Myeloproliferative Neoplasms

15

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Contents

15.1 Introduction

Human immunodeficiency virus (HIV) infection is linked to an increased risk of both acquired immunodeficiency syndrome (AIDS)-defining malignancies (ADMs) and non-AIDS-defining malignancies (nADMs). One subset of these nADMs are myeloproliferative neoplasms (MPNs), in which there is an overproduction of red blood cells (RBCs), platelets, or a subset of white blood cells (WBCs). Many patients with MPNs are asymptomatic at the time of medical

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evaluation, and their diagnosis is established after routine blood testing reveals an anomaly. Others present to medical attention complaining of headache, fatigue, weight loss, and early satiety in the backdrop of splenomegaly, bleeding, and thrombotic complications and clonal evolution.

In this chapter, we will discuss MPNs. Case reports describing MPNs in HIV-infected patients are rare. Subsequently, there is neither ample knowledge regarding the natural history of MPNs in this population nor is there abundant clinical experience in using standard chemotherapies in conjunction with highly active antiretroviral therapy (HAART). Although there is perhaps no inherent reason why people living with HIV/AIDS (PLWHA) should be predisposed to these disorders, we expect more instances of MPNs in this population as these individuals achieve survival rates comparable to the general population.

We focus on the classification of MPNs and the importance of cytogenetics and molecular studies in refining the diagnosis. Chronic myeloid leukemia (CML), which is associated with the Philadelphia chromosome, has been described in only a handful of case reports in the context of HIV infection. We will narrow our discussion to briefly mention the Philadelphia-negative MPNs: polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). For these disorders, even less is known regarding their clinical course and natural history in the backdrop of HIV infection.

15.2 Classification

Among the classic MPNs, CML is genetically characterized by the reciprocal chromosomal translocation between chromosomes 9 and 22, t (9; 22). This translocation is associated with a shortened chromosome 22 (the Philadelphia chromosome [Ph]) in 95 % of instances. In the remaining cases, t (9; 22) can be identified by either fluorescence in situ hybridization or reverse transcriptase polymerase chain reaction (PCR) techniques for detection of *BCR-ABL*, a tyrosine kinase protein [1]. While cytogenetic abnormalities are common in PMF and uncommon in ET, no specific cytogenetic abnormality in the MPNs other than CML has yet been established [2].

Janus kinase-2 (JAK-2) mutations are found in virtually all patients with PV and approximately 50 % of those with either ET or PMF. This finding has greatly aided in the diagnosis of MPNs [3]. Further studies identified JAK- signal transducers and activators of transcription (STAT) pathway mutations in the thrombopoietin receptor and the calreticulin gene in JAK-2 non-mutated MPNs [4]. The diagnosis of PV is entertained when there is an unexplained increase in hematocrit/RBC mass in conjunction with presence of a JAK-2 mutation along with a decreased serum erythropoietin level [5].

PMF (agnogenic myeloid metaplasia, chronic idiopathic myelofibrosis) is characterized by the presence of bone marrow fibrosis that cannot be attributed to another myeloid disorder such as CML, PV, ET, or myelodysplastic syndromes

(MDS). ET is a diagnosis of exclusion, representing clonal or autonomous thrombocytosis not classifiable as PV, PMF, CML, or MDS [6].

The MPNs, and PMF in particular, are often accompanied by leukoerythroblastic changes on peripheral blood smear. The characteristic laboratory changes associated with a myelophthisic bone marrow process include nucleated red blood cells and teardrop forms, giant platelets, and immature white blood cells (e.g., myelocytes, metamyelocytes, occasionally promyelocytes and myeloblasts) (Fig. 15.1).

Within the context of the MPNs, an elevated RBC mass is specific for PV. Occasionally, both CML and MDS may present with either isolated thrombocytosis suggesting ET or associated bone marrow fibrosis suggesting PMF [7]. As a result, the diagnostic workup of patients with suspected MPN should always include cytogenetic studies and careful morphologic evaluation to exclude the presence of t (9; 22) and MDS, respectively. The accurate diagnosis and classification of MPNs are prerequisites for appropriate risk-based therapy and should be based on an integrated approach following the World Health Organization (WHO) guidelines that, in addition to clinical, cytogenetic, and molecular evaluation, includes a bone marrow examination [8] (Figs. 15.2, 15.3, and 15.4).

