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Anemia in myelofibrosis: Current and emerging treatment options

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ABSTRACT

Myelofibrosis (MF) is a clonal hematologic malignancy with progressive bone marrow fibrosis. Clinical manifestations of MF include splenomegaly, constitutional symptoms, and anemia, whose pathogenesis is multifactorial and largely due to ineffective erythropoiesis and is clinically associated with poor quality of life and reduced overall survival. The only curative treatment for MF is allogenic stem cell transplantation; however, few patients are eligible. Disease management strategies for MF-related anemia have limited effectiveness, and Janus kinase (JAK) inhibitors may induce or worsen related anemia. Thus, there is a significant unmet need for the treatment of patients with MF-related anemia. This review summarizes current and emerging treatments for anemia in MF, including luspatercept and KER-050 (transforming growth factor-β ligand traps), momelotinib and pacritinib (JAK inhibitors), pelabresib (a bromodomain extra-terminal domain inhibitor), PRM-151 (an antifibrotic agent), imetelstat (a telomerase inhibitor), and navitoclax (a BCL-2/BCL-xL inhibitor). Therapeutic combinations with ruxolitinib may offer another treatment approach.

1. Introduction

Myelofibrosis (MF) is a chronic myeloproliferative neoplasm (MPN) that can arise de novo (primary MF) or occur post polycythemia vera (PPV) or post essential thrombocythemia (PET) (Passamonti et al., 2017; Tefferi, 2021). The clinical manifestations of MF are severe anemia, hepatosplenomegaly, cytopenia, cachexia, bone pain, splenic infarct, pruritus, thrombosis, bleeding, and constitutional symptoms (e.g., fever, night sweats, fatigue) (Tefferi, 2021). MF is characterized by clonal proliferation of hematopoietic stem cells resulting in extramedullary hematopoiesis, atypical megakaryocytic hyperplasia, and ineffective erythropoiesis. An array of growth factors released by abnormally expanded megakaryocytes induce fibroblastic proliferation and promote bone marrow fibrosis (Verstovsek et al., 2016), leading to a suboptimal environment for erythropoiesis and compensatory extramedullary hematopoiesis that is less effective. Thus, ineffective erythropoiesis contributes to MF-related anemia, a hallmark symptom of MF (Ciurea et al., 2007; Tefferi, 2021). MF is associated with high morbidity due to progressive marrow failure, progression to acute myeloid leukemia, thrombotic and hemorrhagic complications, infections, transfusion-dependent anemia, and thrombocytopenia (Ballen et al., 2010; Barbui et al., 2010; Kc et al., 2017). Treatment for MF is challenging and mortality due to MF-related complications is high (Asher et al., 2020; Diaz and Mesa, 2018; Tefferi et al., 2012). Currently, the only curative therapy is allogenic stem cell transplantation, but this is an option only for younger and fit patients and is associated with high risk of treatment-related death and morbidity (Asher et al., 2020; Ballen et al., 2010; Barbui et al., 2010; Gagelmann et al., 2019; Kc et al., 2017). Current treatments for MF-related anemia include red blood cell (RBC) transfusions, erythropoiesis-stimulating agents (ESAs), androgens, steroids, splenectomy, and immunomodulatory drugs (IMiD® agents), all of which are associated with multiple side effects and have limited efficacy and durability of response. Advances in understanding of the pathogenesis of MF-related anemia have led to several novel therapies being developed (Fig. 1). This review provides an overview of results from trials of current and emerging therapeutic agents for MF-related anemia.

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2. Anemia in MF

2.1. Prevalence of anemia in MF

The incidence of MF-related anemia varies considerably between studies and may be influenced by the proportion of primary versus secondary MF (i.e., PPV-MF and PET-MF) in studied patient populations. Several studies have found the prevalence of anemia, defined as hemoglobin (Hb) level < 10 g/dl at the time of diagnosis, to be 35–38% in patients with MF (Cervantes et al., 2009; Passamonti et al., 2010; Tefferi et al., 2012). In patients within 1 year of diagnosis in one study, 58% were anemic, and 24% and 46% required RBC transfusions at the times

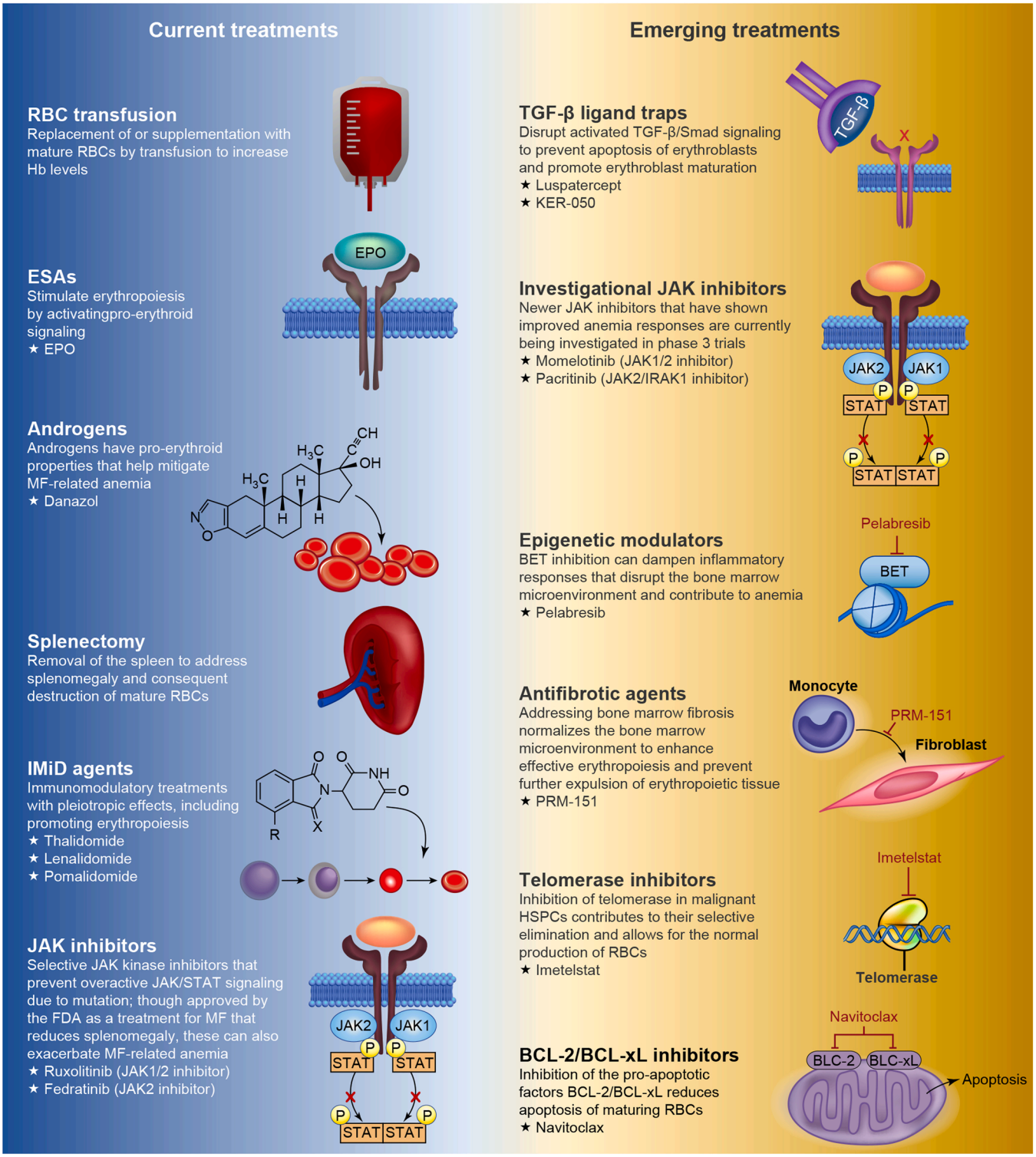

Fig. 1. Current and emerging treatments for anemia in myelofibrosis. Abbreviations: BET, bromodomain and extra-terminal domain; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; FDA, US Food and Drug Administration; Hb, hemoglobin; HSPC, hematopoietic stem and progenitor cell; IMiD, immunomodulatory drug; JAK, Janus kinase; MF, myelofibrosis; RBC, red blood cell; STAT, signal transducer and activator of transcription; TGF-β, transforming growth factor beta.

of initial diagnosis and referral, respectively. In patients beyond 1 year of diagnosis, 64% were anemic and 45% required RBC transfusions (Tefferi et al., 2012). Of the patients who were not anemic at diagnosis, 47% developed anemia after a median of 3.3 years after diagnosis (Passamonti et al., 2010). In another study, 87% of 722 patients with primary MF were anemic at the time of referral: 37% had severe anemia (Hb < 8 g/dl or transfusion-dependent), 16% had moderate anemia (Hb 8 to < 10 g/dl), and 47% had mild anemia (Hb ≥ 10 g/dl, but below sex-adjusted normal value) (Barraco et al., 2016). In a study of 1109 consecutive MF patients stratified using the same definitions of anemia severity, anemia was present in 950 (86%) patients, of which 35%, 14%, and 37% of patients had mild, moderate, and severe anemia, respectively (Nicolosi et al., 2018). In patients with PPV-MF and PET-MF, the median value of Hb is around 11 g/dl and tends to decrease over time (Mora et al., 2018a). Hb is lower in patients with PET-MF (Passamonti et al., 2017), in female patients (Barraco et al., 2018) and in those with higher degree of bone marrow fibrosis (Mora et al., 2020), and its value is independent of the presence of cytogenetic abnormalities (Mora et al., 2018b).

