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REVIEW

Hematologic toxicities of small molecule tyrosine kinase inhibitors

Nicholas A. Barber · Wais Afzal · Mojtaba Akhtari

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Abstract Small molecule tyrosine kinase inhibitors (TKIs) are potent anti-cancer targeted therapies. TKIs are considered safe and efficacious therapeutic modalities, and are generally tolerated well. However, they are associated with certain side effects including hematologic toxicities such as anemia, macrocytosis, neutropenia, thrombocytopenia, hemolytic anemia, bone marrow aplasia and necrosis. Thrombotic microangiopathy, arterial thromboembolism and splenic infarction can also occur following treatment with TKIs. Cytopenias are the most common adverse effects associated with these agents, and other hematologic toxicities are not frequent. It is essential for clinicians to monitor patients closely, and recognize those side effects as early as possible, in order to improve efficacy of small molecule TKIs and optimize outcomes. This article summarizes hematologic toxicities associated with the commonly used small molecule TKIs. It also provides practical strategies for the management of these toxicities.

Keywords Small molecule tyrosine kinase inhibitors · Hematologic · Toxicities · Adverse effects

Introduction

Receptor tyrosine kinases are cell-surface enzymes that bind to specific growth factors that initiate cell proliferation, cell cycle progression, and inhibition of apoptosis. Currently, there are over 50 receptor tyrosine kinases described in the literature [1]. A number of these tyrosine kinases are implicated in the pathogenesis of a variety of malignancies. Understanding of these pathways has led to the development of small molecule tyrosine kinase inhibitors (TKIs) that target malignant pathways. A growing number of these agents are prescribed by oncologists and hematologists and newer generation TKIs continue to be investigated.

Currently approved TKIs that target the *BCR-ABL*, epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), human epidermal growth factor receptor (HER2), and anaplastic lymphoma kinase (ALK) pathways and their corresponding disease indications are listed in Table 1. These oral agents have transformed the therapeutic options and natural history of a number of solid and hematologic malignancies. Similar to most targeted therapies, small molecule TKIs tend to be better tolerated than traditional chemotherapies. Although TKIs have specific targets that cause less "traditional" side effects such as nausea, vomiting, alopecia, and neuropathies, these drugs are not without unique toxicity profiles.

Hematologic toxicities from TKIs are common. Although myelosuppression is the most common hematologic adverse effect of these agents, a number of other toxicities have been described and are summarized in Table 2. Grading of toxicity is established by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v3.0 (CTCAE) and are shown in Table 3 [2]. Because the list of available TKIs and indications for their use is growing, it is essential for the clinician to understand these complications and their management. This review discusses the hematologic toxicities of the commonly used small molecule TKIs, and it also provides practical strategies for the management of these toxicities.

N. A. Barber · W. Afzal · M. Akhtari (✉)
Division of Hematology and Oncology, Department of Internal Medicine, University of Nebraska Medical Center,
987680 Nebraska Medical Center,
Omaha, NE 68198-7680, USA
e-mail: mojtaba.akhtari@unmc.edu

Table 1 Small molecule tyrosine kinase inhibitors (TKIs)

Agent	Target tyrosine kinase	Disease
Imatinib	BCR-ABL, c-kit, PDGFR	CML, Ph + ALL, Others
Dasatinib	BCR-ABL, SFK	CML, Ph + ALL
Nilotinib	BCR-ABL	CML
Gefitinib	EGFR	NSCLC
Erlotinib	EGFR	NSCLC, pancreatic cancer
Sorafenib	VEGFR, c-kit, FLT-3	HCC, RCC
Sunitinib	VEGFR, c-kit, FLT-3	RCC, GIST, pancreatic neuroendocrine
Axitinib	VEGFR	HCC, RCC
Pazopanib	VEGFR, PDGFR	RCC
Crizotinib	ALK	NSCLC
Lapatinib	HER2	Breast Cancer

PDGF platelet-derived growth factor receptor, *SFK* SRC family kinases, *EGFR* epidermal growth factor receptor, *VEGFR* vascular endothelial growth factor receptor, *ALK* anaplastic lymphoma kinase, *HER2* human epidermal growth factor receptor 2, *CML* chronic myeloid leukemia, *Ph* + Philadelphia chromosome positive, *ALL* acute lymphocytic leukemia, *NSCLC* non-small cell lung cancer, *HCC* hepatocellular carcinoma, *RCC* renal cell carcinoma, *GIST* gastrointestinal stromal tumor

Inhibitors of the *BCR-ABL* pathway

The 9:22 chromosomal translocation [Philadelphia chromosome (Ph)] results in constitutive activation of the *BCR-ABL* tyrosine kinase pathway. Uninhibited activation of this pathway promotes the immature myeloid cell proliferation and survival that is responsible for chronic myelogenous leukemia (CML) [3]. Imatinib, dasatinib, and nilotinib inhibit *BCR-ABL* tyrosine kinase activity by competitively binding to the intracellular ATP binding site preventing leukemic cell production. These drugs have revolutionized the outlook of patients with CML [4–8]. In contrast to some of the non-hematologic toxicities such as fluid retention and hepatotoxicity that tend to be agent specific, the hematologic toxicities of the BCR-ABL TKIs are a class effect.

