Chapter 11
Myeloid Malignancies

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Abstract Myeloid malignancies comprise the various myeloid proliferative stem cell disorders. In this chapter, the side effects of the currently used drugs are given as used in the general hematologic clinic. For the various disorders covered, the side effects of the medications are pleomorphic; therefore, for the tyrosine kinase inhibitors in chronic myeloid leukemia, a tabulated summary is given. Hematopoietic stem cells, autologous as well as allogeneic, are not covered. These treatment modalities are used in very specialized units, and the patient's follow-up during the first few months is also done through these units, which are very familiar with the therapies.

Keywords Myelodysplastic syndromes • Acute myeloid leukemia Polycythemia vera • Essential thrombocythemia • Chronic myeloid leukemia

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Myelodysplastic Syndrome

5-Azacytidine

5-Azacytidine [1–6] is a hypomethylating agent that has been approved in the treatment of myelodysplasia with low-intermediate and high-intermediate International Prognostic Scoring System (IPSS) in the United States. In the European Union, 5-azacytidine has been approved for myelodysplasia with high IPSS only. Some data about its efficacy in chronic myelomonocytic leukemia or in acute myeloid leukemia with low blast count have also been noted.

The side effects of 5-azacytidine are listed below. Hematologic toxicity that results mainly in anemia or thrombocytopenia is observed in most patients. Leukopenia or grade III neutropenia occurs in about one patient out of five and may lead to febrile neutropenia or opportunistic infections. Invasive fungal infections remain an issue in patients receiving 5-azacytidine treatment; therefore, prophylactic antifungal treatment with activity against aspergillus should be discussed in selected patients.

Agranulocytosis or irreversible aplasia are exceptional but are a cause of infectious mortality.

Fever may occur at the time of injection but is mostly related to infection. Nausea and vomiting occur frequently but may be reduced with adequate antiemetic medication.

A recurring problem in patients receiving subcutaneous 5-azacytidine is skin reaction at the infusion site. These reactions can vary from rash to pruritic plaques. Most skin rashes disappear with topical antihistamines or anti-inflammatory creams. The injection technique, however, influences the prevalence of skin lesions. Correct injection that avoids skin contact with the product lowers the occurrence of rash and pruritic plaques by more than a half.

The following are side effects of 5-azacytidine treatment:

Hematologic

- Very frequent (>50 % of patients): anemia, thrombocytopenia
- Frequent (>20 % of patients): leukopenia, neutropenia

- Rare (5–10 % of patients): lymphadenopathies, hematomas
- Very rare (<5 % of patients): agranulocytosis, aplasia, splenomegaly

General

- Very frequent (>50 % of patients): fever
- Frequent (>20 % of patients): fatigue, anorexia, injection site pain
- Occasional (>10 % of patients): epistaxis, febrile neutropenia, weight loss, sweating
- Rare (5–10 % of patients): herpes simplex, hypotension
- Very rare (<5 % of patients): anaphylactic shock, opportunistic infections (blastomycosis, toxoplasmosis), dehydration, systemic inflammatory response

Gastrointestinal

- Very frequent (>50 % of patients): nausea, vomiting
- Frequent (>20 % of patients): diarrhea, constipation, pharyngitis
- Occasional (>10 % of patients): abdominal pain and tenderness
- Rare (5–10 % of patients): stomatitis, oral petechiae, mouth hemorrhage
- Very rare (<5 % of patients): gastrointestinal hemorrhage

Renal

- Rare (5–10 % of patients): dysuria, urinary tract infections
- Very rare (<5 % of patients): renal failure, hematuria

Pulmonary

- Frequent (>20 % of patients): cough, dyspnea
- Occasional (>10 % of patients): chest pain, upper respiratory tract infection, pneumonia, rhinorrhea
- Rare (5–10 % of patients): wheezing, pleural effusion

