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Novel Therapies for Myelofibrosis

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Abstract

Purpose of Review—To provide a contemporary update of novel agents and targets under investigation in myelofibrosis in the JAK inhibitor era.

Recent findings—Myelofibrosis (MF) is a clonal stem cell disease characterized by marrow fibrosis and a heterogeneous disease phenotype with a variable degree of splenomegaly, cytopenias, and constitutional symptoms that significantly impact quality of life and survival. Overactive JAK/STAT signaling is a hallmark of MF. The only approved therapy for MF, JAK1/2 inhibitor ruxolitinib, can ameliorate splenomegaly, improve symptoms, and prolong survival in some patients. Therapeutic challenges remain, however. Myelosuppression limits the use of ruxolitinib in some patients, eventual drug resistance is common, and the underlying malignant clone persists despite therapy. A deeper understanding of the pathogenesis of MF has informed the development of additional agents.

Summary—Promising targets under investigation include JAK1 and JAK2, downstream intermediates in related signaling pathways, epigenetic modifiers, pro-inflammatory cytokines, and immune regulators.

Keywords

myelofibrosis; myeloproliferative neoplasms; novel therapies; JAK inhibitors; drug development

Introduction

Myelofibrosis (MF) is a heterogeneous disease within the family of BCR-ABL negative myeloproliferative neoplasms (MPNs) characterized by dysregulated proliferation of myeloid cells, aberrant deposition of reticulin and collagen in the bone marrow, and excess production of pro-inflammatory cytokines. The resulting clinical manifestations vary between individuals and include progressive cytopenias, extramedullary hematopoiesis resulting in splenomegaly, constitutional symptoms (i.e. fatigue, pruritus, and night sweats), psychosocial symptoms, acute leukemic transformation, and shortened life expectancy (1-3).

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Current MF therapies are often ineffective in controlling symptoms or altering the natural history of the disease.

Insights into molecular mechanisms of MPN pathogenesis have spurred drug development in the field. Dysregulation of the JAK/STAT pathway is central to MPN development, and driven by activating mutations in Janus kinase 2 (*JAK2*), calreticulin (*CALR*), or myeloproliferative leukemia virus (*MPL*) in over 90% of MF cases (4, 5). Alterations in additional cellular processes such as DNA methylation (i.e. *TET2, DNMT3A* mutations), histone modification (*ASXL1, EZH2* mutations), RNA splicing (*U2AF1, SF3B1, SRSF2* mutations), and signaling through other pathways (RAS/RAF/MEK/ERK, PI3K/AKT/mTOR, LNK) further contribute to MF initiation or progression and may explain some of the variability in the disease phenotype (6). This complexity and heterogeneity in disease biology provides both challenges and opportunities for drug development in MF.

Current Risk-Adapted Approach to Treatment

There are currently few standard treatment options for patients with MF. Allogeneic hematopoietic stem cell transplantation (alloHSCT) provides the only potentially curative treatment modality, however its use in the MF population is marred by potential toxicities due to advanced age (median age at diagnosis is 67 years), comorbidities, and poor functional status resulting from disease symptomatology (7). Other treatment modalities are aimed at reducing symptoms and improving blood counts, with little effect on the underlying malignant clone or on patient survival. Ruxolitinib is an oral inhibitor of JAK1/2 with the ability to reduce spleen size and improve symptoms in some patients, and has been associated with a modest survival advantage (8, 9). A number of other agents have been used to improve cytopenias or reduce splenomegaly with variable success, including erythropoietin stimulating agents, androgens (i.e. danazol), immunomodulators (i.e. thalidomide), and hydroxyurea.

Management decisions for patients with MF are dictated by individual patient symptoms and the risk of disease transformation or patient death. These risks are assessed using either the Dynamic International Prognostic Scoring System (DIPSS) which incorporates age, white blood cell count, hemoglobin level, circulating blast cells, and constitutional symptoms, or the newer DIPSS-Plus that adds karyotype, red blood cell transfusion requirement, and thrombocytopenia (10, 11). Using the DIPSS-Plus tool, patients are assigned low, intermediate-1, intermediate-2, or high risk scores corresponding to median overall survival times of 15.4 years, 6.5 years, 2.9 years, and 1.3 years, respectively. These disparate outcomes highlight the heterogeneity among patients with MF, and underscore the importance of risk-directed treatment algorithms (12). Presently, there is no evidence that early treatment of asymptomatic patients improves survival, and therefore management of asymptomatic low risk patients is generally supportive and expectant. Ruxolitinib is approved by the United States Food and Drug Administration (FDA) for intermediate or high risk MF, however it is often used in lower risk patients with significant disease-related symptoms and has been included in the 2017 inaugural National Comprehensive Cancer Network (NCCN) guidelines for MF for any symptomatic patient, provided that the platelet count is >50 10^9/L (12). AlloHSCT has been shown to improve long-term outcomes among

those with intermediate-2 or high-risk disease, and should therefore be offered to those deemed eligible (13). For those with low risk disease, alloHSCT is associated with inferior 5-year survival rates when compared to those treated without transplant. For those with intermediate-1 risk disease, the risk-benefit ratio of alloHSCT remains unclear, and may be considered on a case-by-case basis. Despite improvements in risk stratification and their application to treatment algorithms for patients with MF, the current therapies prove inadequate for many. Development of novel agents and approaches for treatment of MF therefore remains a significant area of unmet need. In this review, we summarize the contemporary drug therapies for MF, with a focus on novel agents and approaches.