Imatinib

Originally developed for CML, imatinib mesylate (Gleevec®, Novartis, East Hanover, NJ) is approved for multiple hematologic and solid malignancies [9]. Before the approval of imatinib in 2001, the prognosis of patients with CML was grim (average of 3–7 years) [3]. Since the introduction of imatinib the 8-year survival is now greater than 85% [6]. Imatinib also inhibits the c-kit and platelet derived growth factor (PDGF) pathways, explaining its role in gastrointestinal stromal tumors (GIST).

Cytopenias

Cytopenias are seen in all disease phases of patients with CML but are more common in patients with advanced disease (accelerated or blast phases) and in those who have received prior cytotoxic therapy.

The rates of grade 3 or 4 cytopenias were high in the original phase II trial of imatinib for late CP CML after interferon alpha failure: neutropenia (35%), thrombocytopenia (20%), and anemia (7%) [4]. Median time-to-develop

Table 2 Hematologic toxicities of small molecule tyrosine kinase inhibitors

Imatinib	**Dasatinib**	**Nilotinib**
Cytopenias	Cytopenias (esp. thrombocytopenia)	Cytopenias
Bone marrow aplasia Gelatinous marrow transformation	Platelet aggregation defects	Bone marrow aplasia
Bone marrow necrosis		
Hemolytic anemia		
TTP		
Macrocytosis		
Gefitinib	**Erlotinib**	**Sorafenib**
Neutropenia	Cytopenias	Cytopenias
Anemia	Microangiopathic hemolytic anemia	Arterial thromboembolism
		Splenic infarction
Sunitinib	**Axitinib**	**Pazopanib**
Cytopenias Arterial thromboembolism	Cytopenias	Cytopenias
TTP/HUS		
Macrocytosis		
Crizotinib		
Neutropenia		

Table 3 Common terminology criteria for adverse events v3.0 (CTCAE) for cytopenias

Grade	1	2	3	4	5
Anemia	10 - LLN g/dL	8–10 g/dL	6.5–8 g/dL	<6.5 g/dL	Death
Neutropenia	1500-LLN/mm^3	1000–1500/mm^3	500–1000/mm^3	<500/mm3	Death
Lymphopenia	800-LLN/mm^3	500–800/mm^3	200–500/mm^3	<200/mm^3	Death
Thrombocytopenia	75,000-LLN/mm^3	50,000–75,000/mm^3	25,000–50,000/mm^3	<25,000/mm^3	Death

Common Terminology Criteria for Adverse Events, Version 3.0 DCTD. NCI, NIH, DHHS March 31, 2003 (http://ctep.cancer.gov). Publish Date: August 9, 2006

and duration of grade 3 or 4 neutropenic or thrombocytopenic episodes were 62 days (duration 21 days) and 57 days (duration 18 days) respectively. Neutropenic fever was reported in 0.75% patients. A six-year follow-up of this trial compared rates of cytopenias during and after the first year of imatinib therapy [10]. Grade 3 or 4 neutropenia was less than half as frequent (13%) during subsequent years of therapy and was less than 1% after 2 years. Prior exposure to interferon alpha as well as late CP likely explains the high rate of cytopenias seen in the initial phase II study. The mean duration of myelosuppression in these patients was approximately 60 days [11].

Patients exposed to prior cytotoxic therapy and those in late CP experience more imatinib-induced cytopenias. This concept is highlighted by data from the IRIS study which investigated imatinib as upfront therapy in CP CML [5, 12]. This trial randomized over 1,000 patients with newly diagnosed chronic phase (CP) CML to either imatinib 400 mg daily or a combination of interferon alpha and cytarabine. The overall frequency of grade 3 or 4 cytopenias with imatinib was much less than the chemotherapy arm: neutropenia (14.3% vs 25%), thrombocytopenia (7.8% vs 16.5%), and anemia (3.1% vs 4.3%) respectively. Similar to earlier experience, the majority of cytopenias were seen within the first 2 years with grade 3 or 4 cytopenias reported in<5% of patients after 2 years.

The severities of imatinib-induced cytopenias seem to be dose-dependent. One phase III trial compared 800 mg daily to 400 mg daily reported almost twice the incidence of grade 3 or 4 cytopenias in the higher dose group [13]. Breccia et al. compared toxicities of patients treated in early or late (after failure of interferon) CP CML and found that grade 3 or 4 cytopenias were seen in 7% and 24% of patients respectively [14]. They also found shorter median duration of cytopenias in early CP CML (10–14 days) compared to LP CML (16–20 days).

The severities of imatinib-induced cytopenias correlate with phase of disease (BP > AP > CP). A phase II trial of imatinib in 229 patients with BP CML reported grade 3–4 neutropenia (64%), thrombocytopenia (62%), and anemia (52%) [15]. In this study, the median days to reach a thrombocytopenic and neutropenic nadir were 37 and 36 respectively. Median days to recovery were 31 for thrombocytopenia and 19 for neutropenia. This report did not include a description of therapy received prior to imatinib but did report a median of over three years since diagnosis. Another phase II study involving 181 pre-treated patients with AP CML (including 29 patients in BP) reported higher rates of grade 3 or 4 cytopenias with two different doses of imatinib: neutropenia (56% with 400 mg, 60% with 600 mg), thrombocytopenia (44% with 400 mg, 43% with 600 mg), and anemia (44% with 400 mg, 47% with 600 mg) [16].

Although the phase II BP CML trial reported neutropenic fever or severe sepsis in 6–17% of patients, it is uncommon in CP CML (less than 1%) [4, 15, 17]. The virtual absence of mucositis as a side effect of imatinib is likely the explanation for this.

