Review article

UDC: 616.155-07-08
doi:10.5633/amm.2021.0212

CONTEMPORARY APPROACH IN THE DIAGNOSIS AND MANAGEMENT OF PRIMARY MYELOFIBROSIS

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Primary myelofibrosis (PMF) is an infrequent chronic myeloproliferative neoplasm. PMF is a result of clonal expansion of myeloid cells and is distinguished by the variable presence of mutations, morphologically by increased proliferation of megakaryocytes, progressive bone marrow fibrosis, hepatosplenomegaly, anemia, leukoerythroblastosis, with constitutional symptoms and shortened survival. World Health Organization defined the current diagnostic criteria for PMF in 2016, which involve a combined assessment of clinical, histological, mutational and laboratory features of diseases. Recently, a several new PMF prognostic scoring systems have started being used in the clinical practice, which are based solely on genetic markers or include clinical variables in addition to mutations and karyotype. In the treatment of myelofibrosis, risk adapted therapy has been applied, which implies the selection of the type of therapy according to the risk category obtained by calculating the valid prognostic scores. Allogenic stem cell transplant remained the only potentially curative therapy for PMF treatment but is suitable only for a small number of high risk patients who have a matching donor. In the last decade, the development and approval of ruxolitinib for the treatment of PMF has been of the greatest importance in the treatment of this disease, although it is a palliative therapy. Ruxolitinib is a potent JAK1/JAK2 inhibitor that leads to decreases in splenomegaly and symptoms and has prolonged overall survival in patients with this disease.

Acta Medica Medianae 2021;60(2):96-105.

Key words: *primary myelofibrosis, prognostic modeling, treatment*

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Introduction

Myeloproliferative neoplasms (MPNs) are clonal diseases of hematopoietic stem cells distinguished by excessive production of terminally differentiated myeloid lineage cells. MPN are associated with clinical conditions that significantly shorten the overall survival and reduce the patient's quality of life (1). Myelofibrosis (MF) belongs to the group of BCR-ABL1 negative clonal myeloproliferative disorders. Myelofibrosis encompasses primary myelofibrosis (PMF), prefibrotic-myelofibrosis (PF-MF), and post-polycythaemia vera myelofibrosis (post PV-MF) or post-essential thrombocythaemia myelofibrosis (post ET-MF) that occur after PV and ET (2, 3). PMF is a heterogeneous disease, not only in terms of clinical and hematological manifestations, but also in terms of prognosis. It is characterized by megakaryocytes proliferation, reactive bone marrow fibrosis, peripheral blood leukoerythroblastosis, anemia, hepatosplenomegaly, and constitutional symptoms (4). MF belongs to a group of rare diseases that usually occur in elderly people, with an average survival of 6 years, which can vary from 1 year to more than 2 decades (5, 6).

The true cause of myelofibrosis is still unknown, but multiple pathogenetic mechanisms are considered responsible for the main features of the disease: genetic mutations, cytokine overproduction and stem cell-derived clonal myeloproliferation (7). In primary myelofibrosis somatic mutations are categorized into two groups: "driver" mutations that are associated with JAK-STAT hyperactivation, JAK2, MPL, and CALR in addition "other" mutations connected to epigenetic dysregulation in some. The existence of mutations in the JAK2 and MPL genes causes constitutive activation of the JAK2/STAT signaling pathway leading to increased production of myeloid and megakaryocyte progenitors. CALR gene encodes calreticulin, a significant role-playing protein in intracellular signaling, gene expression regulation, Ca2+ storage, apoptosis, cell adhesion and autoim-

mune response (8). Research has shown that in PMF, 45%-68% of patients are carriers of the JAK2 V617F mutation, MPL mutations occur in 5%-10% and CALR mutations hold 25%-35% of patients. It is assessed that around 9% of patients with PMF have no "driver" mutations, when the disease is referred to as "triple-negative" PMF, which is considered to be an indicator of a poor prognosis. Superior overall survival of CALR-mutated MF compared to JAK2-mutated or "triple-negative" patients has been reported in several studies (9, 10, 11). In a large Italian study by Rumi et al. (12), the median overall survival was longest in patients with a CALR mutation of 17.7 years, while the shortest survival of 3.2 years was found in triple-negative patients.