2.2. Pathogenesis of anemia in MF

The development of anemia in MF is a multifactorial process (Fig. 2) that is not completely understood. Pathogenesis includes bone marrow fibrosis, reduced effective erythropoiesis (due to displacement of hematopoietic progenitor cells from the bone marrow to extramedullary sites), splenomegaly (which contributes to the destruction of mature RBCs), and an increase in plasma volume resulting in dilutional anemia (Naymagon and Mascarenhas, 2017; Tefferi, 2021). Loss of RBCs through bleeding (e.g., from esophageal varices) also contributes to MF-related anemia. In addition, the proinflammatory bone marrow niche of patients with MF, resulting largely from abnormal cytokine production by megakaryocytes, plays an important role in disrupting the bone marrow microenvironment and leads to impaired erythroid differentiation. Abnormal cytokine production also results in disrupted iron metabolism via the increased production of hepcidin, further impeding functional erythropoiesis and contributing to anemia (Naymagon and Mascarenhas, 2017). One study of patients with MF and essential thrombocythemia (ET) found that a large proportion of anemic patients with MF (35%) had functional iron deficiency, though this was rare in patients with ET (1 of 23 patients) (Birgegard et al., 2019). The study further found a significant negative correlation between Hb levels and the levels of proinflammatory cytokines, including interleukin (IL)− 2, IL-6, and tumor necrosis factor alpha (TNFα), in all 80 patients with MF taking part in the study, including in the subgroup of patients with anemia. Levels of IL-6 were significantly higher in anemic patients with MF (not receiving transfusions) compared with non-anemic patients ($P = 0.02$) (Birgegard et al., 2019).

2.3. Quality of life in MF patients with transfusion-dependent anemia

Most patients with MF eventually require RBC transfusions to manage their anemia, and the level of RBC transfusion dependence is inversely correlated with quality of life (QoL) (Elena et al., 2011; Kochhar et al., 2015; Tefferi et al., 2014). Patients receiving regular RBC transfusions (defined here as ≥ 2 units per 8 weeks during the 16 weeks before the study) generally have been shown to have chronic anemia associated with fatigue, lower QoL, excess morbidity, and cardiovascular mortality, as well as iron overload (Fenaux et al., 2020). Fatigue is the symptom most often reported by patients with MPN-associated anemia, and can be caused by the disease, the severity of anemia, or exacerbated by treatment (Tefferi et al., 2014). In several patient surveys, fatigue was consistently found to be the most prevalent and often QoL-limiting symptom (Asher et al., 2020). More severe RBC transfusion dependence, defined as transfusion of > 6 RBC units in a 12-week period for patients whose pre-transfusion Hb level was < 8.5 g/dl in the absence of bleeding or treatment-induced anemia, has even greater detrimental effects on QoL. Patients who respond to treatments for anemia have reported improved QoL, as measured by the Functional Assessment of Cancer Therapy–Anemia (FACT-An) questionnaire (Tefferi et al., 2014).

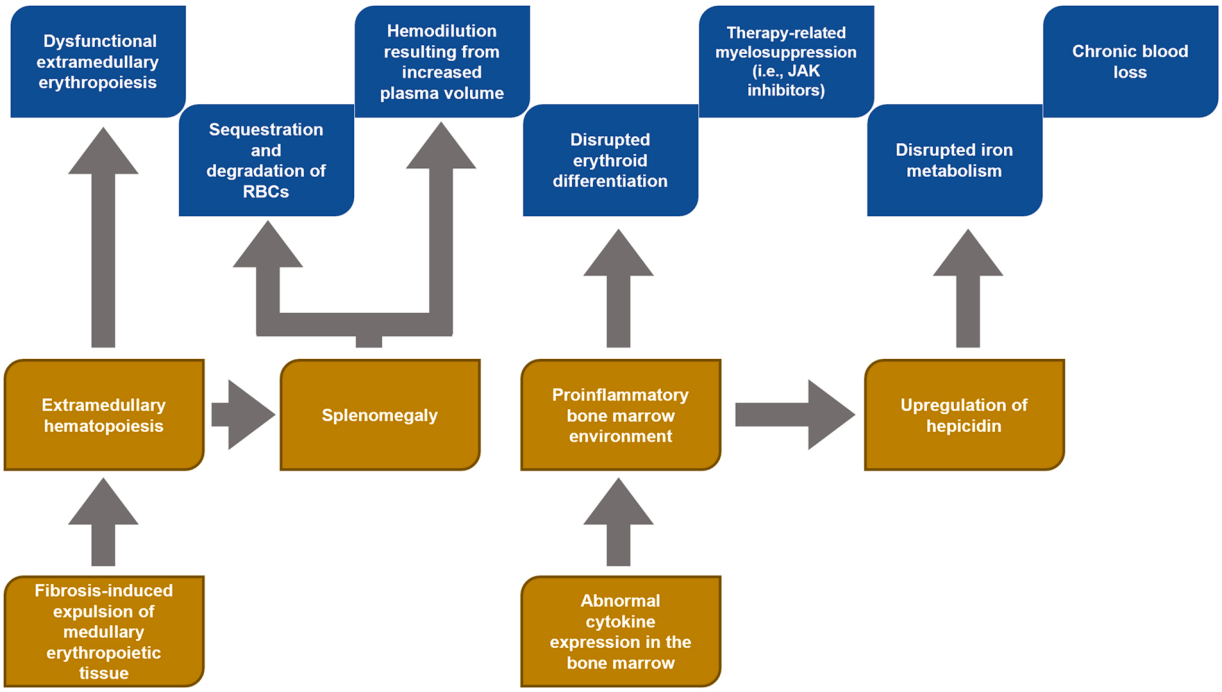

Fig. 2. Causes of anemia in myelofibrosis. Abbreviations: JAK, Janus kinase; RBC, red blood cell. Adapted from Naymagon and Mascarenhas (2017).

2.4. Prognostic role of anemia in MF

A Hb level < 10 g/dl is considered a risk factor in the International Prognostic Score System (IPSS) (Cervantes et al., 2009), the Dynamic International Prognostic Score System (DIPSS) and DIPSS-plus (Gangat et al., 2011; Passamonti et al., 2010), and in the Mutation-Enhanced International Prognostic Scoring System (MIPSS70) (Guglielmelli et al., 2018). In the IPSS, presence of anemia at diagnosis is a negative prognostic factor for survival. In the DIPSS, developing anemia during the disease confers a risk category of at least intermediate-1 and doubles the hazard ratio for survival compared with other prognostically detrimental variables such as age, leukocytosis, and constitutional symptoms (Passamonti et al., 2010). RBC transfusion-dependent anemia is also an additional independent risk factor in the DIPSS-plus model (Gangat et al., 2011). Anemia is also of prognostic value in patients with PPV-MF and PET-MF according to the Myelofibrosis Secondary to PV and ET-Prognostic Model (MYSEC-PM), developed in this patient setting (Passamonti et al., 2017).

Anemia is likely a marker of more advanced or aggressive disease, and patients with MF who develop RBC transfusion requirements are typically at an advanced disease stage. Data from the COMFORT-I (NCT00952289) and COMFORT-II (NCT00934544) ruxolitinib studies found that the presence of anemia at baseline was associated with worse survival, regardless of treatment (Gupta et al., 2016). In another study, median survival was 2.6 years in patients who received RBC transfusions at diagnosis compared with 8 years in those who did not (hazard ratio 3.9, 95% confidence interval 2.5–6.1; $P < 0.001$) (Elena et al., 2011). After adjusting for IPSS categories in multivariate Cox's proportional hazard regression, transfusion dependence retained an independent effect on survival. Significant associations have been found between anemia and advanced age, lower platelet count, the presence of constitutional symptoms, the presence of mutant *U2AF1*, and the absence of Janus kinase 2 (*JAK2)* mutation and *CALR* type 1/type 1-like mutation (Barraco et al., 2016; Nicolosi et al., 2018; Tefferi et al., 2017). Other factors associated with anemia are lower leukocyte counts, higher circulating blast percentages, and higher clinical and cytogenetic risk categories (Nicolosi et al., 2018).

