New therapeutic agents marketed in the second half of 2011: Part 2

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Abstract

Objective: To provide information regarding the most important properties of the new therapeutic agents marketed in the second half of 2011.

Data sources: Product labeling supplemented selectively with published studies and drug information reference sources.

Data synthesis: 13 new therapeutic agents were marketed in the United States during the second half of 2011, 6 of which were considered in part 1 of this two-part series. The other 7 agents are considered in this article: vemurafenib, vandetanib, ruxolitinib phosphate, crizotinib, brentuximab vedotin, belatacept, and deferiprone. Indications and information on dosage and administration for these agents are reviewed, as are the most important pharmacokinetic properties, drug interactions, and other precautions. Practical considerations for the use of these new agents are also discussed. When possible, the properties of the new drugs are compared with those of the older agents marketed for the same indications.

Conclusion: Five of the new drugs considered in this article are antineoplastic drugs that have properties that distinguish them from older agents. Vemurafenib is the second agent marketed in 2011 for the treatment of patients with unresectable or metastatic melanoma, joining ipilimumab. Vemurafenib is specifically indicated in patients with the BRAF V600E mutation (as detected by an FDA-approved test), which is present in approximately one-half of melanomas. Vandetanib is the first drug to be demonstrated to be effective in the treatment of patients with medullary thyroid cancer. Ruxolitinib is an inhibitor of Janus-associated kinases and is the first drug to be approved for the treatment of myelofibrosis, a rare disease involving the bone marrow. Crizotinib is the first drug to inhibit the kinase produced by the abnormal anaplastic lymphoma kinase (ALK) gene and has been approved for the treatment of patients with non–small-cell lung cancer that is ALK positive, as detected by an FDA-approved test. Brentuximab vedotin is the first drug to be approved for the treatment of systemic anaplastic large cell lymphoma and also is indicated for use in patients with Hodgkin’s lymphoma following failure of other regimens. Two other agents are also considered in this article: belatacept acts as a selective T-cell (lymphocyte) costimulation blocker and is used in combination with other immunosuppressants for prophylaxis of organ rejection in adult patients receiving a kidney transplant. Deferiprone is an iron chelator that is administered orally for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.

Keywords: New drugs, Food and Drug Administration, drug development, pharmaceutical marketing, risk assessment.
Preassessment questions
Before participating in the activity, test your knowledge by answering the following questions. These questions also will be part of the CPE exam.

1. Which of the following agents is associated with the occurrence of cutaneous squamous cell carcinoma as an adverse event?
   a. Crizotinib
   b. Ruxolitinib
   c. Vemurafenib
   d. Brentuximab vedotin

2. Which of the following agents should only be used in patients who are Epstein-Barr virus seropositive?
   a. Brentuximab vedotin
   b. Belatacept
   c. Vandetanib
   d. Ruxolitinib

3. Which of the following statements is correct regarding brentuximab vedotin?
   a. It is a prodrug that is converted to its active form by plasma esterases.
   b. Peripheral neuropathy is commonly experienced with its use.
   c. Its use should be avoided in patients with impaired renal function.
   d. Concurrent use with a strong cytochrome P450 3A4 inducer should be avoided.

Antineoplastic agents

Vemurafenib
Melanoma is the most dangerous form of skin cancer and is the leading cause of death from skin disease. Early-stage disease is often curable; however, the prognosis for patients with late-stage (metastatic) melanoma is very poor. Although certain antineoplastic agents (e.g., dacarbazine) have been used in the treatment of metastatic melanoma, they have been of limited benefit. Ipilimumab (Yervoy), a monoclonal antibody marketed earlier in 2011, is the first drug to be demonstrated to prolong survival in patients with metastatic melanoma.

A protein designated as BRAF is an important component of a pathway involved in normal cell growth and survival. Mutations that keep the BRAF protein in an active state may cause excessive signaling in the pathway resulting in uncontrolled cell growth. These mutations of the BRAF protein are thought to occur in approximately one-half of melanomas and an estimated 8% of solid tumors.

The mutation of BRAF that has been implicated in many cases of melanoma is designated as the BRAF V600E mutation. The recognition of the role of this BRAF mutation in the occurrence of metastatic melanoma, as well as the poor prognosis for patients experiencing this disease, have resulted in the development of a new therapeutic agent that has been designed to target and inhibit this mutation of the BRAF protein.

Vemurafenib (Zelboraf—Roche) is administered orally and inhibits some mutated forms of BRAF serine–threonine kinase, including BRAF V600E. It also has been reported to inhibit other kinases in vitro, but whether these actions are of clinical importance is not known. Vemurafenib is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. At the same time that vemurafenib was approved, FDA also approved the cobas 4800 BRAF V600 Mutation Test (Roche), a diagnostic test used to identify patients eligible for treatment. The new drug should only be used in patients whose melanoma carries a BRAF V600E mutation, and its use is not recommended in patients with wild-type BRAF melanoma.

The effectiveness of vemurafenib was demonstrated in a study in patients with treatment-naive, BRAF V600E mutation–positive, unresectable or metastatic melanoma who were treated with the new drug or dacarbazine. The major efficacy outcome measures were overall survival and investigator-assessed progression-free survival. The risk of death in the patients treated with vemurafenib was reduced by 56% compared with those receiving dacarbazine. At the time of this analysis, median overall survival of the patients treated with the new drug had not yet been reached, and was 7.9 months for those treated with dacarbazine. Patients treated with vemurafenib also had a 74% reduced risk of the disease getting worse or dying (progression-free survival). The median progression-free survival was 5.3 months for those treated with vemurafenib compared with 1.6 months for those treated with dacarbazine.

Investigator-assessed response rate (i.e., tumor shrinkage) in patients treated with vemurafenib was 48.4% (1% complete responses and 47.4% partial responses) compared with 5.5% (partial responses) for those treated with dacarbazine. In another study in patients who had received systemic therapy previously, use of vemurafenib resulted in tumor shrinkage in 52% of participants (2% complete responses and 50% partial responses).

