REVIEW ARTICLE

Recent New Drug Approvals, Part 2: Drugs Undergoing Active Clinical Studies in Children

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The objective of this 2-part review is to provide information about drugs that have been recently approved by the US Food and Drug Administration. Part 1 reviewed recently approved drugs with pediatric indications. Part 2 reviews drugs recently approved only in adults and have published or ongoing studies in children.

INDEX TERMS drug approval, drug industry, Food and Drug Administration, pediatrics

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INTRODUCTION

This is the second article in a 2-part series that reviews recently approved drugs. The first article reviewed drugs that when approved by the US Food and Drug Administration (FDA) contained labeling for use in children. This second part reviews drugs that have been approved for use only in adults and have published or ongoing clinical studies in children as reported in ClinicalTrials.gov.

This review is divided into 2 sections. The first section includes new drugs with potential for use in children. Oncology drugs are discussed separately in the second section because they present a unique problem: children often have different types of cancer than those found in adults. Currently, the Pediatric Research Equity Act only requires drug companies to perform studies in children for the approved adult indication. A proposed solution would be to require newly approved drugs in adults to be studied in children with similar disease pathways or gene mutations.

Tables 1 and 2 provide a summary of select adult trials that contributed to drug approval and pediatric published and ongoing studies for each drug.

NEW DRUGS WITH ACTIVE PEDIATRIC TRIALS

Deferiprone (Ferriprox)

Iron is an essential element in many physi-

ologic functions including oxygen transport, energy production, oxidative metabolism, DNA synthesis, and oxygen storage in muscle. Iron can also cause harm by catalyzing the formation of free radicals that attack cell membranes, DNA, and proteins. These harmful effects are increased in states of iron overload. The concern for iron overload is important in patients with thalassemias because ineffective hemoglobin synthesis can result in chronic anemias that are treated with multiple blood transfusions. Repeated blood transfusions can cause iron overload, which can then result in cardiac toxicity, liver fibrosis and cirrhosis, and endocrinopathies.¹

Deferoxamine was the first iron chelator approved for human use. It requires parenteral administration and is typically given as a subcutaneous or intravenous infusion for 8 to 12 hours for 5 to 7 days per week. The first oral chelator approved for human use, deferasirox, is administered once daily and is approved for use in children 2 years of age and older. A second oral iron chelator, deferiprone (Ferriprox, ApoPharma USA, Inc, Rockville, MD), was approved for human use on October 14, 2011.

Indication(s)

Deferiprone is indicated for the treatment of adults with transfusion iron overload due to thalassemias when current chelation therapy is inadequate.² Deferiprone has been studied in children 1 to 10 years of age (n=100) for 6 months

Table 1. New Drugs With Active Pediatric Trials

Study	Design	Population	Dose	Primary Outcome(s)
Deferiprone				
EIAly et al, 2010 ³	Uncontrolled, safety and efficacy study	Thalassemia and sickle cell disease with iron overload, ages 1-10 yr (n=100)	50-100 mg/kg/day in 3 divided doses (liquid formulation, 100 mg/mL)	Significant decline in serum ferritin concentrations from baseline after 6 mo of therapy (p<0.0005). Most common AEs: GI intolerance (11%), increased ALT (12%), mild neutropenia (6%)
NCT00293098 ⁴	Expanded access study for compassionate use in patients with thalassemia and iron-induced heart disease	Treatment of iron overload in children (ages not specified)	75 mg/kg/day in 3 divided doses	<i>Study in progress</i>
NCT00897221 ⁵	Phase 2, multicenter, open-label, single treatment, safety and efficacy study	Friedreich ataxia, ages 7-35 yr, (estimated enrollment: n=36)	20 or 40 mg/kg/day (liquid formulation, 100 mg/mL)	Occurrence of AEs. <i>Study completed; no study results posted</i>
Ezogabine				
Porter et al, 2007 ⁷	Multicenter, randomized, parallel-group, blinded, placebo controlled trial	Inadequately controlled partial-onset seizures, ages 16-70 yr (n=399)	600 mg/day, 900 mg/day, 1200 mg/day, or placebo in 3 divided doses	Significant decrease (p<0.001 overall difference across treatment arms) in monthly seizure frequency from baseline: 23% (600 mg), 29% (900 mg), 35% (1200 mg), and 13% (placebo). Most common AEs: somnolence, dizziness confusion
Gil-Nagel et al, 2012 ⁶	Multicenter, randomized, double-blind, placebo-controlled trial	Partial-onset seizures (≥4 seizures per mo), ages 18-75 yr (n=538)	600 mg/day, 900 mg/day, or placebo in 3 divided doses	Median seizure reduction of 27.9% for 600 mg/day (p=0.007) and 39.9% for 900 mg/day (p<0.001) compared to 15.9% for placebo. Discontinued due to AEs: 17% (600 mg), 26% (900 mg), 8% (placebo). Most common AEs were dizziness, somnolence, headache, and fatigue
French et al, 2011 ⁸	Multicenter, randomized, parallel-group, double-blind, placebo controlled trial	Simple or complex partial-onset seizures (≥4 seizure per mo), ages 18-75 yr (n=306)	1200 mg/day or placebo in 3 divided doses	44% reduction in seizure frequency compared to 17.5% for placebo (p<0.001). Most common AEs: dizziness, somnolence, fatigue, confusion
NCT01494584 ⁹	Phase 2, open-label, multiple-dose pharmacokinetic study	Uncontrolled partial-onset seizures or Lennox-Gastaut syndrome, ages 12-17 yr, (estimated enrollment: n=16)	Dose escalation (doses not specified)	Steady-state pharmacokinetics, safety, and tolerability. <i>Study in progress</i>
NCT01668654 ¹⁰	Phase 3, open-label, long-term safety extension study	Partial-onset seizures or Lennox-Gastaut syndrome, age ≥12 yr, (estimated enrollment: n=500)	Weight-based dosing in 3 divided doses (dose not specified)	Incidence of AEs. <i>Study in progress</i>

Table 1. New Drugs With Active Pediatric Trials (cont.)

Study	Design	Population	Dose	Primary Outcome(s)
Fidaxomicin				
Louie et al, 2011 ¹⁹	Prospective, multicenter, double-blind, randomized, parallel-group trial	<i>Clostridium difficile</i> infection, age ≥16 yr (n=629)	Fidaxomicin 200 mg twice daily or vancomycin 125 mg four times daily for 10 days	Non-inferior clinical cure rate for fidaxomicin (88.2%) compared to vancomycin (85.8%). Lower recurrence rate with fidaxomicin (15.4%) than vancomycin (25.3%) (p=0.005). AEs similar for both groups.
Cornely et al, 2012 ¹⁸	Multicenter, double-blind, randomized, non-inferiority trial	<i>C difficile</i> infection, age ≥16 yr (n=535)	Fidaxomicin 200 mg every 12 hr or vancomycin 125 mg every 6 hr for 10 days	Non-inferior clinical cure rate for fidaxomicin (87.7%) compared to vancomycin (86.8%). AEs similar for both groups.
NCT01533844 ²¹	Multicenter, prospective observational non-interventional feasibility study	Term neonates with suspected <i>C difficile</i> -associated disease, age <28 days, (estimated enrollment: n=60)	None	Feasibility of intervention and pharmacokinetic study with fidaxomicin oral suspension. Incidence and clinical aspects of <i>C difficile</i> . <i>Study in progress</i>
NCT01591863 ²⁰	Phase 2, open-label uncontrolled study assessing the safety, tolerability, and pharmacokinetics of fidaxomicin	<i>C difficile</i> -associated diarrhea, ages 6 mo to 18 yr, (estimated enrollment: n=32)	32 mg/kg/day to a maximum of 400 mg/day in 2 divided doses (oral suspension or tablets)	Safety and tolerability, fidaxomicin and metabolite plasma and fecal concentrations. <i>Study in progress</i>
Icatibant				
Lumry et al, 2011 ²⁷	Phase 3, randomized, double-blind, placebo-controlled study (FAST-3)	Type I or II hereditary angioedema, age ≥18 yr	Single subcutaneous injection of icatibant 30 mg or placebo	Median time to ≥50% reduction in symptom severity: 2 hr for icatibant vs 19.8 hr for placebo (p<0.001)
Cicardi et al, 2010 ²⁶	Two double-blind, randomized, multicenter trials, FAST-1 (icatibant vs placebo) and FAST-2 (icatibant vs oral tranexamic acid)	Type I or II hereditary angioedema, age ≥18 yr, FAST-1 (n=56), FAST-2 (n=76)	FAST-1: Single subcutaneous injection of icatibant 30 mg or placebo. FAST-2: Single subcutaneous injection of icatibant 30 mg or tranexamic acid 3 g daily for 2 days	Time to clinically significant relief of symptoms: FAST-1: icatibant 2.5 hr vs placebo 4.6 hr (p=0.14). FAST-2: icatibant 2 hr vs tranexamic acid 12 hr (p<0.001)
NCT01386658 ²⁹	Phase 3, multicenter, open-label, non-randomized, single-arm study	Children and adolescents with acute hereditary angioedema, ages 2 to 17 yr (estimated enrollment: n=36)	Single subcutaneous dose of icatibant 0.4 mg/kg (max dose of 30 mg)	Pharmacokinetic profile, safety, efficacy. <i>Study in progress</i>
Linagliptin				
Product information ³²	Eight double-blind, placebo-controlled, clinical safety and efficacy studies	Type 2 diabetes, ages 20-80 yr; approximately 3800 patients	Linagliptin 5 mg PO daily	Clinically significant improvements in HbA1c, fasting plasma glucose, and 2-hr postprandial glucose, compared to placebo