Bone marrow aplasia

Although virtually all patients who develop cytopenias from imatinib recover within 2 months of dose reduction or discontinuation, bone marrow aplasia (BMA), including two fatal cases, has been described [18, 19]. Srinvas et al. reported the largest series of 44 patients. These patients underwent bone marrow biopsy after 4 weeks of persistent pancytopenia that developed between 3–6 months of imatinib. Five patients (two in CP, two in BP, and one in AP) had BMA (5–10% cellularity). All five patients were positive for BCR-ABL by RT-PCR at the time of marrow analysis. The three patients who were in CP or AP developed aplasia after 6 months of therapy whereas the two patients in BP developed aplasia after 3 months. Long-term follow-up was not included in this series.

Gelatinous marrow transformation and bone marrow necrosis

Gelatinous marrow transformation (GMT) is a rare manifestation of multiple malignant and non-malignant diseases [20]. Two cases of GMT in patients taking imatinib for CP CML have been reported. The mechanism for this process

is not well understood but may be secondary to leukemic cell production of hyaluronic acid or direct bone marrow stroma toxicity (i.e., imatinib). The existence of GMT in these two patients did not portend a worse prognosis.

Multiple cases of bone marrow necrosis (BMN) have been reported in patients taking imatinib for CML and Ph + ALL [21, 22]. BMN has been reported in CML patients before the development of imatinib which a TKI-independent mechanism [23, 24].

Other hematologic toxicities

Both Coombs' positive and negative hemolytic anemia has been reported in patients taking imatinib [25, 26]. In the latter, the patient responded to steroids and was able to continue imatinib for metastatic GIST. Thrombotic thrombocytopenic purpura (TTP) was also implicated in a patient receiving imatinib for idiopathic hypereosinophilic syndrome [27].

Macrocytosis has been reported in a case series of patients taking imatinib for GIST [28]. All patients taking imatinib developed macrocytosis and the percentage increases in mean corpuscular volume (MCV) after 3, 6, 9, and 12 months of therapy were 0.7%, 5.6%, 5.9%, and 5% respectively. Inhibition of c-kit, and perhaps other pathways promoting erythroid differentiation are the proposed mechanism.

Drug discontinuation and dose modifications

Hematologic intolerance to imatinib leading to dose modifications, treatment delays, and therapeutic substitutions with newer generation TKIs are not uncommon. Most of the time myelosuppression is the cause. In the IRIS study only 2% of patients discontinued imatinib because of drug related adverse events [29]. Hamdan et al. presented an abstract in 2007 that analyzed dosing trends for 216 patients on imatinib for CML (87% in CP) treated between 2000 and 2005 [30]. Twenty-one percent of patients started on 400 mg daily required dose reductions. Neutropenia, anemia, and nausea were the most frequent causes. More than half of the patients who started at a dose of 600 mg/day required dose reductions mostly because of thrombocytopenia and gastrointestinal bleeding. Forty-six (74%) resumed therapy after a median interruption of 21 days and the remaining 16 patients permanently discontinued imatinib.

Clinical significance of therapy related cytopenias

The presence of imatinib-induced neutropenia (<1,000 neutrophils/mm^3) at 3 months after the initiation of therapy, along with a poor cytogenetic response, are independent predictive factor for blast transformation and decreased survival [31]. A follow-up of the original phase II imatinib study found that any episode of grade 3 or 4 myelosuppression, especially those that lasted longer than 2 weeks, was associated with lower rates of major (58% vs 75%) and complete (36% and 63%) cytogenetic responses [11]. Treatment delays and discontinuation as a result of severe myelosuppression and a greater tumor burden at the initiation of treatment are both implicated in these unfavorable outcomes.

Second-generation BCR-ABL inhibitors

Dasatinib (Sprycel®, Bristol-Myers Squibb, Princeton, NJ) and nilotinib (Tasigna®, Novartis, East Hanover, NJ) are second generation BCR-ABL TKIs. They are currently approved for newly diagnosed CP Ph + CML and imatinib resistant Ph + CML. Dasatinib is also approved for imatinib refractory Ph + ALL.

Dasatinib

Hematologic toxicities are common with dasatinib. In addition to cytopenias, dasatinib has been implicated in a number of other hematologic adverse effects.

Cytopenias The original phase II dasatinib trial involving imatinib-resistant or intolerant CP-CML patients reported frequent grade 3–4 cytopenias (49% neutropenia, 47% thrombocytopenia, and 22% anemia)[32]. Not surprisingly, grade 3 or 4 neutropenia and thrombocytopenia are seen in up to 85% of patients receiving dasatinib for AP and BP CML [33, 34]. Similar to imatinib, this is likely explained by greater disease burden and prior imatinib exposure. In support of this, the more recent phase III trial of dasatinib versus imatinib as upfront therapy for CP-CML reported similar rates of grade 3 or 4 neutropenia (21% and 20% respectively) [35]. However, when compared to imatinib dasatinib had a higher rate of thrombocytopenia (19% vs 10%) and anemia (10% vs 7%). In both groups three-fourths of those who developed cytopenias did so within 4 months of starting therapy and stopping therapy was required in only four patients on dasatinib. No cases of neutropenic fever were reported in this study.

The explanation for the increased incidence of thrombocytopenia with dasatinib appears to be more complex than imatinib or nilotinib. In addition to a relative decrease in healthy marrow in untreated CML dasatinib appears to specifically impair effective thrombopoiesis [36]. This in vitro study showed that dasatinib was associated with increased megakaryocytes in the marrow but prevented normal migration to the peripheral circulation and proplatelet formation.