"Driver" mutations may be associated with "other" mutations whose effect on pathogenesis has not yet been fully elucidated like ASXL1, SRSF2, IDH1/2, EZH2, TET2, DNMT3A and CBL. It is widely accepted that "other" mutations have affected disease progression and leukemic transformation while "driver" mutations are all-important for the MPN phenotype. The ASX1, EZH2 and SRSF2 mutations have been related with shorter survival, and AXL1, SRSF2 and IDH1/2 mutations with increased risk of leukemic transformation compared with patients without mutations (9, 13). The previously mentioned mutations are included in the group of so-called High Molecular Risk (HMR) mutations, and it was found that 24%-35% of patients carry one mutation and 7%-9% carry at least 2 mutations (14). The presence of U2AF1Q157 mutation was shown to be correlated with shorter overall survival and anemia, but not with poor leukemia-free survival, in contrast to other high molecular risk mutations (15).

This article will address the impact of genetic mutations on the diagnosis and development of new prognostic models in patients with myelofibrosis. The application of risk adapted therapy and different current treatment options will also be analyzed.

Diagnosis

The latest classification of myeloid malignant diseases by the World Health Organization of 2016 recognizes two categories: acute myeloid leukemia and linked neoplasms and chronic myeloid neoplasms, with the latter category including MPN to which PMF belongs (16). World Health Organization defined the current criteria for PMF diagnosis in 2016 (17) which present a complex evaluation of clinical, histological, mutational and laboratory features as represented in Table 1.

Table 1. World health organization (WHO) 2016 revised diagnostic criteria for primary myelofibrosis

Primary myelofibrosis (prefibrotic)	Primary myelofibrosis (overtly fibrotic)
Major criteria 1. Typical megakaryocyte changes, an accompanied by ≤ grade 1 reticulin/collagen fibrosis 2. Not meeting the WHO criteria for other myeloid neoplasms 3. Presence of JAK2, CALR or MPL mutations, or presence of other clonal markers, or absence of evidence for reactive bone marrow fibrosis	**Major criteria** 1. Typical megakaryocyte changes, an accompanied by ≥ grade 2 reticulin/collagen fibrosis 2. Not meeting WHO criteria for other myeloid neoplasms 3. Presence of JAK2, CALR or MPL mutations, or presence of other clonal markers, or absence of evidence for reactive bone marrow fibrosis
Minor criteria a. Anemia not attributed to a comorbid condition b. Leukocytosis ≥ $11x10^9$/L c. Palpable splenomegaly d. Increased serum lactate dehydrogenase	**Minor criteria** a. Anemia not attributed to a comorbid condition b. Leukocytosis ≥ $11x10^9$/L c. Palpable splenomegaly d. Increased serum lactate dehydrogenase e. Leukoerythroblastosis
Diagnosis requires meeting all 3 major criteria and one minor criterion	Diagnosis requires meeting all 3 major criteria and one minor criterion

The difference from the previous WHO diagnostic criteria of 2008 is the definition of prefibrotic myelofibrosis as a new entity of the disease. Prefibrotic MF and ET remain entities that are frequently difficult to distinguish but this can be achieved using histomorphological findings and occurrence of minor clinical criteria (18). In addition, it is necessary to make a difference between prefibrotic and overtly

fibrotic PMF on the basis of clinical data of prodromal stages of PMF which are distinguished by mild anemia, minimal splenomegaly, absence of leukoerythroblastosis but with the presence of thrombocytosis and a morphological presence of fibrosis grade 0-1 (17, 19).

Prognostication in myelofibrosis

PMF prognostic models have been devised and introduced into clinical practice to suggest the most suitable therapy for each patient individually (20). The International Prognostic Scoring System (IPSS) has been in use since 2009 (5) and developed with the purpose of assessing the prognosis at the initial diagnosis time. IPSS uses five predictors for shortened survival: age > 65 years, hemoglobin < 10 g/dL, leukocyte count > 25×10^9/L, circulating blasts ≥ 1% and the presence of constitutional symptoms. Depending on the presence of unfavorable factors, four risk categories of low, intermediate-1, intermediate-2 and high were defined, which correlated with median survivals from 11.3 years to 2.3 years.