Table 1. New Drugs With Active Pediatric Trials (*cont.*)

Study	Design	Population	Dose	Primary Outcome(s)
NCT01342484 ³³	Phase 2, randomized, double-blind, placebo-controlled, parallel-group, dose-finding study	Type 2 diabetes and insufficient glycemic control, ages 10-17 yr (estimated enrollment: n=117)	Linagliptin 1 mg or 5 mg PO once daily for 12 wk	Comparison of glucose-lowering effect (change in HbA1c) of small dose (1 mg), large dose (5 mg), and placebo. <i>Study in progress</i>
Rivaroxaban				
Patel et al, 2011 ³⁶	Multicenter, randomized, double-blind, double-dummy trial (ROCKET AF)	Adults with non-valvular atrial fibrillation at increased risk for stroke (n=14,264)	Rivaroxaban 20 mg PO once daily vs dose-adjusted warfarin	Incidence of stroke or systemic embolism: 1.7% per yr for rivaroxaban and 2.2% per yr for warfarin (p<0.001)
Eriksson et al, 2008 ³⁵	Phase 3, randomized, double-blind, safety and efficacy study (RECORD 1)	DVT prophylaxis in adults undergoing elective total knee replacement (n=3153 for superiority analysis, n=4433 for safety analysis)	Rivaroxaban 10 mg PO once daily vs enoxaparin 40 mg subcutaneously once daily	Composite number of DVT: 1.1% for rivaroxaban and 3.7% for enoxaparin (p<0.001). Occurrence of major bleeding: 0.3% for rivaroxaban and 0.1% for enoxaparin (p=0.18)
NCT01145859 ³⁸	Phase 1, single-dose, pilot pharmacokinetic and pharmacodynamic study	Venous thromboembolism, ages 6 mo to 18 yr (estimated enrollment: n=48)	Weight-adjusted dose with equivalent exposure compared to 10 mg or 20 mg in adults	Pharmacokinetic (AUC and C _{max}) and pharmacodynamic (PT, aPTT, and anti-factor Xa) parameters. <i>Study in progress</i>
NCT01684423 ³⁹	Phase 2, open-label, active-controlled, randomized study	Venous thromboembolism, ages 6 mo to 17 yr (estimated enrollment: n=50)	Weight-adjusted dose with equivalent exposure compared to 20 mg in adults (tablets and oral suspension)	Number of major and clinically relevant non-major bleeding events after 31 and 60 days. <i>Study in progress</i>
Roflumilast				
Bateman et al, 2006 ⁴⁵	Phase 2/3, randomized, double-blind, parallel-group, safety and efficacy study	Adults with mild to moderate asthma (n=693)	Roflumilast 100 mcg, 250 mcg, or 500 mcg once daily for 12 wk	Change from baseline FEV ₁ : Roflumilast 500 mcg was superior to 100 mcg (p=0.02). Significant improvement from baseline in all dose groups (p≤0.06)
Neville et al, 2008 ⁴³	Open-label, single-dose, crossover dose-escalation pharmacokinetic study	Stable mild to moderate asthma, ages 6-16 yr (n=25)	Roflumilast 100 mcg in period 1 and 250 mcg in period 2 (separated by washout period) once daily	No difference between age groups for pharmacokinetic parameters; parameters were similar to adults. Few AEs reported; all assessed as unrelated or unlikely related to roflumilast
NCT00163475 ⁴¹	Phase 3, randomized, double-blind, safety and efficacy study (the MOVE-study)	Stable asthma, ages 12-70 yr (estimated enrollment: n=511)	Roflumilast 500 mcg once daily for 6 wk (morning vs evening administration)	Mean change in FEV ₁ . <i>Study completed, no results posted</i>
NCT00163527 ⁴²	Phase 3, randomized, double-blind, parallel assignment, safety and efficacy study	Chronic asthma, taking small-dose inhaled corticosteroids, ages 12-70 yr (estimated enrollment: n=2054)	Roflumilast once daily for 24 wk (no dose specified)	Mean change in FEV ₁ . <i>Study completed, no results posted</i>

AEs, adverse events; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AUC, area under the curve; C_{max}, peak concentration; DVT, deep vein thrombosis; FEV₁, forced expiratory volume in 1 second; GI, gastrointestinal; HbA1c, glycosylated hemoglobin; max, maximum; PO, orally; PT, prothrombin time; Xa, activated factor X

Table 2. New Oncology Drugs With Active Pediatric Trials

Study	Design	Population	Dose	Primary Outcome(s)
Brentuximab				
Younes et al, 2012 ⁵²	Phase 2, open-label, single-arm trial	Relapsed or refractory HL after ASCT, ages 15-77 yr (n=102)	1.8 mg/kg IV (for 30 min) once every 3 wk	Overall response rate: 75% (34% complete response) for median duration of 6.7 mo
Pro et al, 2012 ⁵¹	Phase 2, multicenter, open-label trial	Relapsed or refractory ALCL, ages 14-76 yr (n=58)	1.8 mg/kg IV (for 30 min) once every 3 wk (16 doses)	Overall response rate: 86% (57% complete response) for median duration of 12.6 mo
NCT01492088 ⁵³	Phase 1/2, open-label, single-agent, multicenter, dose-escalation study	Relapsed or refractory ALCL (phase 2) or HL (phase 1), ages 2-18 yr, (estimated enrollment: n=42)	IV infusion every 21 days for up to 16 cycles (no dose specified)	AEs (phase 1), pharmacokinetics (phase 1), complete and partial response (phase 2). <i>Study in progress</i>
NCT01421667 ⁵⁴	Phase 2, single-arm, open-label multicenter trial	CD30-positive non-Hodgkin lymphoma, ≥6 yr of age, (estimated enrollment: n=75)	1.8 mg/kg IV once every 3 wk	Overall response rate (study in progress)
NCT01461538 ⁵⁵	Phase 2, open-label, multicenter trial	CD30-positive non-lymphomatous malignancies, ≥6 yr of age, (estimated enrollment: n=80)	1.8 mg/kg IV every 3 wk vs 2.4 mg/kg IV every 3 wk	Objective response rate. <i>Study in progress</i>
NCT01196208 ⁵⁶	Expanded access study to allow brentuximab treatment to patients assigned to placebo in a phase 3 study (SGN35-005 protocol)	Relapsed or refractory HL or ALCL, ≥6 yr of age	1.8 mg/kg IV every 3 wk	Objective response rate. <i>No study results posted</i>
NCT00947856 ⁵⁷	Phase 2, multicenter, open-label, safety and efficacy study	CD30-positive hematologic malignancies (previously in a brentuximab study), ≥6 yr of age, (estimated enrollment: n=125)	1.2 mg/kg or 1.8 mg/kg IV every 21 days	Incidence of AEs, best clinical response. <i>Study in progress</i>
Crizotinib				
Study A (product information) ⁶²	Open-label, multicenter, single-arm study	Locally advanced or metastatic ALK-positive NSCLC, ages 29-82 yr (n=136)	250 mg PO twice daily (median duration of treatment: 22 wk)	Objective response rate: 50% (1 complete and 67 partial responses), median duration of response: 41.9 wk
Study B (product information) ⁶²	Open-label, multicenter, single-arm study	Locally advanced or metastatic ALK-positive NSCLC, ages 21-79 yr (n=119)	250 mg PO twice daily (median duration of treatment: 32 wk)	Objective response rate: 61% (2 complete and 69 partial responses), median duration of response: 48.1 wk
Kwak et al, 2010 ⁶³	Open-label, multicenter, 2-part phase 1 trial (part 1: dose escalation; part 2: expanded cohort efficacy study)	Advanced ALK-positive NSCLC, ages 25-78 yr (n=82)	250 mg PO twice daily (median duration of treatment: 6.4 mo)	Overall response rate: 57% (1 complete and 46 partial responses), estimated 6-mo progression-free survival of 72%