JAK Inhibitors

Ruxolitinib

JAK1/2 inhibitor ruxolitinib remains the only FDA approved agent for MF, and sets the standard against which novel agents are measured. The COMFORT-I and COMFORT-II trials demonstrated clinical benefit from ruxolitinib compared to placebo (COMFORT-I) or best available therapy (COMFORT-II), including spleen volume reduction (SVR), decrease in total symptom score (TSS), improvement in quality of life measures, and improvement or stabilization of bone marrow fibrosis (table 1) (14-16). Follow up at 5 years revealed sustained responses with median response duration among the ruxolitinib-randomized patients of 3.2 years in both studies (8, 9). Improvement in overall survival (OS) was also shown in the ruxolitinib groups even after crossover (not reached versus 3.8 years in COMFORT-I; not reached versus 4.1 years in COMFORT-II).

Despite meaningful clinical benefits conferred by ruxolitinb, challenges remain. First, the effects on the malignant clone appear to be minimal. Molecular responses as measured by JAK2 mutant allele burden are uncommon (17). Second, anemia and thrombocytopenia limit the use and dose of ruxolitinib in certain populations. Both thrombopoietin and erythropoietin signaling involve JAK2, and therefore thrombocytopenia and anemia are expected and dose-related (18). Despite this limitation, low-dose ruxolitinib has proven to be relatively safe in those with baseline platelet counts of 50–100 × 10^9/L, and the agent is still associated with a favorable response profile even at low doses in this population (18). Third, the eventual development of resistance to JAK inhibitors presents a therapeutic challenge. Long term follow up from the COMFORT-II trial showed that the probability of maintaining a response to ruxolitinib at 5 years was 0.48 (95% confidence interval 0.35-0.60), and the median response duration was 3.2 years (8). Multiple mechanisms of resistance to JAK inhibition have been described, including up-regulation of parallel pathways, heterodimerization of activated JAK2 with other JAK kinases including JAK1 and TYK2, and point mutations in the kinase domain of JAK2 that have been identified in cell lines but have not yet been seen in patients (19-23). Investigation of rationally designed combination therapies to prevent or overcome resistance is therefore warranted.

Other JAK Inhibitors

The number of other JAK inhibitors in development has unfortunately dwindled over time due to toxicity concerns and failure to meet efficacy endpoints in larger trials. However,

several investigational JAK inhibitors of interest persist. Table 1 describes features and key results of clinical trials with select JAK inhibitors.

Pacritinib, a JAK2/FLT3 inhibitor, garnered interest due to its lack of myelosuppression noted in early clinical trials (24). Two phase 3 trials, PERSIST-1 and PERSIST-2, have been performed. In PERSIST-1, patients with higher-risk MF were randomized to pacritinib versus best available therapy (BAT) (25). The primary endpoint of ≥35% reduction in SVR was met by 19% in the pacritinib arm versus 5% in the BAT arm, with minimal myelosuppression (Table 1) even among patients with baseline cytopenias. PERSIST-2 focused exclusively on patients with platelets $<100 \times 10^9$/L, and randomized patients to two doses of pacritinib (200 mg BID or 400 mg once daily) or BAT, which could include ruxolitinib (26). Prior treatment with ruxolitinib was allowed as well. Patients in the pacritinib arm achieved greater reductions in spleen volume, TSS, and transfusion requirements at 24 weeks (Table 1). The FDA imposed a full clinical hold on pacritinib in February 2016 due to concerns regarding excess fatalities, cardiac events, and hemorrhagic events. The clinical hold was lifted in January 2017. Pacritinib remains an attractive agent due to potential for use in thrombocytopenic patients, however further studies to clarify the safe and effective dose and schedule are warranted.

Momelotinib is a JAK1/2 inhibitor with the attractive feature of improving anemia, likely due to reduction in hepcidin production by the liver (27). SIMPLIFY-1, a phase 3 head-to-head trial of momelotinib versus ruxolitinib in JAK inhibitor-naïve patients with MF met its primary endpoint in demonstrating noninferiority in SVR responses at 24 weeks, however failed to meet its secondary endpoint of TSS reduction (28). In a second phase 3 study, SIMPLIFY-2, patients previously exposed to ruxolitinib were randomized to momelotinib versus BAT, which included ruxolitinib in most (29). This trial failed to meet its primary endpoint of superiority of momelotinib in terms of SVR responses, however did show a reduction in TSS and improvement in anemia. As a result of these somewhat disappointing phase 3 results, momelotinib is no longer in development and the therapeutic void for patients with MF and anemia remains unfilled.

Several additional JAK inhibitors are under investigation in earlier clinical phases. NS018 is a selective inhibitor of JAK2 and Src that showed a favorable toxicity profile and promising efficacy signals in phase 1; the phase 2 portion of this study is ongoing (30). A phase 2 study of JAK1 inhibitor itacitinib demonstrated the ability of selective JAK1 inhibition to improve splenomegaly and symptoms related to MF while preserving hemoglobin levels (31). A multicenter phase 2 study evaluating itacitibine alone or in combination with low-dose ruxolitinib after ruxolitinib failure is planned (NCT03144687).