3. Current treatments

Current treatments for MF-related anemia, their rates of efficacy, and limitations are detailed in Table 1. Due to differences in patient populations and the measures used to define treatment response, comparisons between clinical studies and assessment of the relative efficacy of different treatment options can be challenging. For clinical studies, patients with MF-related anemia are usually classified as either RBC transfusion dependent or independent. Transfusion dependence is defined by the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet as a transfusion requirement of ≥ 6 RBC units in the 12 weeks prior to study enrollment, for an Hb level < 8.5 g/dl, in the absence of any bleeding or treatment-induced anemia, and the latest transfusion within 28 days of study enrollment. Transfusion independence is classified as the absence of RBC transfusion during any consecutive 12-week interval during treatment (in a study) while maintaining Hb level > 8.5 g/dl (Naymagon and Mascarenhas, 2017; Tefferi et al., 2013). Regarding treatment response, an anemia response in transfusion-dependent patients is defined as the achievement of transfusion independence, whereas anemia response in transfusion-independent patients is defined by an increase in Hb of ≥ 2 g/dl (Naymagon and Mascarenhas, 2017; Tefferi et al., 2013). In this review, these are the definitions used for treatment response unless otherwise specified.

3.1. ESAs

Anemia in patients with MF can be treated with ESAs, which stimulate erythropoiesis by activating pro-erythroid signaling (Tsiara et al., 2007). However, studies evaluating the effect of this treatment have been small with variable response rates ranging from 16% to 85% in retrospective series. Factors predictive of a response to ESA treatment include low baseline serum erythropoietin levels and low RBC transfusion requirements; however, even among patients eligible for treatment, response rates are not predictable, and patients eventually become refractory to ESA treatment. A study of 163 patients with MF-related fibrosis treated with ESA therapy reported anemia response (according to IWG-MRT criteria) in 86 patients (53%) and a median duration of response of 19.3 months (Hernández-Boluda et al., 2017). Many patients with MF are also not likely to be considered for ESA treatment due to having high baseline serum erythropoietin levels; in patients with serum erythropoietin levels > 500 mU/ml, treatment with ESAs is not recommended (Devos et al., 2022). Overall, ESAs are not commonly used to treat MF-related anemia due to their limited efficacy in transfusion-dependent patients, the risk of vascular complications, and the potential to exacerbate splenomegaly (Tefferi, 2021).

3.2. Androgens

Androgens have pro-erythroid properties that have been leveraged in the treatment of MF-related anemia, though the exact mechanism of their effect is not fully understood (Al-Sharefi et al., 2019). Two well-established androgens that can be used to treat patients with MF-related anemia are testosterone enanthate and oral fluoxymesterone. More recently, the synthetic attenuated androgen danazol was shown to have superior safety and tolerability with similar efficacy to the other androgens (Cervantes et al., 2015; Tefferi, 2021), and response rates around 30%, including 44% in RBC transfusion-independent and 19% in transfusion-dependent patients. Danazol is well tolerated but is contraindicated in patients with androgen-dependent tumors, thrombosis or a history of thrombosis, patients with markedly impaired cardiac hepatic or renal function, and in pregnancy/breastfeeding. Although androgen response rates are limited, their favorable safety profile makes them a worthwhile treatment option to consider for this patient population (Cervantes et al., 2015). Indeed, danazol is currently being used as the comparator to the JAK inhibitor momelotinib in the phase 3 MOMENTUM study (NCT04173494; Verstovsek et al., 2021).

3.3. Steroids

Steroids are used for the treatment of MF-related anemia because they suppress inflammatory stimuli associated with MF pathogenesis. Few trials have evaluated prednisone in this patient population, and although response rates were similar to those observed with danazol, systemic steroid treatment is associated with side effects, including hyperglycemia, cushingoid changes, infectious complications, and psychiatric disturbances (Hernández-Boluda et al., 2016).

3.4. Splenectomy

Splenectomy is an effective treatment option for treating splenomegaly in patients with MPNs. Reports of splenectomy eliminating splenomegaly-related symptoms, improving anemia, thrombocytopenia, and portal hypertension have been published; however, splenectomy is also associated with a significant risk of complications. Experience from a single center on a large series of patients reported that although splenectomy was associated with a response rate of 37.6% (defined as becoming transfusion independent or Hb > 10 g/dl) in patients with MF who had anemia, a 9% incidence of perioperative mortality and 30.5% overall morbidity was observed with the most common complications being postoperative thrombocytosis, thrombohemorrhagic phenomena, and increased risk of in-hospital mortality due to complications (Tefferi et al., 2000). Careful evaluation of the risks versus potential benefits of splenectomy should be conducted before this treatment strategy is

Table 1
Current therapies and disease management practices for MF-associated anemia.

Agent (s)	Trial	Response rate[a]	Disease criteria	Line of therapy / concomitant therapy	Limitations
ESAs	(Huang and Tefferi, 2009) (n = 43)	23% (0% among TD and 37% [only in patients with BL Hb < 10 g/dl]; $P = 0.007$)[b]	PMF and documentation of a CBC prior to therapy and follow-up that is adequate to assess response	–	Should be avoided in TD patients or those with BL Hb < 10 g/dl
	(Tsiara et al., 2007) (n = 20)	60%[c]	CIMF diagnosed according to criteria proposed by the Italian Consensus Conference for the Diagnosis of CIMF	All had prior corticosteroids, hydroxyurea, interferon-α, or androgens; they did not respond or lost response to treatment, and were being regularly transfused with packed RBC to maintain post-transfusion Hb levels of at least 10 g/dl	Limited eligibility (response in patients with low s-Epo), failure to maintain response
	(Cervantes et al., 2006) (n = 20)	40%[d]	MF with myeloid metaplasia and anemia	First-line in 6 patients, previous therapies included hydroxyurea (n = 7), danazol (n = 7), anagrelide (n = 2), splenectomy (n = 1). Some patients had received > 1 prior therapeutic	No patients with appropriate s-Epo levels responded
	(Cervantes et al., 2004) (n = 20)	45% (4 CR [20%] and 5 PR)[e]	MF with myeloid metaplasia and anemia	First choice treatment in 3 patients, remaining 17 patients had received prior therapies	Limited eligibility (response in TI and those with higher Hb at BL)
	(Hernández-Boluda et al., 2017) (n = 163)	53%[f] (29% among TD patients, 57% among TI patients)	MF with transfusion-dependent anemia or Hb levels < 10 g/dl at the start of ESA treatment	Previous therapies included hydroxycarbamide (n = 110), JAK inhibitors (n = 32), danazol (n = 11), immunomodulators (n = 2), splenectomy (n = 3). Concomitant treatment with cytoreductive agents allowed; combination of ESAs with other drugs to treat anemia excluded	
Androgens (danazol)	(Cervantes et al., 2015) (n = 50)	44% among TI patients, 19% among TD patients[f]	MF according to the current criteria of the WHO in PMF and the criteria of the International Consensus in PPV and PET MF (Barosi et al., 2008; Tefferi et al., 2007)	Danazol was not started at the same time as other therapies. However, previously instituted therapy was maintained in 19 patients, including hydroxyurea (n = 11), low-dose prednisone (n = 5), and anagrelide (n = 3)	Frequent mild resolving transaminitis with rare severe cholestatic hepatitis and adenocarcinoma (Hernández-Boluda et al., 2016)
Splenectomy	(Tefferi et al., 2000) (n = 223)	37.6%[g] among patients who had splenectomy for anemia 30% among patients who were TD at the time of surgery became TI by 6 months postoperatively, and the benefit was sustained in 23% at latest follow-up	MF with myeloid metaplasia		Bleeding, infection, thrombosis, postsplenectomy hepatomegaly. Morbidity (30.5%) and mortality (9%)
Immunomodulators	(Abgrall et al., 2006) (n = 52) Thalidomide vs placebo	Improvement in Hb level: 1 patient in each group, reduction in RBC transfusion: 3 vs 5 patients[h]	Myeloid metaplasia with MF with anemia	–	Tolerance of thalidomide was significantly correlated with the severity and liver involvement of the disease
	(Mesa et al., 2010) (n = 48) Lenalidomide	19% among all anemic patients[i]	PMF or PET/PPV MF with BL Hb < 10 g/dl or RBC TD (1 transfusion in the 2 months before enrollment)	All patients received concomitant prednisone	Myelosuppression was the main toxicity with 88% with incidence of grade 3 or 4 hematologic toxicity
	(Tefferi et al., 2017) (n = 229) Pomalidomide vs placebo	16% vs 16% ($P = 0.87$)[j]	PMF or secondary MF and TD	–	Rare edema and neutropenia
	(Schlenk et al., 2017) (n = 98) Pomalidomide (2 dose regimens)	39% vs 24%[j]	MF with myeloid neoplasia	Prednisolone added if no response after 3 months (cohort 1) or 3 or 6 months (cohort 2 based on initial randomization)	

Abbreviations: BL, baseline; CBC, complete blood count; CIMF, chronic idiopathic myelofibrosis; CR, complete response; ESA, erythropoietin stimulating agent; Hb, hemoglobin; IWG-MRT, International Working Group for Myelofibrosis Research and Treatment; JAK, Janus kinase; MF, myelofibrosis; PET, post essential thrombocythemia; PMF, primary myelofibrosis; PR, partial response; PPV, post polycythemia vera; RBC, red blood cell; RUX, ruxolitinib; s-Epo, serum erythropoietin; TD, transfusion dependent; TI, transfusion independent; WHO, World Health Organization.