Bleeding Initial phase I and II studies reported bleeding episodes in up to 24% of patients taking dasatinib [34, 37]. Bleeding complications were more common in patients with AP or BP and in doses greater than 140 mg daily. The gastrointestinal tract was involved in over 80% of cases. Interestingly, 37% of episodes occurred in patients with platelet counts greater than 100,000/mm^3. In an effort to explain this through in vitro and in vivo studies, Gratacap et al. observed that dasatinib initiates a complex and reversible inhibitory effect on platelet aggregation [38]. The mechanism for this is thought to be through inhibition of the SRC Lyn kinase that normally mediates VWF/GPIb-IX-V induced platelet activation. The SRC family kinases are a known target pathway for dasatinib. However, despite a higher incidence of bleeding in early trials and an increase in thrombocytopenia with dasatinib the number of bleeding episodes in the phase III study was comparable to imatinib (5%).

Nilotinib

Nilotinib (formerly AMN107) is a selective TKI of *BCR-ABL*. In preclinical studies nilotinib was shown to be 30-fold more potent than imatinib and myelosuppression is the most frequently seen hematologic toxicity [39].

Cytopenias Initial phase I and II studies of nilotinib involving patients with prior *BCR-ABL* inhibitor exposure reported significant myelosuppression and specifically thrombocytopenia. The phase I trial which included patients with imatinib-resistant Ph + CML and ALL reported grade 3 or 4 anemia (6%), neutropenia (9%), and thrombocytopenia (25%) [40]. In the phase II study of nilotinib in imatinib resistant CP-CML 29% of patients experienced grade 3 or 4 neutropenia and thrombocytopenia [41]. Dose interruptions and reductions were required in 10% and 19% of patients respectively. Hematopoietic growth factors or platelet transfusions were required in 5% and 10% of patients respectively. In a post-hoc analysis of this trial only 18% of patients who had experienced hematologic intolerance during prior imatinib therapy discontinued nilotinib due to grade 3 or 4 thrombocytopenia. A similar phase II study involving imatinib-resistant patients with AP-CML reported significant grade 3 or 4 thrombocytopenia (35%), neutropenia (21%), and anemia (13%) [42]. Dose interruptions and reductions were required in 16% and 24% of patients respectively and growth factor support or platelet transfusions were required in 28% of patients. In the randomized phase III CP-CML upfront therapy trial comparing two different doses of nilotinib (300 mg and 400 mg) to imatinib more thrombocytopenia (10,12% vs 9%) but less neutropenia (10,12% vs 20%) and anemia (3% vs 5%) was observed [43]. All grade 3 or 4 cytopenias developed within 2 months of starting therapy. No cases of febrile neutropenia were reported in any of these trials.

Two cases of nilotinib-induced bone marrow aplasia (BMA) have been reported [44, 45]. One patient had achieved a major cytogenetic remission after 9 months of imatinib but developed non-hematologic intolerance, so was switched to nilotinib. The patient subsequently developed massive hematochezia and pancytopenia and bone marrow examination revealed <5% cellularity. The other patient was switched to nilotinib due to both disease progression and intolerance to both imatinib and dasatinib. The patient initially developed cytopenias on nilotinib 400 mg twice daily and then had disease progression when the dose was reduced to once daily. Six months after increasing the dose back to 400 mg twice daily the patient developed a complete cytogenetic response and BMA with 5% cellularity. His dosing regimen was modified but he had persistent and recurrent BMA seen on subsequent marrow analysis and re-challenging with nilotinib. He required supportive care with G-CSF and transfusions, and he is currently on bosutinib. Similar to imatinib, the mechanism for prolonged marrow suppression is not well understood.

Etiology of myelosuppression associated with inhibitors of the *BCR-ABL* pathway

The mechanisms for imatinib-, dasatinib-, and nilotinib-induced cytopenias in patients with CML may be explained by a number of mechanisms. Cytopenias develop acutely during therapeutic elimination of leukemic marrow cells resulting from a hypocellular marrow that exists until normal hematopoiesis resumes. Because all three *BCR-ABL* TKIs induce impressive hematologic responses, this is likely a shared mechanism. This phenomenon has been confirmed by interim marrow analysis of patients recently started on imatinib [46–48]. One of these reports involved an analysis of bone marrow samples of 52 patients receiving imatinib in multiple phase II studies. The investigators reported a decrease in cellularity to ≤50% in 41 (77%) of these patients. This also supports the fact that there is a decreasing incidence of cytopenias over time and that patients with advanced disease experience more severe myelosuppression.

Also contributing to myelosuppression is direct inhibition of multiple tyrosine kinase pathways that promote normal hematopoiesis. Specifically, inhibition of the c-Abl pathway causes cell-cycle arrest and prevention of normal apoptosis of CD34+ cells [49]. In addition, all three agents inhibit PDGFR and c-Kit pathways which have also displayed roles in normal hematopoiesis [50, 51]. The inhibition of c-Kit may explain why a small number of patients treated with imatinib for GIST who have normal

baseline marrow function and are treated with imatinib develop cytopenias (grade 3 or 4 neutropenia 5%, anemia 2%) [52].

Recommended management of BCR-ABL TKI-induced myelosuppression

Recommendations for monitoring and therapy modification

Guidelines for monitoring hematologic toxicities from *BCR-ABL* TKIs have been suggested by institutional experts and pharmaceutical industry [53–57]. Currently it is recommended that complete blood counts be done weekly for the first month, monthly during month 2 and 3, and every 3 months thereafter. Package inserts for these agents recommend differing monitoring intervals (Table 4).

