JAK inhibitors in myeloproliferative neoplasms

L. Knoops, S.N. Constantinescu

Discovery of JAK2 V617F as the main molecular event in BCR-ABL negative myeloproliferative neoplasms gave an impetus to screening for JAK2 inhibitors and testing them in myelofibrosis, the most severe of these diseases. Besides JAK2 V617F, other mutants of JAK2 and of cytokine receptors rarely found in myeloproliferative neoplasms are candidates for inhibition by JAK2 inhibitors, such as mutants in exon12 of JAK2, responsible for a minority of polycythaemia vera cases, and mutations in thrombopoietin receptor, which are at the basis of 3-8% of essential thrombocythaemia and myelofibrosis cases that are negative for JAK2 V617F. We briefly review the current ATP-competitive JAK2 inhibitors that are now in clinical trials and their positive effects on quality of life of myelofibrosis patients. We discuss perspectives of searching for inhibitors tailored specifically for JAK2 V617F, that would be predicted to have a stronger effect in eradicating the mutant clone, and reduce allele burden. On the other hand, since JAK2 V617F does not seem to confer an obvious advantage to mutated hematopoietic stem cells, such inhibitors are predicted to reduce phenotype and symptomatology, but not to cure the disease.

(Belg J Hematol 2011;2:27-35)

Introduction

The Janus kinases (JAKs) are a family of 4 non-receptor tyrosine kinases that play an essential role in mediating cytokine signalling. JAKs associate with cytokine receptors that lack intrinsic kinase activity to mediate cytokine-induced signal transduction via the activation of the STAT transcription factors and other signalling pathways (*Figure 1*, page 28).[1,2] The 4 family members (JAK1, 2, 3 and TYK2) associate with different cytokine receptors (*Table 1*, page 29). The possible involvement of JAK dysregulation in oncogenesis was suggested by a mutation in the Drosophila JAK kinase, hopscotch, which was inducing leukaemia in the fly.[3] In 2005, several studies demonstrated that a unique acquired activating somatic mutation of JAK2 (V617F) was found in 95% of polycythaemia vera (PV) patients and in about half of essential thrombocythaemia (ET) and primary myelofibrosis (PMF) patients.[4-7] Mutations of the homologous V617F residue in JAK1 and TYK2 were shown to activate those Janus kinases.[8] This and other mutations of JAK1 were subsequently described in acute lymphoblastic leukaemia and activating mutations of JAK3 were detected in a megakaryoblastic leukaemia cell line.[9-11] Based on the excellent results obtained

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Conflict of interest: the authors have nothing to disclose and indicate no potential conflicts of interest.

Key words: JAK2 V617F, myelofibrosis, myeloproliferative neoplasm, tyrosine kinase inhibitor

by BCR-ABL tyrosine kinase inhibitors in chronic myeloid leukaemia, these discoveries led naturally to the development of JAK inhibitors to treat haematological malignancies with activated JAK-STAT signalling.

Rationale for using JAK2 inhibitors in myeloproliferative neoplasms

BCR-ABL negative myeloproliferative neoplasms (MPNs) were defined as key targets for JAK inhibition because of the high frequency of the JAK2 V617F mutation found in these patients. The V617F mutation of JAK2 induces excessive activation of cytokine receptor-kinase complexes, and constitutive activation EPOR-JAK2 and TPOR-JAK2 complexes is believed to be involved in the polycythaemia and thrombocythaemia phenotypes of MPNs.[1,12,13] Furthermore, it has been suggested that signalling dysregulation via TpoR and possibly G-CSFR contribute to myelofibrosis. A causal role of JAK2 V617F in the induction of myeloproliferation was proven by mouse models, in which the JAK2V617F mutation was expressed in haematopoietic progenitors via a retroviral vector.[14-16] These mice developed a myeloproliferative disorder characterised by polycythaemia, hyperleukocytosis and splenomegaly. This MPN progresses to myelofibrosis in about 3 months.[17] The mutation does not appear to have a major impact on the biological properties of the haematopoietic stem cells, while JAK2 V617F greatly impacts progenitors at late stages of differentiation.[18-20] JAK2 V617F inhibition will therefore probably counteract the myeloproliferation process but will not eradicate stem cells harbouring the mutation (*Figure* 2, page 30). Moreover, JAK2 V617F negative subclones seem to cooperate to the pathophysiology of the disease and can be responsible for transformation into AML.[21,22]

