6].

It is very important to distinguish ET from pre-PMF, which is the entity defined for the first time by the 2016 WHO criteria [1]. This is possible only with the close correlation of clinical, molecular and histopathological data. Compared to ET, patients with pre-PMF have a higher risk of transformation to AML and shorter overall survival (OS) [9]. Passamonti et al. [10] analyzed the course of disease among 605 patients with ET (follow-up 4,596 person-years). Leukemia occurred in 14 patients (2.3%) at a median 11 years after diagnosis of ET; the risk was 2.6% at 10 years. Age >60 years (p =0.02) was significantly correlated with the development of leukemia. Cytotoxic treatment did not imply a higher risk of leukemia. Among 605 patients with ET analyzed by Gangat et al. [5] followed for a median of 84 months, leukemic transformation was observed in 20 patients (3.3%). In multivariate analysis, hemoglobin level below normal and platelet count ≥1,000 $\times 10^9$/L were identified as independent risk factors for leukemic transformation.

The European Collaboration on Low-dose Aspirin in Polycythemia Vera (ECLAP) prospective project included 1,638 patients with PV [6]. AML/myelodysplastic syndrome (MDS) was diagnosed in 22 patients after a median of 2.5 years from recruitment in the study and a median of 8.4 years from the diagnosis of PV. Older age was confirmed as the main independent risk factor. Exposure to radioactive phosphorus (P32), busulphan, and pipobroman were also identified as risk factors of progression to AML compared to treatment with phlebotomy or interferon. Tefferi et al. [11] analyzed the course of PV in a group of 545 patients. A total of 50 (3%) cases of post-PV AML were documented and occurred at a median of 10.8 years (range 0.5–22.3) from diagnosis. Cumulative hazard of leukemic transformation was 2.3% at 10 years and 5.5% at 15 years. Risk factors included older age, abnormal karyotype, and leukocytes >15 $\times 10^9$/L. Leukemic transformation was associated with treatment exposure to pipobroman or P32/chlorambucil. Similarly to previous large retrospective and population-based studies, they did not observe an association between leukemic transformation and hydroxyurea use [6, 12].

Bonicelli et al. [12] observed transformation to AML in 30 (9.2%) of 327 PV patients (median follow up 11 years). The median time from PV diagnosis was 55.4 months (range: 27–262 months) and the cumulative risk of leukemia was 8%, 14% and 17% after 10, 15 and 20 years, respectively. Using Cox multivariate analysis, only female sex was identified as a risk factor of AML, whereas age >70 years, leukocytosis >13 $\times 10^9$/L and thrombosis at diagnosis remained significant predictors of survival.

In recent years, the introduction of the NGS (next-generation sequencing) technique has allowed the identification of many additional (except for driver mutations) somatic mutations in patients with MPN. These include mutations of genes involved in the post-translational modification of histones (*ASXL1*; frequency 10–35%, *EZH2*; frequency 7–10%), DNA methylation (*TET2, DNMT3A, IDH1 /2*), mRNA splicing (*SRFS2, SRF3B1, U2AF, ZRSR2*) and DNA repair processes (*TP53*). Recent publications have highlighted the prognostic contribution of so-called high molecular risk (HMR) mutations (*ASXL1, EZH2, SRSF2, IDH1/2, U2AF1*) [13–17]. Tefferi et al. [14] showed that spliceosome mutations *SF3B1, SRSF2* in ET and *SRSF2* in PV adversely affect OS. They also revealed that *TP53* mutations predicted leukemic transformation in ET. Luque Paz et al. identified three molecular groups associated with a distinct time to leukemic transformation in PV and ET [13]. Short-term transformations were mostly characterized by a complex molecular landscape and mutations in *IDH1/2, RUNX1*, and *U2AF1* genes, whereas long-term transformations were associated with mutations in *TP53*, *NRAS*, and *BCORL1* genes. Considering the important role of molecular landscape on prognosis in PV and ET, Tefferi et al. [14] constructed the three-tiered mutation-enhanced international prognostic systems (MIPSS) which takes into account male sex, leukocyte count ≥11 $\times 10^9$/L, HRM in ET, and age >60 years, thrombosis history, leukocyte count ≥15 $\times 10^9$/L in PV.

Assessment of risk factors for blast transformation in patients with MF

Among classic myeloproliferative neoplasms, the highest risk of blast transformation concerns patients with MF and amounts to approximately 20% [4, 7]. Myelofibrosis is a disease with a very heterogeneous course; therefore, it is important to properly assess the risk of blast transformation and implement an appropriate, risk-adjusted therapy.

It seems that the type of driver mutation influences the course of PMF. Patients with type 1 *CARL* mutation are younger, have a higher platelet count, lower leukocytosis, require less frequent red blood cell transfusions, have fewer unfavorable epigenetic mutations, are in lower risk groups, and have significantly longer OS compared to patients with *JAK* (+) and *MPL* (+) [15–17]. On the other hand, 'triple negative' patients have a particularly poor prognosis as they have a significantly shortened OS and an increased risk of leukemic transformation [18, 19]. Also, patients with the previously described HMR mutations have a shorter OS and a higher risk of blast transformation [15–17].