Guidelines for the management of *BCR-ABL* inhibitor-induced cytopenias are complex and are based on category 2B evidence. A number of groups, including the FDA and the National Comprehensive Cancer Network (NCCN) have published guidelines on the management of imatinib, dasatinib, and nilotinib induced cytopenias (Table 5) [9, 46, 55–57]. General principles for the management of toxicities include: 1) more aggressive disease should afford greater tolerance for hematologic toxicities in order to avoid treatment disruptions; 2) neutropenic complications are rare in BCR-ABL induced neutropenia; 3) blood products and growth factor support is generally encouraged in higher risk patients; 4) grade 1 or 2 myelosuppression does not require modification of therapy; 5) and that intolerance to one agent merits a trial on another. Also, a bone marrow biopsy should be considered if the clinician suspects that cytopenias are due to disease response rather than drug toxicity. Differentiating the cause may improve long-term outcomes [11]. Mauro et al. recommend a stepwise approach to *BCR-ABL* TKI therapy modification for all phases of CML (Figs. 1 and 2) [46].

The role of myeloid growth factors

The rationale for using granulocyte-colony stimulating factor (G-CSF) is to avoid infectious complications and to allow for uninterrupted therapy. Although not formally indicated for such use, improvement in imatinib-induced neutropenia through the use of filgrastim has been reported [58]. In this series the majority of patients experienced improved hematologic tolerance leading to increased adherence and cytogenetic response. As a result, the guidelines include G-CSF as an option in the management of imatinib-induced neutropenia. In a more provocative report it has been suggested that G-CSF may have improve disease outcomes by stimulating "dormant", but otherwise TKI resistant, leukemic cells into a susceptible state [59].

Inhibitors of the epidermal growth factor receptor (EGFR) pathway

Hematologic toxicity with oral EGFR inhibitors is a rare occurrence. The two most common agents in this category are gefitnib (Iressa®, AstraZeneca, Osaka, Japan) and erlotinib (Tarceva®, Genentech, Inc, South San Francisco, CA). Both agents rarely cause myelosuppression.

Gefitinib

Gefitinib is approved in Europe and Asia for EGFR-mutant advanced non-small cell lung cancer (NSCLC). The IPASS study showed gefitinib to be superior to conventional chemotherapy in minimal or never smokers with advanced adenocarcinoma of the lung [60]. Although less frequent compared with the chemotherapy arm, grade 3 or higher neutropenia (3.7%) and anemia (2.2%) were reported.

Erlotinib

Erlotinib is currently approved for advanced NSCLC and pancreatic cancer. The phase III TRIBUTE trial showed that when added to conventional first-line chemotherapy erlotinib has superior overall survival in never smokers [61]. Although not statistically compared, the incidences of all cytopenias were slightly higher in the group that received erlotinib in addition to chemotherapy (anemia 51.7% vs 41.8%, thrombocytopenia 18.2% vs 15.9%, neutropenia 34.9% vs 33.2%, and febrile neutropenia 4.3% vs 1.9% respectively). A phase II study comparing erlotinib to standard chemotherapy as frontline therapy in 103 frail patients with NSCLC reported grade 3 or 4 anemia and thrombocytopenia in one patient [62]. Although not formally

Table 4 Hematologic monitoring in small molecule tyrosine kinase inhibitors

Imatinib	CBC weekly for the first month, biweekly for the second month, as clinically indicated thereafter
Dasatinib	CBC weekly for the first 2 months, monthly thereafter, or as clinically indicated
Nilotinib	CBC every 2 weeks for the first 2 months, then monthly

Prescribing information. Gleevec (imatinib mesylate). East Hanover, NJ: Novartis Pharmaceuticals Corporation, 04/2011; Sprycel (dasatinib). Princeton, NJ: Bristol Myers Squibb Company, 2010; Tasigna (nilotinib). Hanover, NJ: Novartis Pharmaceuticals, 2010

Table 5 NCCN guidelines for the management of imatinib, nilotinib, and dasatinib induced cytopenias

	Imatinib	
Neutropenia	Thrombocytopenia	Patients with AP/BP
Hold until ANC ≥ 1500/mm^3, then resume at the starting dose of 400 mg. If recurrence of ANC <1000/mm^3, hold until ANC ≥1,500/mm^3, then resume at reduced dose of 300 mg	Hold until Plt ≥ 75,000/mm^3, then resume at starting dose of 400 mg. If recurrence of plt <50,000/mm^3, hold until plt ≥75,000/mm^3, then resume at r educed dose of 300 mg.	Rule out disease related cytopenias. If not related to disease, reduce dose to 400 mg. if cytopenia persists 2 weeks, reduce dose further to 300 mg. If cytopenias persist for 4 weeks, stop imatinib until ANC ≥1,000/mm^3 and platelet count ≥20,000/mm^3, and then r esume treatment at 300 mg.
	Nilotinib	
Neutropenia	Thrombocytopenia	
Hold until ANC ≥1,000/mm^3,resume at prior dose if recovery occurs within 2 weeks, or reduce dose to 400 mg daily, if ANC is <1,000/mm^3 for more than 2 weeks.	Hold until Plt ≥50,000/mm^3, resume at prior dose if recovery occurs within 2 weeks or reduce dose to 400 mg daily if platelet count is <50,000/mm^3 for more than 2 weeks.	
	Dasatinib	
Neutropenia	Thrombocytopenia	Patients with AP/BP
Hold until ANC ≥1,000/mm^3, resume at starting doseif recovery occurs within 7 days or reduce one dose level if ANC <500/mm^3 for more than 7 days.	Hold until Plt ≥50,000/mm^3, then resume at starting dose if recovery occurs within 7 days or reduce one dose level if platelet count <25,000/mm^3 for more than 7 days.	Rule out disease related cytopenias. If not related to disease, hold until ANC ≥1,000/ mm^3 and platelet count ≥20,000/mm^3, resume at original starting dose or reduce one dose level if cytopenia persists. If cytopenia is related to leukemia, consider dose escalation to 180 mg daily