Beyond JAK Inhibitors

DNA Hypomethylating Agents

Epigenetic alterations, such as CpG island hypermethylation causing inactivation of tumor suppressor genes, have been implicated in the pathogenesis of many malignancies including MF (32-34). DNA hypomethylating agents (HMAs) such as azacitidine and decitabine are postulated to exert their effects, in part, through reactivation of hypomethylated genes. Both

are FDA approved for the treatment of myelodysplastic syndrome (MDS), and are also frequently used for the treatment of acute myeloid leukemia (AML). Modest clinical responses have been reported with HMAs in patients with MF. A phase 2 study evaluated the effects of azacitidine in 34 patients with MF; 76% had received previous treatment (35). Clinical improvement (CI) was seen in 21%, and a partial response (PR) was achieved in 1 patient (3%). No complete responses (CR) were seen, and no improvement in bone marrow fibrosis was identified. Myelosuppression was common with this standard, 7-day azacitidine regimen. Another study administered azacitidine on a shortened 5-day schedule to 10 patients with MF, and no improvement was reported (36).

Low-dose subcutaneous decitabine (0.3 mg/kg/day on days 1-5 and days 8-12) has shown some evidence of efficacy. In this Phase II trial in MF, of 19 evaluable patients, a 37% overall response rate was reported (37). Myelosuppression was significant, though reversible. In a retrospective report, standard dose decitabine (20 mg/m^2 intravenously daily on days 1-5) resulted in clinical benefit in 9 (82%) of patients with high risk MF, but no partial or complete responses, and benefits were maintained for a median of 9 months (38). Other case reports have described efficacious use of decitabine in controlling symptoms, improving splenomegaly, and decreasing transfusion requirements. (39).

Combination studies of JAK inhibitors and HMAs for chronic phase MF are underway. Clinical responses have been reported with either azacitidine or decitabine in combination with ruxolitinib in intermediate-2 or high risk MF (40, 41). A phase II study combining low-dose azacitidine with ruxolitinib for patients with chronic phase MF or myelodysplastic syndrome/myeloproliferative neoplasms (MDS/MPN) is ongoing (NCT01787487).

HMAs may be particularly useful in cases of accelerated or blast phase disease, where ORR as high as 52% has been reported with azacitidine (42) and encouraging activity has been reported in retrospective series with decitabine (38, 43). Two phase 1 studies of decitabine plus ruxolitinib in accelerated or blast phase MF demonstrated that the combination was tolerable and promising (44, 45), and a phase 2 portion through the Myeloproliferative Disorders Research Consortium is ongoing (NCT02076191).

Histone Deacetylace Inhibitors

Histone deacetylace inhibitors (HDACi) represent another epigenetic-targeted therapy under investigation for MF. As single agents, vorinostat, panobinostat, givinostat, and pracinostat have all demonstrated modest clinical activity (46-51). The most common class toxicities of HDACi include cytopenias, fatigue, and diarrhea. Two clinical trials investigating the combination of HDACi and JAK inhibitors are ongoing (NCT01693601 and NCT01433445). Preliminary results of the Phase 1b trial of the combination of panobinostat and ruxolitinib have been reported (52). Among 61 patients with MF, 57% and 39% achieved SVRs ≥35% at 24 weeks and 48 weeks, respectively. Improvement in bone marrow fibrosis occurred in 4 of 12 evaluable patients, and ≥20% decrease in JAK2 mutant allele burden was seen in 5 out of 17 tested patients.

PI3K/AKT/mTOR Pathway Inhibitors

The PI3K/AKT/mTOR signaling pathway and the JAK/STAT signaling pathways are intricately connected, and both are both aberrantly activated in MPN (53). Small molecule inhibitors of PI3K, AKT, and mTOR have all been subjects of preclinical investigation in MF, with encouraging results (54-56). In a phase I/II clinical trial, mTOR inhibitor everolimus induced responses in 23% (1 PR, 6 CI) (57). Pre-clinical synergy has been demonstrated with combinations of PI3K/AKT/mTOR inhibitors and JAK inhibitors, prompting several ongoing combination studies including PI3K inhibitor buparlisib with ruxolitinib (NCT01730248), PI3K inhibitor INCB050465 and ruxolitinib (NCT02718300), and selective PI3Kδ inhibitor TGR-1202 and ruxolitinib (NCT02493530). Early results from the buparlisib and ruxolitinib phase 1b study have been reported, and the combination was reasonably well tolerated (58). Clinical responses were noted, with palpable spleen length reduction of ≥50% in 82% of JAK inhibitor naïve and 55% of JAK inhibitor pre-treated patients.

RAF/MEK/ERK Pathway Inhibitors

In parallel to the PI3K/AKT/mTOR pathway, the RAF/MEK/ERK signaling pathway is also activated by increased JAK/STAT signaling and contributes to impaired cellular differentiation and increased proliferation (59-61). In a CALR deleted murine model with a MPN phenotype, treatment with the MEK inhibitor trametinib alone significantly reduced bone marrow fibrosis (62). Combining MEK inhibitor selumetinib with ruxolitinib has been shown to significantly inhibit malignant cell growth and rescue hematopoietic stem cell function, as well as prolong survival in a NRAS mutant murine model with a MDS/MPN phenotype (63). While clinical experience with MEK inhibitors in MF is limited, modest single-agent activity in AML has been demonstrated (64, 65). Further investigation of RAF/MEK/ERK pathway inhibitors in MF, in rationally designed combinations, is warranted and a trial combining the MEK inhibitor selumetinib (table 2) with the DNA hypomethylating agent azacitidine will soon be underway.

