short review

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Brief update on systemic therapies in myeloproliferative neoplasms

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Summary Over the past years we have gained considerable insights into the biology and consequent therapeutic options in myeloproliferative neoplasms. In this review we aim to highlight the most relevant recent developments in this field with special focus on primary as well as secondary myelofibrosis and polycythemia vera.

Keywords JAK inhibitors · Hepcidin mimetics · Interferon-alfa · Secondary myelofibrosis · Polycythemia vera

Abbreviations

AE	Adverse events
Allo-SCT	Allogeneic stem cell transplantation
BAT	Best available therapy
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
GI	Gastrointestinal
JAKi	Janus kinase inhibitor
MF	Myelofibrosis
MPN	Myeloproliferative neoplasms
PV	Polycythemia vera
SVR_{35}	Spleen volume reduction of 35%
TSS_{50}	Total symptom score reduction of 50%

Introduction

Myeloproliferative neoplasms (MPN) are a group of seven separate entities with a pronounced heterogeneity with regard to their clinical phenotype, prognosis and therapeutic options [1]. In comparison to the wide range of novel targeted therapeutic agents and cellular therapies emerging in the hematology field, therapeutic options for classical MPN are still rather limited, such as phlebotomy, acetylsalicylic acid (ASA), hydroxyurea, the first-in-class JAK1/2 inhibitor ruxolitinib and allogeneic stem cell transplantation (allo-SCT) [2, 3]. However, especially regarding primary and secondary myelofibrosis (MF) as well as polycythemia vera (PV), some very promising novel agents and targets are currently being investigated.

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Myelofibrosis

Fedratinib

Fedratinib was approved in 2019 as the second JAK inhibitor (JAKi) after ruxolitinib [4, 5]. Approval was based on the JAKARTA trials. The single-arm phase II JAKARTA-2 as well as the randomized JAKARTA phase III trial evaluated fedratinib in intermediate-1 or higher primary or secondary MF patients with platelet counts $\geq 50 \times 10^9$/l [4, 5]. Results from the JAKARTA phase III study in JAKi-naïve patients demonstrated a significantly higher proportion of fedratinib-treated patients achieving a spleen volume reduction of at least 35% (SVR_{35}) at week 24 as well as a significant reduction in the symptom score total symptom score (TSS) from baseline when compared to placebo [6]. The most common adverse events (AEs) were hematologic and gastrointestinal side effects [6]. Importantly, fedratinib was placed on hold due to safety concerns with suspicion of Wernicke encephalopathy in 2013, leading to significant delay of the JAKARTA studies and also of approval [4, 7]. The hold was finally lifted in 2017 after generation of additional safety data [7]. In conclusion, fedratinib represents an important addition to ruxolitinib therapy when thiamine levels are monitored care-

fully. However, the main difficulty with both agents is still the leading toxicity being hematologic side effects. This is especially problematic in a group of patients where practically all will suffer from anemia and 2/3 will experience thrombocytopenia during the course of the disease [8, 9]. Based on the survival advantage shown for ruxolitinib, the latter still remains the first-line therapy of choice in symptomatic MF, whereas fedratinib should be considered in patients with moderately low platelets and in ruxolitinib-resistant or intolerant individuals.

In the recent past, some very promising new therapeutics appeared particularly for cytopenic MF.

Pacritinib

Pacritinib is a new emerging inhibitor of JAK2, IRAK1, NF-kB and inhibitor of ACVR1 [8, 10]. It was approved by the FDA in 2022 for intermediate or high-risk MF patients with low platelet counts $<50\times10^9$/l [11]. The pivotal study leading to FDA approval was the phase III PERSIST-2 trial. Eligibility criteria involved primary or secondary MF in intermediate-1 risk disease or higher, with thrombocytopenia ($<100\times10^9$/l), TSS >13 and splenomegaly of at least 5 cm below the costal margin [12]. A total of 311 patients were randomized to pacritinib in two dosing schemes, either 400 mg QD or 200 mg BID, versus best available therapy (BAT) [12]. BAT included mainly ruxolitinib (45%) and hydroxyurea (19%) [12]. Applying the now approved dose of 200 mg BID, there was a significant difference in SVR_{35} compared to BAT at week 24 (22 vs. 3%, $p=0.001$) [12]. In addition, there was an advantage in TSS reduction of pacritinib with a significantly higher percentage of patients achieving a TSS reduction of 50% or more (TSS_{50}) at week 24 (32 vs. 14%, $p=0.01$) [12]. Importantly, the investigators also demonstrated a significant reduction in red blood cell (RBC) transfusion dependence with pacritinib versus BAT [12]. Using pacritinib 200 mg BID, the proportion of patients who achieved RBC transfusion-independence with previous transfusion dependence at baseline was higher with pacritinib at week 24 compared to BAT (22 vs. 9%) [12]. The most common adverse events were hematologic toxicities, gastrointestinal (GI) adverse events, fatigue and peripheral edema [12]. In 2016 a full clinical hold was placed on pacritinib by the FDA due to issues with bleeding as well as cardiovascular events and deaths, which was lifted in 2017 [12]. Analogous to the JAKARTA-2 study, these concerns caused early termination and intermittent discontinuation of the pacritinib trials [12]. Collectively, pacritinib thus constitutes a highly interesting novel therapeutic option in severely cytopenic MF with potential benefits for transfusion-dependent patients. Unfortunately, due to difficulties with the generation of the required additional data, the company withdrew its application for EMA-approval in 2017 [13].