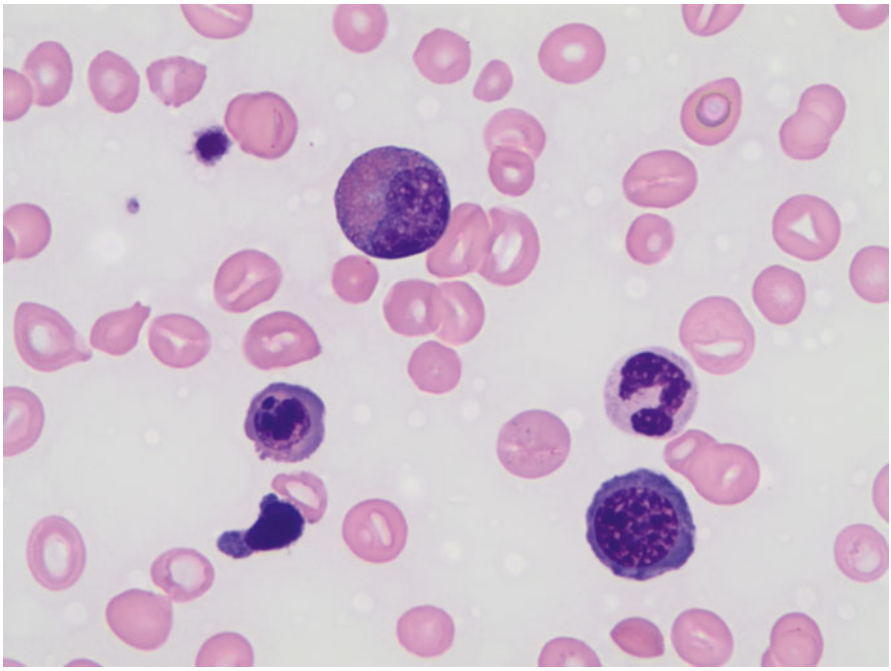

Fig. 15.1 Leukoerythroblastic peripheral blood smear (Image and description courtesy of Dr. Dick Hwang, Virginia Mason Medical Center)

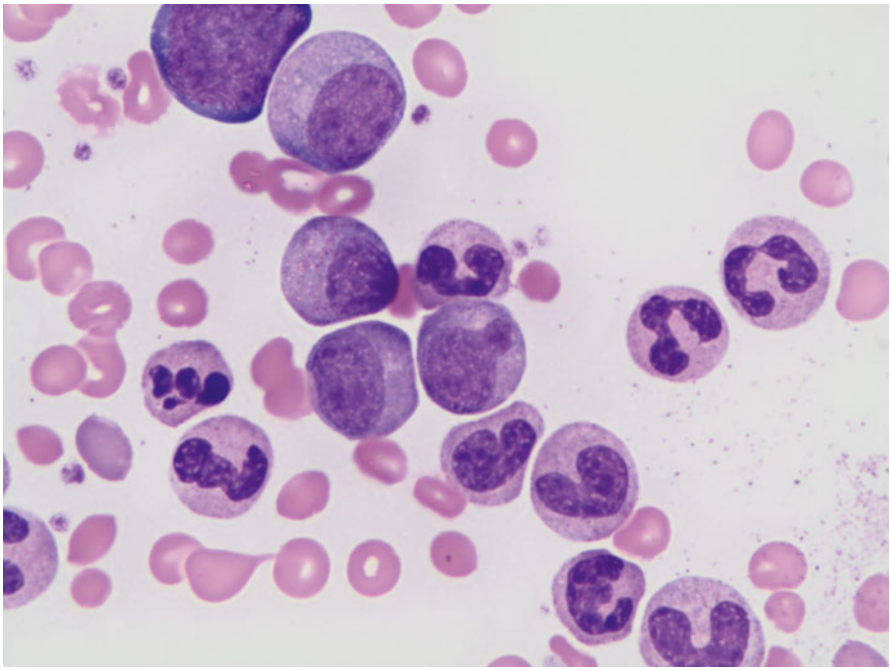

Fig. 15.2 Chronic myeloid leukemia (CML) (Image and description courtesy of Dr. Dick Hwang, Virginia Mason Medical Center)

15.3 Chronic Myeloid Leukemia

The American Cancer Society estimates that in 2015 in the United States, roughly 6600 new cases of CML will be diagnosed, which is slightly higher than 10 % of all new leukemia cases. The disease is more common in men than women and the average age at diagnosis is 64 years [9].

The goals of treatment for CML have changed radically over the past decade and can be summarized as follows [10]:

1. Hematologic remission defined as a normal complete blood count and the absence of splenomegaly
2. Cytogenetic remission (normal karyotype with 0 % Ph+ cells)
3. Molecular remission (negative PCR result for the mutational *BCR/ABL* mRNA), which represents efforts to cure and prolongation of patient survival

Typically, CML has three clinical phases: an initial chronic phase, during which the disease process is easily controlled, a transitional and unstable course (accelerated phase), and finally, a more aggressive course (blast crisis), which is usually fatal. In all three phases, supportive therapy with transfusions of RBCs or platelets may be used to relieve symptoms and improve quality of life.