Hedgehog Inhibitors

The hedgehog signaling pathway contributes to normal hematopoiesis, and overactive hedgehog signaling has been implicated in the pathogenesis of both malignant and fibrotic diseases (66, 67). Small molecule inhibitors of several hedgehog signaling proteins have shown clinical activity in MF. Early results of a phase 1/2 study of glasdegib as a single agent in patients with MF after JAK inhibitor therapy showed a favorable toxicity profile of the drug, with modest single-agent responses (68). The main toxicities noted were dysguesia, muscle spasms, alopecia, decreased appetite, and fatigue. No patient achieved SVR ≥35%, but 5 (24%) did have some degree of improvement in splenomegaly. Favorable symptom responses were seen, as 8 (38%) had ≥20% decrease in TSS. This study is ongoing (NCT02226172). Combinations of hedgehog pathway inhibitors and JAK inhibitors are also underway. Preliminary results from a phase 1b/2 study of sonidegib in combination with ruxolitinib in 27 patients with MF showed that 56% of patients achieved a SVR of ≥35% at any time during treatment (NCT01787552)(69).

Telomerase Inhibitors

Telomeres are repetitive DNA sequences that cap chromosomes, protect coding DNA, and shorten with each cycle of cell division (70). Many malignant cells express telomerase, a holoenzyme responsible for maintaining telomere length. Imetelstat is an oligonucleotide that binds the RNA template of telomerase and competitively inhibits enzymatic activity telomerase activity (71, 72). Imetelstat was investigated in a pilot study of 33 patients with intermediate-2 or high-risk MF, about half of whom were previously treated with ruxolitinib (73). Complete or partial remissions were seen in 7 patients (21%), with median response durations of 18 months and 10 months for those who achieved complete and partial remissions, respectively. Among the 4 patients who achieved a CR, bone marrow fibrosis was reversed in all 4 and molecular responses occurred in 3. Imetelstat was relatively well tolerated in this population, with the most common toxicities being cytopenias and transaminitis. A phase II study of 2 doses of imetelstat in patients with intermediate-2 or high-risk MF previously treated with a JAK inhibitor is ongoing (NCT02426086). Favorable responses to imetelstat have also noted in patients with essential thrombocythemia, however this indication has not been pursued further, likely due to the relatively indolent course associated with ET (74).

Anti-Fibrosing Agents

Targeting the complex pathogenic mechanisms that result in bone marrow fibrosis remains challenging. One novel therapeutic target is pentraxin 2, an endogenous protein that regulates differentiation of monocytes into fibrocytes and pro-fibrotic macrophages at sites of tissue damage (75-77). PRM-151 is a recombinant form of pentraxin 2 that was initially developed as an agent for pulmonary fibrosis, but has since been studied in MF. In a phase 2 study of PRM-151 in combination with ruxolitinib in patients with intermediate-1 or higher risk disease, 35% experienced an objective response, defined as CI (15%) and/or reduction in bone marrow fibrosis (23%) (78). Improvements in anemia (40%), spleen size (26%), and symptoms (38%) were also noted. A second stage of this study evaluating 3 dose levels is ongoing (NCT01981850).

Several other potential targets involved in fibrotic processes have been identified, however clinical results have been somewhat disappointing to date. Lysyl oxidase like (LOXL) is an amine oxidase enzyme that catalyzes a key step in the formation of crosslinks between collagen and elastin. In preclinical models, LOXL levels were found to be elevated, and inhibition of LOXL led to improvement in marrow fibrosis (79, 80). In a phase II study, a humanized antibody against LOXL2, simtuzumab, was well tolerated but failed to reduce marrow fibrosis or achieve clinical improvement (81).

Cytokine transforming growth factor-β (TGF-β) has been implicated in both the fibrotic and proliferative aspects of myelofibrosis (82). Sotatercept, a first-in-class activin receptor type IIA (ActRIIA) ligand trap, causes sequestration of TGF-β ligands and improvement in erythroid differentiation. A phase 2 study is ongoing in patients with MF-associated anemia, and interim results showed an anemia response in 5/14 (36%) evaluable patients, but effects on bone marrow fibrosis are not yet known (NCT01712308) (83). A phase I study of fresolimumab, a TGF-β-neutralizing monoclonal antibody, was initiated but the drug was

withdrawn after 3 subjects were treated at the lowest planned dose level due to management decisions on the part of the pharmaceutical company. At that low dose, the agent was well tolerated and one patient experienced hematologic improvement, achieving transfusion independence (84). While the clinical experience with TGF-β targeted agents is limited, this remains an interesting avenue for future investigation, particularly in anemic patients.

Immunotherapy

Immune dysregulation is a central feature of MPNs, and immune based approaches to treatment are therefore appealing. Allogeneic stem cell transplantation (alloHSCT) remains the only potentially curative therapy for MF, and the only immunotherapeutic strategy known to be effective for MPN. However, only a minority of MF patients will be eligible due to older age at diagnosis, comorbid disease burden, or poor functional status (often caused by underlying MPN). Even among those well enough to undergo alloHSCT, the long-term outlook remains disappointing due to toxicity and refractory/relapsed disease, with expected 5 year OS of less than 50% in most studies (85-89).