NCCN. National Comprehensive Cancer Network: clinical practice guidelines in oncology. Chronic myelogenous leukemia. Version 2.2012:1–75. http://www.nccn.org/professionals/physician_gls/PDF/cml.pdf (Last accessed 2011 Nov)

reported, microangiopathic hemolytic anemia was reported in two patients in the original pancreatic cancer trial [63].

Inhibitors of the vascular endothelial growth factor (VEGF) pathway

Sorafenib and sunitinib

Sorafenib (Nexavar ®, Bayer, Berkeley, CA) and sunitinib (Sutent®, Pfizer Inc, New York, New York) are inhibitors of the VEGF and platelet derived growth factor (*PDGF*) pathways. Sorafenib is currently approved for hepatocellular carcinoma (HCC) and advanced renal cell carcinoma (RCC) and sunitinib is approved for metastatic RCC, GIST, and pancreatic neuroendocrine tumors.

Cytopenias

Sorafenib and sunitinib inhibit the FMS-like tyrosine kinase 3 (FLT-3) and c-kit pathways, which promote hematopoiesis. In the original SHARP trial that showed a survival benefit for sorafenib over placebo in HCC grade 3 or 4 thrombocytopenia was the only significantly reported cytopenia (4% sorafenib vs <1% placebo) [64]. However, a recent meta-analysis of randomized trials and safety data profiles of sorafenib reported all-grade and high-grade (3 or 4) anemia (43.9% and 2%), neutropenia (18% and 5.1%), thrombocytopenia (25.3% and 4%), and lymphopenia (34.1% and 13.1%) respectively [65].

The phase III study comparing sunitinib to interferon alfa in metastatic RCC reported more grade 3 or 4 neutropenia (12% vs 7%) and thrombocytopenia (8% vs 0%) but less lymphopenia (12% vs 22%) [66]. This higher rate of myelosuppression in sunitinib compared to sorafenib is explained by its greater inhibition of FLT-3 [67].

Other hematologic toxicities

Multiple cases of sunitinib-induced TTP/HUS, including one fatality, have been reported [68–71]. These cases involved patients with metastatic RCC. Compromised renal endothelium is the proposed mechanism. Immune thrombocytopenic purpura (ITP) was reported in a woman after 3 weeks of sunitinib given during a clinical trial for metastatic breast cancer [72]. Her ITP resolved after drug discontinuation.