Table 2. New Oncology Drugs With Active Pediatric Trials (*cont.*)

Study	Design	Population	Dose	Primary Outcome(s)
NCT00939770 ⁶⁴	Multicenter, open-label, phase 1 dose-escalation study followed by a phase 2 study	Relapsed or refractory solid tumors, primary CNS tumors, and ALCL, ages 1-21 yr, (estimated enrollment: n=196)	Doses (not specified) administered PO twice daily (28-day cycles)	Maximum tolerated dose and recommended phase 2 dose, toxicities, and pharmacokinetics. <i>Study in progress</i>
NCT01606878 ⁶⁷	Phase 1, multicenter, open-label, dose-escalation study	Relapsed or refractory solid tumors or ALCL, ages 1-21 yr, (estimated enrollment: n=58)	Doses (not specified) administered PO twice daily	AEs and maximum-tolerated dose when administered with combination chemotherapy. <i>Study in progress</i>
NCT01644773 ⁶⁸	Phase 1, open-label, dose-escalation study	Diffuse intrinsic pontine glioma and high-grade glioma, ages 2-21 yr, (estimated enrollment: n=42)	Doses administered PO twice daily. Starting dose: 130 mg/m ² (increased by approximately 30% up to 6 dosage concentrations)	Maximum tolerated dose. <i>Study in progress</i>
Ipilimumab				
Hodi et al, 2010 ⁷²	Phase 3, randomized, double-blind, multicenter trial	Unresectable stage III or IV melanoma, previously treated, >18 yr of age (n=676)	Ipilimumab 3 mg/kg + gp100 vs ipilimumab 3 mg/kg alone vs gp100 alone	Survival was 10 mo for ipilimumab + gp100, 10.1 mo for ipilimumab alone, and 6.4 mo for gp100 alone. Grade 3 or 4 AEs: 10%-15% for ipilimumab and 3% for gp100 alone
NCT01445379 ⁷³	Phase 1, open-label, dose-escalation study	Solid malignant tumor resistant to standard therapy, ages 1-21 yr, (estimated enrollment: n=34)	Four planned dose concentrations up to largest dose tolerated in adults (doses not specified)	Tolerance and toxicity profile; pharmacokinetics. <i>Study in progress</i>
NCT01696045 ⁷⁴	Phase 2, open-label, safety and efficacy study	Previously treated or untreated unresectable stage III or IV malignant melanoma, ages 12-17 yr, (estimated enrollment: n=30)	10 mg/kg once every 3 wk for 4 doses then every 12 wk till progression or unacceptable toxicity	Overall survival at 1 yr. <i>Study in progress</i>
Vandetanib				
Wells et al, 2012 ⁷⁸	Phase 3, multicenter, randomized, double-blind, placebo-controlled trial	Unresectable locally advanced or metastatic medullary thyroid carcinoma, >18 yr of age (n=331)	300 mg/day	Median progression-free survival: 30.5 mo (predicted) for vandetanib vs 19.3 mo for placebo (p<0.001). AEs: diarrhea, rash, nausea, hypertension, and headache
NCT00514046 ⁷⁹	Phase 1/2, open-label, safety and efficacy study	Unresectable medullary thyroid carcinoma, ages 5-18 yr (estimated enrollment: n=21)	150 mg/m ² once daily in 28-day cycles	Objective response, change in tumor markers, change in tumor-related diarrhea, safety, maximum tolerated dose, and pharmacokinetics. <i>Study in progress</i>

Table 2. New Oncology Drugs With Active Pediatric Trials (*cont.*)

Study	Design	Population	Dose	Primary Outcome(s)
NCT00472017 ⁸⁰	Phase 1, open-label, safety and efficacy study	Newly diagnosed brainstem glioma receiving concurrent radiation therapy, ages 2-21 yr (estimated enrollment: n=35)	Vandetanib once daily, dose escalation (doses not specified)	Maximum tolerated dose and dose-limiting toxicity. <i>Study completed; no study results posted</i>
Vemurafenib				
Chapman et al, 2011 ⁸⁶	Phase 3, randomized trial	Previously untreated, unresectable stage IIIC or stage IV BRAF V600–positive melanoma, >18 yr of age (n=675)	Vemurafenib 960 mg orally twice daily vs dacarbazine 1000 mg/m ² IV every 3 wk	Overall survival at 6 mo: 84% for vemurafenib and 64% for dacarbazine. Common AEs with vemurafenib: arthralgia, rash, fatigue, alopecia, nausea, diarrhea
Sosman et al, 2012 ⁸⁷	Phase 2, multicenter, open-label trial	Previously treated BRAF V600–positive melanoma, >18 yr of age (n=132)	Vemurafenib 960 mg orally twice daily	Overall response rate of 53% (6% complete response, 47% partial response). Most common AEs: arthralgia, rash, fatigue, photosensitivity, alopecia
NCT01519323 ⁸⁹	Phase 1, open-label, multicenter, single-arm, dose-escalation study	Stage IIIC or IV BRAF V600–positive melanoma, ages 12-17 yr (estimated enrollment: n=27)	Vemurafenib twice daily, dose escalation (doses not specified)	Maximum tolerated dose. <i>Study in progress</i>
NCT01636622 ⁸⁸	Phase 1, open-label, safety and efficacy study	Advanced solid tumor or BRAF-positive lymphoma, >12 yr of age, (estimated enrollment: n=96)	Vemurafenib 480 mg twice daily every 3 wk (combination therapy with carboplatin (dosed by AUC) and paclitaxel 100 mg/m ²)	Maximum tolerated dose. <i>Study in progress</i>

AEs, adverse events; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ASCT, autologous stem cell transplant; AUC, area under the curve; CNS, central nervous system; gp100, glycoprotein 100 peptide vaccine; HL, Hodgkin lymphoma; IV, intravenous; NSCLC, non-small cell lung cancer; PO, orally

who received 50 to 100 mg/kg/day,³ but it is not currently approved for pediatric patients. Deferriprone use was associated with a significant decrease in serum ferritin concentrations and a toxicity profile similar to that of adult studies.³