Enhancement of anti-tumor immunity represents one of the most exciting recent advances in oncology. Many solid tumor and hematologic malignancies have evolved mechanisms by which they avoid immune recognition. Under normal circumstances, T cell surface receptors such as cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and programmed cell death protein 1 (PD-1) interact with their associated ligands (i.e. PD-L1) and act as checkpoints to recognize “self” and prevent activation of effector T cells (90). Malignant cells often aberrantly express these ligands, thereby selectively evading immune recognition.

Clinical experience with immune checkpoint inhibitors in several solid tumor malignancies and Hodgkin lymphoma has been encouraging and has led to FDA approval of several agents. In AML and MDS, modest clinical responses have been reported with anti-CTLA4 and anti-PD-L1/anti-PD-1 agents alone and in combination with hypomethylating agents (91, 92). The role of immune checkpoint inhibitors in MF remains unproven, however several clinical studies are ongoing. These include a single-center phase 1 study of anti-PD-L1 monoclonal antibody durvalumab (NCT02871323), which is now closed to accrual and a phase 2 study of anti-PD-1 antibody nivolumab (NCT02421354), both in patients with MF after JAK inhibitor failure, intolerance, or ineligibility. A phase 2, multi-center study of anti-PD-1 agent pembrolizumab in advanced MF is also planned (NCT03065400).

Immune checkpoint inhibition may hold some promise in the post-transplant relapse setting. A phase 1 study of anti-CTLA4 agent ipilimumab in patients with a variety of hematologic malignancies who experienced disease relapse after alloHSCT reported several complete responses (5/22 treated at the effective dose level), in addition to several partial responses (2/22) and several decreases in tumor burden in patients who did not qualify as responders (6/22) (93). Of note, only one patient with an MPN was included in this study, and that patient did not experience an objective response. A phase 1 study of either ipilimumab or nivolumab in patients with relapse of a hematologic malignancy (including MPN) after alloHSCT is ongoing (NCT01822509).

Outside of immune checkpoint inhibitors, other antigen-specific immunotherapies including monoclonal antibodies, antibody-drug conjugates, cancer vaccines, and chimeric antigen receptor T-cell (CAR-T) therapies have proven effective for various solid tumor and lymphoid malignancies. However, such strategies have been problematic in myeloid malignancies. The antigenic heterogeneity and antigen shift over time that is characteristic of myeloid disorders presents a significant challenge to the development of antigen-targeted therapies (94). In addition, immune-mediated toxicities may be particularly limiting in patients with myeloid malignancies who are often older and less fit at diagnosis. Despite these limitations, several antibody-drug conjugates have shown promise in AML, and Natural Killer Group 2D (NKG2D) CAR-T cell therapy is under investigation for AML and MDS (NCT02203825) (95). It has yet to be seen whether similar therapies may have a role in the treatment of MF.

Other Novel Agents

Proviral integrations of Moloney virus (PIM) kinases are a family of serine/threonine kinases that regulate JAK/STAT signaling (96). In addition to affecting the JAK/STAT pathway, the PIM kinases also contribute to oncogenesis through phosphorylation of cell cycle regulators, activation of anti-apoptotic proteins, and enhancement of MYC expression (97-99). PIM kinases appear to be important in MPN pathogenesis, and may represent a therapeutic target. Two family members, PIM1 and PIM2, have been found to be upregulated in MPN (100). PIM inhibitors have shown preclinical synergy with JAK inhibitors, as well as the ability to overcome JAK inhibitor resistance in MPN cell lines (101, 102). A phase 1b study of ruxolitinib plus PIM inhibitor PIM447, or ruxolitinib plus CDK4/6 inhibitor ribocicilib (LEE011), or the combination of all three is underway in several non-U.S. countries (NCT02370706). Other kinase inhibitors under investigation in MF include the aurora kinase inhibitor-alisertib (Table2), based on its potential role in megakaryocytic differentiation in MF.

Anti-apoptotic proteins represent another potential target for MF therapy. Members of the B-cell lymphoma 2 (BCL-2) family of proteins inhibit the mitochondrial apoptosis pathway and promote erythropoietin-independent erythropoiesis in MPN (103). Activation of the JAK/STAT pathway mediates the transcription of BCL-2 family proteins and therefore contributes to anti-apoptotic signaling (104). The BCL-2 inhibitor venetoclax has shown activity in AML as a single agent and in combinations, and has received an FDA breakthrough therapy designation for this indication (105). Obatoclax, a pan-BCL-2 inhibitor, was studied in 22 patients with MF (106). Clinical activity was minimal, with no complete or partial responses though 1 patient (4%) experienced hematologic improvement. In mouse models of JAK2 mutant MPNs, combined targeting of JAK and BCL-2 family proteins led to disease regression, and was able to overcome resistance to single-agent JAK inhibition (107). Combination studies with JAK inhibitors or HMAs may be useful for the future and are in development, however the myelosuppressive potential of BCL-2 inhibitors may be limiting in patients with MF.

Novel Nonpharmacologic Approaches

Adjuvant nonpharmacologic psychosocial and lifestyle interventions have anecdotally shown promise in decreasing symptom burden in patients with MPNs, including MF. Interest in formally studying these interventions has piqued in recent years.

Physical activity during cancer treatment has been shown to improve various quality of life measures (108, 109). These benefits are likely generalizable to hematologic malignancies including MPNs (110). In a feasibility study of an online-streaming yoga program, 244 patients with MPNs were asked to perform 60 minutes of yoga per week over 12 weeks, following instructional yoga videos designed either specifically for MPN patients or with splenomegaly in mind (111). Actual yoga participation averaged about 51 minutes per week, and was associated with significant improvements in total symptom burden, fatigue, depression, anxiety, and sleep. A subsequent randomized study utilizing an at-home yoga program is planned, with endpoints including symptom measures, activity levels as measured by Fitbit tracking, and cytokine assessments.