[a] Due to differences in patient populations and efficacy assessments, direct comparisons of results between studies may be difficult.

[b] Response was defined as ≥ 2.0 g/dl increase in Hb level or becoming TI over a minimum of a 1-month period.

[c] Response was defined as Hb levels increased over 2 g/dl within 12 weeks after enrollment or RBC transfusion requirements reduced by 50% within the same interval.

[d] CR was Hb normalization (≥ 12 g/dl) and PR was a Hb increase of ≥ 2.0 g/dl in non-TD patients or a ≥ 50% reduction in transfusion requirements, defined by the European Myelofibrosis Network (Barosi et al., 2005).

[e] CR defined as transfusion cessation with normal Hb levels and PR as a transfusion decrease ≥ 50% and Hb > 10 g/dl maintained for ≥ 8 weeks.
[f] The response was assessed using the recently revised criteria of the IWG-MRT, according to which anemia response (included in the category of "clinical improvement") is considered in 2 different situations: (1) transfusion cessation, in TD patients, and (2) an Hb increase > 2 g/dl, in TI patients, both lasting for a minimum of 12 weeks (Tefferi et al., 2013).
[g] Quantitative improvement consisted of either having no further need for RBC transfusions or achieving a durable increase of Hb > 10 g/l in Hb level.
[h] Main outcome measure was a 2 g/l increase in Hb or 20% reduction in transfusions.
[i] Response assessments while on the study used the IWG-MRT criteria (Tefferi et al., 2013).
[j] Primary endpoint was the proportion of patients achieving RBC TI defined as ≥ 84 consecutive days with no RBC transfusion.

recommended (Tefferi et al., 2000); splenectomy is generally considered a last-resort treatment option for managing MF-related anemia.

3.5. IMiD agents

IMiD agents including thalidomide, lenalidomide, and pomalidomide have demonstrated efficacy in treating anemia, thrombocytopenia, and in some instances, splenomegaly. Several phase 1/2 clinical trials have investigated IMiD agents either alone or in combination with steroids in patients with MF (Abgrall et al., 2006; Masarova et al., 2017; Mesa et al., 2010; Schlenk et al., 2017; Tefferi et al., 2017) (Table 1). Owing to the large variability in study designs and response criteria, no clear consensus on the efficacy of IMiD therapy has emerged. For example, a phase 2 study of pomalidomide in 96 patients with MPN-associated MF and anemia reported response rates of up to 39% (Schlenk et al., 2017), but a phase 3 randomized study of pomalidomide in 229 RBC transfusion-dependent patients with MPN-associated MF found no difference in the response rate between pomalidomide and placebo (16% vs 16%; $P = 0.87$) (Tefferi et al., 2017). Studies have shown that IMiD agents improve erythropoiesis, with beneficial effects on anemia, and sometimes thrombocytopenia (Masarova et al., 2017); however, IMiD agents are also associated with multiple adverse events (AEs), including neutropenia, thrombocytopenia, neuropathy, fatigue, constipation, bone marrow suppression, gastrointestinal toxicity, and rash. Initial investigation of concomitant dosing of ruxolitinib with lenalidomide (NCT01375140) produced little improvement and had low tolerability (Daver et al., 2015). Thus, sequential dosing of ruxolitinib with thalidomide (NCT03069326) is being used in an ongoing trial and has shown promising efficacy with improvements in anemia and thrombocytopenia (Rampal et al., 2019). Combination with pomalidomide (NCT01644110), both low dose and dose escalation, has also shown clinical benefit with reduced toxicity (Stegelmann et al., 2019).

3.6. JAK inhibitors

Given the role of mutation-induced overactive JAK-signal transducer and activator of transcription (STAT) signaling in the pathogenesis of MF, it is unsurprising that JAK inhibitors are effective treatment options that improve symptoms and confer a survival advantage for patients with advanced disease (Bose and Verstovsek, 2020). However, these treatments do not improve anemia and can, in fact, have negative impacts on MF-associated anemia – similarly unsurprising given the importance of the JAK-STAT pathway in erythropoietin-mediated signaling (Naymagon and Mascarenhas, 2017) – and thus warrant mention.

Ruxolitinib, a JAK1/2 inhibitor approved in 2011, was the first JAK inhibitor to be approved for the treatment of MF. Ruxolitinib was investigated versus placebo in the phase 3 COMFORT-I study in patients with intermediate-2- or high-risk MF (Verstovsek et al., 2012). The study met its primary endpoint of ≥ 35% spleen volume reduction from baseline (SVR35) at week 24 (41.9% of patients receiving ruxolitinib compared with 0.7% of patients who received placebo; $P < 0.0001$). Treatment with ruxolitinib also resulted in symptom response (≥ 50% reduction in total symptoms score from baseline [TSS50]) in 45.9% of patients versus 5.3% of patients receiving placebo. In the subsequent COMFORT-II study comparing ruxolitinib with best available therapy (BAT), only patients treated with ruxolitinib achieved SVR35 after either 24 weeks (32% vs 0% receiving BAT; $P < 0.001$) or 48 weeks (28% vs 0% receiving BAT) of treatment (Harrison et al., 2012). A prespecified pooled analysis of 3-year data from the COMFORT studies accounting for the variations in time on treatment due to patient crossover evaluated effects of ruxolitinib on overall survival. A survival advantage was observed for patients who were randomized to ruxolitinib compared with those randomized to control (placebo or BAT) (Vannucchi et al., 2015). However, anemia and thrombocytopenia occurred in patients treated with ruxolitinib in both studies, resulting in dose adjustments and a small number of discontinuations (Harrison et al., 2012; Verstovsek et al., 2012). Similar efficacy and safety results were observed in the phase 3b expanded-access JUMP study (NCT01493414; Al-Ali et al., 2020). In an effort to understand the implications of ruxolitinib-associated anemia, a post hoc analysis of the pooled COMFORT data was performed. This analysis found that 61% of patients treated with ruxolitinib who did not have anemia at baseline developed postbaseline anemia, and 69% of patients treated with ruxolitinib who had anemia at baseline saw their anemia worsen (Gupta et al., 2016). The analysis also revealed that the survival advantage associated with ruxolitinib applied to both patients with and without anemia at baseline, and that new or worsening postbaseline anemia, which could have resulted from ruxolitinib treatment, did not affect overall survival (Gupta et al., 2016).

Despite its lack of impact on survival, the anemia associated with ruxolitinib is a limitation of this treatment. Patients with new or worse anemia may require dose adjustments or interruptions to their treatment, as observed for a small number of patients in the clinical trials. Anemia also contributes to treatment discontinuation in real-world experience: in an analysis of results from clinical practice across 20 hematology centers, 27.5% of patients discontinued ruxolitinib due to treatment-related AEs, 10.5% of which were specifically due to treatment-related anemia (Palandri et al., 2020). The addition of interventions to address treatment-related anemia may be of use in order to maximize the benefits of ruxolitinib treatment. Favorable results have been reported for combination treatment of ESAs with or after initiation of ruxolitinib; 54% of patients met the definition of response, with an additional 15% exhibiting minor improvements in anemia. Of the responders, 76% continued to respond after 5 years, a longer response time than is typically seen for ESAs alone (Crisà et al., 2018). These types of combination treatments may be useful for optimizing the dosing of ruxolitinib. Alternate dosing strategies of ruxulitinib itself to mitigate its effects on anemia are also under investigation: a new ruxolitinib dosing strategy of a reduced starting dose and delay in titration to increase dosing is being investigated in the phase 2 REALISE study (NCT02966353; Cervantes et al., 2021).