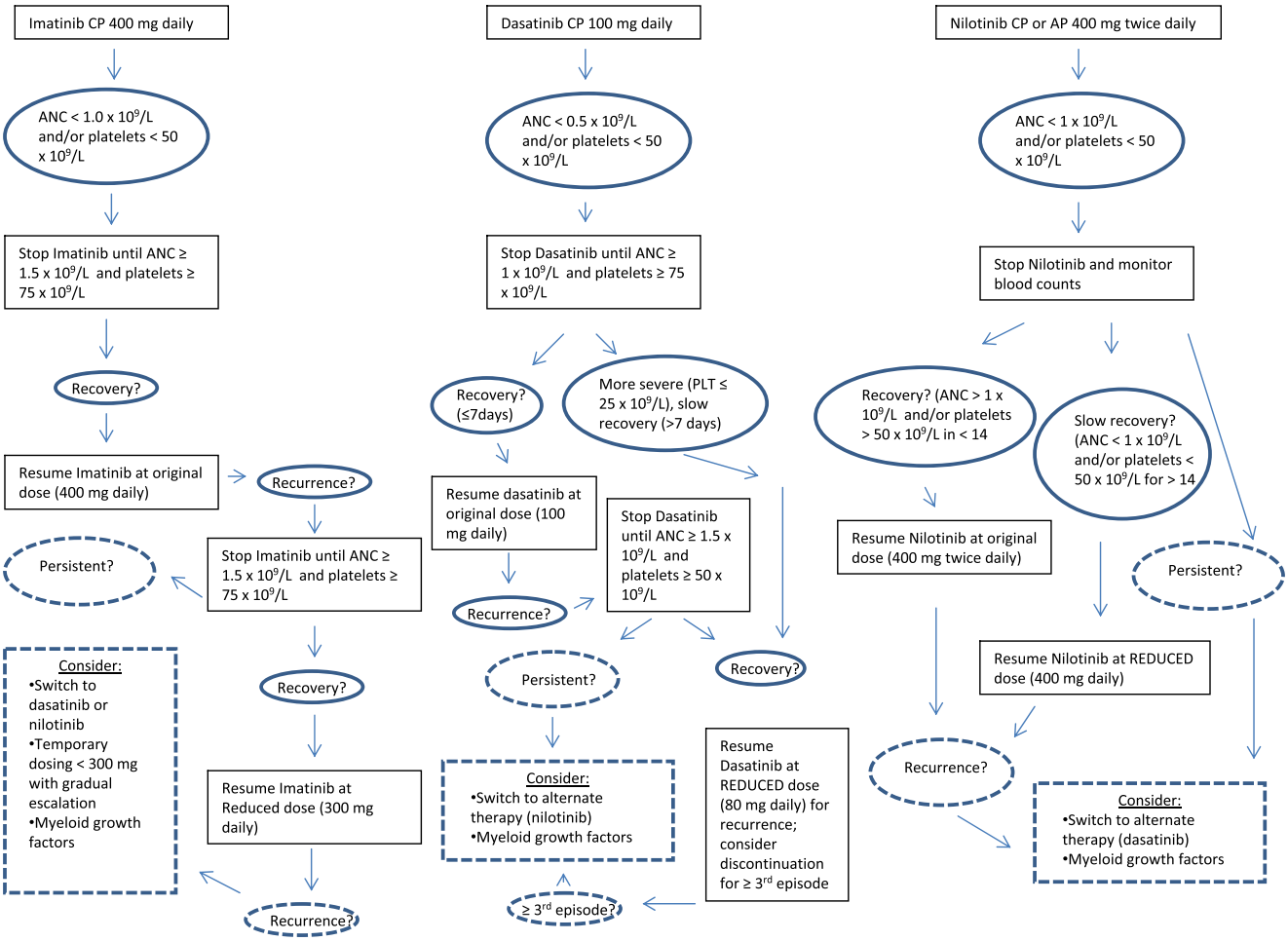

Fig. 1 Myelosuppression management guidelines, chronic and accelerated phase disease. From Mauro et al. [46] with permission from Elsevier

Macrocytosis has also been described in patients taking sunitinib [28, 73]. An institutional case series of all patients treated with sunitinib for RCC, breast cancer, and GIST reported development of macrocytosis in all cases. The mean percentage increase in MCV at 3, 6, 9, and 12 months of therapy were 12.4%, 16.8%, 16.6%, and 12.7% respectively. Similar to imatinib, the likely mechanism for this is inhibition of the c-kit pathway. Macrocytosis was reversible upon drug discontinuation.

Both sorafenib and sunitinib have been associated with an increased risk of arterial thromboembolic events (ATEs). A relative risk (RR) of 3.03 for arterial thrombosis, myocardial ischemia, myocardial infarction, cerebral ischemia, cerebral infarction, and cerbrovascular accident was observed when compared to a control group [74]. The rates of ATEs were similar when data was stratified for malignancy and specific TKI. The proposed mechanism for this is endothelial disruption. In addition, a case of partially reversible splenic infarction was reported in a patient taking sorafenib for HCC [75].

Axitinib

Axitinib is an oral inhibitor of *VEGFR* −1, -2, and −3 that is currently being investigated in metastatic RCC and HCC. A phase II study has shown clinical responses in patients with metastatic RCC refractory to sorafenib [76]. This study reported grade 1 or 2 cytopenias (anemia 64.3%, lymphopenia 49.1%, thrombocytopenia 19.6%, and neutropenia 10.9%) and only grade 3 or 4 lymphopenia (16.4%). Phase III trials are ongoing in metastatic RCC and HCC.

Pazopanib

Pazopanib (Votrient®, GlaxoSmithKline, Research Triangle Park, NC) is a selective inhibitor of multiple tyrosine kinases, including VEGFR −1, -2, and −3, and *PDGFR*, and others that are involved in angiogenesis. It is approved for advanced RCC. In the original phase III trial grade 3 or 4 neutropenia and thrombocytopenia were infrequent (< 2%) [77]. Minimal anti-FLT-3 activity can explain the limited myelosuppression with pazopanib [67].

