Molecular drug targets in myeloproliferative neoplasms: mutant ABL1, JAK2, MPL, KIT, PDGFRA, PDGFRB and FGFR1

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Abstract

Therapeutically validated oncoproteins in myeloproliferative neoplasms (MPN) include BCR-ABL1 and rearranged PDGFR proteins. The latter are products of intra- (e.g. FIP1L1-PDGFRA) or inter-chromosomal (e.g. ETV6-PDGFRB) gene fusions. BCR-ABL1 is associated with chronic myelogenous leukaemia (CML) and mutant PDGFR with an MPN phenotype characterized by eosinophilia and in addition, in case of FIP1L1-PDGFRA, bone marrow mastocytosis. These genotype–phenotype associations have been effectively exploited in the development of highly accurate diagnostic assays and molecular targeted therapy. It is hoped that the same will happen in other MPN with specific genetic alterations: polycythemia vera (JAK2 V617F and other JAK2 mutations), essential thrombocythemia (JAK2 V617F and MPL515 mutations), primary myelofibrosis (JAK2 V617F and MPL515 mutations), systemic mastocytosis (KIT D816V and other KIT mutations) and stem cell leukaemia/lymphoma (ZNF198-FGFR1 and other FGFR1 fusion genes). The current review discusses the above-listed mutant molecules in the context of their value as drug targets.

Keywords: V617F ● polycythemia ● thrombocythemia ● myelofibrosis ● eosinophilia ● mastocytosis

Introduction

Myeloid malignancies are stem cell-derived clonal disorders and include three broad clinicopathologic categories: acute myeloid leukaemia (AML), myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPN). Such classification is however operational and not precise; for example, some patients present with histologic features that are reminiscent of both MPN and MDS and are assigned the diagnosis of ‘MDS/MPN’ overlap [1]. The history of MPN dates back to 1951 when William Dameshek coined the term ‘myeloproliferative disorders (MPD)’ as a clinicopathologic category that included chronic myelogenous leukaemia (CML), polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) [2, 3]. These ‘classic’ MPD are...
now included in an expanded category of ‘MPN’, according to the World Health Organization (WHO) classification system, which also includes systemic mastocytosis (SM) and chronic neutrophilic (CNL) and eosinophilic (CEL) leukaemias (Table 1) [4]. Current classification of chronic myeloid neoplasms is semi-molecular although primarily based on myeloid cell morphology and presence or absence of effective haematopoiesis; Fig. 1 illustrates the histological hallmarks that distinguish MDS, MPN and MDS/MPN.

Pathogenetic breakthroughs in MPN began in 1960 when the Philadelphia (Ph) chromosome was described in CML [5, 6]. This historic discovery later (1980–1990) led to the identification of BCR-ABL1 as the disease-causing mutation in CML [7–9]. In 1993 and 1994, stem cell factor receptor (KIT) and platelet-derived growth factor receptor-α (PDGFRα) mutations were associated with SM (KITD816V and KITV560G) [10] and an MPN phenotype characterized by eosinophilia and monocytosis (ETV6-PDGFRα) [11]. In 1998, a fibroblast growth factor 1 (FGFR1) mutation was described in stem cell leukaemia/lymphoma (SCLL; ZNF198-FGFR1). In 2003, FIP1L1-PDGFRα, a karyotypically occult platelet-derived growth factor receptor-α (PDGFRα) mutation, was described in association with an MPN phenotype characterized by eosinophilia and mastocytosis [12]. The molecular pathogenesis of BCR-ABL1-negative classic MPN remained elusive until early 2005 [13–16] when several groups reported a Janus kinase 2 (JAK2) gain-of-function (GOF) mutation in PV, ET and PMF. In 2006, a GOF thrombopoietin receptor (MPL) mutation (MPLW515L) was reported in JAK2V617F-negative PMF [17]. In 2007, other JAK2 mutations (exon 12 mutations) in JAK2V617F-negative patients with PV were described [18]. Additional MPL and JAK2 exon 12 mutations have since been added to the list [19–21].

The above-listed revelations in putative disease-causing or disease-promoting genetic changes have ignited much interest in the development of molecular targeted therapy in MPN. Proof-of-principle in this regard has already been accomplished with the use of imatinib mesylate (IM) in CML [22] and PDGFR-rearranged MPN [12, 23]. On the other hand, therapeutic targeting of KITD816V or mutant FGFR1 has not been as successful whereas phase I/II clinical trials evaluating anti-JAK2 drugs are currently ongoing. In this review, I will provide a clinically relevant overview of mutant molecules of interest in adult MPN and discuss the current state of affairs in regards to targeted therapy.

**BCR-ABL1**

The stage for the discovery of BCR-ABL1 in CML was set in 1960 when Peter Nowell and David Hungerford described the Ph chromosome [5]. In 1967, Philip Fialkow and colleagues applied polymorphisms in the X-linked glucose-6-phosphate dehydrogenase (G-6-PD) locus to establish CML as a stem cell-derived clonal disorder [24]. In 1972, Janet Rowley clarified the constitution of the Ph chromosome as a reciprocal translocation between chromosomes 9 and 22; t(9;22)(q34;q11) [25].

In 1982, the human homologue (ABL1; 225 kb total gene size) of v-abl was mapped to chromosome 9 [26] and shown to be involved in the Ph translocation [27]. In 1984, the chromosome
22 breakpoint was mapped to a 5.8 kb area and named the ‘breakpoint cluster region (bcr)’, which is part of the BCR gene (135 kb total gene size) [28, 29]. In 1990, retroviral infection of haematopoietic stem cells with BCR-ABL was shown to induce CML-like disease in mice [7–9].