A second JAK inhibitor approved to treat MF is fedratinib, which targets JAK2. Despite initial promising results, the JAKARTA study investigating the safety and efficacy of fedratinib in JAK inhibitor-naïve patients with intermediate-2- or high-risk primary, PPV, or PET MF was placed on clinical hold due to suspected cases of Wernicke encephalopathy. The hold has since been lifted following review of additional safety data (Bose and Vestovsek, 2020; Pardanani et al., 2021). Reanalysis of the JAKARTA trial results demonstrated an SVR35 response rate of 37% in patients treated with fedratinib compared with 1% in patients treated with placebo; the TSS50 response rate was 40% with fedratinib versus 9% with placebo. The most common AEs were diarrhea, nausea, anemia, and vomiting, reflecting fedratinib's additional inhibitory

activity on FLT3 (Bose and Vestovsek, 2020; Pardanani et al., 2021). Anemia was the only grade 3 or higher AE to occur in more than 5% of patients. The JAKARTA 2 study, which further investigated fedratinib for the treatment of patients who were intolerant or resistant to ruxolitinib, was also interrupted by the clinical hold, resulting in some patients not reaching the end of planned treatment. Of evaluable patients, 55% achieved a spleen response, including 53% of patients resistant and 63% of patients intolerant to ruxolitinib (Harrison et al., 2017). As observed previously, the most common hematologic AEs were anemia and thrombocytopenia, and the most common non-hematologic AEs were gastrointestinal symptoms. Similar to ruxolitinib, fedratinib treatment does not improve MF-associated anemia, thus trials to investigate combined JAK2 inhibitor treatment with an agent to address anemia, such as the INDEPENDENCE study (NCT04717414), which will include combined dosing with luspatercept, will provide important information.

4. Emerging treatments for MF and their effects on anemia

Treatments under investigation in clinical trials and their response rates and toxicities are detailed in Table 2.

4.1. Transforming growth factor-β ligand traps

Transforming growth factor-β (TGF-β) inhibits erythroid differentiation by inducing apoptosis in erythroblasts. In MF, TGF-β levels are upregulated, which contributes to pathogenesis of the disease, including anemia (Tefferi and Vainchenker, 2011; Zermati et al., 2000). Luspatercept, a first-in-class erythroid maturation agent that binds several endogenous TGF-β superfamily ligands to diminish Smad2/3 signaling, is European Medicines Agency (EMA) and US Food and Drug Administration (FDA) approved to treat anemia in select populations of patients with β-thalassemia or with lower-risk myelodysplastic syndromes (MDS) with ring sideroblasts (Kubasch et al., 2021). In a phase 3 study of luspatercept in patients with lower-risk MDS and ring sideroblasts who require regular RBC transfusions (NCT02631070), 38% and 13% of patients in the luspatercept and placebo arms, respectively, achieved RBC transfusion independence (RBC-TI) for ≥ 8 weeks ($P < 0.001$). In addition, more of the patients treated with luspatercept than those treated with placebo achieved RBC-TI for ≥ 12 weeks during weeks 1–24 (28% vs 8%; $P < 0.001$), and weeks 1–48 (33% vs 12%; $P < 0.001$) (Fenaux et al., 2020). Luspatercept, with or without ruxolitinib, recently demonstrated promising efficacy in preliminary analysis of an ongoing phase 2 study of patients with MPN-associated MF and anemia (NCT03194542). Of the patients who were not receiving RBC transfusions, 2/20 patients (10%) not receiving ruxolitinib and 3/14 patients (21%) receiving ruxolitinib achieved an increase in Hb level of ≥ 1.5 g/dl compared with baseline over 12 consecutive weeks. Of the patients who were receiving transfusions (2–4 units of RBC/28 days in the 12 weeks before the study), 2/21 patients (10%) not receiving ruxolitinib and 6/19 patients (32%) receiving ruxolitinib achieved RBC-TI over any 12 consecutive weeks. A reduction in the need for transfusion of > 50% was obtained in 8 patients (38%) receiving ruxolitinib and 10 patients (53%) not receiving ruxolitinib (Gerds et al., 2019). In a longer-term analysis, nearly a quarter of patients receiving RBC transfusions achieved more than one ≥ 12-week episode of RBC-TI with luspatercept. The incidence of grade 3–4 AEs with luspatercept was low, and the most common AEs included hypertension, bone pain, and diarrhea (Gerds et al., 2020a). Recruitment for a phase 3, placebo-controlled trial of luspatercept in patients with transfusion-dependent MF with anemia receiving JAK2 inhibitor therapy (INDEPENDENCE trial) is currently ongoing (NCT04717414) (Mesa et al., 2021a).

KER-050 is a novel inhibitor of the TGF-β superfamily that acts as a modified ActRIIA ligand trap to promote hematopoiesis through inhibition of ligands such as activins and growth differentiation factors. Preclinical data suggest that a research form of KER-050 (RKER-050) acts as a modulator of RBC maturation that can rapidly increase RBCs, Hb, and hematocrit in murine models of age-associated anemia and chronic conditions, such as MDS (Feigenson et al., 2020a). RKER-050 showed rapid recovery in a model of acute bleeding with effects on both erythropoiesis and thrombopoiesis and is believed to stimulate terminal maturation of late-stage erythroid precursors and expand and promote differentiation of early-stage erythroid precursors. Additionally, RKER-050 increases erythropoietin levels. The ability of RKER-050 to target multiple stages of erythropoiesis makes it an interesting therapeutic candidate for MF and related anemia (Feigenson et al., 2020b). A phase 2, multicenter, open-label study to evaluate the safety and efficacy of KER-050 as monotherapy or in combination with ruxolitinib is ongoing (NCT05037760).

4.2. JAK inhibitors under investigation

Momelotinib is a selective, small-molecule inhibitor of JAK1 and JAK2 kinases. In addition, preclinical murine models of anemia showed that momelotinib inhibits the TGF-β family member activin A receptor type 1 (ACVR1), resulting in decreased expression of hepcidin, improving erythropoiesis (Bassiony et al., 2020). The efficacy of momelotinib versus ruxolitinib was evaluated in the phase 3 SIMPLIFY 1 trial (NCT01969838) in JAK inhibitor-naive patients with MF. Momelotinib was found to be noninferior to ruxolitinib for spleen response (SVR35 at week 24) but not for symptom response (TSS50 at week 24). Regarding effects on anemia, momelotinib was superior to ruxolitinib in reducing rates of RBC transfusion need (66.5% vs 49.3%; $P < 0.001$) (Mesa et al., 2017a), although the high transfusion response rate in the ruxolitinib group has been viewed with skepticism (Naymagon and Mascarenhas, 2017). In an updated analysis of SIMPLIFY 1, the proportion of patients receiving transfusions of ≤ 4 RBC units was 85% with momelotinib and 62% with ruxolitinib ($P < 0.0001$). Furthermore, momelotinib increased the likelihood of not requiring RBC transfusion by a factor of 9.3 compared to ruxolitinib ($P < 0.0001$). Grade ≥ 3 AEs occurred in 25% versus 43.5% of patients receiving momelotinib and ruxolitinib, respectively, and the rates of patients experiencing AEs resulting in drug discontinuation were 13.1% and 5.6%, respectively (Bassiony et al., 2020). In the phase 3 SIMPLIFY 2 study (NCT02101268), momelotinib was compared with best alternative therapy (BAT) in patients with MF who had suboptimal responses to ruxolitinib or experienced hematologic toxicity. The study failed to meet its primary endpoint of SVR35 at week 24. However, at week 24, 26% versus 6% of patients treated with momelotinib versus BAT had TSS50, and 43% versus 21% of patients in the momelotinib and BAT groups, respectively, achieved RBC-TI ($P = 0.0012$). Momelotinib alleviated symptoms, improved anemia responses, and reduced the need for RBC transfusions (Harrison et al., 2018). Long-term momelotinib treatment data from SIMPLIFY 1, SIMPLIFY 2, and an extended access protocol have found low rates of high-grade toxicities, and safety was similar for momelotinib compared with ruxolitinib in SIMPLIFY 1 and SIMPLIFY 2. Furthermore, reduced transfusion burden was seen with momelotinib compared with ruxolitinib in the long-term clinical data, indicating that momelotinib may be an effective treatment option in MF-related anemia (Gupta et al., 2020; Harrison et al., 2020; Mesa et al., 2019; Verstovsek et al., 2021). Concerning the impact of anemia response on survival, SIMPLIFY 1 showed that patients who achieved RBC-TI by week 24 (responders) in the momelotinib group show an overall survival advantage, with median overall survival not reached and 3-year survival of 80% (hazard ratio 0.30; $P = 0.0001$) compared with momelotinib RBC-TI non-responders (Mesa et al., 2021b). Momelotinib is currently being evaluated (enrollment closed) and compared with danazol in the phase 3 MOMENTUM study in patients with symptomatic anemia who have previously been treated with a JAK inhibitor (NCT04173494); the primary endpoint is symptom reduction (Verstovsek et al., 2021). A recent report of results after 24 weeks of treatment showed that 31% of

Table 2
Emerging treatments and their response rates in clinical trials.