Clinical Pharmacology

Deferriprone is a chelating agent with affinity for ferric ion (Fe⁺⁺⁺) forming a 3:1 chelator to iron complex (Figure 1). No clinical studies have assessed the relationship between the dose of deferriprone and the amount of iron eliminated from the body. Following oral administration, the peak serum concentration occurs about 1 hour after dosing in fasted individuals and 2 hours in fed individuals. Food decreases the maximum

concentration about 40% and the area under the concentration curve by 10%. Deferriprone is rapidly eliminated predominately by metabolism via glucuronidation with an elimination half-life of 1.9 hours. Protein binding is less than 10%.²

Dosage and Administration

Deferriprone is available as a 500-mg scored, film-coated tablet. The initial recommended dose is 25 mg/kg (rounded to the nearest 250 mg, half tablet), orally three times daily for a total of 75 mg/kg/day. The dose can be increased every 2 to 3 months to a maximum dose of 33 mg/kg, three times daily for a total of 99 mg/kg/day. Although deferriprone does not carry pediatric labeling, the dosing chart provided in

Figure 1. Iron chelation by deferiprone. DFP, deferiprone; Fe, iron.

the product label goes down to a dosing weight of 20 kg.² In the pediatric study by ElAlfy et al,³ a dose of 50 to 100 mg/kg/day (in 3 divided doses) was used. In addition, a liquid formulation was given, but this product is not commercially available in the United States.³ The ongoing pediatric studies^{4,5} report daily dosing ranges between 20 to 75 mg/kg/day.

Comments

Deferiprone has a boxed warning of agranulocytosis/neutropenia. The absolute neutrophil count (ANC) should be measured before beginning therapy and weekly during therapy. Deferiprone therapy should be interrupted for an ANC $< 1.5 \times 10^9/L$ or symptoms of an infection. For an ANC $< 0.5 \times 10^9/L$ consider hospitalization and do not resume therapy without a careful assessment of the risks and benefits. Avoid the concurrent use of other drugs that are associated with neutropenia.²

Although studies assessing the effect of deferiprone on QT interval have not been conducted, deferiprone should be used with caution in patients at risk for QT prolongation. One patient with a documented history of QT prolongation experienced torsades de pointes during deferiprone treatment.²

The most common adverse reactions occurring in greater than 5% of patients include neutropenia, nausea, abdominal pain/discomfort, vomiting, elevated alanine aminotransferase, arthralgia, and chromaturia. Other less common side effects include agranulocytosis, diarrhea, dyspepsia, weight gain, elevated aspartate aminotransferase, changes in appetite, back pain, arthropathy, and headache.²

Although not studied, deferiprone should not be given within 4 hours of ingesting foods, mineral supplements, and antacids that contain polyvalent cations (iron, aluminum, and zinc).²

Ezogabine (Potiga)

The search for new, more effective, and better-tolerated antiepileptic drugs for the treatment of inadequately controlled seizures remains a major therapeutic quest. Current antiepileptic drugs target voltage-dependent sodium or calcium channels, enhance γ -aminobutyric acid (GABA), antagonize T-type calcium channels, or reduce glutamate-induced receptor excitation. Ezogabine (Potiga, GlaxoSmithKline, Research Triangle Park, NC) was approved June 10, 2011. It has a novel mechanism in which it binds to voltage-gated potassium channels to regulate neuronal excitability.

Indication(s)

Ezogabine (retigabine) is indicated for adjunctive treatment of partial-onset seizures in patients 18 years of age and older. Safety and efficacy of ezogabine were established in adults in 3 multicenter clinical studies.⁶⁻⁸ Ezogabine, is currently being investigated in 2 open-label studies in pediatric patients to evaluate the pharmacokinetics⁹ and safety and tolerability^{9,10} in patients with uncontrolled partial-onset seizures or Lennox-Gastaut syndrome.

Clinical Pharmacology

The mechanism of action of ezogabine is not completely understood, but *in vitro* studies suggest that it may enhance transmembrane potassium currents by activating KCNQ channels (a type of ion channel), which are thought to stabilize the resting membrane potential to reduce brain excitability.^{11,12} Other studies¹¹ indicate ezogabine may also augment GABA-mediated channels. Ezogabine is rapidly absorbed after oral administration, with an oral bioavailability

of about 60%. High-fat meals can increase peak concentrations but do not affect the extent of absorption. Studies suggest ezogabine is 80% bound to plasma protein, but this does not appear to be clinically significant with respect to displacement of other medications. Ezogabine is well distributed throughout the body and is extensively metabolized by glucuronidation and acetylation.¹¹

Dosage and Administration

In adults, the recommended starting dose is 100 mg three times daily (300 mg/day) for the first week. The dose should be titrated weekly by no more than 150 mg/day to a goal dosage between 200 and 400 mg three times daily (600-1200 mg/day). Little improvement has been observed with doses between 900 mg/day and 1200 mg/day, and the larger dose was associated with an increase in adverse events and drug discontinuation. No dose adjustment is needed for mild renal or hepatic impairment but is required with moderate or severe changes in renal or hepatic function. When ezogabine is discontinued, the dose should be reduced slowly over a period of at least 3 weeks to minimize the potential for withdrawal or increased seizure frequency. Ezogabine is available as 50-mg, 200-mg, 300-mg, and 400-mg tablets and it may be taken with or without food.¹¹

Comments

Several warnings and precautions should be considered in patients taking ezogabine. In clinical trials, ezogabine was associated with urinary retention (approximately 2%), so urologic symptoms should be monitored closely, especially in patients with other risk factors for urinary retention. Confusion (4%), psychosis (<1%), and hallucinations (<1%) were also reported in trials more commonly than with placebo. The effects were dose related and often presented within the first 8 weeks of therapy. Also, rapid titration was associated with an increased risk of neuropsychiatric symptoms. Dizziness (23%) and somnolence (22%) were reported and these effects also appeared to be dose related. Most of these effects were mild or moderate in nature, most commonly occurred in the titration phase, and diminished with continued use. Ezogabine has also been shown to cause QT prolongation, so QT interval should be monitored in high-risk

patients. As with other antiepileptic medications, ezogabine may increase the risk of suicidal thoughts or behavior, so patients should be informed of this risk and advised to seek medical attention if signs or symptoms of depression or mood changes develop.¹¹

Other reported adverse reactions include diplopia, blurred vision, gastrointestinal disturbances, fatigue, infection (specifically influenza), and weight gain. Most of these reactions appear to be dose related.¹¹

The safety and efficacy of ezogabine in patients younger than 18 years have not been established, but in animal studies, young rats appear to have increased sensitivity to urinary retention and neurotoxicity, compared to adult rats.¹¹

Fidaxomicin (Difcid)

Clostridium difficile is one of the most common infectious causes of antibiotic-associated diarrhea and typically occurs after broad-spectrum antibiotic use.¹³ Illness severity varies greatly, but severe disease can be associated with ileus, toxic megacolon, and even death.¹⁴ In children, there is an increasing trend in incidence of *C difficile* infection, but in contrast to adults, there does not appear to be an increasing trend in severity of illness.¹⁵ According to the Infectious Diseases Society of America, first-line treatment options include metronidazole and oral vancomycin.¹⁶ *In vitro*, fidaxomicin (Difcid, Optimer Pharmaceuticals, Inc, San Diego, CA), which was previously referred to as OPT-80, has been shown to be 8 times more potent than vancomycin against clinical isolates of *C difficile*.¹⁷ It was approved May 27, 2011.

