In This Issue

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Ipilimumab for Pediatric Unresectable or Metastatic Melanoma

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Background: Melanoma in pediatric patients, defined by the National Cancer Institute as patients less than 20 years old, is a rare but serious health concern.[1] Melanoma accounts for 7.1% of cancers in patients ages 15 to 19 years, affecting 5 to 6 per million under the age of 20. Unresectable stage III and IV metastatic melanoma in pediatric patients are difficult to treat and lack curative options.[2] Ipilimumab (Yervoy®; Bristol-Meyers Squibb) is a recombinant, fully human monoclonal antibody.[3] A study in adult patients with metastatic melanoma demonstrated increased survival when treated with ipilimumab, which led to its approval by the Food and Drug Administration (FDA) for adult patients in 2011.[4] Since malignant melanoma tumors in children have similar immunologic features as those in adults, ipilimumab was studied in the pediatric population and received FDA approval for the treatment of unresectable or metastatic melanoma in patients aged 12 and older in July 2017.[2,3]

Mechanism of Action: Ipilimumab is a first-in-class monoclonal antibody immune checkpoint inhibitor.[3] Cancer cells evade the immune system by using checkpoint proteins, such as programmed death receptor 1 (PD1) or Cytotoxic T Lymphocyte Antigen 4 (CTLA-4) to "turn off" the immune system's T cells preventing them from attacking carcinogenic tissue. Immune checkpoint inhibitors prevent T cell deactivation by interfering with these checkpoint proteins. For example, ipilimumab helps to maintain T cell antitumor immune response by binding to CTLA-4 blocking its interaction with its ligands, CD80 and CD86.

Key Clinical Trial: A phase 2 study examined the efficacy and safety of ipilimumab at doses of either 3 mg/kg (n=4) or 10 mg/kg (n=8) in pediatric patients ages 12 to 18 years, with stage III or IV malignant melanoma.[5] For the 3- and 10-mg/kg groups, the median age was 13- and 15-years, respectively. After 1 year of treatment, three out of four patients on 3 mg/kg and five out of eight patients on 10 mg/kg were alive. Two patients on 10 mg/kg had partial responses and one patient from each group had stable disease. Treatment-related side effects were reported in two of four and seven of eight patients in the 3- and 10-mg/kg groups, respectively. There was one grade 3-4 immune-related adverse event (irAE) with 3 mg/kg dose and five irAEs with the 10 mg/kg dose. The most common AEs were hepatitis and pyrexia. Despite early termination due to low enrollment, the authors concluded that ipilimumab was an effective treatment for melanoma in patients aged 12 to 18 years of age with a safety profile similar to that observed in adults.

Safety: The most common AEs (≥5%) associated with ipilimumab include fatigue, diarrhea, pruritus, rash, and colitis.[3] At higher doses of 10 mg/kg, AEs include nausea, vomiting, headache, weight loss, pyrexia, decreased appetite, and insomnia. It is important to note that ipilimumab carries a Boxed Warning for severe and fatal irAEs, which may involve any organ system. Similar to adults, pediatric patients re-

(Continued on page 2)

(Continued from page 1)

ceiving ipilimumab may develop drug-related enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy.[2] Patients should be assessed for these disease states and be evaluated at baseline and before each dose.[3] If a severe irAE occurs, ipilimumab should be permanently discontinued and systemic high-dose corticosteroid therapy should be initiated. Additionally, ipilimumab can cause fetal harm; patients should be advised to use contraception.

Dosing and Administration: The recommended dose of ipilimumab for adult and pediatric patients with unresectable or metastatic melanoma is 3 mg/kg given intravenously over 90 minutes every 3 weeks for a maximum of four doses.[3] If toxicities occur, doses may be delayed; however all treatment must be administered within 16 weeks of the first dose. Ipilimumab should be diluted in normal saline or dextrose 5% and water to a final concentration between 1 to 2 mg/mL and administered through a low-protein-binding in-line filter.[3]

Availability and Cost: Ipilimumab is available as a 5 mg/mL intravenous solution in 10- or 40-mL vials.[3] The suggested wholesale price of the 50 mg/10 mL vial is about $8,350 and the 200 mg/40 mL vial is about $33,420.[6] Therefore, the cost for a 70 kg patient to complete the therapy consisting of 3 mg/kg every 3 weeks for four cycles would be approximately $140,000.