The role of diet in MPNs remains largely unexplored. Certain dietary patterns have been associated with lower levels of proinflammatory cytokines, however it remains unclear whether these findings can be exploited for clinical benefit (112-114).

Mood disturbances such as anxiety and depression are common among patients with MPNs (115). No prospective studies have evaluated pharmacologic or non-pharmacologic methods of addressing mood disturbances in this population. Acceptance and commitment therapy (ACT), a multi-pronged psychosocial intervention, has demonstrated utility in several cancers and chronic medical and psychiatric conditions (116-118). A feasibility and health-related quality of life study of ACT in patients with MPNs is planned.

Conclusion

Discoveries of molecular mechanisms of MPN pathogenesis have led to the development of the first targeted therapy for MF, ruxolitinib. While ruxolitinib improves symptoms and splenomegaly with modest effects on survival, significant areas of unmet therapeutic need remain within this heterogeneous disease and future research should be aimed at filling these gaps. First, JAK pathway inhibitors should be developed and utilized to maximize clinical benefit. Cytopenias prevent many patients from receiving ruxolitinib, and therefore a second generation of JAK pathway inhibitors with less myelosuppressive potential is needed. Even in those who do receive ruxolitinib and achieve clinical benefit, the MF clone persists in nearly all and drug resistance eventually develops in most. Prevention and management of this resistance with novel agents or combinations is needed. Efforts to develop more potent and specific inhibitors of mutant JAK2 are ongoing, however promising clinical candidates have yet to emerge (119).

Second, methods to selectively target and eradicate the underlying malignant clone in MF must be prioritized. Select molecular, epigenetic, and immunologic targets under clinical investigation and their associated pharmacotherapies are depicted in figure 1, but thus far all of these approaches fall short of inducing deep molecular responses across subgroups of

patients. A better understanding of the roles of immune dysregulation and the stem cell microenvironment in MF is needed to guide further therapeutic development. Gene editing may be a future direction for MPN research, however biological, technical, and ethical issues limit clinical applications at the present time (120, 121).

Despite these challenges, the current pace of drug development for MF provides cause for excitement. A search of open, interventional studies for MF returned a list of 131 current ongoing clinical trials (122). Table 2 illustrates the breadth of ongoing trials of novel agents for MF therapy. In addition to pharmacotherapy, psychosocial and lifestyle interventions will likely prove integral to MF management. The phenotypic heterogeneity of MF necessitates a heterogeneous set of treatment options, and a deeper understanding of disease biology will be key to individualizing these treatment plans and improving outcomes for patients with MF.

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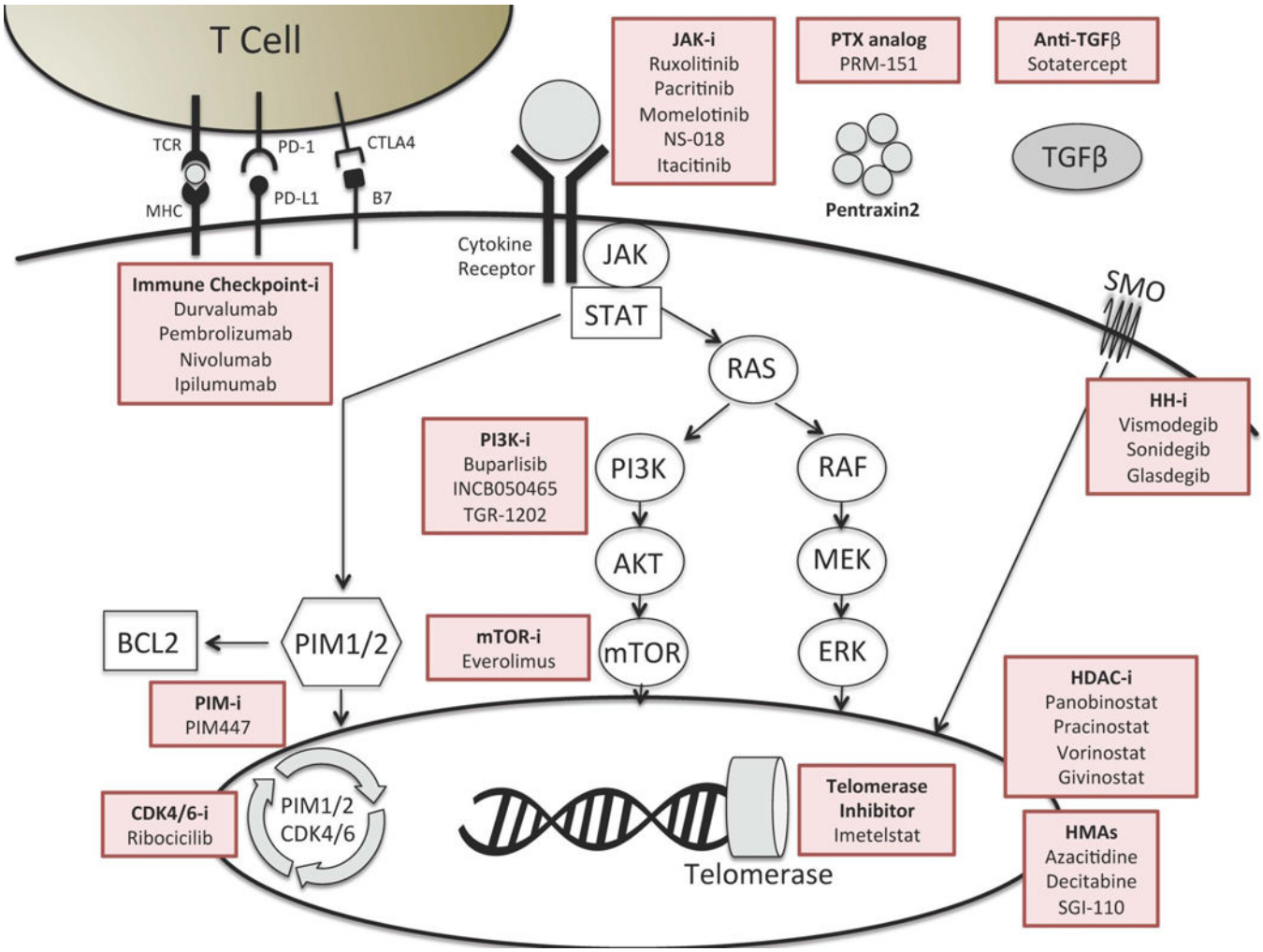