Fidaxomicin has been shown to be non-inferior to vancomycin for *C difficile* infection^{18,19} and was associated with a significantly lower rate of recurrence with some strains.¹⁹

Indication(s)

Fidaxomicin has been approved for treatment of *C difficile*-associated diarrhea (CDAD) in adults (18 years of age or older). Fidaxomicin has been studied in patients 16 years of age and older,^{18,19} and there are currently 2 ongoing studies in children. In a phase 2 open-label study,²⁰ investigators are assessing the safety, tolerability, and the pharmacokinetics of fidaxomicin in patients aged 6 months to 18 years. Fidaxomicin is also being investigated for possible use in

neonates with CDAD in an observational, non-interventional feasibility study.²¹

Clinical Pharmacology

Fidaxomicin is a macrolide antibiotic and is bactericidal against *C difficile* *in vitro*. It acts locally in the gastrointestinal tract and has minimal systemic absorption at therapeutic doses. Metabolism is not dependent on cytochrome P450 enzymes but occurs through hydrolysis, and an active metabolite is formed (OP-1118). Fidaxomicin and its active metabolite are mainly excreted through feces. In controlled trials, renal impairment did not affect plasma concentrations, so no adjustment is recommended based on renal function. The effects of hepatic impairment have not been evaluated, but because fidaxomicin is not significantly metabolized through the liver, dose adjustment does not appear to be necessary based on hepatic function.²²

Dosage and Administration

Fidaxomicin is available as a 200-mg oral tablet and the recommended adult dose is 200 mg orally twice daily. It may be administered with or without food.²² Fidaxomicin 32 mg/kg/day in 2 divided doses (maximum of 400 mg/day) is currently being studied in pediatric patients.²⁰ In this study an oral suspension is being used in patients younger than 6 years, but this product is not commercially available in the United States.

Comments

In clinical trials, there was no significant difference in safety between fidaxomicin and vancomycin. The most commonly reported adverse events associated with fidaxomicin were mild gastrointestinal symptoms (nausea, vomiting, diarrhea, and abdominal pain).^{18,19} Other adverse events that have rarely been reported with use of fidaxomicin are gastrointestinal hemorrhage, anemia, and neutropenia.²²

Icatibant (Firazyr)

Hereditary angioedema (HAE) is a rare autosomal dominant disease presenting with recurrent self-limiting episodes of skin and mucosal swelling/edema. This edema is caused by the absence (type I HAE) or decreased (type II HAE) function of C1-esterase inhibitor, which plays a major role in regulation of the factor XII/kallikrein

proteolytic cascade that results in bradykinin production.²³⁻²⁵

Indication(s)

Icatibant (Firazyr, Shire Orphan Therapies, Inc, Lexington, MA) was approved August 25, 2011, for acute attacks of HAE in adults (18 years of age or older)²⁶⁻²⁸ and is currently being studied in a phase 3 clinical trial for use in pediatric patients with HAE.²⁹

Clinical Pharmacology

Icatibant is a competitive bradykinin B2 receptor antagonist (Figure 2). Bradykinin is a vasodilator thought to be responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain. Icatibant inhibits bradykinin from binding the B2 receptor, which results in resolution of the clinical symptoms of an acute HAE attack.²⁸

Icatibant intravenous doses of 0.4 and 0.8 mg/kg infused for a period of 4 hours elicited an inhibition response to bradykinin challenge for 6 to 8 hours after the end of the infusion time. From this analysis, icatibant 30 mg injected subcutaneously is thought to be effective for at least 6 hours. Effect on QTc interval was evaluated by using 30- and 90-mg subcutaneous dosing and was found to be below the threshold for concern. The dose of 90 mg represented the maximum dosing to be administered in a 24-hour period.²⁸

Intravenous and subcutaneous administrations have been evaluated to determine the pharmacokinetic profile of icatibant. The absolute bioavailability of a single 30-mg subcutaneous dose of icatibant is approximately 97%. In 96 healthy subjects, this dose produced a mean maximum concentration (C_{max}) of 974 ng/mL after approximately 45 minutes, an elimination half-life of 1.4 ± 0.4 hours, and a volume of distribution of 29.0 L. There was no accumulation noted after 3 doses given 6 hours apart.²⁸

Icatibant is extensively metabolized to inactive metabolites, with primary excretion in the urine. There is no need to adjust dosing due to hepatic or renal impairment. Icatibant does not appear to inhibit cytochrome P450 isoenzymes (CYP) and does not induce CYP1A2 or 3A4. However, there is a potential concern for drug interaction when administered concurrently with an angiotensin-converting enzyme (ACE) inhibitor. Icatibant may attenuate the antihypertensive effect of ACE

Figure 2. Icatibant inhibition of the bradykinin cascade.

inhibitors. There are no clinical data to support this as current trials have excluded patients taking ACE inhibitors.²⁸

Dosage and Administration

The recommended dosage for adults is 30 mg subcutaneously every 6 hours with a maximum of 3 doses in a 24-hour period. Icatibant is available in single-use, prefilled syringes containing icatibant 30 mg in 3 mL and is packaged with a 25-gauge needle. Pediatric dosing has not been currently established, but a phase 3 clinical trial is underway, evaluating a dose of 0.4 mg/kg up to a maximum of 30 mg subcutaneously as a 1-time dose.²⁹

Comments

Three controlled trials in adults provided safety data evaluating 223 patients who received icatibant (n=113), placebo (n=75), or comparator (n=38). The most commonly reported adverse event is related to injection site reactions (97% vs 33%) in patients receiving icatibant vs placebo. Other reported adverse events in greater than 1% of treated patients included pyrexia, transaminase increases, dizziness, tiredness, and rash.

The safety of self-administered icatibant was also evaluated in an open-label trial including 56 patients with HAE. There was no difference in the safety profile of icatibant when comparing patients who self-administered vs patients who received icatibant from a health care professional. Patients experiencing laryngeal edema should still seek additional medical treatment after self-administration of icatibant.²⁸

Linagliptin (Tradjenta)

The incidence of type 2 diabetes mellitus in children is increasing dramatically. Rates are higher in non-white groups, with American Indian youths having the highest reported incidence (4.5 per 1000 for all US American Indians and 50.9 per 1000 for Pima Indians from Arizona). Retrospective studies have reported an incidence of 7.2 per 100,000 for African Americans and whites aged 10 to 19 years in 1994. Type 2 diabetes also accounted for 8% to 46% of all new cases of diabetes (regardless of type) in pediatric center referrals.³⁰ During 2002-2005, there were 3600 newly diagnosed cases of type 2 diabetes annually among youths. However, type 2 diabetes is still extremely rare in children younger than 10 years.³¹

Indication(s)

Linagliptin (Tradjenta, Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT) was approved May 2, 2011, for adults as an adjunct to diet and exercise to improve glycemic control in patients diagnosed with type 2 diabetes mellitus.³² A phase 2 dose-finding study is currently underway in pediatric patients aged 10 to 17 years with type 2 diabetes mellitus.³³

Clinical Pharmacology

Linagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor, which ultimately inhibits the degradation of incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 and GIP increase insulin release in a glucose-dependent manner and decrease circulating concentrations of glucagon. These incretin hormones regulate glucose homeostasis and are secreted at low basal concentrations with an immediate increase in production in response to a meal. In the presence of both euglycemia and hyperglycemia, GLP-1 and GIP increase insulin production and secretion from pancreatic beta cells. In addition to the effect on pancreatic beta cells, GLP-1 decreases glucagon secretion from pancreatic alpha cells, which reduces glucose output from the liver and decreases fasting plasma glucose and glycosylated hemoglobin (HbA1c). Improvements were also noted in 2-hour postprandial glucose measurements when compared to measurements for patients taking placebo.³²

Oral bioavailability is approximately 30% and is not affected by administration with food. The volume of distribution at steady state is approximately 1110 L and protein binding is concentration-dependent, decreasing from 99% to from 75% to 89% at 1 nmol/L and ≥ 30 nmol/L, respectively. This is due to saturation of binding to DPP-4. Protein binding is not affected by renal or hepatic impairment. Linagliptin is primarily excreted unchanged and elimination occurs via the enterohepatic system (80%) or urine (5%). Renal clearance is approximately 70 mL/min. There is no dosage adjustment necessary in patients with hepatic or renal impairment.³²

Linagliptin is a weak to moderate inhibitor of CYP3A4 and a P-glycoprotein (P-gp) substrate. There is no recommendation for dosage adjustment of linagliptin when given concomitantly with other medications. Inducers of CYP3A4 or

P-gp decrease exposure to linagliptin, and alternative therapy is recommended.³²

Dosage and Administration

Linagliptin is available as a 5-mg oral tablet and the recommended dosage in adults is currently 5 mg once daily to be taken with or without food.³² Dosing in pediatric patients has not yet been established, but dosing regimens of 1 mg and 5 mg once daily are currently being evaluated.³³

Comments

Linagliptin is not indicated for use in patients diagnosed with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. This oral agent has not been studied in combination with insulin. Nasopharyngitis was reported in 5% or more of patients. Other less common adverse events reported include pancreatitis and hypoglycemia. If a patient is receiving an insulin secretagogue, one should consider lowering the dose of the insulin secretagogue as the risk for hypoglycemia was reported more often in combination with a sulfonylurea than for those patients treated with sulfonylurea and placebo.³²

Rivaroxaban (Xarelto)

Venous thromboembolism rates in the hospitalized pediatric population have risen by 70% from 2001 to 2007.³⁴ Enoxaparin is a viable option but is not available orally and requires monitoring. Rivaroxaban (Xarelto, Janssen Pharmaceuticals, Inc, Titusville, NJ) was approved July 1, 2011. It is an oral agent that does not require extensive monitoring.