In the year 2010, the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) (6) established a dynamic prognostic model (DIPSS) based on the same five variables as IPSS, that may be used whenever during the disease and be helpful for treatment decision-making. In DIPSS for hemoglobin < 10 g/dL two negative points were awarded. In low risk patients the respective median of survival was not attained, while in high risk patients it was 1.5 years. Next year, the DIPSS-plus system additionally included an unfavorable karyotype presence that contained +8, -7/7q, i(17q), inv(3), -5/5q-, 12p- or an 11q23 rearrangement, transfusion dependency and thrombocytopenia. There are also four risk categories for DIPSS-plus, with appropriate median survivals from 15.4 years to 1.3 years (21).

During the year 2018, MIPSS70 (mutation-enhanced international prognostic scoring system for transplant-age patients), a newer prognostic model, was being utilized. It encompassed clinical features plus mutations and karyotype to be pertinent for transplant decision making in patients with PMF. Table 2 summarizes a few of the latest prognostic models in PMF.

Table 2. Novel prognostic models in myelofibrosis

Prognostic models	MIPSS70	MIPSS70+ version2.0	GIPSS	MPN personalized risk calculator
Criteria	Hb < 100 g/L (1 point) WCC > 25×10^9/L (2points) PB blasts ≥ 2% (1point) Constitutional Sx (1point) Plt < 100×10^9/L (2points) BM fibrosis Gr ≥ 2 (1point) Absence of *CALR* Type 1/like mutations (1point) HMR category (1point) ≥ 2HMRmutations (2points)	Severe anemia (2points) Moderate anemia (1point) PB blasts ≥ 2% (1point) Constitutional Sx (2points) VHR karyotype (4points) Unfavorable karyotype (3points) ≥ 2 HMR mutations (3points) One HMR mutation (2points) Type 1/like CALR absent (2 points)	VHR karyotype (2points) Unfavorable karyotype (1point) Type1/like CALAR absent (1point) ASXL1 mutation (1point) SRS2 mutation (1point) U2AF1Q157 mutation (1point)	Age at diagnosis Hb WCC Platelet count Gender Prior Thrombosis Splenomegaly *JAK2 V617F* *MPL* *CALR* *JAK2 Exon 12* Other mutation [a]
Risk groups (median survival)				
Very low Low Intermediate-1 Intermediate Intermediate-2 High Very high	0-1 point (27.7y) 2-4 points (7.1y) ≥ 5 points (2.3y)	0 point(not reached) 1-2 points (16.4y) 3-4 points (7.7y) 5-8 points (4.1y) ≥ 9 points (1.8y)	0 point (26.4y) 1 point (8.0y) 2 points (4.2y) ≥ 3 points (2y)	N/A as risk personalized and not grouped

MIPSS-Mutation enhanced international prognostic scoring system;
MIPSS70+ version 2.0: mutation and karyotype enhanced international prognostic system;
GIPSS-Genetic inspired prognostic scoring system; Hb-Hemoglobin; WCC-white cell count; PB-peripheral blood;
Sx-symptoms; HMR: high molecular risk mutations include ASXL1, SRSF2, EZH2, IDH1, IDH2 and, in addition, for GIPSS and MIPSS70+ version 2.0, U2AF1Q157;
VHR: very high risk karyotype. Severe anemia: Hemoglobin < 8 g/dL in women and < 9 g/dL in men. Moderate anemia: Hemoglobin 8-9.9 g/dL in women and 9-10.9 g/dL in men.

MIPSS70 includes nine variables, tree genetic and six clinical risk factors. MIPSS70 prognostic model has tree risk categories with appropriate median survival rates from 2.3 years to 27.7 years (22). MIPSS70+ prognostic model includes 7 independent variables, of which four aregenetic (CALR type 1/like mutation absence; HMR presence; more than 2 HMR presence; and "unfavorable" karyotype) and three are clinical risk factors (hemoglobin < 10 g/dl; circulating blasts ≥ 2%; and constitutional symptoms). There are four levels of risk categories in MIPSS70+, low (0-2 points), intermediate (3 points), high (4-6 points), and very high risk (≥ 7 points) with an approximated average survival of 20 years, 6.3 years, 3.9 years, and 1.7 years (23). A few months later, the same authors presented revised MIPSS70+ version 2.0 because they had recognized U2AF1Q157 as an added HMR mutation (23) and defined new hemoglobin thresholds accommodated for sex and severity (24), so this score includes 5 genetic and 4 clinical factors. MIPSS70+ version 2.0 considered five risk patient groups with significantly different median survival of 1.8 years to 16.4 years and "median not reached" (25).