Both vemurafenib and ipilimumab represent important advances in the treatment of metastatic melanoma. Because the two drugs provide their benefits via different mechanisms of action, their concurrent use is being evaluated to determine whether additional benefits are possible compared with the use of either agent alone or their sequential use.

The most frequently reported adverse events (and their frequency in the study in treatment-naive patients) with the use of vemurafenib included arthralgia (53%), alopecia (45%), fatigue (38%), rash (37%), nausea (35%), and photosensitivity reactions (33%). Patients should be advised to avoid sun exposure while taking the drug and to wear protective clothing and use a broad spectrum UVA/UVB sunscreen and lip balm (sun protection factor [SPF] of at least 30) when outdoors to help protect against sunburn.

Cutaneous squamous cell carcinomas were experienced by 24% of the patients in the clinical studies and usually developed early in the course of treatment. These events were managed with excision, and patients were able to continue treatment without dosage adjustment. All patients should receive

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a dermatologic evaluation before initiating therapy and every two months during treatment. Monitoring should be considered for 6 months following discontinuation of therapy. A small number of patients experienced skin lesions that were reported as new primary malignant melanoma, and these lesions also were managed with excision and without dosage adjustment.

Severe dermatologic reactions have been reported infrequently, including one case of Stevens-Johnson syndrome and one case of toxic epidermal necrolysis, as well as serious hypersensitivity reactions, including anaphylaxis, in patients treated with vemurafenib. Treatment should be permanently discontinued if one of these events occurs.

The use of vemurafenib has been associated with the occurrence of exposure-dependent QT prolongation. Its use is not recommended in patients with uncorrectable electrolyte abnormalities, long QT syndrome, or who are taking other medications known to prolong the QT interval. An electrocardiogram (ECG) and electrolytes, including potassium, magnesium, and calcium, should be evaluated before starting treatment with vemurafenib and after dosage modification. Monitoring of ECGs should occur 15 days after treatment initiation and then monthly during the first 3 months of treatment, followed by every 3 months thereafter or more often as clinically indicated.

Adverse events involving the eyes have been experienced by some patients, including uveitis, blurred vision, iritis, and photophobia. Treatment with corticosteroid and mydriatic ophthalmic drops may be needed for the management of uveitis, and patients should be routinely monitored for signs and symptoms of this adverse event. Liver laboratory abnormalities have been attributed to the use of vemurafenib, and liver enzymes (transaminases and alkaline phosphatase) and bilirubin should be monitored before starting treatment, and monthly during treatment, or as clinically indicated.

Vemurafenib may cause harm to the fetus if it is administered during pregnancy, and it is classified in Pregnancy Category D. Women of childbearing potential and men should be advised to use appropriate contraceptive measures during treatment and for at least 2 months following discontinuation of treatment. Whether the drug is excreted in human milk is unknown, but a decision should be made whether to discontinue nursing or not use the drug. The effectiveness and safety of vemurafenib in patients younger than 18 years have not been established.

Vemurafenib has been administered without regard to food, but its bioavailability has not been determined. It is a cytochrome P450 (CYP)3A4 substrate, although the extent to which the drug is metabolized is not known. Vemurafenib and its metabolites represented 95% and 5% of the components in plasma, respectively, and approximately 95% of a dose is recovered in the feces, with only 1% being recovered in the urine. The clearance of the drug in patients with mild and moderate renal or hepatic impairment is similar to that in patients with normal renal or hepatic function. However, data are limited regarding its use in patients with severe renal or hepatic impairment.

The concurrent use of vemurafenib with CYP3A4 inhibitors or inducers has not been evaluated. However, the potential for interactions exists, and caution should be exercised when they are used concomitantly. The new drug is a moderate CYP1A2 inhibitor and a weak CYP2D6 inhibitor, and it may increase the exposure of other drugs that are substrates for these metabolic pathways. It also is a CYP3A4 inducer and has been reported to reduce the exposure of midazolam, a CYP3A4 substrate. The concomitant use of vemurafenib with agents with narrow therapeutic windows that are metabolized by CYP1A2, CYP2D6, and CYP3A4 is not recommended. If concurrent use cannot be avoided, caution should be exercised and a reduction in dosage of the concomitant CYP1A2 or CYP2D6 substrate drug should be considered. Vemurafenib has been reported to cause an 18% increase in the exposure of S-warfarin, a CYP2C9 substrate, and additional International normalized ratio monitoring should be considered.

Vemurafenib is supplied in film-coated tablets in a 240-mg potency. The recommended dosage is 960 mg (four tablets) twice a day. The first dose should be taken in the morning and the second dose in the evening, approximately 12 hours later. The tablets should be swallowed whole with a glass of water and should not be chewed or crushed. If a dose is missed, it can be taken up to 4 hours before the next dose to maintain...
the twice-daily regimen. The occurrence of adverse events or prolongation of the QT interval may require a reduction in dosage, treatment interruption, or discontinuation of treatment, and the product labeling should be consulted for the specific recommendations. Reducing the dosage below 480 mg twice a day is not recommended. Treatment with vemurafenib should be continued until disease progression or unacceptable toxicity occurs.

Vandetanib

Approximately 45,000 new cases of thyroid cancer were diagnosed in the United States in 2010, and about 1,700 patients died from the disease. Medullary thyroid cancer is one of the rarer forms of thyroid cancer, representing less than 5% of cases. It involves specific types of cells in the thyroid gland and can occur spontaneously or be part of a genetic syndrome. Total thyroidectomy is the first-line therapy, but some patients have unresectable disease. Antineoplastic drugs such as dacarbazine and doxorubicin have been used for treatment but with only limited benefit.

Vandetanib (Caprelsa—AstraZeneca) is indicated for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. It is the only drug that has been approved by FDA for this type of cancer. Vandetanib is a kinase inhibitor that inhibits the activity of tyrosine kinases, including members of the epidermal growth factor receptor family, vascular endothelial cell growth factor receptor, rearranged during transfection, and other kinases. It is thought to reduce tumor cell-induced angiogenesis and tumor vessel permeability and to inhibit tumor growth and metastasis.