Agent and mechanism of action	Trial	Response[a]			Toxicity
		SVR35	TSS50	Additional efficacy measures	
Luspatercept Binds to TGF-β superfamily ligand	**Phase 2 study** Cohort 1: non-TD no RUX (n = 20); cohort 3A: non-TD + RUX (n = 14); cohort 2: TD no RUX (n = 21); cohort 3B: TD + RUX (n = 19) (Gerds et al., 2019)	–	–	Hb increase ≥ 1.5 g/dl at every assessment: 10% (cohort 1), 21% (cohort 3A).[b,c] Mean Hb increase of ≥ 1.5 g/dl: 15% (cohort 1), 57% (cohort 3A).[b] Achievement of RBC-TI ≥ 12 weeks: 10% (cohort 2), 32% (cohort 3B).[b] ≥ 50% reduction in RBC transfusion burden: 38% (cohort 2), 53% (cohort 3B)[b,d]	Hypertension, bone pain, diarrhea
Momelotinib JAK1, JAK2, ACVR1 inhibitor	**SIMPLIFY-1** MOM vs RUX (n = 432) (Mesa et al., 2017a)	26.5% vs 29% at ($P = 0.011$; noninferior)	28.4% vs 42.2% ($P = 0.98$; noninferiority was not met)	Transfusion rate, TI, and TD improved with MOM (nominal $P \leq 0.19$ for all)	Anemia, thrombocytopenia, infections, peripheral neuropathy
	SIMPLIFY-2 MOM vs BAT (n = 156) (Harrison et al., 2018)	7% vs 6% ($P = 0.90$)	26% vs 6% (nominal $P = 0.0006$)	TI: 43% vs 21% ($P = 0.0012$)	Anemia, thrombocytopenia, peripheral neuropathy
	MOMENTUM MOM vs DAN (n = 195) (Verstovsek et al., 2022)	23.1% vs 3.1% ($P = 0.0006$; superior)	Least-squares mean from mixed model for repeated measures: −9.36 vs −3.13 ($P = 0.0014$; superior)	Rate of TI: 30.8% vs 20.0% ($P = 0.0064$, one-sided; noninferior)	Thrombocytopenia, anemia, infection
Pacritinib JAK2, FLT3, IRAK1, CSF1R inhibitor	**PERSIST-1** PAC vs BAT (n = 327) (Mesa et al., 2017b)	19% vs 5% ($P = 0.0003$)	19% vs 10% ($P = 0.24$)	TI: 25% vs 0% ($P = 0.043$)	Anemia, thrombocytopenia, diarrhea, cardiac failure (20% vs 21%)
	PERSIST-2 PAC vs BAT (n = 311) (Mascarenhas et al., 2018)	18% vs 3% ($P = 0.001$)		RBC transfusion burden in patients not TI at BL was 19% (PAC QD); 22% (PAC BID) vs 9% (BAT). Clinical improvement in Hb and reduction in transfusion burden were greatest with PAC QD. TI in 2 patients in the PAC groups	Thrombocytopenia, anemia, GI events, cardiac events
	PAC203 (phase 2) PAC 100 mg QD, PAC 100 mg BID, 200 mg BID (n = 164) (Gerds et al., 2020a)	0, 1.8%, 9.3%; among patients with platelet count $< 50 \times 10^3$/μl: 0, 0, 16.7%	7.7%, 7.3%, 7.4%; median percent reduction in TSS: –3%, 16%, and 27%	TD to TI: 13%, 13%, 9%. Reduction in transfusion burden: 17.9%, 35.5%, 14.7%	Diarrhea, thrombocytopenia, anemia, neutropenia, bleeding, cardiac events
Pelabresib (CPI-0610) BET inhibitor	**MANIFEST (phase 2)**[e] Arm 1: Pelabresib monotherapy in patients relapsed/refractory/intolerant to RUX (non-TD n = 27; TD n = 16) (Talpaz et al., 2020)	Non-TD: 23.8%; TD: 0	Non-TD: 47.4%; TD: 8.3%	TD to TI: 21.4% of TD patients	Thrombocytopenia, anemia, nausea, diarrhea, respiratory tract infections
	Arm 2: Pelabresib as an "add-on" to RUX in patients with suboptimal response to RUX (non-TD n = 26; TD n = 44) (Verstovsek et al., 2020)	Non-TD: 22.2%; TD: 20.8%	Non-TD: 36.8%; TD: 46.2%	TD to TI: 34.4% of TD patients	Thrombocytopenia, anemia, diarrhea, respiratory infections
	Arm 3: Pelabresib in combination with RUX in JAK inhibitor-naïve patients (n = 64) (Mascarenhas et al., 2020)	63.3%	58.6%	–	Anemia, thrombocytopenia, diarrhea, respiratory infections, nausea
PRM-151 Antifibrotic, recombinant human pentraxin-2	**Phase 2 study** PRM-151 ± RUX (Verstovsek et al., 2018)	Mean best percent change by palpitation in spleen size from baseline was −37%	Mean best percent reduction in TSS was −54%	Reticulin fibrosis improved in 9 patients and collagen fibrosis in 7 patients	–
	Phase 2 study PRM-151 0.3 mg/kg, 3 mg/kg, or 10 mg/kg (Verstovsek et al., 2019)	–	–	BMF improvement by ≥ 1 grade in 30%, 28%, and 25%. ≥ 50% reduction in RBC transfusions or Hb increases of ≥ 10 g/l for ≥ 12 consecutive weeks in 16–29%[f]	Fatigue, cough, thrombocytopenia, and abnormal weight loss
Imetelstat Telomerase inhibitor	**Pilot study** 9.4 mg/kg (Tefferi et al., 2015)	35%[g]	–	CR or PR in 21%. Bone marrow fibrosis reversed in all 4 patients with CR and a molecular response occurred in 3 of the 4 patients. TD to TI for ≥ 3 months in 31%	Thrombocytopenia, neutropenia, anemia, elevated bilirubin, alkaline phosphatase, aspartate aminotransferase
	IMbark (phase 2)[h] 9.4 mg/kg, 4.7 mg/kg IV every 3 weeks (n = 107) (Mascarenhas et al., 2021)	9.4 mg/kg arm: 10.2% 4.7 mg/kg arm: 0%	9.4 mg/kg arm: 32.2% 4.7 mg/kg arm: 6.3%	BMF improvement by ≥ 1 grade in 40.5% (9.4 mg/kg arm) and 20.0% (4.7 mg/kg arm). Anemia response in 6.8% (9.4 mg/kg arm, 1.7%	Thrombocytopenia, anemia, neutropenia, nausea

(*continued on next page*)

Table 2 (*continued*)

Agent and mechanism of action	Trial	Response[a]			Toxicity
		SVR35	TSS50	Additional efficacy measures	
				without clinical improvement) and 4.2% (4.7 mg/kg arm)	
Navitoclax Antiapoptotic, binds BCL2 family	**REFINE (phase 2)**[i] Single arm NAV + RUX (n = 34) (Harrison et al., 2021)	27%	30%	BMF improvement by ≥ 1 grade in 33%. Improvement of Hb of ≥ 2 g/dl or TI occurred in 64% of patients[j]	Thrombocytopenia, diarrhea, fatigue, anemia, pneumonia

Abbreviations: ACVR1, activin A receptor type 1; BAT, best available therapy; BET, bromodomain and extraterminal domain; BID, twice daily; BL, baseline; BMF, bone marrow fibrosis; CR, complete response; DAN, danazol; GI, gastrointestinal; Hb, hemoglobin; IV, intravenous; JAK, Janus kinase; MOM, momelotinib; NAV, navitoclax; PAC, pacritinib; PR, partial response; QD, once daily; RBC, red blood cell; RUX, ruxolitinib; SVR35, ≥ 35% spleen volume reduction from baseline; TD, transfusion dependence; TGF-β, transforming growth factor beta; TI, transfusion independence; TSS50, ≥ 50% reduction from baseline in total symptoms score.

[a] Due to differences in patient populations and efficacy assessments, direct comparisons of results between studies may be difficult.

[b] Versus BL based on central laboratory assessment over 12 weeks, within 24 weeks.

[c] In order for response to be counted, Hb level was required to be maintained at ≥ 1.5 g/dl at every assessment over the entire 12-week treatment period.

[d] Minimum 4 RBC unit reduction.

[e] Data cutoff: April 17, 2020.

[f] In patients with TD or Hb < 10 g/dl and TI at BL.

[g] Spleen response defined as > 50% reduction in the distance below the left costal margin for ≥ 12 weeks as measured by physical examination.

[h] Data cutoff: April 26, 2018.

[i] Data cutoff: August 30, 2020.

[j] Among patients with Hb < 10 g/dl or TD at BL.

patients receiving momelotinib in the MOMENTUM study attained RBC-TI compared with 20% of patients receiving danazol ($P = 0.0064$ [one-sided]) (Verstovsek et al., 2022).