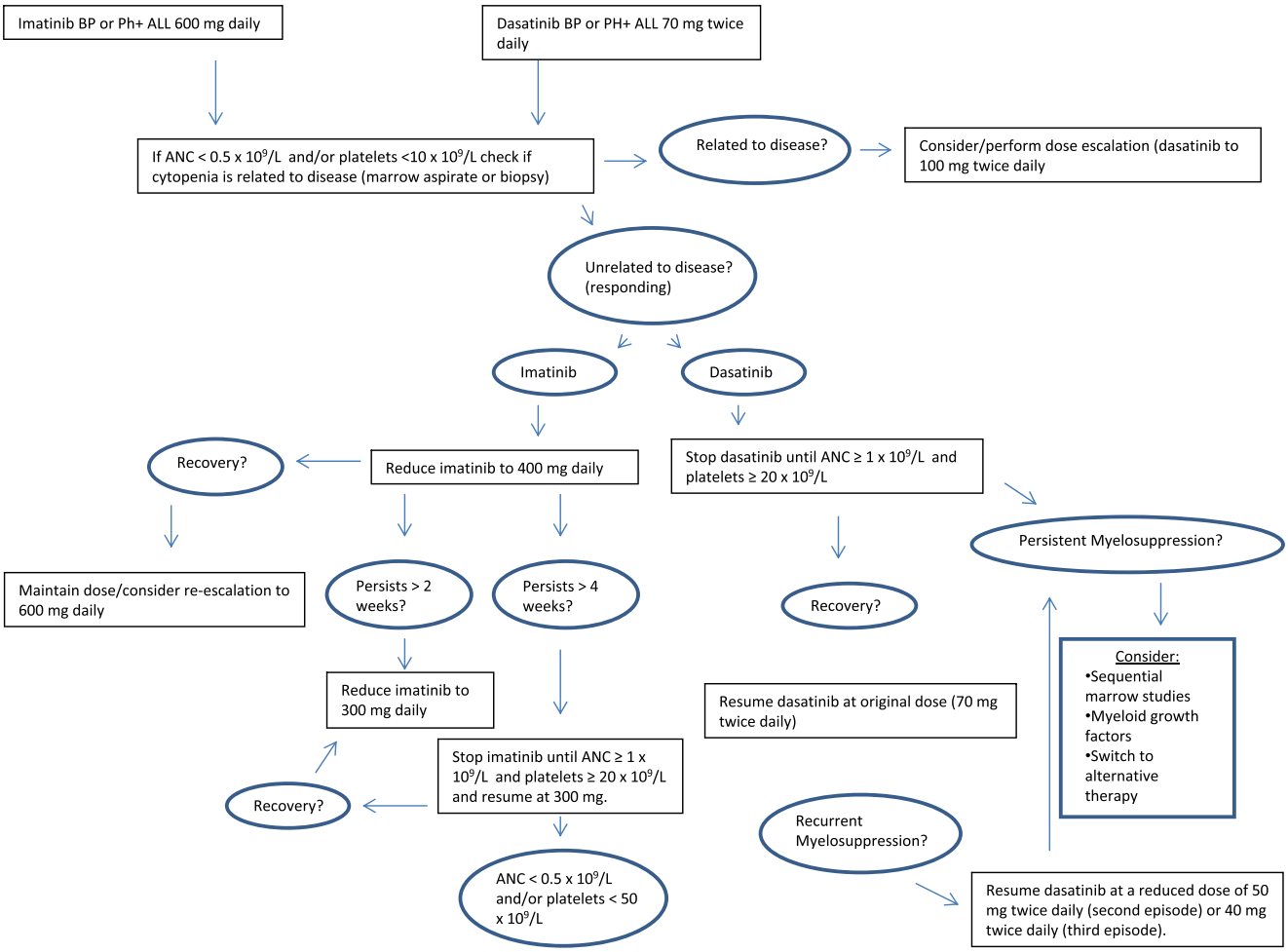

Fig. 2 Myelosuppression management guidelines, blast phase and Ph+ ALL. From Mauro et al. [46] with permission from Elsevier

Other tyrosine kinase inhibitors

Crizotinib

Crizotinib (Xalkori®, Pfizer, New York, NY) is a selective anaplastic lymphoma kinase (*ALK*) inhibitor that has recently been approved for *ALK*-positive advanced or metastatic non-small cell lung cancer (NSCLC) based on early phase II data [78, 79]. It has also shown promise in anaplastic large cell lymphoma [80]. Minimal grade 3 or 4 neutropenia (1–4%) was the only reported hematologic toxicity in these trials.

Lapatinib

Lapatinib (Tykerb®, GlaxoSmithKline, Research Triangle Park, NC) is an oral small molecule HER2 TKI that is approved for hormone-positive and HER2-positive advanced breast cancer and HER2-overexpressing breast cancer. None of the pivotal phase III trials involving lapatinib added to chemotherapy, trastuzumab, or letrazole reported an increase in cytopenias or other types of hematologic toxicities when compared to these therapies alone [81–84].

Conclusions

Understanding of tyrosine kinase-mediated oncogenesis and the introduction of receptor-specific small molecule TKIs have led to some of the recent triumphs in cancer therapy. The currently approved TKIs are proving to be successful and in some cases provide durable responses in a variety of solid and hematologic malignancies. And often of equal importance to patients are the superior tolerability and quality of life these agents afford compared to conventional chemotherapy.

The *BCR-ABL* TKIs can cause dose and agent-limiting cytopenias that may be due to either direct myelosuppression or eradication of a diseased hypercellular marrow lacking healthy hematopoietic precursors. Severity of myelosuppression typically correlates with burden of

disease, prior cytotoxic and TKI therapy, and advanced phases of disease. Prolonged bone marrow aplasia, bone marrow necrosis, and gelatinous marrow transformation have been documented with these agents. Neutropenic fever is uncommon due to the absence of mucositis. The severity of myelosuppression has been associated with worse disease outcomes in CML, likely due to treatment delays. Myeloid growth factor administration may improve treatment continuity and outcomes. Frequent upfront monitoring for cytopenias is recommended until complete blood count stability is observed. Management guidelines for TKI-induced cytopenias, including myeloid growth factor administration, are well established. Other less common hematologic problems associated with imatinib include hemolytic anemia and TTP/HUS. Second generation TKIs also cause myelosuppression and dasatinib can cause bleeding due to inhibition of normal platelet aggregation.

The EGFR TKIs gefitinib and erlotinib are rarely associated with cytopenias. The VEGFR TKIs, especially sunitinib, have been associated with cytopenias. The degree of myelosuppression correlates to the degree of FLT-3 inhibition also seen with these agents. Both sorafenib and sunitinib increase the risk of arterial thromboembolic events. Sorafenib has caused splenic infaction and Sunitinib has also been implicated in TTP/HUS and ITP.

Drug-induced hematologic toxicity is seen with many anti-cancer therapies and TKIs are no exception. Continuous patient monitoring, effective patient-clinician communication and patient education are very important in optimizing patient care and quality of life. Early recognition of these toxicities and their management in every day practice is crucial to assure safety and optimal outcomes.

Conflict of interest statement None of the authors have any conflict of interest to declare.

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