Targets for JAK2 inhibition are not restricted to V617F positive MPNs. In PV, the minority of patients (3%) that are V617F negative harbour other mutations in JAK2, like exon 12 mutations around K539L.[23] In PMF and ET, activating mutations of the TpoR were described in about 5% of the patients.[24-27] These mutations always target the W515 residue, that was shown to be required to maintain TPOR inactive in the absence of TPO.[25] The increased TPOR activity induced by W515/L/A/K mutations requires an intact JAK2 kinase activity.[28] In PMF patients lacking known mutations of the receptor-JAK complexes, STAT3 constitutive activation was found, suggesting that TpoR and JAK2 are still involved in the myeloproliferation process.[29] Furthermore, approximately 30% of MPN patients have been shown to overexpress in their platelets miR-28, a microRNA that targets TpoR and several other mRNAs coding for key proteins involved in megakaryocyte differentiation.[30] Among the MPNs, JAK2 V617F-negative ET appears to be associated with miR-28 overexpression, suggesting that these patients might also have constitutive STAT5 activation, since expression of the host gene of miR-28 is dependent on constitutive STAT5 activation.[30]

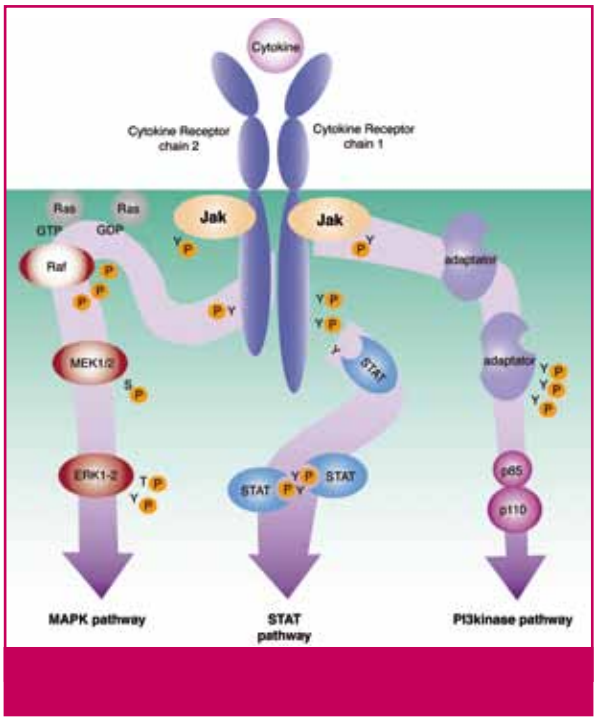

Figure 1. Schematic representation of cytokine receptor-JAKs signal transduction pathways. Upon cytokine binding, cytokine receptor changes conformation and JAKs are activated by cross-phosphorylation at tyrosine residues. This leads to tyrosine phosphorylation of receptors and of signalling molecules mediating intracellular cytokine effects. Many cytokines activate the JAK-STAT, the MAP kinase and the PI-3-kinase pathways. However, other pathways can be activated by cytokine receptors and the pattern of pathway activation varies depending on the particular receptor.

Table 1. Cytokine receptors subfamilies. Cytokine receptors subfamilies are represented, with their ligands and their associated JAKs.

Subfamily	Ligands	Jak kinases
Homodimeric receptors	EPO	JAK2
	GH	JAK2
	Prl	JAK2
	TPO	JAK2
βc	IL-3	JAK2
	IL-5	JAK2
	GM-CSF	JAK2
gp 130	IL-6	JAK1, JAK2
	IL-11	JAK1
	OSM	JAK1, JAK2
	LIF	JAK1, JAK2
	G-CSF	JAK1, JAK2
	IL-12	JAK2, TYK2
	IL-23	?
	Leptin	JAK2
	CTNF	JAK1, JAK2
γc	IL-2	JAK1, JAK3
	IL-4	JAK1, JAK3
	IL-7	JAK1, JAK3
	IL-9	JAK1, JAK3
	IL-15	JAK1, JAK3
	IL-21	JAK1, JAK3
Other	IL-13	JAK1, JAK2
CRF2	IFN α/β/ω/Limitin	JAK1, TYK2
	IFN γ	JAK1, JAK2
	IL-28 α/β	JAK1, TYK2
	IL-29	JAK1, TYK2
	IL-10	JAK1, TYK2
	IL-19	JAK1, ?
	IL-20	JAK1, ?
	IL-22	JAK1, TYK2
	IL-24	JAK1, ?
	IL-26	JAK1, TYK2