In a significant percentage of patients with PMF (30–50%), karyotype abnormalities occur at the time of diagnosis. The most common aberrations include del (13q), del (20q), trisomy 8, trisomy 9, del (12p), and 1q abnormalities. Complex karyotypes occur in about 15% of cases [20]. The presence of certain cytogenetic abnormalities, such as complex karyotype, chromosome 5 and 7 abnormalities, are associated with a significantly higher risk of transformation to AML [20].

So far, prognostic indices such as IPSS (International Prognostic Scoring System), and DIPSS (Dynamic International Prognostic Scoring System), and DIPSS plus, have been used to assess the prognosis of patients with PMF [21–23]. Due to the growing understanding of the prognostic significance of mutations, several prognostic indices have been published that also take into account molecular changes. In 2018, Guglielmelli et al. [24] proposed the MIPSS70 and MIPSS70 plus indices, taking into account both clinical data and molecular and cytogenetic tests. The MIPSS70 index takes into account the following risk factors: Hb <100 g/L, leukocytes >25 $\times 10^9$/L, platelets <100 $\times 10^9$/L, peripheral blood blasts >2%, bone marrow fibrosis >grade 2, presence of constitutional symptoms, absence of type 1 *CALR* mutation, presence of HMR epigenetic mutation, and presence of at least two HMR mutations. Depending on the number of risk factors, patients are classified into three risk groups: low, intermediate, or high, with median OS of 27.7; 7.1, and 2.3 years, respectively. The MIPSS70-plus index additionally takes into account changes in karyotype. Currently, it is recommended to use the new version of MIPSS70+ (MIPSS70+ vs. 2.0 index) [25]. This additionally takes into account the division into very unfavorable and unfavorable karyotype as well as moderate and severe anemia. Tefferi et al. [26] proposed a prognostic model that takes into account only molecular and cytogenetic changes. This is known as GIPSS (Genetically Inspired Prognostic Scoring System for primary myelofibrosis). As risk factors, it considers changes in karyotype, absence of type-1 *CALR* mutations, and presence of epigenetic mutations *ASXL1, SRSF2* and *U2AF1Q157.*

In the case of myelofibrosis secondary to PV or ET, a separate prognostic scale, MYSEC-PM (Myelofibrosis Secondary to PV and ET-Prognostic Model), is recommended [27].

It should be emphasized that, whenever possible, molecular risk factors should be taken into account, especially when deciding whether to qualify patients for allo-SCT. New prognostic indices allow for a more accurate assessment of the expected survival time. It has been shown that, using the MIPSS70 index, nearly 30% of patients with low and intermediate risk-1 according to IPSS are in a high-risk group, with an expected OS of only 2.3 years [24]. All patients with high-risk myelofibrosis eligible for transplantation should be offered this treatment option before the disease progresses to an accelerated or blast phase.

Treatment of MPN blast phase

Patients in the blast phase of MPN have a poor prognosis, with an expected OS of several months. Post MPN AML is more often characterized by unfavorable changes in karyotype than in *de novo* disease [4, 7, 8]. Tefferi et al. [8] retrospectively reviewed the results of treatment of 410 MPN-BP patients: 248 from the Mayo Clinic and 162 from Italy. Among 248 patients with MPN BP from the Mayo Clinic, cytogenetic information was available in 172 cases, of which 140 (81%) were reported as abnormal and 32 (19%) as normal; among the 140 abnormal cases, 56 (40%) were labelled 'high risk' based on the presence of monosomal karyotype or monosomy 7 (n =46), or single or multiple abnormalities including inv(3)(q21.3q26.2)/t(3;3)(q21.3;q26.2) (n =5), or i(17)(q10) (n =5). Median OS in the entire group of patients was only 3.6 months, with no improvement over the last 15 years. Multivariate analysis performed on the Mayo cohort identified high risk karyotype, platelet count <100 $\times 10^9$/L, age >65 years and transfusion need as independent risk factors for survival. Intensive chemotherapy (AML-like induction chemotherapy) resulted in complete remission (CR) or CR with incomplete count recovery (CRi) rates of 35% and 24%, respectively; treatment-specified 3-year/5-year survival rates were 32%/10% for patients receiving allo-SCT (n =24), 19%/13% for patients achieving CR/CRi but who were not transplanted (n =24), and 1%/1% in the absence of both allo-SCT and CR/CRi (n =200) (p <0.01). Similar results were presented by Kennedy et al. [28]: among 75 patients with MPN-BP, 39 received AML-like induction chemotherapy followed by allo-SCT in eligible patients (17 of 39). The 36 other patients were treated with hypomethylating agents (HMA), novel agents, or supportive care. Two-year survival was 25.6% in the intensive treatment group compared to 3% for the rest. Moreover, survival was significantly better in the transplant group (2-year survival of 47% vs. 15%; p =0.03). The MPN Subcommittee of the Chronic Malignancies Working Party of the European Society for Blood and Marrow Transplantation studied 46 patients with MPN-BP who received allo-SCT [30]. Before SCT, 42 patients (91%) received induction chemotherapy. Of the 38 patients evaluable for response, nine (24%) achieved CR, 10 (26%) achieved partial response (PR), and 19 (50%) were refractory or had progressive disease at the time of SCT. The 3-year progression-free (PFS) and OS rates were 26% and 33%, respectively. The only significant factor for survival was CR vs. no CR before transplantation (69% vs. 22%, p =0.008); however, CR was achieved only in eight patients.