Indication(s)

Rivaroxaban is indicated in adults for prophylaxis of deep vein thrombosis (DVT) in patients undergoing knee or hip replacement surgery³⁵ and in patients with non-valvular atrial fibrillation³⁶ to reduce the risk of stroke and systemic embolism.³⁷ Two clinical trials^{38,39} are currently underway, evaluating the use of rivaroxaban in children with venous thromboembolism.

Clinical Pharmacology

Rivaroxaban is an orally bioavailable factor Xa inhibitor (Figure 3). It selectively blocks factor Xa (activation of factor X to factor Xa is central in the coagulation cascade) and does not require a cofactor, such as antithrombin III,

Figure 3. Rivaroxaban is a competitive reversible antagonist of activated factor X (Xa).

for activity. This drug exhibits dose-dependent absolute bioavailability. Systemic exposure does not increase further in doses >50 mg. Due to the dose-dependent nature of rivaroxaban, the 10-mg tablet can be taken with or without food, whereas the 15-mg and 20-mg tablets are recommended to be taken with the evening meal.³⁷

Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and P-gp. Avoidance of concomitant administration with rivaroxaban and drugs with combined P-gp and strong CYP3A4 inhibitor activity is recommended, as this may increase bleeding risk. Patients with renal impairment (creatinine clearance [CrCL] < 80 mL/min) taking P-gp and weak to moderate CYP3A4 inhibitors may also have increased bleeding risks owing to increase in exposure.

Dosage and Administration

Rivaroxaban is available as an oral tablet in 3 strengths: 10 mg, 15 mg, and 20 mg. For non-valvular atrial fibrillation, the recommended adult dose is 20 mg orally once daily with the evening meal. In patients receiving rivaroxaban for DVT prophylaxis, the recommended adult dose is 10 mg daily with or without food.³⁷ Dosage adjust-

ment in renal impairment is recommended and is based on indication and CrCL. Rivaroxaban should be avoided in patients with moderate to severe hepatic impairment (Child-Pugh B or C, respectively).³⁷ Two ongoing pediatric studies^{38,39} are evaluating a weight-adjusted dose with equivalent exposure, compared to 10-mg or 20-mg dosing in adults.

A preliminary study showed better comparability in prolonging activated partial thromboplastin time values between neonatal cord and adult samples than with heparin, suggesting that establishing a rivaroxaban dose in neonates may be relatively easy. This is likely due to rivaroxaban's anticoagulant effect independent of antithrombin III activity.⁴⁰

Comments

Rivaroxaban does increase the risk of bleeding, which can be serious or fatal, and there is no known antidote. The most commonly observed adverse reactions were bleeding complications. When used for prophylaxis, most major bleeding complications (≥60%) were noted during the first week postoperatively. Non-hemorrhagic complications reported in ≥1% of treated patients

Figure 4. Roflumilast-selective phosphodiesterase 4 inhibition increases intracellular cyclic adenosine monophosphate concentration, decreasing inflammatory activity, [adenosine triphosphate (ATP)].

included surgical wound secretion, extremity pain, muscle spasms, syncope, pruritus, and blisters. Also, one study in acute medically ill patients reported cases of pulmonary hemorrhage and pulmonary hemorrhage with bronchiectasis. Postmarketing surveillance has also identified Stevens-Johnson syndrome, anaphylaxis, cholestasis, and agranulocytosis, but incidence of these adverse events has not been established.³⁷

Roflumilast (Daliresp)

Chronic obstructive pulmonary disease (COPD) can be a very debilitating disease characterized by chronic bronchitis or emphysema, primarily caused by smoking. Several medications used for the treatment of COPD are also used in the treatment of bronchial asthma. Since asthma is prevalent in children, roflumilast (Daliresp, Forest Pharmaceuticals Inc, St Louis, MO) has been studied in pediatrics for this condition.^{41–43} It was approved on March 1, 2011.

Indication(s)

Roflumilast is indicated in adults for the treat-

ment of severe COPD associated with chronic bronchitis to reduce the risk of exacerbations.⁴⁴ Although roflumilast is not FDA approved for the treatment of asthma, several studies have been completed, assessing the safety and efficacy of roflumilast in adolescent and adults with chronic stable asthma.^{41,42,45}

Clinical Pharmacology

Roflumilast and its active metabolite are selective phosphodiesterase-4 inhibitors, which cause an increase in intracellular cyclic adenosine monophosphate (cAMP) (Figure 4). The exact mechanism of action is unknown, but it is thought the therapeutic effect is related to this increase in cAMP. Oral bioavailability is approximately 80%; therefore, it can be taken with or without food. There is no need for adjustment in renal failure, but dosing is contraindicated in moderate to severe hepatic impairment (Child-Pugh B or C).⁴⁴

Dosage and Administration

Roflumilast is available as a 500-mcg white

round tablet. The recommended adult dosage is 500 mcg orally daily. It can be taken with or without food.⁴⁴ A dose of 500 mcg orally once daily has been evaluated in two phase 3 clinical trials in asthmatic persons, which included pediatric patients 12 years of age and older.^{41,42} In addition, an open-label, single-dose pharmacokinetic study evaluated the use of 100 mcg and 250 mcg in asthmatic children aged 6 to 16 years. They reported pharmacokinetic parameters similar to those reported in adults.⁴³

Comments

In adult clinical trials, sputum neutrophil and eosinophil reduction occurred in patients with COPD, as well as increases in FEV₁. In addition, there were significant reductions in the number of COPD exacerbations.⁴⁶ Roflumilast is not to be used for relief of acute bronchospasm as it does not cause bronchodilation. There is a warning that advises about the risk of psychiatric events, including suicidality, in patients treated with roflumilast. It is recommended that the risks and benefits be carefully weighed before prescribing this medication to someone with a history of depression or suicidal thoughts. Weight should be monitored regularly, as weight loss has been associated with its use. The most commonly reported adverse reactions ($\geq 2\%$) include diarrhea, weight loss, nausea, headache, back pain, influenza, insomnia, dizziness, and anorexia. Adverse reactions occurring at a rate of 1% to 2% and greater when compared to placebo include, but are not limited to, abdominal pain, vomiting, muscle spasms, sinusitis, urinary tract infection, tremor, anxiety, and depression.^{44,47}

NEW ONCOLOGY DRUGS WITH ACTIVE PEDIATRIC TRIALS

Brentuximab vedotin (Adcetris)

Anaplastic large cell lymphoma (ALCL) and Hodgkin lymphoma tumor cell membranes highly express the protein CD30, which is a cell membrane protein of the tumor necrosis factor receptor family. Monoclonal antibodies directed against specific tumor antigens have become an important class of chemotherapy drugs, since they can bind to both the primary tumor and any metastases.⁴⁸ These antibodies exert their antitumor effect either directly by cell-mediated cytotoxicity or indirectly by delivery of radiation

or toxins to the tumor cell. CD30 monoclonal antibodies have demonstrated limited activity in clinical studies,^{49,50} but the potency has been enhanced by the development of an antibody-drug conjugate, brentuximab vedotin (Adcetris, Seattle Genetics, Inc, Bothell, WA), which was approved August 19, 2011.