Role in Therapy: Currently, ipilimumab is the only FDA-approved treatment for unresectable or metastatic carcinoma in pediatric patients. Although its approval was based on limited pediatric data from a very small clinical trial, it remains a viable therapy for a disease state with very few effective treatment options.[7]

Formulary Status: Ipilimumab is on the Pediatric CCHS Formulary restricted to the Department of Hematology and Oncology for outpatient use only in patients ≥ 12 years of age with unresectable or metastatic melanoma using its FDA-approved dosing (3 mg/kg every 3 weeks for four doses). It is also on the Adult CCHS Formulary restricted to the Department of Hematology and Medical Oncology for adult outpatient use only using the FDA-approved dosing (3 mg/kg every 3 weeks for four doses).

References:

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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Enasidenib (IDHIFA®)	Antineoplastic Agent	AML	Restricted to the Department of Hematology and Medical Oncology for outpatient use only in patients with AML and identified IDH mutation Note: Patients are instructed to bring home supply or obtain outpatient prescription if admitted to the hospital as an inpatient.
Fibrinogen concentrate (RiaSTAP®)	Blood Product Derivative	Severe Post-Partum Hemorrhage	Restricted to Staff Anesthesia in the setting of severe post-postpartum hemorrhage in conjunction with the Massive Transfusion Protocol and to the Department of Hematology and Medical Oncology
Inotuzumab ozogamicin (Besponsa®)	Antineoplastic Agent	ALL	Restricted to the Department of Hematology and Medical Oncology for patients with ALL
Naltrexone extended-release injectable suspension (Vivitrol®)	Opioid Antagonist	Management of Alcohol and Opioid Dependence	Restricted to physicians certified in Addiction Medicine for use in outpatients for the management of alcohol and opioid dependence
Rituximab and hyaluronidase subcutaneous injection (Rituxan Hycela™)	Antineoplastic Agent	CLL Lymphoma	Restricted to the Department of Hematology and Medical Oncology for outpatient use only
Sulfur hexafluoride lipid-type A microspheres for injectable suspension (Lumason®)	Diagnostic Agent	Cardiac Imaging Hepatic Imaging	For use in liver lesions restricted to patients who: 1) Cannot have an MRI or CT contrast (e.g., allergies or poor renal function) 2) Cannot have an MRI due to implanted device(s) 3) Need to avoid or minimize ionizing radiation exposure
Tranxemic acid (oral) (Lysteda®)	Antifibrinolytic Agent	Orthopedic Surgery	Restricted to the Department of Orthopedic Surgery
Vecuronium	Neuromuscular Blocker Agent	Neuromuscular Blockade	Note: Added to CCHS Formulary due to the inconsistent availability of rocuronium.

AML=Acute Myeloid Leukemia IDH=Isocitrate Dehydrogenase ALL=Acute Lymphoblastic Leukemia
CLL=Chronic Lymphocytic Leukemia MRI=Magnetic Resonance Imaging CT=Computed Tomography

Changes to Restrictions of Medications on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes to Restrictions**
Daratumumab (Darzalex®)	Antineoplastic Agent	Relapsed/Refractory Multiple Myeloma Plasma Cell Leukemia	Old restriction: Restricted to the Department of Hematology and Medical Oncology for outpatient use only **Modified restriction: Restricted to the Department of Hematology and Medical Oncology** **Note: It may be used for inpatients who cannot be discharged due to disease burden, or for inpatients with plasma cell leukemia.**
Diatrizoate meglumine diatrizoate sodium (Gastrografin®)	Iodinated Contrast Media	Treatment of Post-Operative Small Bowel Obstruction and Ileus	Old restriction: Oral gastrografin is restricted to Pulmonary and Critical Care Medicine **Modified restriction:** **1) Restricted to Pulmonary and Critical Care Medicine** **2) Restricted to Colorectal Surgery and General Surgery for the treatment of post-operative small bowel obstruction and ileus**
Rituximab (Rituxan®)	Antineoplastic Agent	Autoimmune Encephalitis	Added to various restrictions listed in Lexicomp: **Modified restriction: Restricted to General Neurology Staff Physicians and NeuroICU Staff Physicians for the management of autoimmune encephalitis as second-line therapy (i.e., following steroids, IVIG, and PLEX)**

IVIG=Intravenous Immune Globulin PLEX=Plasma Exchange

Product Standardizations on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Standarization**
Generic digoxin (Lanoxin®)	Antiarrhythmic Agent	Atrial Fibrillation Heart Failure	Due to a significant cost increase for brand-name Lanoxin®, CCHS pharmacies will be carrying generic digoxin. The same digoxin generic manufacturer product will be carried by all CC inpatient, ambulatory, and specialty pharmacies.
Rabies immune globulin (HyerRAB®)	Immune Globulin	Post-Exposure Rabies Prophylaxis	In order to reduce cost and standardize products across CCHS, HyperRab® was selected as the rabies immune globulin product. Imogam® will be removed from the CCHS Formulary.