Because PV and ET patients have prolonged survival with standard treatment, it was not the ideal population to test new compounds that could potentially be harmful with long-term use. In contrast, PMF patients have shorter survival and no treatments are able to change the natural course of the disease. The survival ranges from <2 to over 15 years on the basis of the presence or absence of clinical adverse features: advanced age, constitutional symptoms, anaemia, leukocytosis and circulating blasts.[31] Because of this unmet medical need in advanced PMF patients, they were chosen for the first trials with JAK2 inhibitors.

Physiological role of JAKs and potential side effects of JAK inhibition

JAKs and cytokine receptors play essential roles in a vast variety of physiological processes. This in complete contrast with the c-ABL kinase, which is targeted by ABL inhibitors like imatinib in CML. In vitro models suggested that c-ABL plays a role in multiple pathways and cellular functions such as DNA repair, cytoskeleton organization, cell

adhesion, proliferation, and apoptosis.[32] c-ABL deficient mice shows neonatal lethality.[33] However, c-ABL does not seem to play an important role in the physiology of adults, allowing complete therapeutic inhibition of ABL without obvious side effects. Furthermore the c-ABL is an intracellular kinase that is independent for activation from growth factor stimulation, while mutated JAK proteins are appended to transmembrane cytokine receptors, and as such they respond to cytokine stimulation and can confer not only cytokine-independence, but also cytokine-hypersensitity.

Inhibiting JAKs will in contrast certainly cause some toxicity. Side effects potentially caused by JAK inhibition can be, to some extent, predicted by the phenotype of JAK knockout mice, keeping in mind that mice are not humans and that marginal differences were noted between cytokine receptors activity in the 2 species. In MPNs, JAK2 is the key target. However, several JAK2 inhibitors also inhibit JAK1.

JAK2 is bound to many cytokine receptors (*Table 1*). JAK2-deficient mice exhibited an embryonic lethal phenotype. Death has been attributed to a block in definitive erythropoiesis, analogous to what has been observed in EPO-/- mice.[34,35] Although haematopoietic precursors can be rescued from JAK2 -/- livers, these cells are unresponsive to Tpo, IL-3 and GM-CSF. Additional studies have revealed defects in the response to IFNγ, but not to IL-6 or IFNα-β.[35] Thus, JAK2 plays a critical role in transducing signals for EPO, Tpo, IL-3, GM-CSF, IL-5 and IFN-γ. JAK2 inhibition is therefore predicted to induce anaemia and thrombocytopenia. The inhibition of IL-3, IL-5 and GM-CSF could interfere with the production and activation of macrophages, mast cells and eosinophils. Mice with these defects showed pulmonary proteinosis and impaired response to parasitic infections.[36,37] IFN-γ was demonstrated as essential in resistance to intracellular pathogens such as *Mycobacterium tuberculosis*.[38,39] Altogether, these data indicate that JAK2 inhibitors could induce significant myelosuppression and sensitivity to different type of infection.

JAK1 associates with numerous cytokine receptor chains (*Table 1*) and is involved in signalling by the majority of cytokines. In line with the pleiotropic function of these receptors, JAK1-deficient mice exhibited an early postnatal lethal phenotype attributable to neurological lesions, probably through