Indication(s)

Brentuximab vedotin is indicated for the treatment of ALCL in adults after failure of at least 1 multiagent chemotherapy regimen. It is also approved for the treatment of Hodgkin lymphoma in adults after failure of either autologous stem cell transplant or 2 prior multiagent chemotherapy regimens. Table 2 summarizes the important characteristics of the adult^{51,52} and pediatric^{53–57} studies evaluating brentuximab.

Clinical Pharmacology

Brentuximab vedotin is an antibody-drug conjugate comprising the anti-CD30 monoclonal antibody conjugated to a small molecule, monomethyl auristatin E (vedotin).⁵⁸ Vedotin is a tubulin polymerization inhibitor that blocks cell division. The conjugate is stable in the bloodstream but releases vedotin when it is internalized into CD30-expressing tumor cells. CD30 cells are highly expressed in hematologic malignancies including Hodgkin lymphoma and ALCL.⁵⁹

The brentuximab vedotin conjugate has a multiexponential decline in serum concentrations with a terminal half-life of 4 to 6 days. There is no accumulation of the antibody-conjugate with multiple dosing every 3 weeks. The time to maximum concentration for vedotin was 1 to 3 days. Vedotin exposures decreased with continued administration of brentuximab vedotin, with 50% to 80% of the exposure of the first dose being observed on subsequent doses.⁶⁰

Dosage

Brentuximab vedotin is available as a lyophilized powder in single-use vials containing 50 mg. The contents of the vial are reconstituted with 10.5 mL of Sterile Water for Injection to yield a single-use solution of 5 mg/mL. The vial is gently swirled to aid dissolution. The recommended dose is 1.8 mg/kg as an intravenous infusion for 30 minutes every 3 weeks for a maximum of 16 cycles or until disease progression or unacceptable toxicity.⁶⁰ For patients weighing more

than 100 kg, the dose should be calculated from a weight of 100 kg. If patients experience grade 2 or 3 neuropathy or grade 3 or 4 neutropenia, the dose should be held until recovery and then restarted at 1.2 mg/kg. The calculated dose should be added to an infusion bag containing a minimum volume of 100 mL of 0.9% sodium chloride, 5% dextrose, or Lactated Ringers Injection to achieve a final concentration of 0.4 mg/mL. After dilution, brentuximab should be infused immediately or stored under refrigeration for up to 24 hours. The solution should not be frozen.⁶⁰

Comments

Brentuximab vedotin has a boxed warning for John Cunningham virus infection resulting in progressive multifocal leukoencephalopathy and death. In addition, brentuximab is contraindicated with concurrent use of bleomycin owing to increased pulmonary toxicity.⁶⁰ The most common side effects reported in $\geq 20\%$ of treated patients include neutropenia, anemia, thrombocytopenia, peripheral sensory neuropathy, fatigue, pyrexia, upper respiratory tract infection, nausea, vomiting, diarrhea, abdominal pain, rash, and cough. Other serious adverse events are infusion-related reactions and the potential for tumor lysis syndrome with rapidly proliferating tumor and high tumor burden.⁶⁰

Crizotinib (Xalkori)

Gene mutations that lead to the proliferation of cancer cells have become the targets for therapeutic interventions. Tyrosine kinases have been an important target because of their role in modulating cell proliferation. Anaplastic lymphoma kinase (ALK) plays an important role in the pathogenesis of solid and hematologic tumors. It was first discovered in ALCL, but ALK has also been found in subsets of B-cell non-Hodgkin lymphoma, neuroblastoma, breast cancer, inflammatory myofibroblastic tumor, and non-small cell lung cancer. Rearrangements of the *ALK* gene can be detected by using fluorescence *in situ* hybridization technology. Several tyrosine kinase inhibitors have been previously developed, including imatinib, gefitinib, erlotinib, lapatinib, sorafenib, and sunitinib.⁶¹

Indication(s)

Crizotinib (Xalkori, Pfizer Inc, New York, NY) was approved August 26, 2011, and is indicated

for the treatment of adults with locally advanced or metastatic non-small cell lung cancer that is ALK positive.⁶² Table 2 summarizes the established efficacy of crizotinib in adults^{62,63} and describes the active pediatric open-labeled trials.⁶⁴

Clinical Pharmacology

ALK is part of a superfamily of leukocyte tyrosine kinase receptors. Translocations in the *ALK* gene result in the expression of fusion oncogenic proteins. Crizotinib is a tyrosine kinase inhibitor that has more selective activity towards ALK than other tyrosine kinases.⁶⁵

Following oral administration, peak crizotinib concentration occurred in 4 to 6 hours, the mean bioavailability was 43%, and the terminal elimination half-life was 42 hours. Steady-state concentration was achieved within 15 days after taking 250 mg dosed twice daily. Elimination is predominately through CYP3A4 metabolism with subsequent conjugation. Coadministration with a strong CYP3A4 inhibitor increases systemic exposure, whereas coadministration with CYP3A4 inducers reduces systemic exposure. Crizotinib is also a moderate inhibitor of CYP3A4.⁶²

Dosage

Crizotinib is available as 200- and 250-mg hard gelatin capsules. The recommended adult dose is 250 mg taken orally twice daily. Treatment is continued for as long as the patient is deriving clinical benefit from therapy. If a dose reduction is required because of excessive toxicities, the dose can be reduced to 200 mg orally twice daily or to 250 mg once daily.⁶² The optimal pediatric dose is not yet known, but several investigators are currently conducting pediatric dose escalation studies.⁶⁶⁻⁶⁸ In these studies, there is no information related to the dosage form that is being used. This is an important consideration in young children who are unable to swallow capsules. This further illustrates the need for pediatric-friendly dosage forms and contributes to the difficulty in studying these medications in pediatric patients.

Comments

Adverse events have been evaluated in 255 patients from the 2 safety and efficacy trials.⁶² Dosing interruptions occurred in about 40% of patients and lasted greater than 2 weeks in about 15% of patients. Dosage reduction was required

in 29% to 44% of patients. The most common adverse events, occurring in $\geq 20\%$ of treated patients, included vision disorder, nausea, diarrhea, vomiting, edema, fatigue, and constipation.⁶² Also, QT prolongation has been reported in patients receiving crizotinib.⁶²

Ipilimumab (Yervoy)

Melanoma is the most severe type of malignant skin cancer and the incidence continues to increase each year. Although melanoma is fairly rare in children, with about 400 new cases per year, the number of newly diagnosed children is increasing.⁶⁹ The treatment options for unresectable or metastatic melanoma are limited. Standard treatment options such as dacarbazine and high-dose interleukin-2 have not prolonged survival.

Cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4) is a cell surface molecule located on T cells. CTLA-4 functions as a natural brake on T lymphocyte activation, which causes immune system impairment. Ipilimumab is a monoclonal antibody targeted to inhibit CTLA-4 activity.⁷⁰

Indication(s)

Ipilimumab (Yervoy, Bristol-Myers Squibb, Princeton, NJ) was approved March 25, 2011, for the treatment of adult patients with unresectable or metastatic melanoma.^{71,72} Ipilimumab is being investigated in 2 ongoing clinical studies in children with advanced or refractory solid tumors⁷³ and stage III or IV malignant melanoma.⁷⁴

Clinical Pharmacology

Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands on antigen-presenting cells (Figure 5).⁷⁵ Blockage of CTLA-4 augments T-lymphocyte activation and proliferation. The effect of ipilimumab on melanoma is thought to be indirect through T-lymphocyte–mediated antitumor activity.

The terminal half-life is 14.7 days and steady-state concentrations are achieved after 3 doses when administered at 3-week intervals with minimum systemic accumulation.