ABL1

ABL1 is a cytoplasmic protein tyrosine kinase (PTK) that plays a role in non-erythroid myelopoiesis [30], cytoskeletal rearrangement and inhibition of cell migration [31]. Wild-type ABL1 exists in two isoforms that can localize to both the cytoplasm and nucleus, influencing cell proliferation/survival and apoptosis [32–34]. ABL1 contains both an SH2 and an SH3 (autoregulatory) domain in addition to the catalytic kinase domain and undergoes a treatment-relevant conformational change when activated by phosphorylation of the activation loop tyrosine residues [35].

BCR-ABL1

The chromosome 9 breakpoints in CML involve a large, ~200 kb region within the ABL1 alternative first exons (1a and 1b), but invariably result in fusion genes that incorporate ABL1 exon 2 [36]. In contrast, the breakpoints on chromosome 22 are clustered within three much smaller regions of the BCR gene [37]: the major breakpoint cluster region (M-bcr; a 5.8 kb region spanning exons 12–16 and resulting in a p210 fusion protein) [28], the minor breakpoint cluster region (m-bcr; upstream of M-bcr and involving the first intron and resulting in a p190 fusion protein) [38, 39] and μ-bcr involving intron 19 that is downstream of M-bcr and resulting in a p230 fusion protein [40]. By far the most frequent chromosome 22 breakpoint in CML is M-bcr and the other two, in the context of CML, are extremely rare. There are usually two junction variants of M-bcr; b2a2 and b3a2, without any documented clinical relevance [41].

BCR-ABL1 gets transcribed as a chimeric mRNA (8.5-kb) as opposed to the normal ABL1 mRNA (a 6- or 7-kb) [42] and subsequently translated to an activated BCR-ABL1 gene product (most commonly 210-kD) instead of the normal ABL1 gene product (145-kD) [43]. BCR-ABL1 localizes to the cytoskeleton and displays an up-regulated tyrosine kinase activity [44] that leads to the recruitment of downstream effectors of cell proliferation and cell survival and consequently leukaemogenesis, as has been demonstrated in cell lines, primary cells and mouse transplant or transgenic models [7, 8, 45–47]. BCR-ABL1 signal transduction involves several adapter molecules (e.g. GRB2, GAB2, CRKL, etc.) and signalling pathways (e.g. Ras, PI3K, JAK-STAT, etc.) that are all thought to contribute to the pathogenesis of CML [35, 48, 49].

Anti-BCR-ABL1 targeted therapy in CML

In 1996, Brian Druker and his colleagues described the in vitro, anti-BCR-ABL1 activity of imatinib mesylate (IM) [22], a

| Table 1 Classification of chronic myeloid neoplasms modified from the 2008 World Health Organization classification scheme [313] |
|---|
| 1. Myelodysplastic syndromes (MDS) |
| 1.1. Refractory cytopenia (RC) with uni-lineage dysplasia (RCUD) |
| 1.1.1. Refractory anaemia (RA) |
| 1.1.2. RA with ring sideroblasts (RARS) |
| 1.1.3. Refractory neutropenia |
| 1.1.4. Refractory thrombocytopenia |
| 1.2. RC with multi-lineage dysplasia (RCMD) |
| 1.3. RA with excess blasts (RAEB) |
| 1.4. MDS with isolated del(5q) |
| 1.5. MDS, unclassifiable |
| 1.6. Childhood MDS |
| 2. Myeloproliferative neoplasms (MPN) |
| 2.1. Classic |
| 2.1.1. Chronic myelogenous leukaemia, BCR-ABL1 positive (CML) |
| 2.1.2. Polycythaemia vera (PV) |
| 2.1.3. Essential thrombocythaemia (ET) |
| 2.1.4. Primary myelofibrosis (PMF) |
| 2.2. Non-classic |
| 2.2.1. Chronic neutrophilic leukaemia |
| 2.2.2. Chronic eosinophilic leukaemia, not otherwise specified (CEL-NOS) |
| 2.2.3. Mastocytosis |
| 2.2.4. MPN, unclassifiable |
| 3. MDS/MPN |
| 3.1. Chronic myelomonocytic leukaemia (CMML) |
| 3.2. Juvenile myelomonocytic leukaemia (JMML) |
| 3.3. Atypical chronic myeloid leukaemia, BCR-ABL1-negative (aCML) |
| 3.4. MDS/MPN, unclassifiable |
| 3.4.1. Provisional entity: RARS and thrombocytosis (RARS-T) |
| 4. Myeloid and/or lymphoid neoplasms with eosinophilia and abnormalities of, |
| 4.1. PDGFRA |
| 4.2. PDGFRB |
| 4.3. FGFR1 (8p11 myeloproliferative syndrome; a.k.a. stem cell leukaemia/lymphoma) |
2-phenylaminopyrimidine class kinase inhibitor that targets ABL1 [50], PDGFR [51], ARG [52] and KIT [53]; the mechanism of action involves competitive inhibition of the ATP binding site of the kinase [54]. Consequently, orally administered IM has been shown to be effective in the treatment of neoplastic diseases with mutations involving the aforementioned kinases: CML [55–61], Ph-positive acute lymphoblastic leukaemia (ALL) [56, 62], gastrointestinal stromal tumours (known to harbour KIT or PDGFR mutations) [63, 64] and PDGFR-rearranged MPN [12, 23, 65–69].

In newly diagnosed patients with chronic phase CML (CP-CML), IM is now recommended as the initial treatment of choice [70]. In the International Randomized Study of Interferon and STI571 (IRIS), interferon alpha/cytarabine combination was compared with IM in 1106 newly diagnosed CP-CML patients. The results of this trial were recently updated in 2006 [71]. IM was found to be superior to combination chemotherapy in terms of both response rates and progression-free survival; the 553 patients initially assigned to IM therapy had been followed for at least 5 years and the best observed rates for complete haematological and cytogenetic remissions were 97% and 82%, respectively. Five-year survival was 89%.