Cardiac

- Rare (5–10 % of patients): tachycardia

Cutaneous

- Frequent (>20 % of patients): injection site erythema, ecchymosis, petechiae
- Occasional (>10 % of patients): pallor, generalized rash, injection site bruising
- Rare (5–10 % of patients): cellulitis, injection site pruritus, injection site swelling, dry skin, skin nodules

Nervous System

- Frequent (>20 % of patients): headache
- Occasional (>10 % of patients): anxiety, depression, insomnia
- Rare (5–10 % of patients): hypoesthesia
- Very rare (<5 % of patients): confusion, convulsions, intracranial hemorrhage

Metabolic

- Occasional (>10 % of patients): hypokalemia

Locomotor

- Frequent (>20 % of patients): rigors, arthralgia, pain in limb, back pain
- Occasional (>10 % of patients): peripheral edema, myalgia

Teratogenic activity is proven in the animal model. An effective contraceptive method is recommended in patients undergoing 5-azacytidine treatment.

Decitabine

The use of decitabine [1, 2, 7], an intravenous hypomethylating agent, is currently restricted to the United States. It is indicated in myelodysplasia, with low-intermediate or high-intermediate IPSS.

The most common side effects are hematologic, with anemia, thrombopenia, and neutropenia occurring in more than 50 % of

the patients. Febrile neutropenia occurs in about 20 % of patients. Opportunistic infections are rare occurrences. Fungal infections like invasive candidiasis have been described in more than 10 % of patients. The issue of antifungal prophylaxis in patients receiving decitabine treatment remains an open question.

Metabolic side effects are rather common and consist mainly of hypoalbuminemia and hyperglycemia and elevation of liver enzymes. Close monitoring of glucose levels is therefore recommended.

The side effects encountered in patients receiving decitabine treatment are as follows:

Hematologic

- Very frequent (>50 % of patients): neutropenia, thrombocytopenia, anemia
- Occasional (>10 % of patients): lymphadenopathy
- Rare (5–10 % of patients): thrombocythemia
- Very rare (<5 %): bone marrow suppression, splenomegaly

General

- Very frequent (>50 % of patients): pyrexia
- Frequent (>20 % of patients): febrile neutropenia, peripheral edema
- Occasional (>10 % of patients): rigors, pain, lethargy, dehydration, anorexia
- Rare (5–10 % of patients): chest discomfort, catheter site erythema, catheter site pain, injection site swelling

Gastrointestinal

- Frequent (>20 % of patients): nausea, vomiting, constipation, diarrhea
- Occasional (>10 % of patients): abdominal pain, oral mucosal petechiae, stomatitis, dyspepsia, ascites
- Rare (5–10 % of patients): gingival bleedings, hemorrhoids, loose stool, tongue ulceration, dysphagia, lip ulceration, abdominal distension, abdominal pain, gastroesophageal reflux, glossodynia
- Very rare (<5 %): cholecystitis

Renal

- Rare (5–10 % of patients): dysuria, urinary frequency

Pulmonary

- Frequent (>20 % of patients): cough
- Occasional (>10 % of patients): pharyngitis, respiratory crackles, hypoxia
- Rare (5–10 % of patients): postnasal drip

Cardiac

- Rare (5–10 % of patients): pulmonary edema
- Very rare (<5 % of patients): myocardial infarction, atrial fibrillation

Cutaneous

- Frequent (>20 % of patients): ecchymosis, petechiae, pallor
- Occasional (>10 % of patients): rash, skin lesions, pruritus, alopecia
- Rare (5–10 % of patients): urticaria, swelling face

Nervous System

- Frequent (>20 % of patients): headache
- Occasional (>10 % of patients): dizziness, hypoesthesia, insomnia, confusion, anxiety
- Rare (5–10 % of patients): blurred vision

Metabolic

- Frequent (>20 % of patients): hyperglycemia, hypoalbuminemia
- Occasional (>10 % of patients): hyperbilirubinemia, hypomagnesemia, hyponatremia
- Rare (5–10 % of patients): hyperkalemia