Figure 1.

Molecular targets for myelofibrosis and their associated agents that have shown promise or are under investigation. Multiple signaling cascades have been implicated in the pathogenesis of MF, including JAK/STAT, PI3K/AKT/mTOR, RAF/MEK/ERK, and Hedgehog (through smoothened receptor SMO). Small molecule inhibitors of various steps in these pathways have either shown a signal of clinical efficacy for MF, or are in clinical development. Targets include JAK (ruxolitinib, pacritinib, momelotinib, NS-018, itacitinib), PI3K (buparlisib, INCB050465, TGR-1202), mTOR (everolimus), or SMO (vismodegib, sonidegib, glasdegib). Epigenetic modulators such as hypomethylating agents (HMAs; azacitidine, decitabine, SGI-110) and histone deacetylase inhibitors (HDAC-i; panobinostat, pracinostat, vorinostat, givinostat) have shown activity in MF, and research continues into optimal dose and combinations of these agents with JAK inhibitors. Inhibitors of immune checkpoint receptors CTLA4 (ipilimumab) and PD-1 (pembrolizumab and nivolumab) or ligand PD-L1 (durvalumab) are also under investigation in various myeloid malignancies including MF. Other ongoing combination studies include small molecule cell cycle inhibitors of PIM1/2 (PIM447) and CDK4/6 (ribocicilib) with JAK inhibitors. Other novel

targets in MF include telomerase (imetelstat), pentraxin-2 (PTX; PRM-151), and TGFβ (sotatercept).

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Table 1

Results of Select JAK Inhibitor Clinic Trials

Agent	Target(s)	Clinical Trial	Patient Characteristics	Key Results	Toxicities
Ruxolitinib (RUX)	JAK 1/2	COMFORT-1 Randomized phase 3 study of RUX vs placebo	Intermediate-2 or high-risk MF RUX (n=155) Placebo (n=154)	Primary endpoint: SVR ≥35% at 24 weeks - Reached in 41.9% of RUX cohort vs 0.7% in placebo cohort Reduction in TSS ≥50% at 24 weeks - 45.9% (RUX) vs 5.3% (placebo) Median spleen response duration 168.3 weeks (RUX) Median OS at 5 years not reached (RUX) vs 200 weeks (placebo) (HR 0.69; 95% CI 0.50-0.96, p=0.025)	G3/4 anemia 45.2% G3/4 thrombocytopenia 12.9% G3/4 neutropenia 7.1% Rate of non-hematologic toxicities similar between RUX and placebo groups
		COMFORT-II Randomized phase 3 study of RUX vs BAT	Intermediate-2 or high-risk MF RUX (n=146) BAT (n=73)	Primary endpoint: SVR ≥35% at 48 weeks - Reached in 28% (RUX) vs 0% (BAT) At 5 years, probability of maintaining spleen response 0.48 (95% CI, 0.35-0.60), median duration of spleen response 3.2 years Median OS at 5 years not reached (RUX) vs 4.1 years (BAT)	Similar to COMFORT-I Any-grade diarrhea 23%
Pacritinib	JAK2/FLT3	PERSIST-I Randomized phase 3 study of pacritinib vs BAT (excluding JAK inhibitors)	Intermediate-1, intermediate-2 or high-risk MF JAK inhibitor naïve No exclusions for cytopenias Pacritinib 400 mg daily (n=220) BAT (n=107)	Primary endpoint: SVR ≥35% at 24 weeks - Reached in 19% (pacritinib) vs 5% (BAT)	G3/4 anemia 17% G3/4 thrombocytopenia 12% G3/4 diarrhea 5% Heart failure 2%
		PERSIST-II Randomized phase 3 study of pacritinib vs BAT (including RUX)	Intermediate-1, intermediate-2, or high-risk MF with platelets $<100\times10^9$/L Previously treated or JAK inhibitor naïve Pacritinib 400 mg daily (n=104) Pacritinib 200 mg BID (n=107) BAT (n=100)	Primary endpoints: SVR ≥35% at 24 weeks -Reached in 18% (pacritinib) vs 3% (BAT) Reduction in TSS ≥50% at 24 weeks - Reached in 25% (pacritinib) vs 14% (BAT)	Toxicities were less frequent in pacritinib BID dosing compared to daily dosing Cardiac AEs in 7% (pacritinib BID), 13% (pacritinib daily), and 9% (BAT) Intracranial hemorrhage 1% (pacritinib daily) *Pacritinib was on full clinical hold 2/2016-1/2017 for fatal toxicity concerns. Further dose finding studies are now planned.
Momelotinib	JAK1/2	SIMPLIFY-I Randomized phase 3 study of momelotinib vs RUX	Intermediate-1 (symptomatic), intermediate-2, or high-risk MF, JAK inhibitor naïve Momelotonib (n=215) RUX (n=217)	Primary endpoint: SVR ≥35% at 24 weeks - Momelotinib non-inferior to RUX for spleen reduction [26.9% (momelotinib) vs 29% (RUX)] Reduction in TSS ≥50% at 24 weeks - Momelotinib was inferior to RUX Transfusion requirements - Momelotinib was associated with decreased transfusion requirements	G3/4 thrombocytopenia (7%) G3/4 anemia (6%) All grade peripheral neuropathy 10% (momelotinib) vs 5% (RUX)