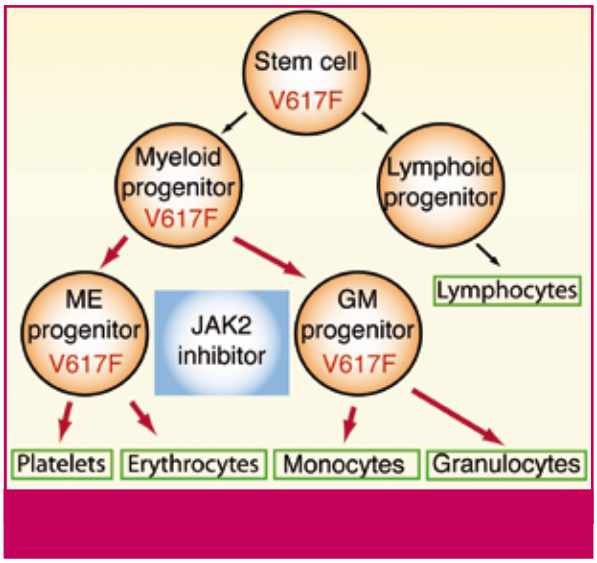

Figure 2. Schematic representation of the JAK2 V617F clonal hematopoiesis and the effect of JAK inhibitor therapy. JAK2 V617F is present in early myeloid progenitors (V617F) but induces the expansion of myeloid progenitors at late stage of differentiation (red arrows), leading to enhanced myelopoiesis and myeloproliferative neoplasms. JAK2 inhibitors block the expansion of the differentiated hematopoietic progenitors and the symptoms of MPNs. The effect of JAK2 inhibitors at the stem cell level is predicted to be weak, and thus JAK2 inhibitors alone are not likely to eradicate the mutated clone.

a loss in LIF function.[40] The response to IL-6 was substantially decreased in JAK1-/- tissues. JAK1-/- mice also exhibited significant defects in thymocyte and B cell production. This impaired lymphopoiesis has been attributed to defective responses to the γ-c family of cytokine receptors, such as IL-2R, -4R, -7R, -9R, -15R, and -21R. These receptor complexes bind JAK1 and JAK3, which are both necessary for proper receptor complex activation. JAK3-/- mice also suffer from severe defects in lymphopoiesis, similar to those observed in mice deficient in γc.[41,42] This murine phenotype is particularly relevant for human disease, because JAK3-defective humans have severe combined immunodeficiency (SCID), which results from a profound T cell defect.[43] The absence of JAK1 also leads to profound defects in the biological response to type I and type II interferon and in the response to IL-10.[40-44] Taken together, it is highly probable that JAK1 inhibition will cause significant immune dysfunction.

The presently used JAK2 inhibitors exhibit different levels of inhibition of other JAKs (*Table 2*). Given the pleiotropic functions of JAK1 and JAK2 in

Table 2. The half maximal inhibitory concentration (IC50) against each of the 4 JAKs is shown for the JAK inhibitors currently under investigation in clinical trials. *NF=not found*.

JAK inhibitor	IC50 (nM)			
	JAK1	JAK2	JAK3	Tyk2
INCB018424[46]	3.3	2.8	322	19
TG101348[48]	105	3	1,002	405
CEP-701[51]	3	1	NF	NF
AZD-1480[50]	1.3	0.26	3.9	NF
SB1518[60]	1,276	22	1,392	NF
CYT387[53]	11	18	155	17
LY2784544	NF	NF	NF	NF
Erlotinib[54]	NF	4,000	NF	NF
XL019[55]	132	2	250	340

human physiology, a complete in vivo inhibition of these kinases in humans seems impossible. This contrasts with BCR-ABL inhibitors for which, given the fact that no vital function for endogenous ABL was described, complete inhibition is the goal. For JAK1 and JAK2 inhibitors, a careful titration will be necessary to find a potential therapeutic window. Furthermore, the intracellular BCR-ABL is not responding to extracellular cues, while the mutant JAKs are scaffolded on cytokine receptors' tails and impart hypersensitivity to cytokines. An increase in cytokine levels might prevent the effects of JAK inhibitors.[45]

JAK2 inhibitors in clinical trials

Only 4 years after the discovery of JAK2 V617F, a number of ATP-competitive inhibitors of JAK2 have been developed by different companies (*Table 2*).