GIPSS prognostic scoring system is based solely on genetic markers. GIPSS encompasses the following variables: "Very high risk" (VHR) karyotype (-7, i(17q), inv(3)/3q21, 12p-/12p11.2, 11q-/11q23,+21, or other autosomal trisomy's, not including +8/+9), "unfavorable" karyotype, absence of type 1/like CALR mutation and presence of ASXL1, SRSF2, or U2AF1Q157 mutation, as interindependent predictors for poor survival. GIPSS recognizes four categories of risk with different survival lengths from 26.4 years to 2 years (26).

Latterly, Grinfeld et al. (27) developed the "MPN personalized risk calculator" which predicts the clinical outcome for each individual patient based on the analysis of available clinical, laboratory and genomic characteristics of patients with myeloproliferative neoplasms. The authors linked disease characteristics and 69 myeloid cancer genes and created prognostic models that allow personal prediction of clinical outcome. This prognostic model showed superior performance compared to the prognostic models used until then. The combination of genetic and clinical characteristics enabled personalized prediction of clinical outcomes and may be helpful in choosing the type and intensity of therapy.

Risk-adapted therapy

During several years, risk adapted therapy was applied in the treatment of myelofibrosis, which implies that the selection of the type of therapy was made according to the risk category obtained by calculating the valid prognostic scores. In patients with determined genetic markers, the use of myelofibrosis treatment algorithm based on the revised MIPSS70+ version 2.0 prognostic scoring system and treatment algorithm based on GIPSS risk stratification is recommended (25, 26). Patients belonging to the high-risk group according to GIPSS correlate with the group of high-risk and very high-risk patients according to MIPSS70 + version 2.0. and involves the use of allogenic stem cell transplant (ASCT) in transplant eligible patients as the only ones potentially curative therapy and therapy that can prolong significant survival of patients with MF (28, 29, 30). A patient who is not a suitable candidate for ASCT due to advanced age and comorbidity or does not have a matching donor should be treated with conventional drugs, study drugs, radiotherapy, or splenectomy. Also, a parallel can be drawn between a group of low-risk patients according to GIPSS and low and very low risk according to MIPSS70+ version 2.0. For patients with MF who are asymptomatic, only regular monitoring of the disease is recommended. Patients belonging to the intermediate risk group according to MIPSS70+ version 2.0 are treated depending on whether they have symptoms that require management. These patients are treated by using conventional therapy based on treatment indications such as anemia, splenomegaly, constitutional symptoms, bone pain or extramedullary hematopoiesis. The prognosis of patients with GIPSS intermediate-1 and intermediate-2 is very diverse, so it requires additional evaluation of the risks by MIPSS70+ version 2.0 application and the treatment algorithm for intermediate risk patients (25, 28, 29).

JAK inhibitor therapies for myelofibrosis

Ruxolitinib

Discovery of the crucial function of dysregulation JAK-STAT signaling in pathophysiology of MF enabled the detection and development of new inhibitors for its treatment. Ruxolitinib directly acts on the basic mechanism of the disease, JAK2 dysregulation, blocks excessive stimulation of the JAK/STAT pathway leading to a decrease in STAT-3/5 activity and Akt/ERK phosphorylation which then causes a reduction of cell expansion and initiation of apoptosis (31). Since 2011, MF patients with intermediate-2 and high-risk disease have been able to be treated with ruxolitinib. It was the first approved JAK1/JAK2 inhibitor causing a reduction in the enlarged spleen and constitutional symptoms and prolonging overall survival in patients with MF. Furthermore, ruxolitinib can reduce hepatomegaly in splenectomized patients, relieves cachexia-related weight loss, and what is particularly significant, reduces the level of cytokines that lead to systemic inflammation in the MF. Although the response rate to ruxolitinib may vary significantly, most patients have benefited from its use. (32).