The effectiveness of vandetanib was evaluated in a placebo-controlled study in which the primary objective was to demonstrate improvement in progression-free survival. The median progression-free survival in patients receiving placebo was 19.8 months, and although it had not been reached in the vandetanib group, it was estimated to be 30.5 months.

Vandetanib also is being studied in patients with lung cancers, brain tumors, and several other types of cancer. However, these are not labeled indications currently.

The use of vandetanib is associated with numerous serious toxicities, and treatment must be monitored closely. It can prolong the QT interval of the ECG, and torsades de pointes and sudden death have been reported in patients receiving treatment. This is the subject of a boxed warning in its labeling, and its use is contraindicated in patients with congenital long QT syndrome. Concurrent use with other drugs that are known to prolong the QT interval (e.g., certain antiarrhythmic agents, moxifloxacin [Avelox]) should be avoided, and the new agent should not be used in patients with hypocalcemia, hypokalemia, or hypomagnesemia. An ECG and serum concentrations of calcium, magnesium, potassium, and thyroid-stimulating hormone (TSH) should be obtained at baseline, at 2 to 4 weeks and 8 to 12 weeks after starting treatment, and every 3 months thereafter. Because of the risks associated with QT prolongation, vandetanib is available only through a restricted distribution program in which prescribers and pharmacies must be certified to participate.

Severe skin reactions, including Stevens-Johnson syndrome, have been reported with the use of vandetanib, and these events have been fatal in some patients. Mild to moderate skin reactions may manifest as rash, acne, dry skin, dermatitis, pruritus, and/or photosensitivity reactions. Patients should be advised to apply sunscreen and wear protective clothing when exposed to the sun. Because of the long half-life (19 days) of vandetanib, sunscreen and protective clothing should be continued for 4 months following discontinuation of treatment with the drug.

Other serious adverse events that have been attributed to vandetanib include interstitial lung disease, ischemic cerebrovascular events, hemorrhagic events, heart failure, and reversible posterior leukoencephalopathy syndrome, and appropriate precautions must be observed in patients at risk. Hypertension, including hypertensive crisis, has been reported, and all patients should be monitored for hypertension. Many of the patients in the clinical studies had prior thyroidectomy, and an increased dosage of the thyroid replacement therapy often is needed. TSH concentrations should be monitored, and if signs or symptoms of hypothyroidism occur, thyroid replacement therapy should be adjusted accordingly.

Diarrhea is the adverse event reported most frequently (57%) in the clinical studies. This may result in electrolyte imbalances and increase the risk of QT prolongation and its related complications. Anti diarrheal agents should be used, and if severe diarrhea develops, vandetanib should be discontinued until the diarrhea improves, at which time therapy should be resumed at a reduced dosage.

Other commonly experienced adverse events with the use of vandetanib included rash (53%), dermatitis/acne (35%), nausea (33%), hypertension (33%), headache (26%), and fatigue (24%). The most frequent laboratory abnormalities included decreased calcium (57%), increased alanine aminotransferase (ALT; 51%), and decreased glucose (24%).

Vandetanib may cause harm to the fetus if administered during pregnancy, and it is classified in Pregnancy Category D. Women of childbearing potential should be advised to avoid becoming pregnant during the period of treatment with the new drug and for 4 months following treatment. Whether vandetanib is excreted in human milk is not known, and a decision should be made whether to discontinue nursing or not use the drug. The effectiveness and safety of vandetanib in pediatric patients have not been established.

Following oral administration, vandetanib accumulates with multiple dosing, with steady state achieved from approximately 3 months. Several metabolites are formed, and unchanged drug and metabolites are detected in plasma, urine, and feces. The drug is slowly excreted, and approximately 70% of a dose is recovered within a 21-day collection period, with about 45% in the feces and 25% in the urine. Its use is not recommended in patients with moderate and severe hepatic impairment, and the dosage should be reduced in patients with moderate and severe renal impairment.
The use of a CYP3A4 inducer (e.g., carbamazepine, rifampin, St. John’s wort) may reduce the exposure and activity of vandetanib unpredictably, and concurrent use should be avoided.

The recommended dosage of vandetanib is 300 mg once a day, with or without food. If a patient misses a dose, the missed dose should not be taken if it is less than 12 hours before the next dose. Treatment should be continued until patients are no longer benefiting from the medication or unacceptable toxicity occurs.

For patients who have difficulty swallowing tablets, the tablets should not be crushed but instead can be dispersed in a glass containing 2 oz noncarbonated water and stirred for approximately 10 minutes until the tablet is dispersed. The dispersion should be swallowed immediately and any residue in the class should be mixed with an additional 4 oz noncarbonated water and swallowed. The dispersion also can be administered through a nasogastric or gastrostomy tube.

In patients with moderate and severe renal impairment, the starting dosage should be reduced to 200 mg once a day. Treatment should be discontinued or the dosage reduced if serious adverse events occur.

Vandetanib tablets are supplied in 100- and 300-mg potencies. Direct contact of crushed tablets with the skin or mucous membranes should be avoided. If such contact occurs, the area should be washed thoroughly.

**Ruxolitinib phosphate**

Myelofibrosis is a rare life-threatening disease involving the bone marrow that is associated with the dysregulation of two enzymes, Janus-associated kinase (JAK)1 and JAK2. These kinases mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. The disease is characterized by the replacement of bone marrow with scar tissue, resulting in blood cells being made in organs such as the liver and spleen, enlargement of the spleen, and occurrence of anemia and thrombocytopenia. The symptoms most often associated with myelofibrosis include fatigue, abdominal discomfort, pain under the ribs, satiety, muscle and bone pain, itching, and night sweats. Treatment options have been limited, with hydroxyurea and glucocorticoids being used off-label but with only limited benefit for some patients.