INCB018424 – INC424 – ruxolitinib:[29,46]

Ruxolitinib was developed by Incyte, and is licensed by Novartis in Europe. It is a potent selective JAK inhibitor with strong activity against JAK1 (IC50 3.3 nM) and JAK2 (IC50 2.8 nM). It is less active on Tyk2 and JAK3. It was the first JAK2 inhibitor introduced in the clinic and entered clinical trials in mid-2007. Dose limiting toxicity is thrombocytopenia. Phase II and III clinical trials are ongoing in MF and PV patients. The results of the pivotal phase I-II trial showing efficacy of JAK inhibitors in MF were recently published.[29]

TG101348 [47,48]

TG101348 was developed by TargeGen, which should be acquired by Sanofi-Aventis. It is a selective and potent inhibitor of JAK2 (IC50=3nM). Its activity on JAK1 is moderate (IC50=35 nM) and it has few effects on JAK3 (IC50=334 nM). The dose limiting toxicity was asymptomatic grade 3 to 4 hyperamylasaemia with or without hyperlipasaemia. A Phase I dose escalation study was performed, and phase II trials are ongoing in MF patients.

CEP-701 - Lestaurtinib:[49]

Lestaurtinib is developed by Cephalon. It is a tyrosine kinase inhibitor structurally related to staurosporine. It is a potent inhibitor of JAK2 (IC50=1 nM), but also of FLT3, RET, TrkA, TrkB and TrkC. CEP-701 was already evaluated in a number of oncology clinical trials and in patients with AML and FLT3-activating mutations. In clinical studies so far, CEP-701 has been relatively well tolerated, with the most common toxicities being nausea, vomiting, anorexia, and diarrhea. A phase II clinical trial in patients with MF is published, with modest efficacy and frequent gastrointestinal toxicity.[49] Phase II studies in MF, PV and ET are ongoing.

AZD1480[50]

AZD1480 is developed by Astra-Zeneca. This pyrazolyl pyrimidine derivate is a potent ATP competitive inhibitor of JAK2 (IC50=0.26 nM), with significant JAK2 selectivity over JAK3 (IC50=3.9 nM) and a marginal selectivity over JAK1 (IC50=1.3 nM). AZD1480 was able to block STAT3 signalling and oncogenesis in solid tumours.[50] A Phase I/II safety trial is recruiting PV, MF and ET patients.

SB1518

SB1518 is developed by S*Bio and is a potent and selective inhibitor of JAK2 (IC50=22 nM). JAK1 and JAK3 are inhibited weakly at much higher concentrations. Phase I-II clinical trials are ongoing for MF patients. The dose limiting toxicity was

diarrhea and nausea.[51]

CYT387[52,53]

CYT387 was discovered by Cytopia Research. CYT387 is active against JAK1 (IC50=11 nM) and JAK2 (IC50=18 nM), but has also activity against other kinases like CDK2, JNK1, PKD3, ROCK2 or TBK1. Dose limiting toxicities were asymptomatic hyperamylasaemia and headache. Phase I/II clinical trials are ongoing for MF patients.

LY2784544

LY2784544 is developed by Elli-Lilly. It is in phase I clinical trials for MF, PV and ET.

Erlotinib (Tarceva®)[54]

Erlotinib is marketed by Genentech in the US and Roche elsewhere. It was developed as an EGFR inhibitor and was approved by the FDA for the treatment of non small cell lung cancer and pancreatic cancer. Erlotinib was shown to inhibit JAK2 V617F at micromolar concentrations (IC50=4 mM). A phase II trial is ongoing in PV patients.

XL019

XL019 is developed by Exelixis. It is a potent and specific JAK2 inhibitor (IC50=2 nM), and was tested in MF patients since mid-2007. These trials were stopped because of the development of neurotoxicity such as formication, peripheral neuropathy or confusional state.[55]

Activity of JAK inhibitors in MPN patients

Reduction of splenomegaly

Marked splenomegaly is a characteristic feature of MF. It is associated with abdominal pain, early satiety and can be complicated by splenic infraction. Moreover, splenomegaly can increase cytopenia due to hypersplenism. Reduction of splenomegaly was observed with all the JAK2 inhibitors tested in MF. This decrease was often rapid and observed in the first weeks of treatment. In the landmark study of INCB018424, 17 of 33 patients (52%) had a rapid ≥50% reduction of splenomegaly lasting for 12 months or more.[29] Similar results were obtained for TG101348, CEP-701, CYT387, SB1518 and XL019.[49,51] The reduction of the spleen volume is dose dependent, and can be limited by dose reduction because of drug-related anaemia or thrombocytopenia. Discontinuation of the treatment induces a fast relapse of splenomegaly, within days for INCB018424. The mechanisms involved in the effects on spleen size are not understood. It is likely that they are related to JAK2 rather than JAK1 inhibition, because JAK2 specific inhibitors like TG101348 also decrease the spleen volume. Spleen reduction is probably not caused by a massive destruction of the neoplastic myeloid progenitors since no increase in the LDH level nor signs of lysis syndrome were observed.