Another novel JAK inhibitor that has shown promising results is pacritinib, which targets JAK2/IRAK1. A phase 2 dose-finding study of pacritinib in patients with MF who are resistant or intolerant to ruxolitinib found that SVR35 rates were highest (9.3%) with 200 mg of pacritinib administered twice per day. In patients with platelets $< 50 \times 10^9$/l, the SVR35 rate was 16.7% (Gerds et al., 2020b). In the PERSIST-1 trial (NCT01773187), pacritinib versus BAT (without JAK inhibitors) in patients with intermediate- to high-risk MF, pacritinib resulted in improvements in both severe thrombocytopenia and anemia, and 25% of patients treated with pacritinib versus 0% of patients who received BAT achieved RBC-TI ($P = 0.043$). The rates of hematologic toxicities were similar between the pacritinib and BAT treatment arms (anemia: 22% vs 20%, respectively; thrombocytopenia: 17% vs 13%, respectively) (Diaz and Mesa, 2018; Mesa et al., 2017b). Pacritinib (400 mg once daily or 200 mg twice a day) was also compared with BAT in the phase 3 PERSIST-2 trial (NCT02055781) in patients with thrombocytopenia. Both dosing schedules were superior to BAT (which in 44% of patients was ruxolitinib) in terms of SVR35 (18% vs 3%, respectively; $P = 0.001$) and TSS50 (25% vs 14%, respectively; $P = 0.08$). Furthermore, transfusion requirements at weeks 12 and 24 were lower in each pacritinib arm versus BAT for patients who received ≥ 1 RBC unit on study; more patients who were not RBC transfusion independent at baseline had reduced RBC transfusion burden at week 24 with both pacritinib doses compared with BAT (Mascarenhas et al., 2018). A phase 3 trial evaluating pacritinib 200 mg twice a day versus the physician's choice of therapy (primary endpoint SVR35; PACIFICA; NCT03165734) is currently recruiting patients with MF and a platelet count $< 50 \times 10^9$/l with limited or no prior exposure to JAK inhibitors.

4.3. Epigenetic modulation: bromodomain and extra-terminal domain inhibitors

Bromodomain and extra-terminal domain (BET) proteins interact with RNA polymerase II and regulate gene expression by binding to acetylated lysine residues on histone tails, which recruits regulatory complexes (Josling et al., 2012). Inhibiting the BET protein BRD4 attenuates the NF-κB pathway, which is involved in MF-related anemia pathology. Inhibiting BET proteins dampens the inflammatory response of bone marrow-derived macrophages and decreases expression of inflammatory cytokines. In a preclinical murine model of MF, NF-κB signaling was repressed by BET inhibition and inflammatory cytokine production was reduced. Combined JAK and BET inhibition led to a reduction in serum levels of inflammatory cytokines, reduced disease burden, and reversed bone marrow fibrosis (Kleppe et al., 2018; Tremblay and Mascarenhas, 2021). Pelabresib (CPI-0610), a novel oral BET inhibitor, is being investigated in patients with MF in the ongoing phase 1/2 parallel arm MANIFEST trial (NCT02158858). In arm 1 of the study, patients who are intolerant, resistant, or refractory to JAK inhibitors received pelabresib monotherapy, stratified by baseline RBC transfusion status (dependent or independent). Results from this arm show that none of the evaluable, transfusion-dependent patients achieved SVR35 at week 24 (median spleen volume change was 17.4%), and 8.3% of evaluable patients achieved TSS50. Notably, 21.4% of evaluable, RBC transfusion-dependent patients achieved RBC-TI. Of evaluable non-transfusion-dependent patients, 23.8% achieved SVR35 at week 24, and 47.4% achieved TSS50. Hematologic treatment-emergent AEs (TEAEs) of any grade were thrombocytopenia (25.6%) and anemia (11.6%) (Talpaz et al., 2020). Arm 2 evaluated pelabresib as an "add-on" treatment to ruxolitinib in patients with MF who have previously demonstrated a suboptimal response to ruxolitinib alone (again stratified by RBC transfusion dependency). At week 24, 20.8% of evaluable transfusion-dependent patients had achieved SVR35, and 46.2% had achieved TSS50; 34.4% of patients who were RBC transfusion dependent achieved RBC-TI. Of non-transfusion-dependent patients, 22.2% and 36.8% achieved SVR35 and TSS50 at week 24, respectively (Verstovsek et al., 2020). In arm 3, pelabresib was evaluated in combination with ruxolitinib in JAK inhibitor-naïve patients who had baseline platelet count $\geq 100 \times 10^9$/l. Of eligible patients, 63.3% achieved SVR35 at week 24 and 58.6% of patients achieved TSS50. The most common hematologic toxicities of any grade were anemia (2.4%) and thrombocytopenia (20.3%), and the incidences of grade ≥ 3 anemia and thrombocytopenia were 17.2% and 4.7%, respectively (Mascarenhas et al., 2020). Pelabresib in combination with ruxolitinib is currently under investigation in the ongoing phase 3 MANIFEST-2 (NCT04603495) study in JAK inhibitor-naive patients with MF.

4.4. Antifibrotic agents

One therapeutic goal in MF is to reduce the extent of bone marrow fibrosis. PRM-151, a recombinant human pentraxin-2 molecule that inhibits differentiation of monocytes to fibrocytes, is an antifibrotic

agent, which has been evaluated in patients with MF in a two-stage phase 2 study (NCT01981850; Verstovsek et al., 2018). During the first stage, patients were treated with PRM-151 with or without ruxolitinib, and in the second stage patients received PRM-151 alone or in combination with ruxolitinib. Interim results from the open-label extension phase of stage 1 show that patients were on study for a median of 30.9 months. The mean best percent change (by palpation) in spleen size from baseline was −37% and a decrease in symptoms, assessed by mean best percent reduction in Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) Total Symptom Score, was −54%. Table 3 presents an explanation of the MPN-SAF tool and other health-related QoL tools used in MF studies. Reticulin fibrosis improved in 9 patients and collagen fibrosis in 7 patients (Verstovsek et al., 2018). In stage 2 of this study, efficacy and safety of PRM-151 were evaluated in patients with MF with advanced disease who were previously treated or ineligible for ruxolitinib. Reduction by ≥ 1 grade in bone marrow fibrosis at any time during the study occurred in 30%, 28%, and 25% of patients receiving 0.3 mg/kg, 3 mg/kg, and 10 mg/kg of PRM-151, respectively. In RBC transfusion-dependent patients, and those with Hb < 10 g/dl and transfusion independent at baseline, 16–29% had a $\geq 50\%$ reduction in RBC transfusions or Hb increase of ≥ 0.1 g/dl for ≥ 12 consecutive weeks. Most common TEAEs included fatigue, cough, thrombocytopenia, and abnormal weight loss (Verstovsek et al., 2019). These findings require further investigation in a larger, randomized controlled trial.

4.5. Telomerase inhibitors

Telomerase is a protein complex that extends the length of telomeres, which protect the terminal regions of chromosomes from degradation. Telomerase activity is present in germline or certain hematopoietic cells, very low or absent in most somatic cells, and can be reactivated in most cancer types. Imetelstat is an oligonucleotide that blocks the template region of telomerase, inhibiting its enzymatic activity (Wang et al., 2018). This inhibition in malignant hematopoietic stem and progenitor cells contributes to their selective elimination, allowing for the normal production of mature RBCs that alleviate anemia (Mascarenhas et al., 2022). Imetelstat was first trialed in a pilot study in patients with high-risk or intermediate-2-risk MF (NCT01731951). Complete or partial remission occurred in 21% of patients, with a median duration of response of 18 months for complete responses and 10 months for partial responses. A $> 50\%$ reduction in spleen size (by palpation) occurred in 35% of patients, and 31% of RBC transfusion-dependent patients achieved RBC-TI for ≥ 3 months. Bone marrow fibrosis was reversed in all 4 patients who had a complete response; additionally, molecular response occurred in 3 of 4 patients. TEAEs included grade 4 thrombocytopenia (18%) and neutropenia (12%), grade 3 anemia (30%), and grade 1/2 elevation in levels of total bilirubin (12%), alkaline phosphatase (21%), and aspartate aminotransferase (27%) (Tefferi et al., 2015). In the phase 2, randomized IMbark study (NCT02426086), 2 doses of imetelstat (9.4 mg/kg and 4.7 mg/kg) were investigated in patients with relapsed/refractory MF. At week 24, SVR35 was achieved by no patients and 6 patients (10.2%) in the low- and high-dose groups, respectively, and TSS50 occurred in 3 patients (6.3%) and 19 patients (32.2%), respectively. Bone marrow fibrosis improved in 20.0% of patients versus 40.5% of patients receiving low- and high-dose treatment, respectively, with median overall survival of 19.9 months compared with 29.9 months, respectively (Mascarenhas et al., 2021). Anemia response (according to IWG-MRT criteria) was reported in 4.2% of patients in the low-dose group and 6.8% of patients in the high-dose group, including 1.7% who achieved anemia response without clinical improvement (ClinicalTrials.gov, 2015). The phase 3, open-label, multicenter IMpactMF study (NCT04576156) to examine overall survival in patients who are refractory to JAK inhibitors receiving imetelstat compared with best available therapy is now recruiting (Mascarenhas, et al., 2022).