Ruxolitinib phosphate (Jakafi—Incyte) is a kinase inhibitor that inhibits JAK1 and JAK2 and is the first drug to be approved for the treatment of myelofibrosis. It is specifically indicated for the treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, postpolycythemia vera myelofibrosis, and postessential thrombocytemia myelofibrosis. In one study, 42% of patients met the primary endpoint of a 35% or greater reduction in spleen volume at 24 weeks compared with less than 1% of the patients receiving placebo. In addition, 46% of patients experienced a 50% or greater improvement in the symptom assessment compared with 5% receiving placebo. In another study, 29% of patients treated with ruxolitinib experienced a 35% or greater reduction in spleen volume at 48 weeks compared with 0% of the patients receiving hydroxyurea or glucocorticoids.

The most important concern with the use of ruxolitinib is the occurrence of hematologic adverse events, including anemia (96%; 87% in those receiving placebo), thrombocytopenia (70%; 31%), and neutropenia (19%; 4%). Patients experiencing anemia may require blood transfusions, whereas thrombocytopenia and neutropenia are generally reversible and managed by withholding the drug or reducing the dosage. A complete blood count and platelet count must be performed before starting treatment, every 2 to 4 weeks until the dosage is stabilized, and then as clinically indicated. Patients also should be assessed for the risk of infections, and treatment with ruxolitinib should not be initiated in patients with active serious infections until the infection is resolved. Herpes zoster was experienced by 2% of patients in the clinical studies, and patients should be informed about the signs and symptoms of this infection and advised to seek treatment as early as possible if these symptoms occur.

Other adverse events that were commonly reported in the clinical studies included bruising (23%), dizziness (18%), headache (15%), and urinary tract infection (9%). Ruxolitinib is classified in Pregnancy Category C and should only be used during pregnancy if the anticipated benefit justifies the risk to the fetus. Whether the new drug is excreted in human milk is unknown, and a decision should be made whether to discontinue nursing or not use the drug. The effectiveness and safety of ruxolitinib in pediatric patients have not been established.

Following oral administration, ruxolitinib is almost completely absorbed. It is partially metabolized, primarily via the CYP3A4 pathway, to two active metabolites that have less pharmacological activity than the parent drug. Approximately 75% of a dose is excreted in the urine as metabolites. The peak serum concentration and bioavailability of ruxolitinib are increased by the concurrent use of a strong CYP3A4 inhibitor (e.g., clarithromycin, itraconazole, ritonavir, grapefruit juice), and the dosage of the new drug should be reduced when one of these agents is used concomitantly.

The recommended starting dosage of ruxolitinib is based on the platelet count. For patients with a platelet count greater than $200 \times 10^9/L$, the starting dosage is 20 mg twice a day, and if the platelet count is between $100 \times 10^9/L$ and $200 \times 10^9/L$, the starting dosage is 15 mg twice a day. The maximum recommended dosage is 25 mg twice a day. If spleen reduction or symptom improvement does not occur within 6 months, treatment should be discontinued.

If a patient also is being treated with a strong CYP3A4 inhibitor, the recommended starting dosage is 10 mg twice a day in patients with a platelet count greater than or equal to $100 \times 10^9/L$. Dosage adjustments also should be considered based on efficacy considerations, occurrence of thrombocytopenia, renal impairment, and hepatic impairment, and the product labeling should be consulted for the specific recommendations. The use of ruxolitinib should be avoided in patients with hepatic impairment who have a platelet count less than $100 \times 10^9/L$ and in patients with moderate or severe renal impairment who...
have a platelet count less than 100 × 10^9/L. It also should be avoided in patients with end-stage renal disease (creatinine clearance <15 mL/minute) not requiring dialysis.

Ruxolitinib phosphate is supplied in tablets in amounts equivalent to 5, 10, 15, 20, and 25 mg ruxolitinib base. If a patient is unable to swallow tablets, ruxolitinib may be administered through a nasogastric tube. One tablet is suspended in approximately 40 mL water with stirring for approximately 10 minutes. Within 6 hours after the tablet has dispersed, the suspension can be administered through a nasogastric tube. The tube should be rinsed with approximately 75 mL water.

**Crizotinib**

Lung cancer is the leading cause of cancer death in the United States. Approximately 85% of lung cancers are non–small-cell lung cancers (NSCLCs), and the vast majority of patients with these cancers are diagnosed with metastatic or advanced disease with a very poor prognosis. Up to 5% of patients with NSCLCs, typically nonsmokers, express the ALK (abnormal anaplastic lymphoma kinase) gene, which can contribute to increased cell proliferation and survival in tumors expressing these proteins.

Crizotinib (Xalkori—Pfizer) is an inhibitor of receptor tyrosine kinases, including ALK, and is the first drug targeted at the translocations within the ALK gene in patients diagnosed with NSCL. It is indicated for the treatment of patients with locally advanced or metastatic NSCL that is ALK positive as detected by an FDA-approved test (a companion diagnostic test [Vysis ALK Break Apart FISH Probe Kit]) that will help determine whether the patient has the abnormal ALK gene. Crizotinib was evaluated in two studies in patients with late-stage ALK-positive NSCL. In one study, the objective response rate was 50% with a median response duration of 42 weeks. In the other study, the objective response rate was 61% with a median response duration of 48 weeks. Almost all of the responses were partial responses, with most of the responses occurring within the first 8 weeks of treatment. The approval of the drug was based on the response rate, and no data were available that demonstrated improvement in patient-reported outcomes or survival.

Crizotinib may cause prolongation of the QT interval of the ECG, and its use should be avoided in patients with congenital long QT syndrome. In patients with congestive heart failure, bradycardia, or electrolyte abnormalities who are taking medications that are known to prolong the QT interval, ECGs and electrolyte concentrations should be monitored periodically.