Locomotor

- Frequent (>20 % of patients): arthralgia
- Occasional (>10 % of patients): limb pain, back pain
- Rare (5–10 % of patients): chest wall pain, myalgia

Infectious

- Frequent (>20 % of patients): pneumonia
- Occasional (>10 % of patients): cellulitis, candidal infection
- Rare (5–10 % of patients): catheter-related infections, urinary tract infection, sinusitis, bacteremia
- Very rare (<5 % of patients): Mycobacterium avium infection

Effective contraceptive methods are recommended for men and women during and for a minimum of 12 months following therapy.

Acute Myeloid Leukemia

Cytarabine

Cytarabine [1, 2, 8–10], an intravenous antimetabolite cytidine analogue, has been widely used as monotherapy or in combination with other agents on the induction of treatment for acute myeloid leukemia. It also has proven efficacy in the treatment of lymphomas, especially mantle cell lymphomas, in which cytarabine-containing regimens have allowed longer progression-free survivals and higher remission rates. Cytarabine is also used in some ALL regimens, mainly in the consolidation phase.

The most common adverse effects are hematologic. Hematologic toxicity occurs regularly in patients receiving cytarabine and consists of deep bone marrow depression. Leukopenia typically follows a biphasic curve, with a first nadir at 7–9 days and a second more profound nadir at days 15–24. Frequent bleeds have been described as a result of thrombopenia.

About 10 % of patients may experience cytarabine syndrome, which consists of fever, myalgia, chest pain, maculopapular rash, conjunctivitis, and malaise. Cytarabine syndrome can evolve to severe hypotension and requires corticosteroid treatment. Discontinuation of the treatment must be discussed according to the severity of symptoms.

Nausea and vomiting frequently occur and require prophylaxis with antiemetic treatments. In patients receiving

high doses of cytarabine (more than 10 g/week), gastroenterologic side effects can be more marked and include diarrhea and severe colitis, ranging from neutropenic colitis to gastrointestinal bleeding. Rare cases of pancreatitis have been described with experimental doses of cytarabine.

Febrile neutropenia is a common finding in patients receiving cytarabine-based regimens. If bacterial causes are the most frequent, invasive fungal infections are a frequent occurrence, especially in AML patients. In selected patients, antifungal prophylaxis active against aspergillosis must be considered.

Central nervous system toxicity occurs mostly in elderly patients receiving high-dose regimens. Cerebellar toxicity is the main feature in patients; it results in ataxia and slurred speech. Infrequently, patients can experience confusion or fatal encephalitis. The use of prophylactic pyridoxine treatment has been debated. Conjunctivitis is also a frequent finding in patients. Prophylactic topical corticosteroids may be useful in patients receiving high-dose cytarabine.

The following toxicities have been described with cytarabine:

Hematologic

- Bone marrow depression: anemia, leukopenia, thrombopenia
- Thrombophlebitis (frequent)

General

- Cytarabine syndrome.
- Severe sepsis may occur from leukopenia.
- Rare: allergic reaction, anaphylactic shock.

Gastrointestinal

- Frequent: anorexia, nausea, vomiting, diarrhea, oral and anal mucositis, hepatic dysfunction
- Rare: esophageal ulceration, bowel necrosis, pancreatitis

Renal

- Rare: renal dysfunction, urinary retention

Pulmonary

- Rare: pneumonia, interstitial pneumonitis

Cardiac

- Rare: rapidly progressive pulmonary edema with cardiomegaly, pericarditis

Cutaneous

- Frequent : rash, alopecia (complete alopecia with high doses)
- Rare: freckling, pruritus, urticaria, skin ulceration, hand-foot syndrome, cellulitis at injection site

Nervous System

- Rare: peripheral neuritis, headache, conjunctivitis, CNS toxicity, such as encephalitis and cerebellitis (CNS complications have been described in high-dose and very high-dose cytarabine)

Metabolic

- Frequent: ASAT and ALAT
- Rare: jaundice

Cytarabine may be used intrathecally. The toxicities of intrathecal medication are roughly the same as for intravenous use. Toxicity is, however, self-limiting. Neurologic complications include paraplegia, necrotizing leukoencephalopathy, blindness, and spinal cord necrosis.