Momelotinib

Another highly interesting novelty in cytopenic MF is momelotinib. Momelotinib is a selective inhibitor of JAK1/2 and ACVR1 [14, 15]. The main obtained data are derived from the phase III SIMPLIFY-1, SIMPLIFY-2 and the MOMENTUM trials [15, 16]. Momelotinib was tested in various clinical scenarios: in JAKi-naïve patients compared to ruxolitinib (SIMPLIFY-1), in ruxolitinib-pretreated patients versus BAT (SIMPLIFY-2) and in anemic, JAKi-pretreated patients in comparison to danazol (MOMENTUM) [14–16]. The latter phase III trial investigated JAKi-pretreated MF patients in intermediate-1 or higher risk disease, with TSS ≥10, anemia (Hb <10 g/dl) and platelet counts of $>25\times10^9$/l [16]. A total of 195 patients were 2:1 assigned to receive either momelotinib 200 mg QD or danazol 300 mg QD [16]. There was a significant advantage of momelotinib compared to danazol in terms of TSS_{50} reduction (25 vs. 9%, $p=0.0095$) as well as a superiority in splenic response (SVR_{35} 23 vs. 3%, $p<0.0006$) at week 24 [16]. Most importantly, momelotinib showed a significant effect on the anemic burden, with achievement of transfusion independence in 27% as compared to 15% in patients that were transfusion-dependent at baseline [16]. Hematologic abnormalities were the most common AE led by anemia, as well as GI toxicities and asthenia [16]. Therapy using momelotinib seems to be feasible in cytopenic patients even with pronounced thrombocytopenia [16]. Thus, momelotinib appears to be a safe and highly interesting novel therapeutic agent in particular in anemic MF patients. The drug is currently under consideration by the FDA, where a decision is expected in June 2023, as well as by the EMA [17, 18].

Combinational therapies

In addition to novel JAKi therapeutics, possible combination partners to ruxolitinib therapy in MF have been investigated in early phase trials such as the Bcl-2 inhibitor navitoclax or the BET inhibitor pelabresib.

The phase II REFINE study patients investigates navitoclax and navitoclax + ruxolitinib in intermediate or high-risk MF patients with or without preceding JAKi therapy [19–21]. Exemplarily, in patients with progression or suboptimal response to ruxolitinib the addition of navitoclax led to a SVR_{35} in 26.5%, a TSS_{50} in 30%, anemia response in 64% and importantly amelioration of bone marrow fibrosis by 1–2 grades in 33% at 24 weeks, suggesting a disease-modifying effect [20]. The most prevalent AE was thrombocytopenia [20].

Similarly, the phase II MANIFEST study evaluates the efficacy of pelabresib with or without ruxolitinib in JAKi-naïve and pretreated MF patients in intermediate-1 or higher risk disease [22]. At 24 weeks,

the group demonstrated in JAKi-naïve patients a SVR_{35} in 68% and TSS_{50} in 56% [22]. In all, 36% of the patients showed a benefit in anemic burden and 28% achieved at least 1 grade improvement in fibrosis [22]. Hematologic toxicities were the most common [22].

Further phase III studies evaluating JAKi combination therapies are awaited and needed in order to acquire more data on efficacy and safety.