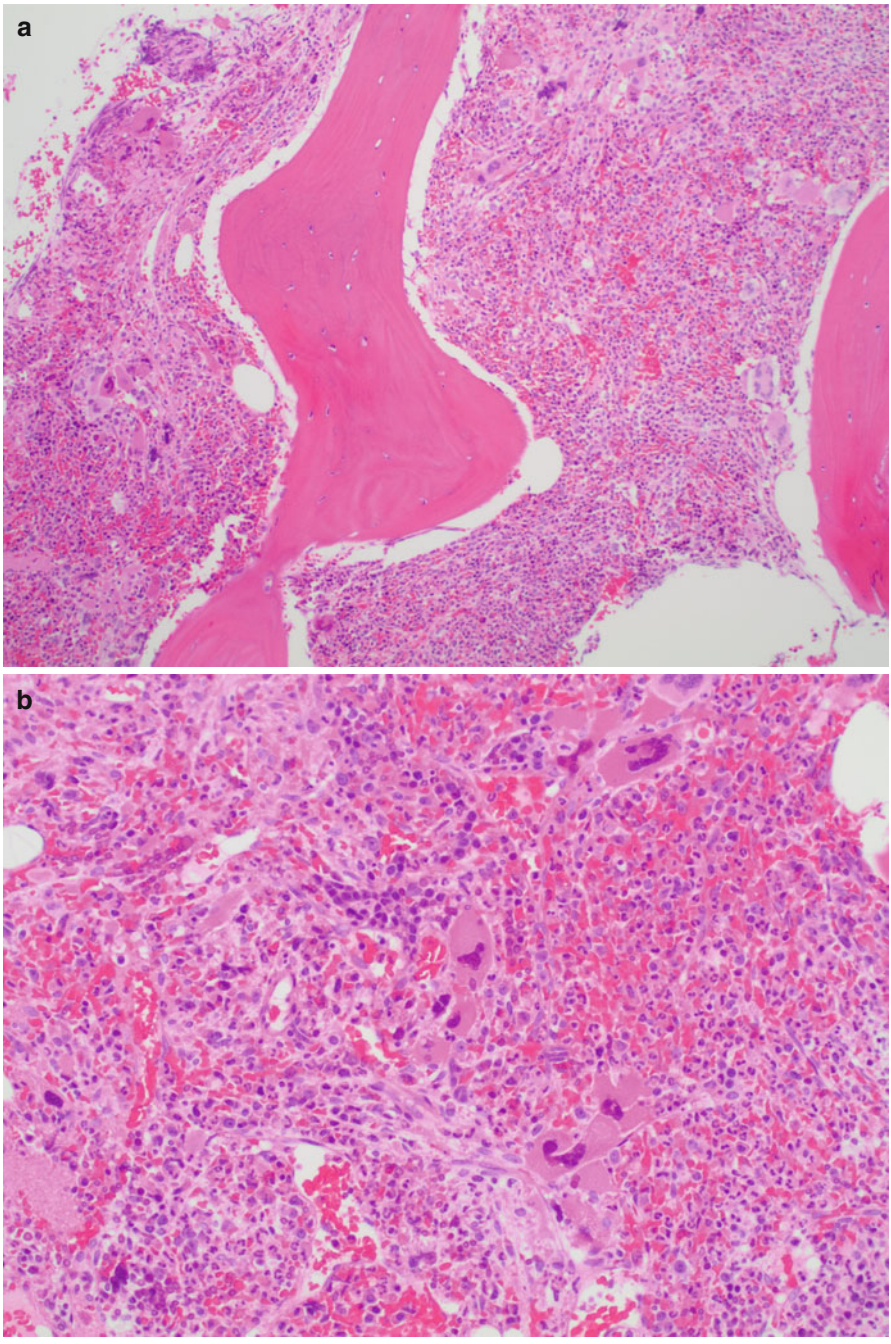

Fig. 15.3 (**a**) Bone marrow biopsy from a patient with primary myelofibrosis with marrow fibrosis and clusters of atypical megakaryocytes 10×. (**b**) Bone marrow biopsy from a patient with primary myelofibrosis 20×. (**c**) Reticulin stain shows moderate reticulin fibrosis (Images and descriptions courtesy of Dr. Dick Hwang, Virginia Mason Medical Center)