Cytarabine displays teratogenic effect in animal models. Women of childbearing age should be advised against conceiving a child during cytarabine therapy. An effective contraceptive method is recommended in both men and women.

Idarubicin

Idarubicin [1, 2, 11–13], an anthracycline-type topoisomerase II inhibitor, has been recommended in combination with other drugs for the treatment of acute myeloid leukemia.

The main side effects of idarubicin treatment involve hematologic toxicity. Severe myelosuppression is a constant and requires treatment with transfusions and granulocyte colony-stimulating factors. Severe febrile neutropenia may result from idarubicin-containing regimens. Idarubicin should be used with extreme caution in patients displaying cytopenias resulting from prior chemotherapies, as cases of permanent bone marrow suppression have been described.

Alopecia is a frequent complication of idarubicin-based chemotherapies.

Cardiac side effects occur frequently and mostly result from restrictive cardiomyopathy with a decline in left ventricle ejection fraction (LVEF). Decline of LVEF depends on the cumulative dose and the age of the patients. Caution should be applied in patients with preexisting cardiomyopathy or in patients who have been treated with anthracyclines previously.

Extravasation of anthracyclines may lead to extended skin necrosis, which may require surgery. In case of extravasation, intermittent cold packs should be applied and surgical advice should be taken.

Secondary neoplasias have been attributed to anthracyclines.

Side effects of idarubicin are as follows:

Hematologic

- Severe myelosuppression

Gastrointestinal

- Frequent: grade I–III nausea, vomiting, mucositis abdominal pain, and diarrhea; grade IV complications are seen in less than 5 % of patients.
- Rare severe enterocolitis with perforation.

Dermatologic

- Frequent: alopecia.
- Occasional: rash, urticaria, and bullous erythrodermous rash of palms and soles. Dermatologic reactions are seen more frequently in patients receiving concurrent antibiotic therapy or with a history of radiotherapy.

Cardiac

- Congestive heart failure, serious arrhythmias, including atrial fibrillation, myocardial infarction

Neurologic

- Very rare (<5 %): peripheral neuropathy, seizures, cerebellar palsy

Pulmonary

- Pneumonitis in less than 5 % of patients

Daunorubicin

Daunorubicin [1, 2, 11, 12] is an intravenous anthracycline that is used in combination with other drugs for the treatment of acute myeloid leukemia.

Side effects of daunorubicin are roughly the same as for idarubicin. Oral mucositis, bone marrow depression, and decrease in left ventricular function, however, seem less severe than with idarubicin in patients older than 60 years of age.

The maximal cumulative dose of daunorubicin is 550 mg/m^2. Some authors propose the dose of 400 mg/m^2 in patients who have undergone radiotherapy encompassing the heart.

Amsacrine

Amsacrine [1,2,14] has been approved for the salvage treatment of AML resistant to anthracyclines. In some European countries, amsacrine is used in the consolidation of AML.

Toxicity of amsacrine is essentially hematologic, resulting in constant pancytopenia requiring supportive treatment with red blood cell transfusion and platelet transfusion as well as granulocyte colony-stimulating factor. Amsacrine should not be used if the patient has previous profound chemo-induced pancytopenia.

Gastrointestinal toxicity is frequent and ranges from simple diarrhea to grade IV neutropenic colitis.

Cardiologic side effects consist mostly of arrhythmias, which can be triggered by coexisting hypokalemia. Close monitoring of the electrocardiogram and of serum kalium levels is recommended if using amsacrine.