Agent	Target(s)	Clinical Trial	Patient Characteristics	Key Results	Toxicities
		SIMPLIFY-II Randomized phase 3 study of momelotinib vs BAT (including RUX)	Intermediate-1 (symptomatic), intermediate-2, or high-risk MF previously treated with RUX Momelotinib (n=104) BAT (included RUX in 88%) (n=52)	Primary endpoint: SVR ≥35% at 24 weeks - Momelotinib was not superior to BAT (including RUX) in improving spleen size in patients previously treated with RUX Reduction in TSS ≥50% at 24 weeks - Momelotinib superior to BAT [26.2% (momelotinib) vs 5.9% (BAT)] Transfusion requirements - Momelotinib was associated with decreased transfusion requirements	G3/4 anemia (13%) G3/4 thrombocytopenia (7%) All grade peripheral neuropathy 11% (momelotinib) vs 0% (BAT)
NS-018	JAK2/Src	Phase 1/2 study of 2 dosing schedules of NS-018 (once daily or BID)	Intermediate-1, intermediate-2, or high-risk MF Previously treated or treatment naive Phase 1 n=48 Phase 2 n=29 (ongoing)	20/36 (56%) evaluable patients with >50% reduction in spleen size by palpation - Includes 9/19 (47%) previously treated with a JAK inhibitor RP2D 300 mg BID. Phase 2 is ongoing.	G3/4 anemia (21%) G3/4 thrombocytopenia (17%)

MF, myelofibrosis; RUX, ruxolitinib; SVR, spleen volume reduction; TSS, total symptom score; OS, overall survival; HR, hazard ratio; CI, confidence interval; G3/4, grade 3/4; RP2D, recommended phase 2 dose

Table 2

Novel Agents for Myelofibrosis in Clinical Development

Class	Agent	Target	Phase	NCT identifier
JAK inhibitors	Itacitinib, alone or with ruxolitinib (+RUX)	JAK1	2	NCT03144687
	Pacritinib	JAK2/FLT3	2	NCT03165734
	NS-018	JAK2/Src	2	NCT01423851
Epigenetic Agents	Pracinostat (+RUX)	HDAC	2	NCT02267278
	Panobinostat	HDAC	1/2	NCT01693601
	IMG-7289	LSD-1	1	NCT03136185
	Azacitidine (+RUX)	DNA methylation	2	NCT01787487
	SGI-110	DNA methylation	2	NCT03075826
PI3K/AKT/mTOR Pathway Inhibitors	INCB050465 (+RUX)	PI3K	2	NCT02718300
	Buparlisib (+RUX)	PI3K	1	NCT01730248
	TGR-1202 (+RUX)	PI3Kδ	1	NCT02493530
Hedgehog Pathway Inhibitors	Vismodegib (+ RUX)	SMO	1/2	NCT02593760
	Sonidegib (+ RUX)	SMO	1/2	NCT01787552
	Glasdegib	SMO	2	NCT02226172
Other Small Molecule Inhibitors	CPI-0610	BET	1	NCT02158858
	PIM447 (+ RUX)	pan-PIM kinases	1b	NCT02370706
	Ribocicilib (+ RUX)	CDK4/6	1b	NCT02370706
	Alisertib	Aurora kinase A	1	NCT02530619
	Selumetinib	MEK kinase	1	*pending
Checkpoint Inhibitors	Durvalumab	PD-L1	1	NCT02871323
	Pembrolizumab	PD-1	2	NCT03065400
	Nivolumab	PD-1	2	NCT02421354
	Nivolumab	PD-1	1/1b	NCT01822509
	Ipilimumab	CTLA4	1/1b	NCT01822509
Other Agents	Imetelstat	Telomerase	2	NCT02426086
	PRM-151	Pentraxin 2	2	NCT01981850
	Sotatercept	TGFβ	2	NCT01712308
	SL-401	IL3 receptor (CD123)	1/2	NCT02268253
	P1101	Peg-Interferon α	2	NCT02370329
	LCL-161	SMAC mimetic	2	NCT02098161

*Clinical trials.gov listing is pending at time of manuscript submission