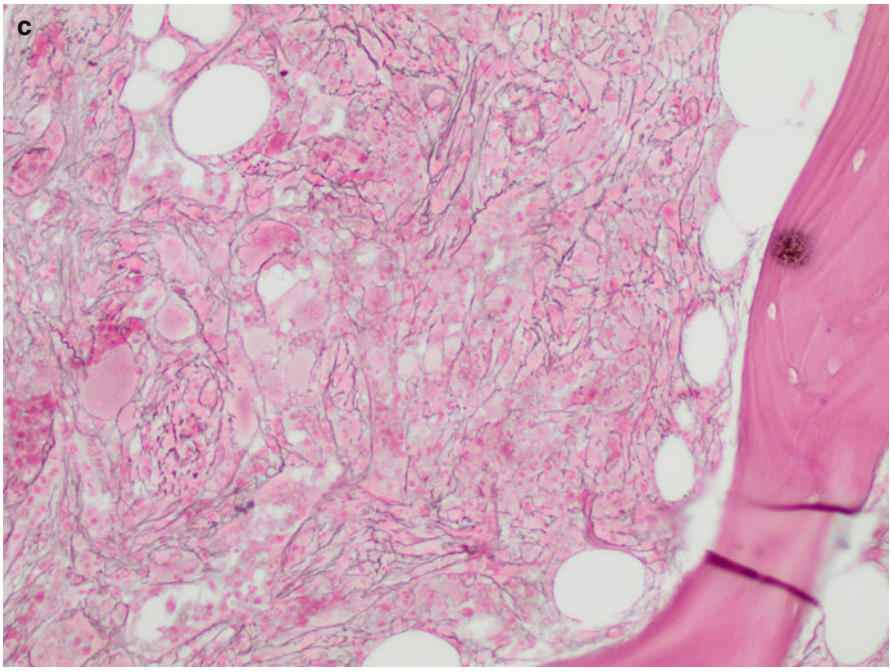

Fig. 15.3 (Continued)

In Western countries, 90 % of patients with CML are diagnosed in the chronic phase. These patients' WBC count is usually controlled with medication (hematologic remission). The major goal of treatment during this phase is to control symptoms and complications due to anemia, thrombocytopenia, leukocytosis, and splenomegaly. The standard treatment of choice until recently has been imatinib, which is a specific small molecule tyrosine kinase inhibitor (TKI) of *BCR/ABL* and is highly effective in all phases of CML [11, 12].

The chronic phase varies in duration, depending on the maintenance therapy used. It usually lasts 2–3 years with hydroxyurea or busulfan therapy, but it may last for longer than 9.5 years in patients who respond well to interferon alpha therapy. Furthermore, the advent of imatinib and the other TKIs has dramatically improved the duration of hematologic and cytogenetic remissions [13].

Some patients with CML progress to a transitional or accelerated phase which may last for several months. The survival of patients in this phase is 1–1.5 years. This phase is characterized by poor control of blood counts with myelosuppressive medication and the appearance of peripheral blast cells (≥15 %), promyelocytes (≥30 %), basophils (≥20 %), and platelet counts less than 100,000 cells/μL unrelated to therapy.

In a retrospective review of all patients diagnosed with CML at the Chris Hani Baragwanath Academic Hospital (CHBAH) in South Africa between 1991 and 2011, 240 patients were identified with CML 18 of whom (7.5 %) were also infected

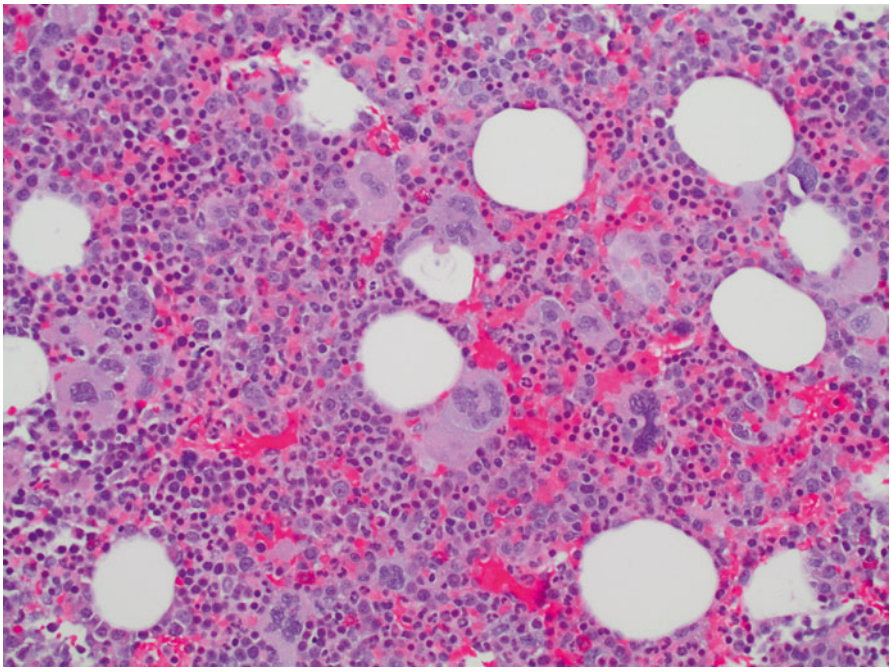

Fig. 15.4 Bone marrow biopsy from a patient with polycythemia vera showing conspicuous hypercellularity for age with erythroid and megakaryocytic hyperplasia. Megakaryocytes show widely separated nuclear lobes (Image and description courtesy of Dr. Dick Hwang, Virginia Mason Medical Center)