Polycythemia vera

Hepcidin mimetics

A promising novel approach in iron-deprived hematopoiesis in PV is the noncytoreductive novel therapeutic class of hepcidin mimetics. Two early phase II trials investigating the first-in-class compound rusfertide provided encouraging results on hematocrit control in PV patients. The REVIVE study includes PV patients with need for therapeutic phlebotomy, while the PACIFIC study likewise includes PV patients with hematocrit levels >48% [23, 24]. The addition of rusfertide induced freedom from phlebotomy, a promising hematocrit control of <45% and normalized ferritin levels in almost all patients [24]. Adverse events were in general mild (grade 1–2), with injection site reactions being the most frequent [23–25]. A transient clinical hold was placed on the development of rusfertide in 2021 due to concerns of secondary malignancies; however the hold was fortunately removed shortly thereafter [23, 26]. Consequently, rusfertide may constitute an interesting future new agent in PV patients with insufficient hematocrit control or intolerance to phlebotomies. A phase III clinical trial is currently underway.

Ropeginterferon alfa-2b in low-risk PV

Another already well-known drug among the therapeutic options in PV patients is ropeginterferon alfa-2b. It has been approved by the EMA and FDA after careful clinical investigation on high-risk PV patients, e.g. within the PROUD-PV trial [27–29]. Here, it has also demonstrated its convincing disease-modifying effect by a substantial drop in JAK2 allelic burden over time, which is not achievable by any other drug so far in PV [29]. Thus, its application may also be reasonable in low-risk PV, to avoid potential long-term harm from the disease, such as transformation to post-PV MF and/or MPN-blast crisis (i.e. secondary AML). An Italian group has recently tested ropeginterferon alfa-2b as a front-line therapeutic agent in low-risk phlebotomy-dependent PV patients [30]. The phase II low-PV study compared standard of care (phlebotomy and aspirin) to standard treatment with additional ropeginterferon alfa-2b in low-risk PV patients ($n=127$) [30]. The effect of the addition of interferon alfa-2b on hematocrit response reached the critical limit of efficacy in this cohort already in the interim analysis, so that patient accrual was terminated early [30]. Even though further phase III studies and longer follow-up are needed to justify this recommendation for common clinical practice, the data are highly convincing and in particular in very

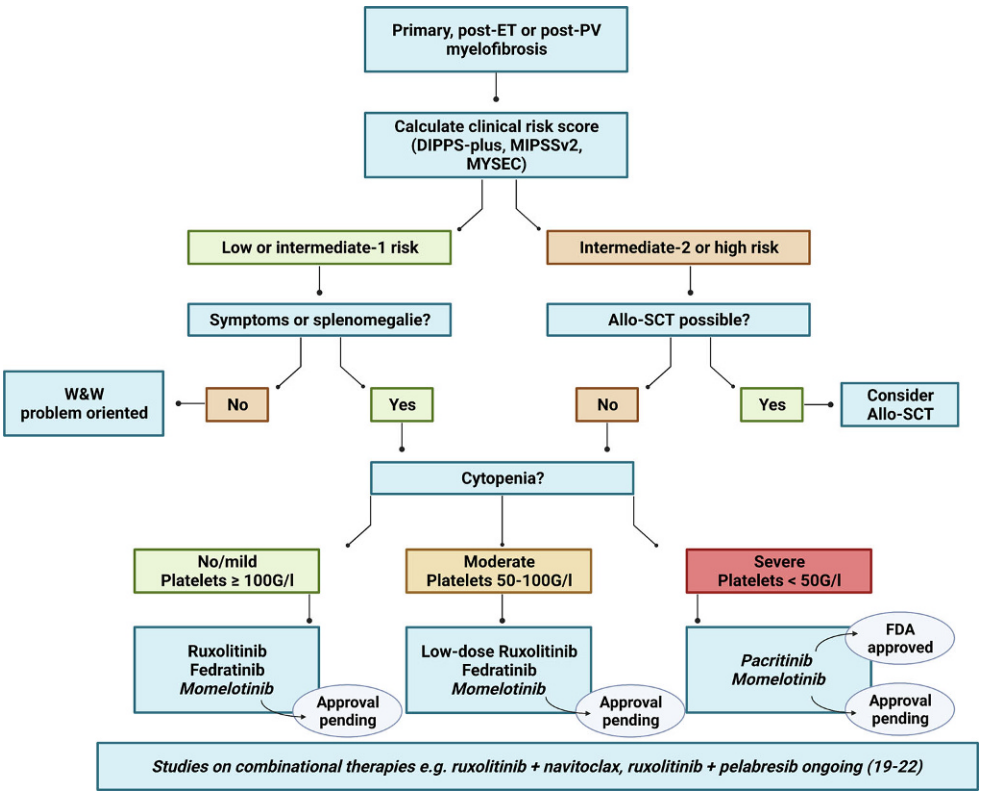

Fig. 1 Treatment algorithm for primary and secondary myelofibrosis. Displayed are established therapeutic strategies for myelofibrosis (MF) patients as well as possible novel evolvements that have not yet been approved. *Allo-SCT* Allogeneic stem cell transplantation, *FDA* U.S. Food and Drug Administrat. (Adapted from the German Onkopedia guidelines [32]. Created with BioRender.com)