**Imatinib resistance and second-generation anti-BCR-ABL1 kinase inhibitors**

IM is not as effective in advanced phase CML as it is in CP-CML [56]. Furthermore, approximately 20% of CP-CML patients either fail treatment, for one reason or another, or transform into advanced disease phase. IM-resistance has operationally been classified into primary (not achieving complete cytogenetic remission) and secondary (loss of response). In each instance, several underlying mechanisms have been implicated and include altered BCR-ABL1/IM cellular concentration ratio due to increased BCR-ABL1 expression or abnormal cellular drug transport, activation of alternative signal pathways, inherent IM-resistance by BCR-ABL1 leukemia stem cells and emergence of IM-resistant BCR-ABL1 mutations. The latter is by far the most frequent and best understood mechanism of IM resistance.

The crystal structure of IM bound to the ABL1 indicates that the drug stabilizes the oncprotein in an enzymatically inactive conformation [54]. BCR-ABL1 mutations induce IM resistance by hindering drug-oncprotein binding at critical contact points or prevent the formation of inactive structural conformation that is required for IM activity [72]. At present, more than 50 BCR-ABL1 mutations have been described and most affect the ABL1 kinase domain; in general four categories of mutations are identified and seven mutations account for two-thirds of the cases (G250, Y253, E255, T315, M351, F359, H396): phosphate-binding loop (e.g. E255, Y253, Q252, G250; affecting ATP binding site); IM binding site (e.g. T315); catalytic domain (e.g. F359); and activation loop (e.g. H396; forcing an active conformation and thus making IM unable to bind) [73]. Not all these mutations are IM-insensitive and some (e.g. T315, E255, Y253) are more resistant than others (e.g. M244, G250, Q252, F317, E355, F359, V379, H396) [74].

The development of second generation kinase inhibitors and better understanding of mutant ABL1 conformation dynamics have had some success in addressing the aforementioned challenges of IM resistance [75–80]. New drugs include more potent ABL1 inhibitors such as nilotinib, dual ABL1/Src inhibitors such as dasatinib and bosutinib, dual ABL1/Lyn inhibitors such as INNO-406, ABL1-substrate binding inhibitors (i.e. non-ATP competitive) such as ONO12380. Most but not all (e.g. T315) ABL1 mutations are sensitive to one or more of the above listed new drugs whose value as salvage therapy for IM-refractory disease is being validated [75–80]. Finally, there is more and more discussion about IM-resistant BCR-ABL1-positive leukaemia stem cells and their dependence on both altered BCR-ABL1 expression and other signalling pathways [81]. Whether or not going after such quiescent leukaemia stem cells is therapeutically essential, in patients achieving complete molecular remissions with currently available drugs, remains to be seen.

**Other ABL1 mutations**

In the context of myeloid malignancies, ETV6 is the only currently known non-BCR fusion partner for ABL1 although other ABL1 fusion proteins have been described in acute lymphoblastic leukaemia (ALL) [82]. ETV6-ABL1, which corresponds to t(9;12)(q34;p13), has been associated with ALL [83–86], AML (with transient response to IM) [87–89] and atypical CML (with minor response to imatinib) [85, 90–92]. Like BCR-ABL1, ETV6-ABL1 encodes for an activated and transforming ABL1 [87, 93]. The PNT oligomerization motif of ETV6 is thought to activate the ABL1 kinase by a similar mechanism to the BCR coiled coil oligomerization domain in the context of the BCR-ABL1.

**JAK2 and MPL mutations**

Like ABL1, JAK2 is a cytoplasmic PTK and mutant JAK2, like mutant ABL1, has now been associated with classic MPN. JAK2 is a member of the Janus family of kinases that were incidentally discovered around 1989 and set aside as ‘just another kinase’ [94]. Their name was later modified to Janus kinases (JAKs) [95] after the Roman god with two faces because they contain two symmetrical kinase-like domains; the C-terminal JAK homology 1 (JH1) domain possesses tyrosine kinase function while the immediately adjacent JH2 domain is enzymatically inert but is believed to regulate the activity of JH1. The possible role of JAK2 mutations in haematological malignancy was first suspected after the observation that a dominant mutation in HOP, a JAK homologue in Drosophila, induced leukaemia-like defects [96].

**Janus kinases**

There are four JAKs (JAK1, JAK2, JAK3 and tyrosine kinase 2) and they all contain seven JH domains organized into four regions; kinase (JH1), pseudo-kinase (JH2), FERM (the N-terminal JH7, kinase (JH1), pseudo-kinase (JH2), FERM (the N-terminal JH7,
JAK2 fusion mutations

GOF JAK2 fusion mutations have been associated with T or pre-B ALL, T-cell lymphoma, AML and MPN-U; these include ETV6-JAK2, t(9;12)(p24;p13), PCM1-JAK2, t(8;9)(p22;p24), BCR-JAK2, t(9;22)(p24;q11.2) and SSBP2-JAK2, t(5;9)(q14.1;p24.1) (Table 2) [106–114]. PCM1 displays multiple coiled-coil motifs and it is believed that these are preserved and function as a dimerization domain in PCM1-JAK2. In ETV-6-JAK2, the chimeric protein includes the Helix-Loop-Helix oligomerization domain of ETV6 fused to the kinase domain of JAK2 and the fusion oncogene induces both T and B cell lymphoid neoplasms in transgenic mice [106, 107, 115, 116]. In a more recent study, expression of ETV-6-JAK2 in human cord blood cells resulted in Epo-independent erythropoiesis in vitro and induction of myelofibrosis in an in vivo xenotransplantation model [117]. In BCR-JAK2, the fusion protein includes the coiled-coil dimerization domain of BCR and the JAK2 kinase domain [112]. The patient in this particular instance had MPN-U and did not respond to imatinib. Another patient with BCR-JAK2 had AML [114]. The BCR-JAK2 fusion in this instance had a different BCR breakpoint, although it was similar to that of BCR-ABL1. The most recently described JAK2 fusion partner, SSBP2, is located at 5q14.1 and the associated phenotype was pre-B ALL [118]. The NH2 terminus of the SSBP2 protein contains a LisH motif that is believed to function as the dimerization domain.