Life-threatening, treatment-related pneumonitis was experienced by four patients (1.6%) in the clinical studies and occurred within 2 months after the initiation of treatment. Patients should be monitored for pulmonary symptoms, and treatment should be discontinued if pneumonitis is diagnosed.

Some patients treated with crizotinib experience hepatic laboratory abnormalities, and liver function tests including ALT and total bilirubin should be monitored once a month and as clinically indicated.

The adverse events most frequently experienced in the clinical studies with crizotinib included vision disorders (64%; e.g., blurred vision, diplopia, reduced visual acuity), nausea (57%), diarrhea (49%), vomiting (45%), constipation (38%), edema (38%), and fatigue (31%). Because of the potential for vision changes, fatigue, and dizziness, patients should be advised to exercise caution regarding driving or operating machinery.

Crizotinib may cause harm to the fetus if administered during pregnancy, and it is classified in Pregnancy Category D. Adequate contraceptive methods should be used by women of childbearing potential and their partners during therapy and for at least 90 days after completing therapy. Whether the new drug is excreted in human milk is not known, and a decision should be made to discontinue nursing or not use the drug. The effectiveness and safety of crizotinib in pediatric patients have not been established.

Following oral administration of a single oral dose of crizotinib, its absolute bioavailability is 43%. The aqueous solubility of the drug is pH dependent, and the concurrent use of drugs that elevate gastric pH (e.g., antacids, histamine H receptor antagonists, proton pump inhibitors) may decrease its solubility and bioavailability. Crizotinib is primarily metabolized via the CYP3A4/5 pathways. Almost two-thirds of a dose of the drug is eliminated in the feces, mostly in the unchanged form, and approximately 22% is recovered in the urine, primarily as metabolites. Its use has not been specifically studied in patients with hepatic or renal impairment.

As a substrate of CYP3A4/5, the action of crizotinib may be increased by strong CYP3A inhibitors (e.g., clarithromycin, grapefruit juice) and reduced by strong CYP3A inducers (e.g., carbamazepine, St. John’s wort), and concurrent use should be avoided. Concurrent use with other CYP3A substrates with a narrow therapeutic index (e.g., cyclosporine, fentanyl) also should be avoided.

The recommended dosage of crizotinib is 250 mg twice a day, and treatment should be continued for as long as the patient is experiencing clinical benefit. If a dose is missed, it should be taken as soon as it is remembered unless it is less than 6 hours until the next dose, in which case the patient should not take the missed dose. Based on tolerability and safety, the dosage may be reduced to 200 mg twice a day and, if necessary, to 250 mg once a day. The product labeling should be consulted for the specific recommendations for adjusting the dosage, or interrupting or discontinuing treatment in patients who develop hematologic toxicities (e.g., thrombocytopenia) and serious nonhematologic toxicities (e.g., QT prolongation, pneumonitis, hepatic laboratory abnormalities).

Crizotinib capsules are supplied in 200- and 250-mg potencies. The capsules should be swallowed whole and should not be opened, crushed, or dissolved.

**Brentuximab vedotin**

Hodgkin’s lymphoma is characterized by the presence of cells known as Reed-Sternberg cells that generally express CD30. Systemic anaplastic large-cell lymphoma (ALCL) is a rare aggressive type of non-Hodgkin’s lymphoma that also expresses CD30. Brentuximab vedotin (Adcetris—Seattle Genetics) is a CD30-directed antibody drug conjugate (ADC) that consists
of an antibody specific for CD30, the microtubule-disrupting agent monomethyl auristatin E (MMAE), and a linker that covalently attaches MMAE to the antibody. ADC binds to the CD30-expressing cells, which is followed by the internalization of the ADC–CD30 complex and the release of MMAE. The binding of MMAE to tubulin disrupts the microtubule network in the cells, resulting in the apoptotic death of the cells.

Brentuximab vedotin is administered intravenously and is indicated for the treatment of patients with Hodgkin’s lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two previous multiagent chemotherapy regimens in patients who are not ASCT candidates. It has also been approved for the treatment of systemic ALCL after failure of at least one previous multiagent chemotherapy regimen, and it is the first drug to be specifically indicated for this disease.

In the clinical study in patients with Hodgkin’s lymphoma, 73% of patients achieved either a complete or partial response, with the median response being 6.7 months. In the study in patients with ALCL, 86% of patients experienced a response (median response 12.6 months).

The use of brentuximab vedotin is associated with a number of serious toxicities, including hematologic complications (i.e., neutropenia [54%], anemia [33%], thrombocytopenia [28%]). Complete blood counts should be monitored before each dose, and more often in patients with grade 3 or 4 neutropenia.

Peripheral sensory neuropathy was experienced by more than one-half of the patients in the clinical studies, and peripheral motor neuropathy also was reported by some patients (15%). Patients should be monitored for symptoms such as paresthesia, discomfort, a burning sensation, and the possible need for adjusting the dosage or interrupting therapy. Of the patients experiencing neuropathy in the clinical studies, 49% had complete resolution, 31% partial improvement, and 20% no improvement.

Other serious adverse events that have been experienced with brentuximab vedotin included progressive multifocal leukoencephalopathy (PML), Stevens-Johnson syndrome, tumor lysis syndrome, and infusion reactions, including anaphylaxis. If anaphylaxis occurs, treatment should be immediately and permanently discontinued. Patients who have experienced a previous infusion-related event should be premedicated (e.g., with acetaminophen, an antihistamine, a corticosteroid) for subsequent infusions.

In addition to peripheral neuropathy and hematologic changes and associated risks, other commonly experienced adverse events with the use of brentuximab vedotin included (with the incidence reported in patients with Hodgkin’s lymphoma) fatigue (49%), upper respiratory tract infection (47%), nausea (42%), diarrhea (36%), pyrexia (29%), rash (27%), cough (25%), abdominal pain (25%), and vomiting (22%). Approximately one-third of the patients in the clinical studies developed anti-brentuximab antibodies, and in some patients, neutralizing antibodies were identified. However, the effect of the antibodies on the efficacy and safety of the drug is not known.