The COMFORT studies, which compared the effectiveness and toxicity of ruxolitinib versus placebo or best available therapy (BAT), were the most significant studies that demonstrated that ruxolitinib reduced spleen volume and disease-related symptoms, in addition to the prolonging of the overall survival of MF patients (33, 34). In the COMFORT-1 study that made comparison of the drug with placebo, it was shown that after 24 weeks of therapy, a decrease in splenomegaly of ≥ 35% was

achieved in 41.9% of patients treated with ruxolitinib vs < 1% for patients treated with placebo. In addition, a reduction in constitutional symptoms of at least 50% with regard to the baseline was demonstrated in 45.9% of patients in group with ruxolitinib compared to 5.3% in group with placebo, and what was particularly significant, this occurred regardless of risk group (33). The COMFORT-2 trial compared ruxolitinib with the best available therapy, showing that after a period of 48 weeks, splenomegaly was reduced by more than 35% in 28.5% of patients in the ruxolitinib group in comparison to 0% in the BAT group. It was also shown that the reduction in constitutional symptoms after 48 weeks was significantly higher in the ruxolitinib treated group of patients. (34). In both studies, the most common hematologic adverse events were ruxolitinib-related moderate to severe anemia and thrombocytopenia, which was corrected by dose adjustment, discontinuation of therapy and substitution therapy. With median follow-ups of approximately three years, the overall survival rate was significantly higher in the ruxolitinib group compared to placebo (35). Correspondingly, after three years of treatment, the estimated probability of survival was higher in the ruxolitinib group in comparison to the therapy considered as the best available, 81% versus 61% (36).

Other JAK inhibitors

Currently, three new JAK inhibitors are examined in phase III clinical trials in terms of their efficacy and safety compared to ruxolitinib. The JAKARTA-2 study (37) examined fedratinib, a JAK2-selective inhibitor, in patients with myelofibrosis who have shown intolerance or resistance to ruxolitinib. In the study group of patients with intermediate or high risk disease, 55% of patients achieved a reduction in spleen volume of more than 35%, while 26% achieved a reduction in disease-related symptoms by more than 50% after 6 months of therapy. In the analyzed group of patients, anemia and thrombocytopenia were the most reported side effects. The PERSIST-2 study (38) examined pacritinib, a JAK2 and Fms-like tyrosine kinase 3 inhibitor, comparing it with the best available therapy for myelofibrosis. In a patient with myelofibrosis and thrombocytopenia, pacritinib has been shown to be more effective in reducing spleen volume and constitutional symptoms compared to the best available therapy. The SIMPIFY-1 study (39) examined momelotinib, a potent and selective JAK1/2 inhibitor compared with ruxolitinib, in patients not previously treated with JAK1/JAK2 inhibitors. After 6 months of follow-up, momelotinib was not inferior to ruxolitinib in decreasing splenomegaly, however, the same did not apply for reduction of symptoms. In this study, patients treated with momelotinib were less transfusion dependent.

Non-JAK inhibitor therapies for myelofibrosis

Allogenic stem cell transplant

Up to the present moment, allogeneic stem cell transplant remained the only therapy that could potentially lead to cure in patients with myelofibrosis. This therapeutic option is applicable to a relatively small number of patients due to their advanced age, poor performance status, comorbidity, and donor availability. All available prognostic information should be used by calculating new prognostic models, such as MIPSS70 and MIPSS70+ version 2.0 which include mutation analysis and assess the clinical outcome and risk-benefit ratio for each patient individually. According to the valid consensus of European Society for Blood and Marrow Transplantation/European LeukemiaNet international working group (40) patients with intermediate-2 or high risk disease and age of less than 70 years are potential candidates to be treated with ASCT. To the contrary, patients with myelofibrosis who have intermediate-1 risk disease and age of less than 65 years may be candidates for treatment with ASCT if there is anemia requiring transfusion, or the presence of peripheral blasts > 2%, or unfavorable cytogenetics.

The study by Ballen K et al. (41) was one of the largest studies examining long-term outcome after the application of ASCT as a possible therapeutic line in PMF. The researchers showed that after 5 years of follow-up in matched related transplants, the progression-free survival rates and overall survival rates were 33% and 37%, while in unrelated transplants these rates were 27% and 30%. A recently published study by Tefferi A et al. (42) showed that after ASCT administration in patients with MF the median survival was almost 10 years, while the 5-year overall survival rate was 62%. This study proved that the very high risk mutations or unfavorable karyotype presence was not affecting survival. In order to predict the post-transplant outcome using multivariate analysis, it was determined that each risk variable that is an integral part of the DIPPS plus model has significance in predicting overall mortality, relapse-free survival, and non-relapse mortality rates (43). JAK inhibitors are now included in pre-ASCT therapy for many patients and their application has been shown to be safe, with no side effects on engrafment and long-term outcome (44).