JAK2V617F

JAK2V617F is an exon 14 G to T somatic mutation. The nucleotide change at position 1849 results in the substitution of valine to phenylalanine at codon 617. JAK2V617F was first described in 2005 in patients with PV, ET and PMF [13–16]. Subsequently, the mutation has also described in other myeloid neoplasms [103, 119]. As of the time of this writing, JAK2V617F has not been reported in lymphoid disorders [120–123], solid tumour [124–126] or secondary myeloproliferation [127, 128]. In general, mutational frequency is estimated at over 95% in PV, 50% in ET or PMF, 20% in certain other MPNs including refractory anaemia with ringed sideroblasts and thrombocytosis (RARS-T) and less than 5% in AML or MDS [104, 129–131].

JAK2V617F induces a PV-like phenotype in murine transplant models: erythrocytosis but not thrombocytosis, low serum Epo level, splenomegaly, extramedullary haematopoiesis, granulocytosis, megakaryocytic hyperplasia and ultimately bone marrow fibrosis and anaemia [14, 132, 133]. However, in a recent study of JAK2V617F transgenic mice, manipulation of mutant gene expression resulted in either an ET (lower expression compared to wild-type allele) or PV phenotype with (equal expression) or without (higher expression) thrombocytosis [134]. Such mutant allele burden-dependent phenotypic variation in transgenic mice was also demonstrated by another study [135].

Current information regarding mutant allele burden in human beings with MPN partially recapitulates what was seen in the above-mentioned experiments with transgenic mice. In other words, mutant allele burden in patients with ET is significantly lower than that seen in patients with either PV or PMF [136–140]. At least in PV, a higher allele burden is the result of JAK2V617F homozygosity, which is accomplished by mitotic recombination [13, 16, 141]. Some have suggested that such homologous recombination and genomic instability in general is facilitated by JAK2V617F [142]. However, the interaction between JAK2V617F homozygosity and mutant allele burden, in terms of phenotypic determination, is currently not clear [143, 144].

In human beings, JAK2V617F occurs at a primitive stem cell level and is chronologically an early event [145–147]. Some but not all [148] studies have suggested JAK2V617F clonal involvement of NK [149], T [150] and B [150] lymphocytes. Regardless, there is evidence to suggest that JAK2V617F may not be the initial clonogenic event in either PV or other MPNs and that its presence might not be mandatory for endogenous colony formation [151–153]. The demonstration of JAK2V617F-negative leukaemia clones arising in JAK2V617F-positive MPN patients lends further support in this regard [154, 155]. In the latter instance, both mutation positive and negative cells were shown to share the same cytogenetic abnormality and thus probably arose from a common ancestral clone [154]. On the other hand, JAK2V617F or other JAK2 mutations might be a necessary component of the PV phenotype, because they are detected in all patients with the disease [20]. Furthermore, recent studies suggest that germline genetic variation [156] and/or the occurrence of other concomitant mutations [19] might explain why the same mutation is present in apparently different disease phenotypes.

Other reported JAK2 exon 14 mutations include D620E (PV, MPN, unclassifiable), E627E (MPN, unclassifiable), K607N (AML), L611S (B-ALL), JAK2DeltaIREED (DS-associated B-ALL), C616Y (PV), V617F from c.1848_1849delinsCT (post-ET MF) and V617F/C618R from c.1849–1851delinsCT > TTTC (PV) [125, 157–163]. In addition, an activating JAK2T875N was described in an AMKL cell line [164]. There is no doubt that the list of such mutations will grow with time and, interestingly, some of the new mutations identified in PV co-existed with JAK2V617F.

JAK2 exon 12 mutations

In 2007, a set of JAK2 exon 12 mutations were described in JAK2V617F-negative patients with PV in whom erythrocytosis was the predominant feature [165]. Because of the latter feature, some of the cases were assigned the diagnosis of ‘idiopathic’ erythrocytosis although their serum Epo level was almost always below the
exon 12 JAK2 mutations were heterozygous but associated with their association with subnormal serum Epo level and the presence of EECS, they fulfil the 2008 WHO diagnostic criteria for PV [171]. Finally, information presented at the 2007 American Society of Hematology (ASH) meeting suggested that JAK2 exon 12 mutations are early, stem cell-derived events involving both myeloid and lymphoid progenitors [190–192] and MPLW515L has been shown to transform cell lines in terms of both cytokine-independent growth and Tpo hypersensitivity, activate JAK-STAT/ERK/Akt and induce PMF-like disease in mice that is characterized by a rapid fatal course, marked thrombocytosis, leukocytosis, hepatosplenomegaly and bone marrow fibrosis [17]. Interestingly, some patients display multiple MPL mutations and others a minor JAK2V617F cloner together with an MPL mutation [187, 193]. Again, these observations support the secondary nature of such mutations and underscore the complexity of pathogenetic mechanisms in MPNs. Finally, preliminary information suggests that MPL mutations favour megakaryocytic/myeloid as opposed to the erythroid skewed proliferation/differentiation seen with JAK2 mutations [151, 191].