Brentuximab vedotin may cause harm to the fetus if it is administered during pregnancy, and it is classified in Pregnancy Category D. Whether the drug is excreted in human milk is not known, and a decision should be made whether to discontinue nursing or not use the drug. The effectiveness and safety of the new drug in pediatric patients have not been established.

A small fraction of the MMAE that is released from brentuximab vedotin is metabolized, primarily via oxidation by CYP3A4/5. The concurrent use of ketoconazole, a strong CYP3A4 inhibitor, has been reported to increase the exposure to MMAE by approximately 34%, and the use of rifampin, a strong CYP3A4 inducer, reduced the exposure to MMAE by approximately 46%.

Brentuximab vedotin is administered by intravenous infusion over 30 minutes, and the recommended dosage is 1.8 mg/kg every 3 weeks. The dosage for patients weighing more than 100 kg should be calculated for 100 kg. Treatment should be continued until a maximum of 16 cycles, disease worsening, or unacceptable toxicity. In patients who experience neutropenia or peripheral neuropathy, the dosage may be reduced (e.g., 1.2 mg/kg) or treatment delayed. Treatment should be discontinued if a patient experiences grade 4 peripheral neuropathy, and growth factor support should be considered for subsequent cycles in patients who experience grade 3 or 4 neutropenia.

Brentuximab vedotin is supplied in single-use vials containing 50 mg of the drug. The vials should be stored in a refrigerator. The contents of each vial should be reconstituted with 10.5 mL Sterile Water for Injection. The volume of reconstituted solution needed to provide the calculated dose should be added to an infusion bag containing a minimum volume of 100 mL to achieve a final drug concentration of 0.4 to 1.8 mg/mL. The reconstituted solution can be diluted with 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or Lactated Ringer’s Injection. Following dilution, the solution may be administered immediately by intravenous infusion, or stored in a refrigerator and used within 24 hours of reconstitution.

Immunosuppressant

Activated T lymphocytes are the most important mediators of immunologic rejection. Belatacept (Nulojix—Bristol-Myers Squibb) is a soluble fusion protein that is produced by recombinant DNA technology. It is a derivative of abatacept (Orencia) and acts as a selective T-cell (lymphocyte) costimulation blocker. It binds to CD80 and CD86 on antigen-presenting cells more avidly than abatacept and blocks CD28-mediated costimulation of T lymphocytes. In vitro, belatacept inhibits T lymphocyte proliferation and the production of the cytokines interleukin-2, interleukin-4, interferon-gamma, and tumor necrosis factor alpha.

Belatacept is administered intravenously and is indicated for prophylaxis of organ rejection in adult patients receiving a kidney transplant. It should be used in combination with basiliximab (Simulect) induction, mycophenolate mofetil (e.g., CellCept), and corticosteroids. In the clinical studies, patients received either belatacept or cyclosporine (e.g., Neoral) in a regimen that also included basiliximab, mycophenolate mofetil, and corticosteroids. The efficacy outcomes for the two regimes
The labeled indications for belatacept are much more limited than those for cyclosporine. The latter agent also is indicated for prophylaxis of rejection in patients receiving liver and heart transplants and for the treatment of patients with rheumatoid arthritis and psoriasis. However, these are not indications for belatacept. Indeed, a boxed warning in the labeling of the new drug indicates that its use is not recommended in patients receiving liver transplants because of an increased risk of graft loss and death.

A boxed warning also appears for belatacept regarding the risk of posttransplant lymphoproliferative disorder, predominantly involving the central nervous system (CNS). The risk of this problem is increased in patients without immunity to Epstein-Barr virus (EBV). Therefore, belatacept should only be used in EBV-seropositive patients, and its use is contraindicated in patients who are EBV seronegative or with unknown serostatus.

Patients receiving immunosuppressants, including belatacept, are at increased risk of serious infections and malignancies, and these are the subjects of a boxed warning in the labeling for the new drug. To reduce the risk of malignancies involving the skin, exposure to sunlight and other ultraviolet light sources should be limited by wearing protective clothing and using a sunscreen with a high SPF. Prophylaxis against cytomegalovirus infection is recommended for at least 3 months after transplantation, and prophylaxis against Pneumocystis jirovecii also is recommended. PML, a rapidly progressive opportunistic infection of the CNS, has been reported with the use of belatacept and should be considered if new or worsening neurological, cognitive, or behavioral signs or symptoms occur.

The adverse events most often reported in the clinical studies of belatacept included anemia (45%), diarrhea (39%), urinary tract infection (37%), peripheral edema (34%), constipation (33%), hypertension (32%), pyrexia (28%), graft dysfunction (25%), cough (24%), nausea (24%), vomiting (22%), headache (21%), hypokalemia (21%), hyperkalemia (20%), and leukopenia (20%). The new drug is less likely than cyclosporine to cause hypertension and dyslipidemia, and appears less likely to reduce renal function. Belatacept is not likely to interact with other medications, and monitoring of serum concentrations is not necessary. The use of live vaccines should be avoided during treatment with belatacept.

Belatacept is classified in Pregnancy Category C and should only be used during pregnancy if the anticipated benefit justifies the risk to the fetus. Whether the new drug is excreted in human milk is unknown, and a decision should be made whether to discontinue nursing or not use the drug. The effectiveness and safety of belatacept in patients younger than 18 years have not been established.

Belatacept is administered by intravenous infusion over 30 minutes. The dose of the drug should be based on the actual body weight of the patient at the time of transplantation and should not be modified during the course of therapy unless a change in body weight of greater than 10% occurs. The initial dosage is 10 mg/kg, but the prescribed dose must be evenly divided by 12.5 mg for the dose to be prepared accurately using the reconstituted solution and the silicone-free disposable syringe provided. A silicone-free syringe is used to avoid the possible development of translucent particles with the use of siliconized syringes.