Removals from the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Removal/ Comments**
Atenolol	Beta Blocker	Hypertension	Reason for removal: There is a shortage of generic atenolol and the brand atenolol (Tenormin®) has significantly increased in price. A beta-blocker dose conversion chart should be utilized to assist prescribers in converting from atenolol to another beta blocker.
Dyazide® (Hydrochlorothiazide and Triamterene)	Potassium-Sparing Diuretic	Hypertension Edema	Reason for removal: Maxzide®-25 and Maxzide® tablets are more cost effective.
Oxymorphone HCl ER (Opana® ER)	Opioid Analgesic	Pain Reliever	Reason for removal: Removed from the market

Therapeutic Interchange on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Therapeutic Interchange**
Intravenous Potassium Chloride (KCl)	Electrolyte	Electrolyte Imbalance	Pharmacists will automatically convert IV to PO orders for potassium chloride for select patients (i.e., those who received PO/enteral medications within the past 8 hours). Oral/enteral options are tablets, oral liquid, and effervescent packets. Exceptions to the automatic interchange are patients with these characteristics: 1. Ventricular arrhythmias 2. Severe hypokalemia (potassium <3 mmol/L or <3.5 mmol/L with symptoms) 3. NPO 4. Difficulty swallowing (e.g., dysphagia, mucositis) 5. Severe nausea/vomiting or received an antiemetic within the last 8 hours 6. Lost PO/enteral access (e.g., NG or Corpak pulled, re-intubated)

IV=Intravenous PO=Oral NPO=Nothing by Mouth NG=Nasogastric

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Eculizumab (Soliris®)	Monoclonal Antibody	Microangiopathic Hemolysis*	Restricted to the Department of Pediatric Hematology/ Oncology and Bone Marrow Transplant for outpatient use only in patients with microangiopathic hemolysis*
Ipilimumab (Yervoy®)	Antineoplastic Agent	Unresectable or Metastatic Melanoma	Restricted to the Department of Pediatric Hematology/ Oncology for outpatient use only in patients at least 12 years of age with unresectable or metastatic melanoma using its FDA-approved dosing (3 mg/kg every 3 weeks for four doses)

*Microangiopathic hemolysis includes thrombotic microangiopathy (TMA) and paroxysmal nocturnal hemoglobinuria (PNH)
FDA=Food and Drug Administration

Removals from the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Atenolol	Beta Blocker	Hypertension	Reason for removal: There is a shortage of generic atenolol and the brand atenolol (Tenormin®) has significantly increased in price.
Intranasal Antihistamines	H_1 Blockers	Allergic Rhinitis	This is a cost savings measure. Patients may bring their own intranasal antihistamines from home.

Changes to Restrictions of Medications on the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Vigabatrin (Sabril®)	Anticonvulsant	Infantile Spasms Refractory Complex Seizures	The Pediatric Neurology Service was added to the current restriction. Modified restriction: 1. Initiation of vigabatrin therapy is restricted to prescribers from the Pediatric Epilepsy Service and **Pediatric Neurology.** The prescriber MUST be registered (certified) with the Vigabatrin REMS Program. 2. Continuation of therapy is restricted to prescribers from the Pediatric Epilepsy Service Vigabatrin REMS Program. However, the pharmacist is allowed to verify and dispense ONE dose ordered by a NON-certified prescriber for continuation of home therapy during OFF-HOURS. The primary service will need to consult with a certified inpatient prescriber from Pediatric Epilepsy Service or **Pediatric Neurology** the next day for approval of subsequent doses for continuation of therapy.

REMS=Risk Evaluation Mitigation Strategy

Standardization of the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Neoral®, Gengraf® and other generic modified cyclosporine capsules and oral liquids	Immunosuppressive Agent	Kidney, Liver, Heart Transplant Rheumatoid Arthritis Psoriasis	Teva generic modified cyclosporine capsules and oral liquid will be used for both inpatient and ambulatory pharmacies.
Sandimmune® Oral Capsules (oral non-modified cyclosporine)	Immunosuppressive Agent	Prophylaxis of Organ Rejection Chronic Rejection	Brand-name Sandimmune® oral capsules will remain on Formulary.
Sandimmune® Injection (Non-modified cyclosporine)	Immunosuppressive Agent	Prophylaxis of Organ Rejection Chronic Rejection	Generic Perrigo Injectable non-modified cyclosporine will be stocked.

FDA=Food and Drug Administration