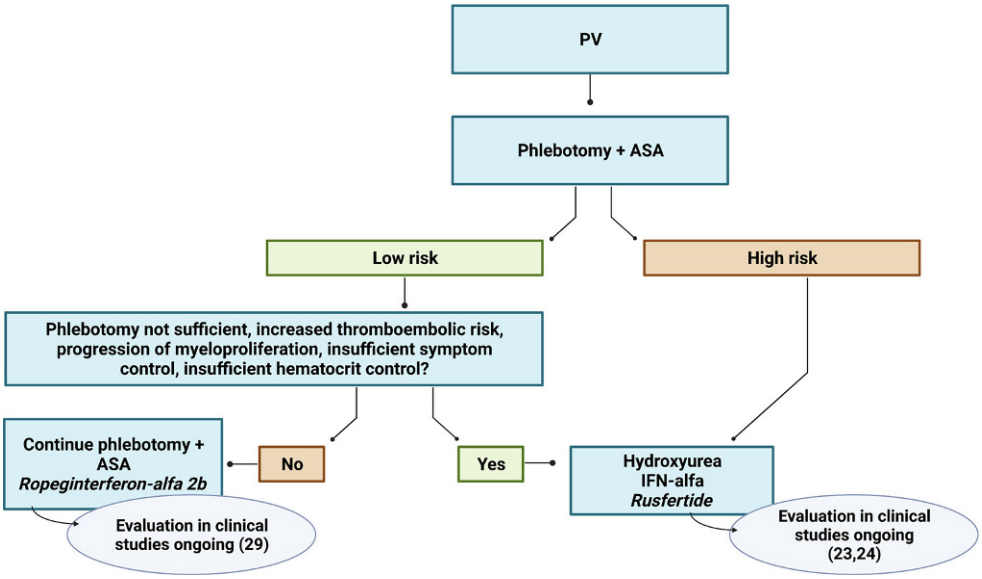

Fig. 2 Treatment algorithm for polycythemia vera (PV). Demonstrated are already approved therapeutic strategies in PV with the addition of possible future treatment developments. *ASA* acetylsalicylic acid. (Adapted from the German Onkopedia guidelines [33]. Created with BioRender.com)

young patients with low tolerability of phlebotomies, high phlebotomy need or additional high-risk genetic markers off-label application in this setting is definitely reasonable.

Conclusions

Clinical developments in the field of myelofibrosis and PV are currently a hot topic in MPN with a variety of emerging novel agents, mainly targeting difficult-to-treat groups, such as cytopenic or ruxolitinib-refractory MF and low-risk PV. Even though not approved by EMA, pacritinib and momelotinib are important novel compounds for cytopenic MF (see Fig. 1). In addition, various other studies in MF are promising, such as the evaluation of novel JAKi (ilginatinib or itacitinib) and combination therapies of JAKi with Bcl-2 inhibitor navitoclax or BET inhibitor pelabresib to achieve a more pronounced anti-fibrotic (disease-modifying) effect [8, 20, 31].

Concerning PV, hepcidin mimetics may further expand the therapeutic horizon in the near future by reducing iron-availability for hematopoiesis and thereby reducing hematocrit and phlebotomy-need. Furthermore, ropeginterferon alfa-2b constitutes a highly interesting extension to conventional treatment in low-risk PV patients, in particular in phlebotomy-intolerant and very young PV patients (see Fig. 2). One may also envision combination of the hematocrit-reducing rusfertide and the disease-modifying ropeginterferon alfa-2b.

Take Home Message

Severely cytopenic myelofibrosis constitutes a challenging entity among the group of MPN. Promising novel therapeutics include JAKi pacritinib and momelotinib. We may also soon see practice-changing developments in polycythemia vera, with one of the most exciting novelties being the evolution of hepcidin mimetics.

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