A dose of 10 mg/kg is administered on day 1 (day of transplantation, before implantation), day 5 (approximately 96 hours after the day 1 dose), and at the end of weeks 2, 4, 8, and 12 after transplantation. Maintenance doses of 5 mg/kg are administered at the end of week 16 and every 4 weeks (±3 days) thereafter.

Belatacept is supplied in vials containing 250 mg of the drug as a lyophilized powder. The vials should be stored in a refrigerator. The contents of a vial should be reconstituted with 10.5 mL Sterile Water for Injection, 0.9% Sodium Chloride Injection, or 5% Dextrose Injection, using the silicone-free disposable syringe provided. The reconstituted solution contains the drug in a concentration of 25 mg/mL. The volume of the reconstituted solution required to provide the dose for infusion should be determined, and this volume of reconstituted solution should be further diluted with a suitable infusion fluid.

Iron chelator

Iron overload is a potentially life-threatening consequence of frequent blood transfusions used in the treatment of rare, chronic blood disorders including thalassemia and sickle cell disease, as well as in other rare anemias and myelodysplastic syndromes. If not treated, excess iron can cause damage to the heart, liver, and endocrine glands.

Iron chelation therapy has been used in the treatment of transfusion-related iron overload, and by binding to iron, the chelating agent facilitates its excretion. Deferoxamine (Desferal) has been a standard therapy, but it must be used parenterally via prolonged infusions. Deferasirox (Exjade) was marketed in 2005 as the first orally effective chelating agent that is selective for iron.

Deferoxprone (Ferriprox—ApoPharma) is an iron chelator that is indicated for oral use in patients with transfusional iron overload caused by thalassemia syndromes when current chelation therapy is not adequate. In clinical studies, it reduced serum ferritin concentrations by at least 20% in more than one-half of patients. However, no controlled trials exist that demonstrate a direct treatment benefit, such as improvement in disease-related symptoms, functioning, or increased survival. Therefore, it is not a first-line therapy.

The labeled indication for deferoxprone is more limited than those for deferasirox and deferoxamine, which also are indicated for the treatment of transfusional iron overload in patients with other chronic anemias, in addition to thalassemia syndromes.

Approximately 2% of the patients in the clinical studies of deferoxprone experienced agranulocytosis, and this is the subject of a boxed warning in its labeling. Neutropenia may precede the development of agranulocytosis, and absolute neutrophil counts should be determined before starting treatment and monitored weekly during therapy. Treatment should be interrupted if infec-
tion develops, and the concomitant use of other drugs known to be associated with neutropenia or agranulocytosis is best avoided.

The adverse events most frequently reported with the use of deferiprone in the clinical studies included nausea (13%), vomiting (10%), abdominal discomfort (10%), arthralgia (10%), and neutropenia (6%). Increased ALT values (6%) have been commonly experienced and should be monitored monthly. Reductions in plasma zinc concentrations also have been reported, and zinc supplementation may be necessary.

Many patients experienced chromaturia, a reddish/brown discoloration of the urine that results from the excretion of the iron–deferiprone complex in the urine. Patients should be informed of this possibility and advised that it is not harmful.

One patient with a history of QT prolongation experienced torsades de pointes during therapy, and caution should be exercised in patients who are at increased risk of prolongation of the QT interval and associated complications.

Deferiprone may cause harm to the fetus if administered during pregnancy, and it is classified in Pregnancy Category D, whereas deferoxamine and deferasirox are classified in Category C. Whether the new drug is excreted in human milk is unknown, but a decision should be made whether to discontinue nursing or not use the drug. The effectiveness and safety of deferiprone in pediatric patients have not been established.

Because deferiprone has the ability to bind polyvalent cations (e.g., iron, zinc, aluminum), an interval of at least 4 hours should separate the administration of the new drug from the administration of medications (e.g., antacids) or supplements containing these cations.

Following oral administration, deferiprone is rapidly absorbed from the upper gastrointestinal tract and appears in the blood within 5 to 10 minutes. Most of a dose is metabolized via the UDP glucuronosyltransferase (UGT)1A6 pathway to a glucuronide derivative that lacks iron binding capacity. The potential exists for a UGT1A6 inhibitor (e.g., silymarin [milk thistle]) to inhibit the metabolism and increase the action of deferiprone. Up to 90% of a dose of the drug is recovered, primarily as the metabolite, in the urine within 24 hours after administration.

The recommended initial dosage of deferiprone is 25 mg/kg three times a day for a total of 75 mg/kg/day. Administering the drug with meals may reduce the possibility of nausea, and patients should be advised to take the first dose in the morning, the second dose at midday, and the third dose in the evening. The maximum dose is 33 mg/kg three times a day for a total of 99 mg/kg/day.

Deferiprone scored tablets are supplied in a 500-mg potency, and the dosage should be rounded to the nearest 250 mg (half tablet).
CPE assessment

Instructions: This exam must be taken online; please see “CPE information” for further instructions. There is only one correct answer to each question. This CPE activity will be available online at www.pharmacist.com no later than March 31, 2012.

1. Which of the following agents has such a long duration of action that precautions regarding certain risks should be observed for 4 months following discontinuation of treatment?
   a. Vemurafenib  
   b. Ruxolitinib  
   c. Belatacept  
   d. Vandetanib

2. With the use of which of the following agents is the determination of platelet counts an important monitoring parameter?
   a. Ruxolitinib  
   b. Deferiprone  
   c. Crizotinib  
   d. Belatacept

3. With the use of which of the following agents is agranulocytosis an important concern?
   a. Vemurafenib  
   b. Deferiprone  
   c. Vandetanib  
   d. Crizotinib

4. Which of the following agents is associated with the occurrence of cutaneous squamous cell carcinoma as an adverse event?
   a. Crizotinib  
   b. Ruxolitinib  
   c. Vemurafenib  
   d. Brentuximab vedotin

5. Which of the following agents should only be used in patients who are Epstein-Barr virus seropositive?
   a. Brentuximab vedotin  
   b. Belatacept  
   c. Vandetanib  
   d. Ruxolitinib

6. Which of the following agents is administered three times a day?
   a. Vemurafenib  
   b. Crizotinib  
   c. Vandetanib  
   d. Deferiprone

7. Which of the following statements is correct regarding vemurafenib?
   a. It acts by inhibiting Janus-associated kinases.
   b. It should only be used in patients with metastatic melanoma whose disease is associated with the BRAF V600E mutation.
   c. It is less effective than dacarbazine but better tolerated.
   d. It is used in a combination regimen with dacarbazine.