with HIV [14]. This proportion of total CML patients with and without HIV infection was much lower than the HIV seroprevalence in the CHBAH population (25 % in 2004 and 28 % in 2008). Based on this data set, the authors concluded that HIV infection does not increase the prevalence of CML. However, in this same data set, they also noted that the median age of HIV-CML patients was younger (37 years) than that of CML patients not infected with HIV (43 years). Eight out of the 18 (44 %) HIV-CML patients had progressed to accelerated or blast phase CML, while less than 10 % of the seronegative CML patients had been diagnosed with accelerated or blast phase.

Although the incidence of CML might not be augmented in the context of HIV infection, this limited data set from South Africa raises the specter that among PLWHA, CML may have a different natural history. Of the 18 HIV-CML patients, 6 were also treated with imatinib at a standard dose of 400 mg/day [14]. After a median follow-up of 15 months, one patient had died (cause not specified), one (17 %) had achieved a major molecular response (MMR), two (33 %) had achieved a major cytogenetic response (MCR), and two (33 %) had achieved a complete cytogenetic response (CCR). However, the response to imatinib in HIV-CML patients was reported to be inferior to that noted in patients with CML without

HIV. Of 44 HIV-negative patients with CML treated with imatinib, 15 (34 %) had achieved a MCR, 7 (16 %) a CCR, 4 (9 %) a MMR, 15 (34 %) had undetectable ABL-BCR transcripts, and 3 (7 %) had achieved less than a MCR.

In a more recent report, three patients diagnosed with chronic phase CML took imatinib in conjunction with HAART [15]. The first patient had been treated with HAART (nevirapine, abacavir, lamivudine, and zidovudine) and had a CD4+ count of 488 cells/mm^3 and a non-detectable HIV viral load when he began imatinib at a dose of 600 mg/day. Three months later, his HIV viral load remained less than 75 copies/mm^3, and cytogenetic analysis showed a minor CR. The second patient had also been treated with HAART (lopinavir-ritonavir, abacavir, lamivudine, and zidovudine) for 3 years when he was diagnosed with CML. He had a non-detectable HIV viral load and a CD4+ count of 508 cells/mm^3 when he received imatinib at a dose of 400 mg/day. Two weeks later, he began erythropoietin supplementation, but when his anemia worsened imatinib was held for 2 weeks and then resumed at a reduced dose of 300 mg/day. His HAART regimen was also revised and efavirenz was substituted for lopinavir-ritonavir and abacavir, and lamivudine and zidovudine were substituted for emtricitabine and tenofovir. A CCR was attained 13 months later, and at a 20-month follow-up, the patient's HIV viral load remained non-detectable and his CD4+ count was 382 cells/mm^3. The third patient had been treated with HAART (nevirapine, abacavir, and lamivudine) for 10 years when he presented to medical attention with isolated leukocytosis and left shifted findings on peripheral blood smear but no overt findings of infection. He had a non-detectable HIV viral load and CD4+ count of 523 cells/mm^3 when he began imatinib at a dose of 400 mg/day. Following CML treatment, he developed persistent anemia, alleviated by recombinant erythropoietin and RBC transfusions. Imatinib was subsequently held for 1 month and then restarted at a dose of 200 mg/day. Over a 16-month period, imatinib was gradually increased 400 mg/day. A CCR was achieved 17 months after treatment started and at 69-month follow-up, the patient's HIV viral load remained non-detectable and his CD4+ count was 440 cells/mm^3. In each of these three cases, imatinib was taken in conjunction with various HAART options and was generally well tolerated.

In these and other case reports, hydroxyurea was used sparingly and imatinib was the TKI employed most frequently to treat HIV-infected patients with CML [16, 17]. Although details of drug-drug interactions have generally not been reported in this context, it is notable that imatinib is mainly metabolized by cytochrome P450 (CYP) 3A4 isoenzyme and concurrent administration of drugs that affect CYP3A4 may incur similar interactions. Other enzymes which play a minor role in the metabolism of imatinib include CYP1A2, CYP2D6, CYPC9, and CYP2C19 [18, 19]. Taking antiretroviral therapies into consideration, serum imatinib levels are likely affected by certain antiretroviral classes that comprise HAART. Nucleoside reverse transcriptase inhibitors and integrase inhibitors have no effect on the substrate CYP3A4; however, non-nucleoside reverse transcriptase inhibitors induce CYP3A4 and protease inhibitors inhibit CYP3A4 [20]. The US Food and Drug Administration (FDA) recommends dose reduction of imatinib by 50 % if patients

are taking a CYP3A4 inhibitor; however, it appears the majority of HIV-infected patients with CML have received full doses of imatinib [18].