Hydroxycarbamide

Hydroxycarbamide is a non-alkylating antiproliferative drug that has its application in the treatment of various hematological, oncological and infectious diseases. Before 2011, hydroxycarbamide

was often used in the treatment of myelofibrosis, but data on its efficacy and safety have been limited. Studies have shown that hydroxycarbamide was effective in reducing constitutional symptoms in 80% of patients and splenomegaly in 40% of patients. The average response duration to hydroxycarbamide is slightly longer than one year, although there may be large differences in the length of response (45). The most common side effects after this therapy were worsening of the anemia, the onset of severe pancytopenia and cutaneous complications such as oral or leg ulcers. Its toxicity is largely dose related, while its potential for leukemic transformation as a single agent is still a matter of controversy (46). According to the recommendations of European LeukemiaNet, resistance and intolerance to hydroxycarbamide in myelofibrosis is precisely defined as not achieving the desired reduction of splenomegaly, uncontrolled myeloproliferation, existence of cytopenias or appearance of signs of non-hematological toxicities (47).

Interferon-alpha

Interferon-alpha (IFN-α) has been shown to have potential to curb clonal myeloproliferation, may inhibit fibrogenic cytokines and angiogenesis in myelofibrosis, with the best results achieved at the onset of the disease. To date, this is the only treatment option in myelofibrosis that is used safely in pregnancy (48). Pegylated interferon therapy use in myelofibrosis leads to a satisfactory therapeutic response and a moderate toxic profile. Constitutional symptoms have been reported to disappear in 82% of patients while spleen size decreases in 46.5% of patients (49). Estimates of overall survival rates of patients having intermediate and high risk myelofibrosis treated with pegylated interferon were significantly higher compared with historical cohorts. Furthermore, the overall survival rate was found to be significantly connected with the pegylated interferon therapy duration (50). Recent studies have shown that new goal in the management of myelofibrosis is achieving minimal residual disease and potentially curing patients using a drug combinations, in which IFN-α predominantly and directly targets the malignant cells while anti-inflammatory agent such as JAK1/2 inhibitors that affect clonal expansion and disease progression (51).

Splenectomy

During disease, most patients with symptomatic splenomegaly become refractory to drugs and may require splenectomy. The results of one large study showed durable remissions after splenectomy with reduction of disease-related symptoms achieved in 67% of patients, transfusion-dependent anemia in 23% and portal hypertension in 50% of patients. In the same study, there was an acceptable operative mortality rate of 9% while the morbidity rate was 31% (52). Recently published Mayo Clinic's results confirmed that the median post splenectomy survival was 18 months and negative prognostic factors for survival were identified: age > 65 years, transfusion dependence, leukocytes > $25x10^9$/L and peripheral blasts ≥ 5% (53). Current guidelines suggest that splenectomy remains an acceptable palliative treatment option for patients having symptomatic splenomegaly that does not respond to therapy, development of splenic infarction, portal hypertension with complications, or severe hypercatabolic syndrome (54, 55).

Splenic irradiation

If patients with myelofibrosis are not acceptable candidates for splenectomy but need further treatment, splenic irradiation is an alternative option when there is massive symptomatic splenomegaly and an appropriate platelet count of more than $50x10^9$/l. The optimal dose and frequency of radiation has not been determined yet, but based on the results of different studies, the use of low-dose intermittent radiation is suggested. In most patients, a mild to moderate reduction in spleen volume is achieved after 6 months. It is considered that radiotherapy should not be used as a substitute for splenectomy (54).

Immunomodulatory drugs

Thalidomide, lenalidomide, and pomalidomide have anti-angiogenic, and immunomodulatory effects on several hematologic diseases including myelofibrosis (56). Examinations have confirmed that low-dose thalidomide or lenalidomide represents a productive treatment for myelofibrosis, because it enables the absence of transfusion dependence, increases the number of platelets and reduces the volume of the spleen in a certain number of patients (57, 58). Overall response rates to thalidomide and lenalidomide were 20% vs. 22% for anemia, 21% vs. 50% for thrombocytopenia, and 31% vs. 33% for splenomegaly, respectively (59, 60). However, their value is diminished by their capacity to cause peripheral neuropathy and myelosuppression. According to a study by Tefferi et al. (61), pomalidomide shows fewer toxic effects in contrast to thalidomide and lenalidomide and its therapeutic activity leads to delicate advancement between pomalidomide therapy with or without steroids and placebo in the treatment of myelofibrosis associated anemia.