Dosage

Ipilimumab is available in 50 mg/10 mL and 200 mg/40 mL single-use vials that should be stored under refrigeration (2°C to 8°C) and protected from light. The required volume of ipilim-

Figure 5. Ipilimumab blocks the immune inhibitory molecule cytotoxic T-lymphocyte antigen-4 (CTLA-4) on activated T cells. Ag, antigen; B7, B7 receptor; CD28 receptor, cluster of differentiation 28 receptor; MHC, major histocompatibility complex; TCR, T-cell receptor.

umab is withdrawn from the vial and further diluted with normal saline to a final concentration of 1 mg/mL or 2 mg/mL. The diluted solution should be stored for no more than 24 hours under refrigeration (2°C to 8°C) or room temperature (20°C to 25°C). The recommended adult dose is 3 mg/kg injected intravenously for 90 minutes every 3 weeks for a total of 4 doses.⁷¹ Pediatric dosing has not been established, but is currently being investigated in a phase 1 open-label dose escalation study in patients aged 1 to 21 years.⁷³ Also, in a phase 2 open-label study including children aged 12 to 17 years with stage III or IV malignant melanoma, ipilimumab 10 mg/kg every 3 weeks for 4 doses, then every 12 weeks, is being assessed.⁷⁴

Comments

The most severe adverse and fatal reactions (black box warning) are immune mediated and include enterocolitis, hepatitis, dermatitis (toxic epidermal necrolysis), neuropathy, and endocrinopathy. Ipilimumab should be permanently discontinued and high-dose systemic corticosteroids initiated. Other reported side effects include diarrhea, pruritus, and fatigue.⁷¹

Vandetanib (Caprelsa)

Medullary thyroid cancer is a rare form of cancer, representing about 4% to 5% of all thyroid cancers. The disease has a high cure rate if surgery is performed at an early stage. Children

represent about 5% of all thyroid cancer cases and commonly present with widespread disease. Thyroid cancer is the third most common solid tumor malignancy and is the most common endocrine neoplasm in children. There are few treatment options for individuals with progressive or unresectable medullary thyroid cancer. Tyrosine kinase inhibitors can be combined with chemotherapy or radiation therapy, and they have the advantages of oral administration and a favorable safety profile. Rearranged during transfection (RET) mutations are important pathways in the development of medullary thyroid cancer and are the target of the tyrosine kinase inhibitor vandetanib.⁷⁶

Indication(s)

Vandetanib (Caprelsa, AstraZeneca Pharmaceuticals LP, Wilmington, DE) was approved April 11, 2011, and is indicated for the treatment of symptomatic or progressive, unresectable medullary thyroid cancer in adults.^{77,78} Vandetanib is being investigated in 2 open-label studies in children with medullary thyroid cancer⁷⁹ and brainstem glioma.⁸⁰

Clinical Pharmacology

Vandetanib is an orally active drug that inhibits the activity of several tyrosine kinases including epidermal growth factor receptor, vascular endothelial cell growth factor, and RET kinase-dependent signaling. These tyrosine kinases play an important role in cellular signaling that promotes tumor proliferation, angiogenesis, and metastasis.⁸¹

Dosage

Vandetanib is available in 100-mg and 300-mg film-coated tablets. The recommended adult dose is 300 mg orally once daily. For individuals with difficulty swallowing tablets, the tablet can be added to a glass with 2 oz of water and stirred for about 10 minutes until the tablet is dispersed. The tablet should not be crushed. The dispersed drug should be swallowed immediately and any residue in the glass should be mixed again with an additional 4 oz of water and swallowed. Patients with renal impairment (CrCL < 50 mL/min) should have the dose reduced to 200 mg. The dose should also be reduced to 200 mg and then to 100 mg if the patient experiences grade 3 or greater toxicity (Common Terminology Crite-

ria for Adverse Events includes QT prolongation, skin reactions, diarrhea, and hypertension).⁷⁷ In one pediatric ongoing study,⁷⁹ vandetanib 150 mg/m² once daily in 28-day cycles is being evaluated in patients with medullary thyroid carcinoma. A dose-escalation study in patients aged 2 to 21 years with brainstem glioma is currently underway to determine the maximum tolerated dose in this patient population.⁸⁰

Comments

The two most common reported adverse events, diarrhea and rash, have been reported in more than 50% of treated patients. Other frequent adverse events occurring in 20% to 50% of treated patients include acne, nausea, hypertension with progression to hypertensive crisis, headache, fatigue, decreased appetite, and abdominal pain. Vandetanib has a block box warning for the potential to cause prolonged QT interval and sudden death.⁷⁷ Because of this risk, vandetanib is available only through a restricted distribution program (CAPRELSA Risk Evaluation and Mitigation Strategy) whereby only physicians and pharmacies that are certified with the program are able to prescribe and dispense vandetanib.⁸²

Vemurafenib (Zelboraf)

Melanoma has one of the highest frequencies (>65%) of the *BRAF* gene mutation. *BRAF* is a proto-oncogene for which acquired mutations are associated with cancer.⁸³ More than 30 mutations of the *BRAF* gene have been identified that are associated with human cancer. About 90% of *BRAF* mutations are V600E-mutated kinase and involve the substitution of glutamic acid (E) for valine (V) at position V600 in the B-raf protein. B-raf protein is involved in cell signaling and growth. There is an FDA-approved test to detect the *BRAF* V600E mutation.⁸⁴

Indication(s)

Vemurafenib (Zelboraf, Genentech USA, Inc, San Francisco, CA) was approved on August 17, 2011, for the treatment of adults with unresectable or metastatic melanoma with *BRAF* V600E gene mutation.⁸⁵⁻⁸⁷ Vemurafenib is also being investigated in children with advanced solid tumors⁸⁸ and with *BRAF* V600-positive melanoma.⁸⁹

Clinical Pharmacology

Vemurafenib is an orally active selective inhibi-

Figure 6. Vemurafenib inhibits BRAF V600E kinase activity in the melanoma cell, blocking growth factor signals that process from the tyrosine kinase receptor. ERK, extracellular signal-regulated kinase; MEK, mitogen-activated protein kinase.

tor of mutated B-raf V600E kinase (Figure 6). The V600E mutation leads to a B-raf protein that is constitutively active, resulting in excessive cell proliferation and resistance to apoptosis. It has no antitumor effect against wild-type B-raf.

Dosage

Vemurafenib is available in 240-mg film-coated tablets. The recommended adult dose is 960 mg orally twice daily. The dose can be taken with or without meals. Dose modification for adverse events or QT prolongation can be made, but it is not recommended to reduce the dose below 480 mg twice daily.⁸⁵ Vemurafenib 480 mg twice daily is being evaluated in pediatric patients older than 12 years.⁸⁸

Comments

The most common adverse events occurring in >30% of patients include arthralgia, rash, photosensitivity, pruritus, fatigue, nausea, alopecia, and skin papilloma. Other frequent adverse events include hyperkeratosis, dry skin, headache, diarrhea, vomiting, and loss of appetite. Cutaneous squamous cell carcinoma occurred in 24% of treated patients, usually occurring early in therapy (median time to appearance, 7 to 8 weeks). Serious adverse events include hypersen-

sitivity reaction, 1 case of Stevens Johnson syndrome, and 1 case of toxic epidermal necrolysis, and QT prolongation.⁸⁵

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ABBREVIATIONS ACE, angiotensin-converting enzyme; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ANC, absolute neutrophil count; cAMP, cyclic adenosine monophosphate; CDAD, *Clostridium difficile*-associated diarrhea; C_{max} , mean maximum plasma concentration; COPD, chronic obstructive pulmonary disease; CrCL, creatinine clearance; CTLA-4, cytotoxic T-lymphocyte antigen-4; CYP, cytochrome P450 isoenzymes; DPP-4, dipeptidyl peptidase-4; DVT, deep vein thrombosis; FDA, US Food and Drug Administration; GABA, γ -aminobutyric acid; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1; HAE, hereditary angioedema; HbA1c, glycosylated hemoglobin; P-gp, P-glycoprotein; RET, rearranged during transfection

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