Experience with newer agents to treat PLWHA and CML are limited (Table 15.1). In a brief case report, an HIV-infected male received nilotinib *not* for CML but rather for acute myeloid leukemia (AML) [21]. During his hospital course, he began antifungal medication, and serum nilotinib levels were carefully monitored along with electrocardiogram determinants of QT prolongation. Like imatinib, kinetic experiments have shown that CYP3A4 and CYP2C8 enzymes are the main contributors to the metabolism of nilotinib, and coadministration with CYP3A4 inhibitors reduce oxidative metabolism of nilotinib by as much as 95 %. The authors reminded clinicians of this important potential drug-drug interaction and suggested a strategy to minimize sudden cardiac death by QT prolongation.

15.4 Polycythemia Vera

PV is a stem cell disorder characterized as a pan-hyperplastic, malignant, and neoplastic marrow disorder. It is most commonly diagnosed in individuals between the ages of 60 and 70 years and is more common in men than women [22, 23]. PV results from uncontrolled blood cell production, especially RBCs, as a result of acquired mutations in an early hematopoietic cell. Because this early cell has the capability to form not only RBCs but also WBCs and platelets, any combination of these cell lines may be affected.

The most prominent feature of PV is an elevated absolute RBC mass because of uncontrolled RBC production. Impaired oxygenation to the tissues as a result of

Table 15.1 Current treatments for chronic myeloid leukemia

Treatment	Suggested dosage	Comments
Imatinib	[a]400 mg/day [b]600 mg/day	First-line TKI treatment for CML approved by the FDA
Dasatinib	[a]100 mg/day [b]140 mg/day	First- or second-line TKI for some imatinib-resistant mutants
Bosutinib	500 mg/day	Second-line TKI for some imatinib-resistant mutants
Nilotinib	300 mg twice daily	First- or second-line TKI; slightly modified version of imatinib
Omacetaxine	1.25 mg/m^2 via subcutaneous injection twice daily	Alkaloid translation inhibitor for treating T315I-mutant CML
Stem cell transplant	Not applicable	Offers curative potential but with greater risks compared to therapy with TKIs; seldom used as initial therapy but considered for patients who have not responded well to other therapies

Suggested dosages retrieved from US Food and Drug Administration (FDA)
[a]Recommended for chronic phase chronic myelogenous leukemia (CML) specifically
[b]Recommended for accelerated or blast phase CML

changes in serum viscosity and sludging of RBCs may lead to headaches, visual impairment, dizziness, vertigo, and claudication [24]. Bleeding complications, seen in approximately 1 % of patients with PV, include epistaxis, gum bleeding, ecchymosis, and gastrointestinal bleeding.

Underlying vascular disease, common in older persons with PV as well as in the aging population of PLWHA, can increase the risk of clotting complications [25]. Blood clots occur in about 30 % of patients even before the PV diagnosis is made. During the first 10 years after a diagnosis of PV, 40–60 % of untreated PV patients may develop blood clots. This is particularly relevant in the context of HIV infection as this may be the first manifestation of a clotting disorder in the backdrop of HIV infection [26]. Roughly three-fourths of PV patients will have splenomegaly and one-third will have hepatomegaly at time of diagnosis. A large proportion will also have plethora, hypertension, fatigue, and pruritus. In addition to the signs and symptoms above, people with PV are at slightly greater risk than the general population for developing leukemia as a result of the disease and/or certain drug treatments.

According to the 2008 revised WHO guidelines, diagnosis of PV requires the presence of both major criteria and one minor criterion or the presence of the first major criterion together with two minor criteria [27].

WHO criteria are described in the following bullets, with major criteria in 1–2 and minor in 3–5:

1. Hemoglobin >18.5 g/dL in men and >16.5 g/dL in women or other evidence of increased RBC volume
2. The presence of JAK2617V F or other functionally similar mutation, such as *JAK2* exon 12 mutation
3. Bone marrow biopsy showing hypercellularity for age with tri-lineage growth (pan-myelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation
4. Serum erythropoietin level below the reference range for normal
5. Endogenous erythroid colony formation in vitro

In reviewing HIV literature, it is often a challenge to discern instances of true PV from secondary causes of elevated RBC mass. In a number of instances, patients were presumed to have PV but secondary causes including testosterone replacement therapy, sleep apnea, chronic dehydration, and smoking were not excluded [28, 29].