The side effects of amsacrine are as follows:

Hematologic

- Very frequent: pancytopenia
- Frequent: febrile neutropenia
- Rare: major hemorrhage

Gastrointestinal

- Frequent: grade I–II nausea or vomiting, grade I–IV mucositis

Renal

- Rare: renal dysfunction, anuria, acute renal failure

Hepatic

- Elevation of serum liver tests, hyperbilirubinemia requiring dose adaptation

Neurologic

- Grand mal seizures in heavily pretreated patients with preexisting neurologic conditions

Cardiac

- Frequent: congestive heart failure, cardiac arrest, ventricular tachycardia

Cutaneous

- Reactions at injection site ranging from simple rash to necrosis

Amsacrine has proven teratogenic in mice. Effective methods of contraception are recommended in both men and women.

Clofarabine (Intravenous)

Clofarabine [1, 2, 15–17], a purine nucleoside analogue, has been approved in the treatment of pediatric ALL. Some studies indicate a benefit in progression-free survival in combination treatment with other drugs in relapsed AML.

Toxicity is mainly hematologic, with febrile neutropenia occurring in about a half of the patients.

Gastrointestinal toxicity is frequent and may lead to severe abdominal pain in 35 % of the patients.

Palmoplantar erythrodysesthesia is a common occurrence and requires topical steroids or topical NSAIDS. Systemic corticosteroids have been discussed as prophylactic treatment.

The side effects of clofarabine are as follows:

Hematologic

- Frequent: bone marrow depression

Cardiologic

- Tachycardia in about a third of the patients
- Pericardial effusion in 35 % of patients

Gastrointestinal

- Frequent: nausea, diarrhea, and vomiting in more than half of the patients. Abdominal pain occurs in 35 % of patients.
- Occasional: sore throat, constipation.

General Disorders

- Fatigue pyrexia and rigors in more than one-third of the patients.
- Mucositis in 17 % of patients.
- Anorexia occurs in 30 % of patients.

Hepatobiliary

- Occasional: jaundice, hepatomegaly

Infectious

- Bacteremia, cellulitis, candidiasis, bacterial, and fungal pneumonia

Neurologic

- Headaches in 44 % of patients
- Rare: somnolence, tremor, depression, anxiety

Respiratory

- Frequent: epistaxis
- Rare: respiratory distress, pleural effusion, cough

Cutaneous

- Frequent: dermatitis, petechiae
- Palmar planter erythrodysesthesia syndrome

Mylotarg (Intravenous)

Mylotarg [1, 2, 18, 19] is a monoclonal anti-CD33 antibody (gemtuzumab) linked to ozogamycin. It has been used as single-agent treatment of elderly patients with CD33-positive AML. Gemtuzumab ozogamycin has been withdrawn from the market owing to an unfavorable risk-benefit ratio.

Acute infusion-related adverse reactions occur frequently and have led in some cases to grade IV adverse events. Frequent (>30 % of patients) side effects are fever, nausea, chills, vomiting, and headache. About 20–30 % of patients experience dyspnea, hypotension, or hypertension, in some cases with hemodynamic instability. Less frequent acute side effects upon injection may be hyperglycemia and hypoxia. Although no antibodies to gemtuzumab have been detected to date, some severe allergic reaction has been described. Two patients have developed antibodies against ozogamycin.

Hematologic toxicity results in profound neutropenia with a mean time to recovery of 40–43 days. Anemia and thrombopenia are longer lasting. Median time to recovery is 50–56 days.

Hepatotoxicity is an issue in about one-third of patients undergoing treatment with gemtuzumab and ozogamycin and results in grade III–IV elevation of liver enzymes or hyperbilirubinemia. Veno-occlusive disease is a well-known but rare side effect of treatment with gemtuzumab and ozogamycin, occurring in about 1 % of patients. Most cases, however, have been described in the context of allogeneic stem cell transplantation.