8. Which of the following statements is correct regarding vemurafenib?
   a. Patients should wear protective clothing and sunscreen and lip balm when outdoors to reduce sun exposure.
   b. It may cause renal toxicity, and creatinine clearance should be monitored regularly.
   c. Doses must be administered with a high-fat meal.
   d. It is primarily eliminated in the urine in unchanged form.

9. Which of the following statements is correct regarding vemurafenib?
   a. It is indicated for the treatment of patients with Hodgkin’s lymphoma.
   b. It acts by inhibiting T lymphocyte proliferation.
   c. Patients should be premedicated with an antihistamine and corticosteroid to reduce the risk of hypersensitivity reactions.
   d. Concurrent use with medications that prolong the QT interval should be avoided.

10. Which of the following statements is correct regarding vemurafenib?
    a. Anemia is often associated with its use.
    b. Blood pressure should be regularly monitored.
    c. It is administered twice a day.
    d. Its action may be increased by the concurrent use of a cytochrome P450 (CYP)3A4 inducer.

11. Which of the following statements is correct regarding ruxolitinib?
    a. It is indicated for the treatment of patients with non–small-cell lung cancer.
    b. Thyroid-stimulating hormone concentrations should be monitored, and thyroid replacement therapy often is necessary.
    c. Patients should be cautioned about the possible occurrence of herpes zoster.
    d. It causes prolongation of the QT interval and electrocardiograms (ECGs) should be monitored.

12. Which of the following statements is correct regarding ruxolitinib?
    a. It is administered subcutaneously.
    b. It is administered once a day.
    c. It is eliminated unchanged in the urine.
    d. Its action may be increased by the concurrent use of a strong CYP3A4 inhibitor.
13. Which of the following statements is correct regarding crizotinib?
   a. It is indicated for the treatment of patients with medullary thyroid cancer.
   b. It has been demonstrated in clinical studies to prolong survival.
   c. It may prolong the QT interval, and ECGs and electrolytes should be monitored.
   d. It is classified as a CD30-directed antibody.

14. Which of the following statements is correct regarding crizotinib?
   a. It acts by inhibiting the ALK (abnormal anaplastic lymphoma kinase) gene.
   b. Dermatological adverse reactions are the most common adverse events associated with its use.
   c. It must be administered apart from food.
   d. Its action may be increased by the concurrent use of omeprazole.

15. Which of the following statements is correct regarding brentuximab vedotin?
   a. It is indicated for the treatment of patients with myelofibrosis.
   b. It is classified as a tyrosine kinase inhibitor.
   c. It acts by disrupting the microtubule network in cancer cells.
   d. It is administered subcutaneously.

16. Which of the following statements is correct regarding brentuximab vedotin?
   a. It is a prodrug that is converted to its active form by plasma esterases.
   b. Peripheral neuropathy is commonly experienced with its use.
   c. Its use should be avoided in patients with impaired renal function.
   d. Concurrent use with a strong CYP3A4 inducer should be avoided.

17. Which of the following statements is correct regarding belatacept?
   a. It is a prodrug that is converted to etanercept following administration.
   b. Its indications include severe rheumatoid arthritis and plaque psoriasis.
   c. It is classified as a selective T-cell costimulation blocker.
   d. Serum concentrations must be monitored.

18. Which of the following statements is correct regarding belatacept?
   a. It should be used in a combination regimen with basiliximab, mycophenolate mofetil, and corticosteroids.
   b. Eligibility to be treated with the drug must be confirmed by a positive response to an FDA-approved test.
   c. Its dosage should be reduced in patients with moderate or severe renal impairment.
   d. Its action is increased by the concurrent use of a strong CYP3A4 inhibitor.

19. Which of the following statements is correct regarding deferiprone?
   a. It is indicated for use in patients with iron deficiency anemia.
   b. It is used in a combination regimen with deferoxamine.
   c. It is converted to ferrous sulfate following administration.
   d. It is used in patients with thalassemia syndromes who receive frequent blood transfusions.

20. Which of the following statements is correct regarding deferiprone?
   a. Absolute neutrophil counts should be monitored during treatment.
   b. It has been demonstrated to increase survival in patients with sickle cell disease.
   c. It should be administered with an antacid to reduce gastrointestinal adverse events.
   d. Hypokalemia is often associated with its use.

CPE information
To obtain 2.0 contact hours of CPE credit (0.2 CEUs) for this activity, complete and submit the CPE exam online at www.pharmacist.com/education. A Statement of Credit will be awarded for a passing grade of 70% or better. You will have two opportunities to successfully complete the CPE exam. Pharmacists who successfully complete this activity before March 15, 2015, can receive credit.

Your Statement of Credit will be available online immediately upon successful completion of the CPE exam.

CPE instructions: Get your documentation of credit now! Posttests can be completed at www.pharmacist.com/education using these steps:
1. Go to Online CPE Quick List and click on the title of this activity.
2. Log in. APhA members enter your user name and password. Not an APhA member? Just click “Create one now” to open an account. No fee is required to register.
3. Go to www.pharmacist.com/CPEMonitor to provide APhA with your required NABP e-Profile ID.
4. Successfully complete the CPE exam and evaluation form to gain immediate access to your documentation of credit.

Live step-by-step assistance is available Monday through Friday 8:30 am to 5:00 pm ET at APhA Member Services at 800-237-APhA (2742) or by e-mailing InfoCenter@pharmacist.com.