There have been very few studies on the impact of HIV infection on the development of PV [30]. In one instance, an HIV-infected male with hemophilia and a 10-year history of PV presented to medical attention with an elevated WBC and was diagnosed with AML. He died from respiratory complications 2 days later [31]. In a second report, a 45-year-old nonsmoking male presented with a hemoglobin of 15.7 g/dl and was subsequently diagnosed with HIV infection [32]. The patient was initially treated with zidovudine and later with didanosine, lamivudine, and saquinavir. Seven years later, he appeared plethoric and with splenomegaly, had an erythrocyte mass of 71 ml/kg, and had an oxygen saturation of 94 %. His hematocrit

was 63 %, leukocytes 12,400, erythropoietin <5 nmol/ml, CD4+ count was 321 cells/mm^3, and his HIV viral load was non-detectable. After a diagnosis of PV, he was treated with a series of phlebotomies to achieve an iron-deficient state coupled with hydroxyurea at a dose of 1 g/day. Despite the potentially myelosuppressive effect of hydroxyurea, his CD4+ count gradually rose to 474 cells/mm^3 and HIV viral load remained non-detectable. At 12-month follow-up, there was no discernible change in CD4+ cell count or HIV viral load, and PV was well controlled.

Therapeutic approaches to PV focus on the following: controlling and maintaining hematocrit levels at <45 % in men and <42 % in women, treating complications of thrombosis and hemorrhage, reducing thrombotic risk and minimizing the risk of leukemogenic transformation, and managing splenomegaly and other disease-related symptoms [33]. If not otherwise contraindicated because of a history of major bleeding or intolerance, aspirin should be given to all patients in a low dose of 75–100 mg/day [34, 35].

To date, no drug has been shown to improve survival or lower risk of leukemic transformation in PV. Whether or not the demonstration of mutant JAK-2 allele burden reduction associated with treatment with interferon alpha or busulfan translates into a survival advantage is currently unclear and cannot be used as a rationale to choose these drugs over hydroxyurea as first-line therapy for high-risk patients. Until new data emerges, hydroxyurea continues to be widely used in response to PV (Table 15.2).

Ruxolitinib is a Janus kinase inhibitor (JKI) with selectivity for subtypes JAK-1 and JAK-2 of this enzyme. Ruxolitinib inhibits deregulated JAK-STAT signaling associated with myelofibrosis leading to modulation of cytokine gene expression. Data regarding the use of ruxolitinib in PV come from a phase II trial and an

Table 15.2 Clinical properties of hydroxyurea

Characteristic	Hydroxyurea
Drug class	Antimetabolite
Mechanism of action	Impairs DNA repair by inhibiting ribonucleotide reductase
Specificity	Affects all cell lines
Pharmacology	Half-life 4 h, renal excretion
Starting dose	15 mg/kg per day orally
Onset of action	Three to 5 days when the usual starting dose is employed (15 mg/kg per day)
Side effects observed in >10 % of patients	Neutropenia, anemia, oral ulcers, hyperpigmentation, rash, nail changes
Side effects observed in ≤10 % of patients	Ankle ulcers, lichen planus-like lesions of the mouth and skin, nausea, diarrhea
Rare side effects	Fever, liver function test abnormalities
Contraindications	Neutropenia, pregnancy, childbearing potential, breast feeding
Annual cost	$1700.00, for 500 mg three times daily dose

Adapted from Tefferi [50] up to date. Accessed May 28, 2015

open-label phase III trial in patients with hydroxyurea-related toxicities or with uncontrolled disease despite hydroxyurea [36]. Based on these studies, ruxolitinib is approved by the US FDA for the treatment of patients with intolerance or resistance to hydroxyurea.

While clinical experience with ruxolitinib for PV patients infected with HIV is lacking, in vitro it does block T-cell activation-mediated HIV replication [37]. Immunologic side effects relevant to PLWHA and who might be considered for ruxolitinib include herpes zoster (shingles; 1.9 %) and opportunistic infections [38]. Metabolic side effects have included weight gain (7.1 %). Laboratory abnormalities have included alanine transaminase (ALT) abnormalities (25.2 %), aspartate transaminase (AST) abnormalities (17.4 %), and elevated cholesterol levels (16.8 %) [39]. Other common adverse events are grade 3–4 anemia (45 %) and thrombocytopenia (10–15 %).

15.5 Essential Thrombocythemia

ET is a MPN in which the body produces too many platelets. ET is the most nondescript of MPNs and the one that can most easily be confused with other entities, since isolated thrombocytosis can be seen in PV, PMF, CML, and more commonly as a complication of many other illnesses. Persistence of thrombocytosis is central to establish an ET diagnosis, along with the exclusion of reactive causes such as iron deficiency and inflammatory states and conditions that frequently comingle with HIV infection [40].