The delayed side effects are as follows:

Hematologic

- Very frequent: grade III–IV neutropenia with
- Anemia and thrombopenia
- More than 13 % of patients experienced grade III–IV bleedings

Infectious

- Frequent: septic shock, pneumonia
- Rare: stomatitis, herpes simplex

Hepatotoxicity

- Grade III–IV increase of liver enzymes or hyperbilirubinemia
- Rare: ascites
- Veno-occlusive disease

Gastrointestinal

- Frequent: constipation, anorexia, dyspepsia, nausea stomatitis

Metabolic

- Frequent: hypokalemia
- Occasional: hyperglycemia, hypocalcemia
- Rare: hypomagnesemia, hypophosphatemia

Respiratory

- Frequent (>20 %): cough, dyspnea, epistaxis
- Occasional (20–30 %): pneumonia, pharyngitis

Cutaneous

- Rare: pruritus, rash

Chronic Myeloproliferative Diseases

The drugs used here are the most common ones for polycythemia vera, essential thrombocythemia, and chronic myeloid leukemia. For the latter disease, a compilation of the side effects is given in a tabulated form.

Hydrea

Hydroxyurea [1, 2, 20–22] is an oral inhibitor of nucleoside reductase and is widely used in melanoma, resistant chronic myeloid leukemia, recurrent carcinoma of the ovary, and myeloproliferative diseases (essential thrombocythemia, polycythemia vera).

Bone marrow toxicity is the major side effect of hydroxyurea. Treatment should not be initiated in patients displaying marked bone marrow depression. Recovery from leukopenia and thrombopenia is rapid after interruption of treatment.

Cutaneous toxicities are rare but may lead to skin ulcers. The development of ulcers requires interruption of hydroxyurea treatment.

In patients treated with hydroxyurea for myeloproliferative syndromes, the rate of secondary leukemias seems slightly increased.

Side effects of hydroxyurea treatment are the following:

Hematologic

- Frequent: neutropenia, thrombopenia, megaloblastic anemia

Cutaneous

- Exacerbation of postirradiation erythema in previously irradiated patients.
- Rare: vasculitic toxicities, ulceration, and gangrene are seen in patients with myeloproliferative disease with a history of interferon.

- Rare: dermatomyositis-like skin changes, maculopapular rash.
- Very rare: alopecia.

Renal

- Dysuria.
- Impairment of renal tubular function with hyperuricemia and increase of creatinine levels. Renal insufficiency should require dose reduction.

Gastrointestinal

- Pancreatitis has been described in patients treated with didanosine or stavudine.
- Occasional: stomatitis, nausea, vomiting, diarrhea, constipation.

Neurologic

- Rare: dizziness, headache, hallucinations, convulsions

Pulmonary

- Very rare: pulmonary fibrosis

Carcinogenesis

- Secondary leukemias have been described in patients receiving long-term treatment.

Laboratory

- Spurious gamma-GT elevations are observed, probably without any clinical consequences.

Multiple fetal malformations have been described in animal models. Men and women considering childbirth should be reassessed for the utility of their treatment, and treatment should be interrupted whenever possible.

Anagrelide

Anagrelide [1, 2, 22–24] is used in essential thrombocythemia to reduce platelet levels.

Main side effects of anagrelide are cardiologic and consist of supraventricular tachycardia. Anagrelide should be used with caution in patients with preexisting heart disease and prescribed only if the potential benefit outweighs the risks.

Interstitial lung disease (allergic alveolitis, eosinophilic pneumonia, and interstitial pneumonitis), though a very rare occurrence, has been associated with anagrelide. Time of onset is between 1 week and several years after initiation of therapy.

Side effects of anagrelide are the following:

Hematologic

- Very rare (1–5 %): anemia, leukopenia, and thrombopenia <100,000/uL. Thrombopenia recovers after treatment discontinuation.