Androgens

Severe anemia has been an important problem in patients with myelofibrosis. Danazol, a synthetic attenuated drug has proved to be useful in the cure of anemia in myelofibrosis. In patients with myelofibrosis, the mode of action of androgens is not fully clarified but is thought to lead to stimulation of bone marrow function. When danazol therapy was conducted at a dose of 600-800 mg per day for 3-6 months, it led to an overall response rate of 40% - 55% of patients and was generally well tolerated. In patients on danazol therapy, monitoring of liver function and periodic imaging of the liver are needed

for early detection of liver tumors in both sexes, while in men screening for prostate cancer should be done (62, 63).

Erythroid-stimulating agents

Human recombinant erythropoietin (EPO) represents an exogenous form of the kidney produced hormone that stimulates erythropoiesis. It has been proved successful in the treatment of MF-associated anemia. If EPO levels are < 500 IU, then EPO replacement therapy can be considered. The starting dose of EPO is 10,000 IU once a week, the dose can be escalated up to 40,000 IU once a week. Analysis of study Cervantes et al. (64) suggested that the overall response rate to human recombinant erythropoietin was 45%-55%, while serum erythropoietin levels < 125U/l, higher hemoglobin concentration, and transfusion independence were associated with a favorable response to human recombinant erythropoietin.

Conclusion

A state-of-the-art approach to patients with primary myelofibrosis is the determination of genetic markers, which play a significant role in diagnosis, prognostic modeling, and treatment decision. Genetic markers have become an integral part of WHO diagnostic criteria and because of their ability to predict survival rates somewhat accurately they have entered new prognostic scoring systems. As of recently, risk adapted therapy has been applied as well as genetic prediction of treatment response. Since most patients with primary myelofibrosis die from this disease, one should strive for more personalized treatments based on genetic markers with the development of more efficient therapies or combinations of therapies that will lead to molecular remission and prolonged overall survival.

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Pregledni rad **UDC: 616.155-07-08**
doi:10.5633/amm.2021.0212

SAVREMENI PRISTUP U DIJAGNOZI I LEČENJU PRIMARNE MIJELOFIBROZE

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Primarna mijelofibroza (PMF) je retka hronična mijeloproliferativna neoplazma (MPN). PMF je rezultat klonske ekspanzije mijeloidnih ćelija i odlikuje se varijabilnim prisustvom mutacija, morfološki povećanom proliferacijom megakariocita, progresivnom fibrozom koštane srži, hepatosplenomegalijom, anemijom, leukoeritroblastozom, konstitucionalnim simptomima i kraćim vremenom preživljavanjem. Svetska zdravstvena organizacija je 2016. godine definisala trenutne dijagnostičke kriterijume za PMF, koji uključuju kombinovanu procenu kliničkih, histoloških, mutacionih i laboratorijskih karakteristika bolesti. Nedavno, nekoliko novih prognostičkih skoring sistema za PMF počeli su da se koriste, koji se zasnivaju isključivo na genetskim markerima ili uključuju kliničke promenljive pored mutacija i kariotipa. U lečenju mijelofibroze primenjuje se terapija prilagođena riziku, što podrazumeva izbor vrste terapije prema kategoriji rizika dobijenoj izračunavanjem važećih prognostičkih skoring sistema. Alogena transplantacija matičnih ćelija ostala je jedina potencijalno kurativna terapija za lečenje PMF, ali je pogodna za mali broj visoko rizičnih bolesnika, koji imaju podudarnog davaoca. U proteklih deset godina, razvoj i odobravanje ruksolitiniba za lečenje PMF bilo je od najveće važnosti u tretmanu ove bolesti, iako je to palijativna terapija. Ruksolitinib je snažan JAK1/JAK2 inhibitor, koji dovodi do smanjenja splenomegalije i simptoma i produžava ukupno vreme preživljavanje kod bolesnika sa ovom bolešću.

Acta Medica Medianae 2021;60(2):96-105.

Ključne reči: *primarna mijelofibroza, prognostičko modeliranje, lečenje*

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