Table 3
Quality of life measures and questionnaires.

Name	Description
MFSAF Myelofibrosis Symptom Assessment Form (Mesa et al., 2009)	• A simple, easy to understand, comprehensive measure specific to the MF population • 7 items focusing on specific MF symptoms: abdominal discomfort, pain under left ribs, early satiety, night sweats, itching, bone or muscle pain, and inactivity • Developed to assess the symptoms of MF and other MPNs (such as PV or ET)
MFSAF 2.0 Myelofibrosis Symptom Assessment Form version 2.0 (Mesa et al., 2021c)	• Version 2.0 measures patient-reported severity of 6 key MF symptoms: night sweats, early satiety, pruritus, pain under the ribs on the left side, abdominal discomfort, and bone or muscle pain, each scored from 0 (absent) to 10 (worst imaginable)
MFSAF 4.0 Myelofibrosis Symptom Assessment Form version 4.0 (Gwaltney et al., 2017)	• Version 4.0 asks respondents to report symptom severity at its worst for each of the 7 items on a 0 (absent) to 10 (worst imaginable) numeric rating scale, and includes 24-hour and 7-day recall formats
MPN-SAF Myeloproliferative Neoplasm Symptom Assessment Form (Scherber et al., 2011)	• Created based on MFSAF to function as a single instrument of patient-reported symptoms for the entire spectrum of patients with MPN, including microvascular symptoms common in patients with ET and PV • Coadministered with the Brief Fatigue Inventory (BFI) • An 18-item instrument monitoring the most debilitating symptoms including night sweats, pruritus/itching, abdominal discomfort, early satiety, bone pain, fever, weight loss or change in appetite, abdominal pain, inactivity, cough, quality of life, headache, concentration problems, dizziness, numbness, insomnia, sad mood, and sexuality problems
MPN-SAF TSS Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (Emanuel et al., 2012)	• An abbreviated 10-item version of the MPN-SAF applying the 10 items deemed most clinically important and characteristic of MPN symptoms • Questions focus on fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fever
MPN-SAF TSS 2.0 Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score version 2.0 (Gerds et al., 2020a)	• Recorded once per day and calculated as the sum of 7 scores related to tiredness, satiety, abdominal discomfort, night sweats, pruritis, bone pain, and left rib pain
EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core 30 items (Aaronson et al., 1993)	• A generic 30-item questionnaire composed of multi-item scales and single items designed to measure cancer patients' physical, psychological, and social functions • 5 multi-item scales: Physical, role, social, emotional, and cognitive functioning • 9 single items: Pain, fatigue, financial impact, appetite loss, nausea/vomiting, diarrhea, constipation, sleep disturbance, and quality of life

Abbreviations: ET, essential thrombocythemia; MF, myelofibrosis; MPN, myeloproliferative neoplasms; PV, polycythemia vera.

4.6. BCL-2/BCL-xL inhibitor (navitoclax)

Navitoclax is an inhibitor of BCL-2/BCL-xL, which are increased with activation of the JAK-STAT signaling pathway, leading to apoptosis of erythroid precursors (Tremblay and Mascarenhas, 2021). Navitoclax has been evaluated in combination with ruxolitinib in a phase 2 (NCT03222609) study in adult patients with MF and splenomegaly who failed ruxolitinib treatment. Thirty-four patients were enrolled in the study (data cutoff of August 30, 2020); all patients experienced TEAEs, the most common being thrombocytopenia (88%; manageable with dose modification), diarrhea (71%), and fatigue (62%). At week 24, 27% of evaluable patients achieved SVR35 (independent of high-molecular-risk mutations) and 30% achieved TSS50. Bone marrow fibrosis improvement by >1 grade at any time during the study occurred in 33% of patients by week 24. Interestingly, Hb levels improved during the study; 64% of patients who had a Hb level <10 g/dl or RBC transfusion dependency at baseline had a Hb improvement of ≥ 2 g/dl or achieved RBC-TI (Harrison et al., 2021). Phase 3 studies comparing the combination of navitoclax and ruxolitinib to ruxolitinib alone in both JAK inhibitor-naive (TRANSFORM-1, NCT04472598) and relapsed/refractory (TRANSFORM-2, NCT04468984) patients are currently ongoing.

4.7. Other investigational agents

Production of hepcidin is controlled by the bone morphogenetic protein type I receptor ACVR1, also known as activin receptor-like kinase-2 (ALK2). Loss of ALK2 in preclinical models resulted in elevated serum iron levels. A novel small molecule ALK2 inhibitor, INCB00928, is currently being evaluated for treatment of anemia. INCB00928 has been shown to inhibit bone morphogenetic protein-induced production of hepcidin with nanomolar activity and exhibited suitable absorption, distribution, metabolism, and excretion properties in rodent studies. In mouse models of anemia, INCB00928 improved RBC count, Hb, and hematocrit levels while decreasing hepcidin levels in a dose-dependent manner. These preclinical findings suggest that ALK2 inhibition with INCB00928 may be a promising treatment, reducing the production of hepcidin and improving MF-related anemia in humans (Chen et al., 2020).

5. Summary

In recent years, advancements in understanding the pathophysiology of MF and MF-related anemia have begun to change the treatment landscape and improve prospects for patients. JAK inhibitors have become an important treatment option for patients with MF, although their ability to exacerbate MF-related anemia adds to the challenge of treating these patients. However, it is possible that an increase in treatment-related anemia linked to JAK inhibitor use may be the cost of better survival associated with the new treatment landscape. Other established MF therapies such as RBC transfusions, ESAs, androgens, and splenectomy have limitations, including limited applicability, poor efficacy, associated toxicities, and mortality. For patients with MF-related anemia, the strong link between anemia and poor QoL and the limited number of treatment options means there is still a significant unmet need in this patient population. Emerging data from trials evaluating therapies for MF-related anemia have shown positive results. Luspatercept has shown promise in a phase 2 trial, specifically in RBC transfusion-dependent patients treated with ruxolitinib. A phase 3 trial with luspatercept in patients with MPN-associated MF is currently underway. New generation JAK inhibitors such as momelotinib and pacritinib have also shown efficacy/less toxicity in terms of anemia responses and are in clinical evaluation. Novel agents such as the BET inhibitor pelabresib, antifibrotic agent PRM-151, telomerase inhibitor imetelstat, and BCL-2/BCL-xL inhibitor navitoclax – either alone or in combination with JAK inhibitor therapy – also offer new treatment options for the management of MF-related anemia. These results, together with positive preliminary data from investigational agents such as KER-050 and INCB00928, provide a positive outlook on the future of treatments for patients with MF-related anemia.

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Author contributions

All authors were involved in all stages of manuscript development, including conceptualization of the outline, drafting, and critical review of the manuscript. The authors are fully responsible for the content and editorial decisions for this manuscript. All authors approved the final draft for submission.

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Fig. 2 is adapted from Fig. 1 of Naymagon and Mascarenhas (2017), which was distributed under the Creative Commons Attribution License 4.0 (CCBY).

Declaration of Competing Interest

Francesco Passamonti has been a member of a speakers' bureau for AbbVie, BMS, Celgene, Janssen, and Novartis; has consulted for AbbVie, AOP Orphan, BMS, Celgene, Janssen, Karyopharma, Kyowa Kirin, MEI Pharma, Novartis, and Roche; and has received research grants from BMS. Claire N. Harrison has received honoraria from AbbVie, AOP Orphan, BMS, Constellation Pharmaceuticals, CTI BioPharma Corp, Janssen, Novartis, and Sierra Oncology; has consulted for AbbVie, AOP Orphan, CTI BioPharma Corp, Galecto, Geron, and Sierra Oncology; has received support for travel from BMS and Novartis; has been a member of an advisory board for Galecto; and has received research grants from BMS, Constellation Pharmaceuticals, and Novartis. Ruben A. Mesa has consulted for Constellation Pharmaceuticals, La Jolla Pharmaceutical, Novartis, Pharma, and Sierra Oncology; and has received research grants from AbbVie, Celgene, Constellation Pharmaceuticals, CTI BioPharma Corp, Genotech, Incyte, Mays Cancer Center P30 Cancer Center Support Grant from the National Cancer Institute (CA054174), Promedior, and Samus. Jean-Jacques Kiladjian received honoraria from Novartis; and has been a member of an advisory board for AbbVie, AOP Orphan, BMS, Incyte, and Novartis. Alessandro M. Vannucchi has been a member of an advisory board for AbbVie, AOP Orphan, Blueprint Medicines, Celgene, Incyte, and Novartis; and has received lecture fees from AbbVie, AOP Orphan, Blueprint Medicines, BMS, GSK, Incyte, and Novartis. Srdan Verstovsek has received research support for the conduct of clinical studies from BMS.

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