Clinical and prognostic correlates of JAK2 and MPL mutations

Virtually all patients with PV carry a JAK2 mutation (97% with JAK2V617F and the rest with JAK2 exon 12 mutations) [20]. In PV, JAK2V617F ‘homozygous’ as opposed to ‘heterozygous’ state has been associated with a higher haemoglobin level, higher leukocyte count, lower platelet count and presence of pruritus [139, 194]. A somewhat similar set of correlations were made for higher mutant allele burden in PV, measured by quantitative

JAK2 mutations associated with trisomy 21 associated acute lymphoblastic leukaemia

A recent report in Lancet described somatically acquired GOF JAK2 mutations (JAK2R683G/S/K; exon 16 and mostly heterozygous) in 16 of 88 (18%) patients with Down’s syndrome-associated B-ALL but only 1 of 216 patients with sporadic ALL [105]. The latter patient had an isochromosome 21q. The mutations caused constitutive JAK-STAT activation and cytokine-independent growth of BaF3 cells that was inhibited by JAK inhibitor 1. Overall prognosis did not appear to be affected.

MPL mutations

MPL (myeloproliferative leukaemia virus oncogene homologue) belongs to the haematopoietin receptor superfamily and enables its ligand, thrombopoietin (Tpo), to facilitate both global haematopoiesis (early expansion of differentiating clones) and megakaryocyte growth and differentiation [175–177]. The gene for MPL maps to chromosome 1p34 and contains 12 exons [178]. Germline MPL mutations have been associated with either familial thrombocytosis (GOF transmembrane domain mutation; S505N) [179] or congenital amegakaryocytic thrombocytopenia (LOF mutations) that often progresses to aplastic anaemia [180–182]. In addition, an MPL single nucleotide polymorphism (G1238T) that results in a K39N substitution is found in approximately 7% of African Americans [183]. Such patients display higher platelet counts and lower MPL expression, when compared to patients without the specific MPL polymorphism [183].

In 2006, a somatic GOF MPLW515L mutation (a G to T transition at nucleotide 1544 resulting in a tryptophan to leucine substitution at codon 515 of the transmembrane region) was described in JAK2V617F-negative PMF [17]. Subsequently, another MPL mutation involving the same 515 codon (MPLW515K) was incidentally discovered during screening for MPLW515L and the prevalence of both mutations was determined at approximately 5% in PMF and 1% in ET [184]. More recent studies have identified other somatic MPL mutations including MPLW515S and MPLS505N (mentioned above in association with familial thrombocytosis) and higher prevalence rates: approximately 4% in ET (9% in JAK2V617F-negative cases) and up to 11% in PMF [185–188]. Most recently, using SNP-array karyotyping, biallelic MPLW515L mutation and uniparental disomy 1p was demonstrated in some patients with RARS-T, thus providing a mechanism of homozygosity similar to that of JAK2V617F [189].

As is the case with JAK2V617F, MPL515 mutations are early, stem cell-derived events involving both myeloid and lymphoid progenitors [190–192] and MPLW515L has been shown to transform cell lines in terms of both cytokine-independent growth and Tpo hypersensitivity, activate JAK-STAT/ERK/Akt and induce PMF-like disease in mice that is characterized by a rapid fatal course, marked thrombocytosis, leukocytosis, hepatosplenomegaly and bone marrow fibrosis [17]. Interestingly, some patients display multiple MPL mutations and others a minor JAK2V617F cloner together with an MPL mutation [187, 193]. Again, these observations support the secondary nature of such mutations and underscore the complexity of pathogenetic mechanisms in MPNs. Finally, preliminary information suggests that MPL mutations favour megakaryocytic/myeloid as opposed to the erythroid skewed proliferation/differentiation seen with JAK2 mutations [151, 191].
assays [137, 140, 195]. The small number of patients with JAK2 exon 12 mutations are more likely to present with isolated erythrocytosis but there is substantial phenotypic overlap with JAK2V617F-positive PV [18, 168].

In ET, the presence of JAK2V617F has been associated with advanced age, higher haemoglobin level, increased leucocyte count and decreased platelet count [136, 196–198]. In mutation-positive patients with ET, JAK2V617F allele burden has been directly correlated with leucocyte count, platelet count and the presence of palpable splenomegaly [136, 139, 140]. Similarly in PV, the presence of JAK2V617F has been associated with an older age at diagnosis and higher leucocyte count [199]. In addition, JAK2V617F ‘homozygous’ PMF patients displayed an even higher incidence of leukocytosis, marked splenomegaly and pruritus [200]. Both PMF and ET patients with MPL mutations were found to be older and more anaemic than their MPL mutation-negative counterparts [186, 188].

JAK2 or MPL mutations in MPNs might not have prognostic relevance. In ET, overall or leukaemia-free survival was not affected by either the presence of JAK2V617F or its allele burden [136, 196]; the impact on the risk of thrombosis or fibrotic transformation is less clear [136, 139, 196, 201]. Equally unclear is the prognostic relevance of JAK2V617F allele burden in PV where a higher mutant allele burden is implicated by some but not by others as an adverse prognostic factor for fibrotic transformation, thrombosis and need for chemotherapy [137, 139, 194, 195]. In PMF, JAK2V617F presence was associated with inferior survival in one but not in another study [199, 202]. Similarly divergent results were reported in terms of leukaemia transformation rate and need for chemotherapy or splenectomy [200, 203]. The most recent study on the subject matter revealed shortened overall and leukaemia-free survival in PMF patients with lower as opposed to higher quartile JAK2V617F allele burden [203].

Anti-JAK2 small molecule therapy

A number of anti-JAK2 drugs have undergone preclinical testing and some have already been introduced into clinical trials [204]. Amongst them, some are JAK2 selective ATP-mimetic small molecules: e.g. TG101209, TG101348, INCB018424, XL019, CEP-701 and SB1518 [205–208]. TG101209, an orally available small molecule JAK2-selective kinase inhibitor, is one of the first compounds to undergo extensive preclinical testing [209]. The drug’s anti-JAK2 kinase activity was estimated at an IC50 of 6 nM, compared to 169 nM for JAK3 [209]. In HEL cells (homozygous for JAK2V617F) and other JAK2V617F-transduced cell lines, TG101209 induced apoptosis and inhibited phosphorylation of JAK2V617F, STAT5 and STAT3 (IC50 of approximately 600 nM) [209]. At similar or lesser drug concentrations, the drug also inhibited colony growth of primary cells from JAK2V617F-positive PV patients and MPLW515L-positive PMF patients [209]. Furthermore, the growth inhibitory effect of TG101209 was relatively selective to mutated-colonies. TG101348, a drug that is very selectively to TG101209, was also shown to display similar in vitro and in vivo anti-PV and anti-MPN activity in the context of JAK2, exon 12, exon 14 JAK2 and MPL mutations [205, 210–212].