A new liposome formulation of cytarabine and daunorubicin used in AML induction therapy is CPX-351. This drug has proven efficacy in the treatment of the elderly, especially in the case of therapy-related AML and with antecedent MDS or chronic myelomonocytic leukemia (CMML) [30]. Therefore, it would be advisable to use it in the case of MPN-BP.

In patients who are not eligible for intensive chemotherapy, HMA such as azacytidine or decitabine can be used [31, 32]. Thepot et al. [31] reported the azacytidine treatment outcomes of 52 patients with MPN-BP who transformed to AML (n =26) or MDS (n =28). Overall response rate (ORR) was 52% (24% CR, 11% PR, 8% marrow CR or CRi, 9% hematologic improvement) and median OS was 11 months. Prognostic factors for CR achievement were the underlying MPN (14% CR for PV vs. 43% for ET; p =0.040) and type of transformation (36% vs. 12% CR in MDS and AML, respectively; p =0.038). Badar et al. [32] conducted a retrospective study of 21 patients with MPN--AML and 13 with MPN-AP treated with decitabine. Six patients (29%) with MPN-AML responded to decitabine (three CR, two CRi, and one PR); median response duration was 7 months. Median OS was significantly higher in those who responded (10.5 vs. 4 months). Among patients with MPN--AP, eight (62%) benefited; median response duration was 6.5 months. Median OS was 11.8 months in responders vs. 4.7 months in non-responders.

Although ruxolitinib monotherapy has very limited efficacy in the advanced stages of MPN [33], its addition to HMA or low doses of cytosine arabinoside may be a therapeutic option [34].

New targeted therapies have recently been approved for treating AML patients, such as venetoclax, IDH1 and IDH2 inhibitors ivosidenib and enasidenib [35–37]. Considering that MF is a disease characterized by the overexpression of the antiapoptotic BCL-2 family of proteins, and IDH mutation occurs in approximately 30% of patients with MF blast phase, it seems that they may turn out to be valuable drugs also for patients with MPN-BP [38–40]. So far, experience with the new drugs is limited, but promising.

Morsia et al. retrospectively analyzed 14 consecutive MPN-BP patients who received venetoclax plus HMA and observed a high rate of ORR [41]. Venetoclax was administered in combination with azacitidine (n =5) or decitabine (n =9). Median age of patients was 67 years with poor-risk cytogenetics in 69% of patients. In 1/2 patients with myeloid sarcoma, partial resolution of the extramedullary tumor was observed. Among the remaining 12 patients, ORR was 42% (n =5) and included CR in three patients (25%) and PR in another two (17%). Cahill et al. retrospectively assessed 15 patients with *IDH1/2*-mutated AML arising from antecedent MPN (seven MPN-BP, one MPN-AP, five MDS--AML, and two CMML-AML) [42]. Thirteen *IDH2* mutated patients received enasidenib as monotherapy (n =12) or combined with azacytidine (n =1). Two *IDH1*-mutated patients received ivosidenib as monotherapy (n =1) or combined with azacytidine (n =1). ORR rate to IDH inhibitor therapy was 40% for the entire group, and 75% for eight patients with MPN-AP/BP (when using the 2012 MPN-BP response criteria). Median OS for all patients was 235 days, and for patients with MPN-AP/BP was not reached.

Conclusions

Allo-SCT, preceded by AML-like induction chemotherapy, is proven to be the only treatment modality that improves at least short-term survival of patients with MPN-BP. However, in the majority of patients SCT is not a feasible option due to advanced age, co-morbidities and poor performance status. For them, the best treatment option remains azacytidine or decitabine. New drugs such as venetoclax and *IDH1/2* inhibitors are raising hopes.

Due to the very poor prognosis of patients in the blast phase of MPN, and the lack of effective treatment options in this phase, care should be taken to prevent transformation.

It is very important that drugs that have leukemogenic potential, such as pipobroman, chlorambucil, and radioactive phosphorus, should be avoided during the chronic phase of the disease. It is also very important to properly assess the risk of transformation (correct diagnosis, new prognostic scales) and select the appropriate therapy early in the course of the disease.

Author's contributions

AG-T — sole author.

Conflict of interest

None.

Financial support

None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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