General

- Frequent (20–30 %): asthenia
- Occasional (10–20 %): dizziness, pain, fever
- Rare (5–10 %): malaise
- Very rare (<5 %): flu-like symptoms, chills, photosensitivity, thromboses

Cardiac

- Frequent (20–30 %): palpitations, edema
- Rare (5–10 %): tachycardia
- Very rare (<5 %): arrhythmia, hypertension, orthostatic hypotension, angina pectoris, heart failure

Pulmonary

- Interstitial lung diseases

Locomotor

- Very rare: arthralgia, myalgia, cramps

Cutaneous

- Rare (5–10 %): pruritus
- Very rare (<5 %): alopecia

Gastrointestinal

- Occasional (10–20 %): nausea, abdominal pain, flatulence
- Rare (5–10 %): vomiting
- Very rare (<5 %): GI hemorrhage, melena, aphthous stomatitis, constipation

Special Senses

- Very rare (<5 %): amblyopia, abnormal vision, tinnitus, diplopia, visual field abnormality

Some cases of pregnancies occurring while on anagrelide treatment have been described with no fetal harm. It is, however, recommended that treatment be stopped during pregnancy or if there is a desire to conceive.

Imatinib, Nilotinib, and Dasatinib [1, 2, 25, 26]

Tyrosine kinase inhibitors are indicated in the treatment of CML. Imatinib and dasatinib have shown efficacy in GIST. Hypereosinophilic syndromes displaying FIP-1L1PDGFR-alpha translocation are also responsive to imatinib.

The spectrum of side effects is comparable between the three molecules. However, the frequency of the respective side effects varies from one molecule to another and may influence treatment decision. Table 11.1 compares the major side effects of imatinib, dasatinib, and nilotinib.

In 2011, a warning was issued by the FDA concerning the risk of pulmonary hypertension in patients receiving dasatinib. Caution is recommended in patients with previous pulmonary hypertension. Close monitoring by cardiac ultrasound is recommended.

TABLE 11.1 Comparative side effects of current tyrosine kinase inhibitors

Side effects	Frequency					
	Imatinib[a]		Nilotinib[b]		Dasatinib	
	All grades	Grade III–IV	All grades	Grade III–IV	All grades	Grade III–IV
Hematologic side effects (%)						
Neutropenia	58–68	20	38–43	10–12	65	21
Thrombocytopenia	56–62	9–10	48	10–12	70	19
Anemia	47–84	5–7	38–47	3	90	10
Nonhematologic side effects (%)						
Peripheral edema	14–36	0	5	0	9	0
Eyelid edema	13	<1	2–5	<1	0	0
Pleural effusion	0	0	0	0	19	1
Periorbital edema	34	0	1–2	0	0	0
Diarrhea	17–60	1	18–22	1	17	<1

Nausea	20–31	0	32–54		8	0
Vomiting	10–14	0	5–9	1	5	0
Myalgia	10–12	0	10	0	6	0
Muscle inflammation	17	<1	NA	NA	4	0
Muscle pain	14–24	<1	6–7	0	11	0
Rash	11–17	1	31–36	1–3	11%	0
Headache	8–10	0	14–21	1	12	0
Fatigue	8	<1	9–11	0–1	10	0
Alopecia	11	0	22–36	0	0	0
Metabolic side effects (%)						

(continued)

TABLE 11.1 (continued)

Side effects	Frequency					
	Imatinib[a]		Nilotinib[b]		Dasatinib	
	All grades	Grade III–IV	All grades	Grade III–IV	All grades	Grade III–IV
Increased bilirubin	10	<1	53–62	4–8	NA	
Increased alkaline phosphatase	33	<1	21–27	0		
Hypophosphatemia	45	8	32–34	5		
Hyperglycemia	20	0	41–36	4–6		
Increased lipase	11	3	24–29	6		
Increased amylase	12	<1	15–18	1		
Increased ALT	20	2	66–73	4–9		
Increased AST	23	1	40–48	1–3		
Increased creatinine	13	<1	5	0		

Adapted from [25, 26]

[a]Ranges for imatinib depend on the study analyzed

[b]Ranges for nilotinib depend on the dosage (300 or 400 mg)

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