In a murine model of polycythaemia vera, oral TG101348 therapy resulted in significant reduction of haematocrit, leucocyte count, extramedullary haematopoiesis, myelofibrosis and JAK2V617F-expressing clones [211]. TG101348, but not TG101209, is currently undergoing phase I/II clinical trial in PMF and post-PV/ET MF.

Several other potent JAK2 inhibitors have also been reported to have in vitro or in vivo (e.g. mouse models) activity against JAK2V617F-driven cell proliferation and signal transduction. Among them, INCB018424, XL019, CEP-701 and SB1518 are currently undergoing clinical trials in patients with advanced stages of PMF or post-PV/ET MF (INCB018424, XL019, CEP-701, PV (XL019, CEP-701), JAK2V617F-positive ET (CEP-701) and acute and chronic haematologic malignancies (SB1518) [208–209, 213, 214]. All of these drugs display potent JAK2 inhibitory activity but their in vitro JAK2 selectivity, in the context of the JAK family of kinases, is different. For example, JAK3 is spared by TG101348, XL019 and INCB018424 but not by CEP-701. Similarly, JAK1 is spared by TG101348 and XL019 but not by INCB018424.

Preliminary results regarding INCB018424 in PMF and post-PV/ET MF are encouraging in terms of the drug’s toxicity profile and its activity against splenomegaly and constitutional symptoms [213]. More follow-up is required to determine the drug’s effect on anaemia, leukoerythroblastosis, myelofibrosis, cytokogenetic abnormalities or JAK2V617F allele burden. Results regarding other JAK2 inhibitors are too early to comment on. Nevertheless, the expected anti-inflammatory cytokine effect of this class of drugs is expected to be a confounding variable in terms of both toxicity and efficacy assessment.

KIT mutations

In 1993, Furitsu and colleagues described a mutant KIT allele with two-point mutations as being responsible for the ligand-independent constitutive activation of KIT in a human mast cell leukaemia cell line (HMC-1); one mutation was located at the JM region at codon 560 and nucleotides 1699–1701 (V560G; GTT→GGT) and the other at the kinase domain at codon 816 and nucleotides 2467–2469 (D816V; GAC→GTA) [10]. One year later (1994), Tsujimura et al. reported a kinase domain point mutation at nucleotide 2468 (GC to TA) resulting in an amino acid substitution at codon 814 (KITD814Y), in a murine mastocytoma cell line, P-815 [215]. In both instances, either the mutations themselves [215] or their corresponding murine constructs (V559G and D814V) [10] were shown to produce constitutive activation of KIT signalling in cell lines.

Nagata and colleagues were the first to describe one of the aforementioned mutations (KITD816V) in blood mononuclear cells from patients with SM and an associated non-mast cell myeloid neoplasm but not in those with indolent or aggressive SM, solitary mastocytoma or chronic myelomonocytic leukaemia.
Activated KIT mutations have been described in a spectrum of haematologic (e.g. mastocytosis, acute leukaemia) and non-haematologic (e.g. gastrointestinal stromal tumour, germ cell tumour) malignancies [232]. Among these, SM is considered an MPN by virtue of its clonal derivation from the haematopoietic stem cell [217–222]. It is currently touted that all patients with MCD carry a KIT mutation but its laboratory detection might be hampered by the use of non-informative cell source or inadequate assay sensitivity [223, 224]. JM KIT mutations have also been described in canine mastocytomas [225].

**Mutant KIT**

Activating KIT mutations have been described in a spectrum of haematologic (e.g. mastocytosis, acute leukaemia) and non-haematologic (e.g. gastrointestinal stromal tumour, germ cell tumour) malignancies [232]. Among these, SM is considered an MPN by virtue of its clonal derivation from the haematopoietic stem cell [234–236]. Observations from several laboratory studies support the oncogenic role of KIT mutations. For example, in murine experiments, D814Y has been shown to induce ligand-independent mast cell growth in vitro, tumourigenicity in vivo, and mast cell differentiation [237]. Similarly, retroviral infection of haematopoietic progenitors with mouse KITD814Y and KITV559G mutants induces autonomous myeloid and mast cell colony formation as well acute leukaemia in murine transplant models [238]. Furthermore, transgenic mice expressing KITD816V restricted to their mast cells display an SM phenotype that closely resembles the clinically heterogeneous disease in man [239]. This is in contrast to another report [240] that suggested a differentiating but not transforming potential for the mutation, which nevertheless probably participates in enhancing mast cell chemotaxis [241] and clustering [236]. Mutant KIT signalling might involve both PI3K [242] and Src [243] participation although utilization of pathway molecules might be different between the wild-type and mutant protein [244].

**Systemic mastocytosis**

The 2008 World Health Organization (WHO) classification system for myeloid malignancies considers SM as a myeloproliferative neoplasm (MPN) [4]. WHO-defined SM should be distinguished from PDGFR-mutated (FIP1L1-PDGFRα, PRKG2-PDGFRB) myeloid malignancy associated with bone marrow mastocytosis and either eosinophilia or basophilia [69, 245]. The latter but not the former are effectively treated by IM. SM is sometimes associated with a clonally related second myeloid neoplasm, which is not surprising considering its origin as a stem cell disease with multi-lineage clonal involvement.