ET can present with headache, visual disturbance, erythromelalgia, or transient ischemic attack. Low-risk ET patients who are asymptomatic often do not need treatment [41]. While most patients with ET enjoy a normal life expectancy, treatment with low-dose aspirin is required for those with vasomotor symptoms. Thrombotic events in low-risk patients with ET are too infrequent to justify the long-term use of potentially harmful agents. The risk may be higher, however, in the presence of cardiovascular risk factors and/or extreme uncontrolled thrombocytosis. Whether or not drug therapy is indicated in this situation remains controversial. On the other hand, approximately 20 % of patients with ET present with major thrombotic events and another 15 % may experience recurrent thrombosis. This complication is most common in patients older than 60. Therefore, cytoreductive therapy in the form of hydroxyurea (and less commonly, anagrelide and interferon alpha) is indicated in these high-risk patients (i.e., age >60 years or history of prior thrombosis); bleeding complications are less frequent and may be prevented by avoiding doses of aspirin greater than 100 mg/day and nonsteroidal anti-inflammatory agents [42].

15.6 Primary Myelofibrosis

PMF is the least common of the MPNs and is characterized by the proliferation of an abnormal clone of hematopoietic stem cells in the bone marrow resulting in fibrosis or the replacement of bone marrow with collagenous connective tissue

fibers. Symptoms include splenomegaly, bone pain, bruising and easy bleeding, fatigue, increased susceptibility to infection, and anemia.

Currently, there are no therapies approved specifically for PMF. However, hematopoietic stem cell transplantation (SCT) is potentially curative and is increasingly being utilized for HIV-infected patients with chemosensitive lymphoid and plasma cell malignancies [43–45]. Allogeneic SCT is associated with high treatment-related mortality and may not be appropriate for older patients with several comorbidities; however, studies utilizing reduced intensity conditioning resulted in a reduction of transplant-related mortality and morbidity [46].

Treatment of PMF is dependent on the individual case and is usually withheld until development of symptoms of disease progression. Cytoreductive therapies such as hydroxyurea, low-dose interferon alpha, and busulfan are effective for hyper-proliferation such as leukocytosis, splenomegaly, and thrombocytosis [42]. Corticosteroids can be given for constitutional symptoms and are also effective for treating PMF-related anemia along with androgens or recombinant erythropoietin [47, 48]. Low-dose thalidomide in conjunction with prednisone has also been shown to be effective treatment for anemia, thrombocytopenia, and splenomegaly in approximately 20–60 % of PMF patients [49]. Experiences treating patients with PMF and HIV infection have not been reported.

Conclusion

There are few cases of MPNs (CML, PV, ET, and PMF) in HIV-infected patients reported in the literature. We briefly review the epidemiology and clinical characteristics associated with these conditions, and we emphasize the importance of cytogenetic and molecular studies when classifying these disorders. CML is characterized by the Philadelphia chromosome, present in 95 % of cases. JAK-2 mutations are found in essentially all patients with PV and approximately 50 % of those with either ET or PMF. Accurate classification and diagnosis are paramount in assigning appropriate risk-based therapy.

Current treatment goals for CML include hematologic remission defined as a CBC which returns to normal values, the absence of splenomegaly, and cytogenetic and molecular remission. Standard treatment is imatinib, which is highly effective in all phases of CML. Available data sets suggest that HIV infection does not increase the prevalence of CML; however, response to imatinib in HIV-CML patients was reported to be inferior to that noted in patients with CML without HIV. Imatinib is metabolized by CYP3A4, and certain antiretroviral classes such as non-nucleoside reverse transcriptase inhibitors and protease inhibitors are known to affect CYP3A4; despite this, imatinib taken in conjunction with various HAART regimens appears to be well tolerated and without significant drug interactions.

The most prominent feature of PV is an elevated absolute RBC mass. There are very few cases that present or study the effect of HIV infection on the development of PV. Hydroxyurea is widely used in response to PV, while alternative treatments include phlebotomy, interferon alpha, or busulfan. Ruxolitinib has also been used for the treatment of patients with intolerance or resistance to

hydroxyurea and has also been demonstrated in vitro to block T-cell activation mediated HIV replication.

ET can easily be confused with other entities since isolated thrombocytosis can be seen in the other MPNs and, more commonly, as a complication of many other illnesses. Most patients with ET maintain normal life expectancy, and only those with vasomotor symptoms or high-risk disease require treatment with low-dose aspirin and hydroxyurea.

PMF is the least common of the MPNs. Treatment of PMF depends on each individual case and can include cytoreductive therapies, corticosteroids, androgens, recombinant erythropoietin, and, rarely, hematopoietic SCT. Accounts of treating patients with PMF and HIV infection have not been reported in the literature.

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