Amelioration inconstitutional symptoms

Quality of life of MF patients is frequently hampered by the presence of constitutional symptoms like night sweats, fevers, fatigue, pruritus or bone pain. Usually, MF patients are in a catabolic state and lose weight. INCB018424, TG101348 and CYT387 induced a rapid and significant improvement of constitutional symptoms, with a rapid disappearance of fatigue, pruritus, abdominal discomfort and night sweats in the majority of patients.[29,51] This effect is probably not dose-dependent as it is observed with the lowest dose of INCB018424. Vestovsek et al. observed that patients also started to gain weight after as few as 2 month of treatment. This weight gain was more pronounced in patients with the lowest body mass index. The median weight gain after one year of therapy was between 6.6 and 9.4 kg, depending on the dose of INCB018424. Like for splenomegaly, the beneficial effect on constitutional symptoms require continuous therapy and symptoms reappeared within days after the treatment was stopped. The mechanisms involved in the decrease of constitutional symptoms include a significant suppression of pro-inflammatory cytokines such as IL-1, TNF-α and IL-6 as observed with INCB018424, probably through JAK1 inhibition. However, this JAK1 inhibition is not the only mechanism since the JAK2 specific inhibitor TG101348 also decrease constitutional symptoms, without significantly reducing plasma cytokine levels.[51]

Anaemia

Because of the essential role of JAK2 in erythropoiesis, JAK2 inhibition will certainly decrease the production of red blood cells. This effect is welcome for PV patients, and advanced patients with elevated blood cell counts and splenomegaly are therefore good theoretical candidates for JAK2 inhibitors. In

MF, myeloproliferation is associated with anaemia, which is of bad prognosis.[31] This anaemia results preliminary from ineffective haematopoiesis, but fibrosis of the bone marrow and hypersplenism are probably contributory. Aggravating the anaemia could be problematic for MF patients. In the clinical trials with JAK2 inhibitors, grade 3 to 4 anaemia appeared in 27% of patients treated with high dose of INCB018424 and 54% of patients treated with high dose of TG101348.[29,51] Anaemia was less frequent with lower doses. Anaemia increased in the first month of treatment, then stabilised or improved with continued treatment. Surprisingly, no anaemia was noticed in preliminary reports from patients treated with CYT387, and some patients even experienced amelioration of anaemia.[51] This suggests that the beneficial effect observed with CYT387 could not be related to a significant JAK2 inhibition.

Effect on platelets and neutrophils

JAK2 inhibition should cause, via the inhibition of TpoR signalling via JAK2, a decrease in the platelet levels. Via the inhibition of the G-CSFR signalling via JAK2, it should decrease the neutrophil levels. Because leukocytosis is of bad prognosis in MF, this effect could be beneficial. Grade 3 to 4 thrombocytopenia is the dose limiting toxicity of INCB018424. It was observed in 60% of patients receiving 25 mg twice daily, and was less frequent with lower dose. This decrease occurred more often in patients with a platelet count of less than 200 x 10^9/l and was reversible within 1 to 3 weeks after dose interruption.[29] Severe thrombocytopenia was less frequent with TG101348, CEP-701 or CYT387 (20-25%).[51] Grade 3 to 4 neutropenia occurred in 10% of patients treated with TG101348. JAK2 inhibitors are very effective to decrease platelets and neutrophil levels when elevated at diagnosis, with more than 50% of normalization for INCB018424 and TG101348.