**Targeted therapy in systemic mastocytosis**

Although several drugs have shown in vitro anti-KIT activity [246–249], the immediately most relevant, in terms of clinical development, include the tyrosine kinase inhibitors IM, nilotinib, dasatinib and PKC412. During in vitro experiments involving both cell lines and primary cells from patients with SM, IM inhibited wild-type KIT and KIT mutants with trans-membrane (F522C) and juxta-membrane (V559G and V560G) but not kinase (D816V or D814V) domain mutations [222, 225, 251]. Similarly, not all juxta-membrane mutations are sensitive to IM (e.g. V559I) [252]. Consistent with these in vitro observations, IM therapy is ineffective in SM associated with KITD816V [253] whereas others have shown activity in MCD associated with the trans-membrane KITF522C mutation [222]. In contrast to the experience from my own institution, Droogendijk et al. treated 11 patients with D816V-positive SM with 400 mg/day of IM and found some ‘clinical improvement’ in some patients [254].

Nilotinib is more potent than IM in its in vitro anti-BCR-ABL activity but is similarly ineffective against KITD816V [255]. Other studies have, however, shown a more promising activity of nilotinib against kinase domain KIT mutations [256]. In contrast, dasatinib has shown potent anti-KIT activity in mast cell and leukaemia cell lines with different KIT mutants including those with D816V [257, 258]. In the largest study of dasatinib therapy in SM [259], the drug was given at a starting dose of 70 mg PO bid to 33 SM patients: 18 indolent, 9 aggressive and 6 with associated non-mast cell myeloid neoplasm. Two (6%) patients, both of whom were D816V-negative, achieved complete remission. Nine (27%) patients experienced symptomatic improvement. The results of another case report series of four patients with SM treated with dasatinib were equally unimpressive [260].

PKC412 has shown in vitro activity against transformed and primary cells with kinase domain KIT mutants (D816Y and D816V) [261, 262]. In a preliminary report, transient improvement in liver function test abnormalities, peripheral blood mast cell percentage and plasma histamine levels were seen in a patient with SM.
treated with PKC412 [263]. Similarly, oral PKC412 (100 mg bid) was administered to 15 SM patients (60% with detectable KitD816V) with evidence of clinical activity in 11 (73%) patients including increase in haemoglobin (n = 1) and reduction of ascites (n = 2) or pleural effusion (n = 2). In four patients, the bone marrow mast cell burden was reported to have decreased from 50–60% to 10–15% range.

PDGFRA mutations

In regards to PDGFRA mutations, the most intensively studied has been the FIP1L1-PDGFRα, a karyotypically occult del(4)(q12), that was described in 2003 as an imatinib-sensitive activating mutation [12]. Subsequent studies have demonstrated the stem cell origin of the particular mutation [264, 265] and functional studies have demonstrated transforming properties in cell lines and the induction of MPD in mice [266, 267]. Cloning of the FIP1L1-PDGFRα fusion gene identified a novel molecular mechanism for generating this constitutively active fusion tyrosine kinase, wherein a ~800 kb interstitial deletion within 4q12 fuses the 5’ portion of FIP1L1 to the 3’ portion of PDGFRA [12]. Molecular studies have shown that the breakpoint in FIP1L1 is relatively promiscuous, whereas the PDGFRA breakpoint is restricted to exon 12 that encodes part of the protein–protein interaction module with two fully conserved tryptophans (WW domain) containing the JM region with resultant disruption of its autoinhibitory activity [268]. Further biochemical analysis has shown that, in contrast with most tyrosine kinase fusions associated with human cancers, the FIP1L1 encoded sequences are dispensable for transformation, and there is no requirement for a dimerization motif; disruption of the autoinhibitory juxta-membrane motif as an invariant consequence of disruption of exon 12 is the basis for constitutive activation of PDGFRα kinase activity [269].

FIP1L1-PDGFRα occurs in a very small subset of patients who present with the phenotypic features of either SM or HES but the presence of the mutation reliably predicts complete haematologic and molecular response to imatinib therapy [67, 69, 270]. FIP1L1-PDGFRα mutation (T674I) that is homologous to the resistance-inducing, ‘gatekeeper’ T315I mutation in BCR-ABL has been described [12, 271, 272] and in vitro salvage with other kinase inhibitors including PKC412 [266] and sorafenib [273] has been demonstrated whereas such activity has not been conclusively shown for nilotinib [274, 275].

PDGFRA activation associated with CEL has also been described with karyotypically apparent fusion mutations including KIF5B-PDGFRα, t(4:10)(q12;p11) [276], BCR-PDGFRα, t(4;22)(q12;q11) [277] and CDK5RAP2-PDGFRα ins(9:4)(q33;q12q25) [278]. In the former instance, the breakpoints involved exon 3 of the kinesin family member 5B and exon 12 of PDGFRα resulting in an in-frame fusion. The patient achieved complete haematological and molecular remission with imatinib therapy [276]. BCR-PDGFRα represents an in-frame fusion with BCR breakpoints in intron 7/exon 12/exon 1 and PDGFRα breakpoint in exon 12/exon 13 and is also sensitive to imatinib therapy [277, 279, 280]. CDK5RAP2-PDGFRα also represents an imatinib-sensitive in-frame fusion involving exon 13 of CDK5RAP2 and intron 9/exon 12 of PDGFRα [278]. As is the case with FIP1L1-PDGFRα, currently known PDGFRα breakpoints are noted to be tightly clustered in the JM region, which once again highlights a key regulatory role for this domain.

FGFR1 mutations

There are at least four members of the FGFR protein family (FGFR1, FGFR2, FGFR3 and FGFR4) with additional variants resulting from alternative splicing. Structurally, FGFRs feature extracellular, trans-membrane, juxta-membrane and kinase domains. FGFRs are functionally important in embryonal development and tissue integrity and germline FGFR mutations result in various birth defects including achondroplasia/hypochondroplasia (FGFR3), Crouzon syndrome (FGFR2) and Kallmann syndrome (FGFR1). Somatic FGFR3 mutations have been described in benign skin tumours, uterine cancer and multiple myeloma and FGFR2 mutations in endometrial carcinoma. In the context of myeloid malignancies, somatic FGFR1 mutations have been
specifically associated with SCLL (also known as the 8p11 myeloproliferative syndrome).

SCLL is an extremely rare disease usually characterized by a mixed myeloid and lymphoid phenotype. The typical presentation is one of aggressive lymphoblastic lymphoma (usually T cell), eosinophilia, monocytosis and other blood and bone marrow evidence of clonal myeloproliferation. The disease rapidly progresses into acute leukaemia (usually myeloid). The hallmark of SCLL is a cytogenetic translocation between chromosome 8p11 and a spectrum of partner chromosomes as outlined in Table 2; these translocations result in fusion oncogenes that always involve exon 9 of FGFR1, located on 8p11 (Table 2) [292–307].

In SCLL, FGFR1 mutation is present in both myeloid and lymphoid lineage cells and some of the associated fusion genes have

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**Table 2 Mutations of putative pathogenetic relevance in myeloproliferative neoplasms**

| JAK2   | MPL   | PDGFA  | PDGFRB | FGFR1     |
|--------|-------|--------|--------|-----------|
| (phenotype) | (phenotype) | (phenotype) | (phenotype) | (phenotype) |
| JAK2V617F (PV, ET, PMF) | MPLW515L/K (PMF, ET) | FIP1L1-PDGFRB del(14q12) (CEL with mastocytosis) | ETV6-PDGFRB t(5;12)(q33;p13) (CMML with eosinophilia) | ZNF 198-FGFR1 t(8;13)(p11;q12) (SCLL) |
| JAK2 Exon 12 mutations | | BCR-PDGFRB t(4;22)(q12;q11) (CEL, MPN-U) | RABAPTN-5-PDGFRB t(5;17)(q33;p13) (CMML) | |
| F537-K539delinsL, H538OK539L, K539L, N542-E543del (PV) | | | HCMOGT-1-PDGFRB t(5;17)(q33;p11.2) (JMML with eosinophilia) | |
| ETV6-JAK2 t(9;12)(p24;13) (AML, MPN-U) | | KIF5B-PDGFRB t(4;10)(q12;p11) (CEL) | CEV14-PDGFRB t(5;14)(q33;q24) (MPN with eosinophilia) | FGFR10P2-PDGFRB ins(12;8)(p11;p11p22) (SCLL) |
| BCR-JAK2 t(9;22)(p24;q11.2) (MPN-U, AML) | | CDK5RAP2-PDGFRB ins(9;4)(q33;q12q25) (CEL) | TP53BP1-PDGFRB t(5;15)(q33;q22) (MPN-U with eosinophilia) | TIF1-FGFR1 t(7;8)(q34;p11) (SCLL) |
| PCM1-JAK2 t(8;9)(p22;p24) (AML, MPN-U) | | | POE4DIP-PDGFRB t(1;5)(q23;q33) (MPN-U with eosinophilia) | MYO18A-FGFR1 t(8;17)(p11;q23) (SCLL) |
| SSBP2-JAK2 t(5;9)(q14.1;p24.1) (pre-B ALL) | | | HIP1-PDGFRB t(5;7)(q33;q11.2) (CMML with eosinophilia) | HERV-K-FGFR1 t(8;19)(p12;q13.3) (SCLL) |
| PV, polycythemia vera; ET, essential thrombocytopenia; PMF, primary myelofibrosis; AML, acute myeloid leukaemia; MPN-U, unclassified MPN; CEL-SM, chronic eosinophilic leukaemia associated with systemic mastocytosis; CMML, chronic myelomonocytic leukaemia; JMML, juvenile myelomonocytic leukaemia; SCLL, stem cell leukaemia-lymphoma syndrome. | | | H4-PDGFRB t(5;10)(q33;q22) (MPN-U) | BCR-FGFR1 t(6;22)(p11;q11) (CML-like MPN) |
| | | | | CEP110-FGFR1 t(8;9)(p12;q33) (SCLL) |
| | | | | CPSF6-FGFR1 t(8;12)(p11;q15) (SCLL) |
been shown to transform cell lines [301, 308–310] and induce SCLL (ZF198-FGFR1) [311] or CML (BCR-FGFR1) [310] like disease in mice. Consistent with this laboratory observation, some patients with BCR-FGFR1 mutation manifest a more indolent, compared to SCLL, disease phenotype [301]. The mechanism of FGFR1 activation in SCLL is similar, in most cases, to that seen with PDGFRB-associated CEL; the tyrosine kinase domain of FGFR1 is juxtaposed to a dimerization domain from the partner gene, although oligomerization motifs are not always identified in the partner gene [307].

SCLL is refractory to usual chemotherapy and some (e.g. PKC412) but not other (e.g. imatinib) kinase inhibitors have been shown to inhibit FGFR1 kinase and downstream effector activity, as well as activation of the downstream effector molecules PLC-γ, STAT5 and phosphatidylinositol 3-kinase/AKT [312]. PKC412 (N-benzoyl-staurosporine) is a small molecule tyrosine kinase inhibitor with activity against FLT3, protein kinase C, CDK2 and receptors for PDGF, FGF and VEGF. The drug has been shown to inhibit ZNF198-FGFR1 kinase and downstream effector activity, reduce proliferation of ZNF198-FGFR1 transformed cell lines and favourably affect survival of mice with ZNF198-FGFR1-induced MPN [312]. Whether or not the drug will work in human beings with SCLL is not currently clear although one PKC412-treated patient experienced an improvement in leukocytosis, lymphadenopathy and splenomegaly over 6 months before receiving allogeneic stem cell transplant [312].

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