JAK2 V617F allele burden

Because ATP-competitive inhibitors such all the above molecules target the kinase domain of JAK2, they inhibit both the wild type and the mutant JAK2. Thus, an important decrease of the V617F allele burden is not expected. Versotvsek et al. observed a mean maximal suppression of 13% from baseline after one year of treatment with INCB018424.[29] This effect appeared to be more pronounced for TG101348, with 7 of 18 patients (19%) having a decrease of more than 50% of the JAK2 V617F allele burden, but more patients need to be studied in the future.[51]

Survival and leukaemic transformation

It is too soon to have data about the survival of patients treated with JAK inhibitors. However, it is not unreasonable to expect that JAK2 inhibitors would become the first medication able to counteract the natural course of MF. In murine models of MPNs, survival of mice was increased with JAK2 inhibitor therapy.[46,48] Results of the INCB018424 trial are also encouraging, since the overall survival of the 153 patients was 84%, with a median follow up of 15 month. 65% of the patients were classified as high risk MF, with a historical median survival of 27 month. There were also only 3 cases of transformation in AML, as compared with an expected AML incidence of 11 cases based on historical controls.

For PV and ET, the context is totally different. In ET, the survival is normal, at least in the first 10 years of follow up. In PV, the survival is only slightly decreased.[56] Therefore, long-term safety of JAK2 inhibitors will be essential before treating this group of patients.

Perspectives

Development of JAK2 V617F specific inhibitors

An inhibitor able to bind uniquely to JAK2 V617F and inhibit its dysregulated activity would be expected to reduce the mutant clone and mimic the effects of imatinib observed in CML. Obtaining such a specific molecule appears to be difficult because the V617F mutation is in the pseudokinase domain of JAK2, and targeting of protein-protein interacting surfaces, such as those between the kinase and pseudokinase domains, is impossible without a crystal structure of the two domains. Only the X-ray structure of the kinase domain has been solved.[57] One observation that might guide the screening efforts is that one helix C residue (F595) is crucial for constitutive activation of JAK2 V617F, but not for cytokine-induced activation of JAK2.[58] F595 is predicted to be located in the vicinity of F617 (<5 Å) and form an aromatic interaction.[58] Interestingly,

Key messages for clinical practice

1. Many JAK inhibitors are in clinical development.
2. No JAK inhibitors are specific for the V617F mutation of JAK2.
3. JAK2 inhibitors decrease splenomegaly and constitutional symptoms in myelofibrosis.
4. Major side effects of JAK1/2 inhibition are anaemia and thrombocytopenia.

F595 is required for constitutive activation of several other JAK2 mutants, suggesting that the region around F595 and helix C might be a good target for specific inhibitors.

Association of treatments

In principle, MPN progenitors might have become addicted to pathways connected to JAK2 activation, such as STAT5, STAT3, Ras-MAP-kinase and others. Synergic inhibition might be obtained by combining an ATP competitive JAK2 inhibitor and another inhibitor blocking specifically such a signalling pathway to which the MPN clone is addicted for proliferation and survival.

Other targets for JAK2 inhibitor resistant patients

Mutations in TpoR W515 induce strong constitutive activation of TpoR and such mutants rapidly trigger an MPN with myelofibrosis in mice.[24,27] The phenotype was prevented by one single point mutation, namely mutation of the cytosolic tyrosine 112 to phenylalanine. This residue was shown to be phosphorylated in TpoR W515A cells and it connects to STAT3 and MAP-kinase ERK1,2 pathways. Since transduction of TpoR W515A Y112F does not induce MPN in mice a small molecule inhibitor that would target phosphorylated Y112 would be predicted to be effective in MPNs with TpoR mutations.[27] Furthermore, knock-in mice that lack Y112 are able to have near-normal steady state platelet numbers, suggesting such a molecule would not necessarily induce thrombocytopenia.[59]

Conclusions

Inhibitors of JAK2 appear to improve quality of life and stabilise evolution of MF patients, with possible decreased evolution of MF to AML. Such inhibitors are non-specific with respect to wild type and mutated JAK2, and as such they cannot be expected to dramatically reduce the allele burden. Furthermore, after more than 1.5 years of clinical trials, it appears that marrow fibrosis and blast levels are not reduced by JAK2 inhibitors. The hallmark effect of JAK2 inhibitors is reduction in spleen size, an effect that is not well understood, that does not require cell lysis, and might involve inhibition of progenitor migration. Given that JAK2 inhibitors are effective in reducing spleen size and improving quality of life of both JAK2 V617F positive and negative MF patients, it is likely that dysregulation of JAK2 pathway is occurring also in JAK2 V617F-negative patients. Finally, since JAK2 inhibitors induce rapid decrease in red blood cells, platelets and granulocyte levels, they might be indicated in high risk forms of PV and ET.

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