PALLIATIVE PEARLS
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Pulmonary Hypertension in Hospice Care
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PATIENT CASE

PM is a 66-year-old woman with a primary diagnosis of pulmonary arterial hypertension (PAH) (WHO functional class III), and history of scleroderma and no known drug allergies. She lives at home with her husband where she is being seen for the first time by the home hospice nurse. Upon review of PM's medications, it is noted she is prescribed Letairis® (ambrisentan) 10mg by mouth daily and Adcirca® (tadalafil) 40mg by mouth daily to manage PAH. These medications are indeed related to the patient's primary diagnosis of PAH however it is not clear to the home hospice nurse if the medications should be continued on hospice care.

CLASSIFICATION OF PULMONARY HYPERTENSION

Pulmonary hypertension (PH) is defined as an elevated mean arterial pressure (mPAP) ≥25 mmHg at rest.[1] PH is considered severe if mPAP is ≥35 mmHg or the mPAP is ≥20 mmHg with an elevated right atrial pressure and/or the cardiac index is <2 L/min/m^2.[2] PH is classified by the World Health Organization (WHO) into five groups based on etiology. A patient's condition is then classified into one of 4 functional classes based on exercise capacity.[3]

Etiology Groupings [1]

- Group 1 - Pulmonary arterial hypertension (PAH): Commonly caused by idiopathic (IPAH) and heritable PAH, drugs and toxins, connective tissue diseases (i.e., scleroderma, rheumatoid arthritis, systemic lupus erythematosus, Raynaud disease), human immunodeficiency virus (HIV), portal hypertension, or congenital heart disease.

- Group 2 - PH due to left heart disease (LHD): Commonly caused by left ventricular systolic or diastolic dysfunction, and mitral and aortic valve disease.

- Group 3 - PH due to chronic lung disease and/or hypoxemia.

- Group 4 - PH due to chronic thromboembolic pulmonary hypertension.

- Group 5 - PH due to unclear multifactorial mechanisms: Commonly caused by chronic hemolytic anemia (i.e., sickle cell disease), myeloproliferative disorders, systemic disorders (i.e., sarcoidosis), metabolic disorders (i.e., glycogen storage disease), chronic kidney disease, or miscellaneous causes.

World Health Organization (WHO) Functional Classification for PH (Exercise Capacity) [3]

- Class I: Without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea, chest pain, or heart syncope.
- Class II: Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in undue fatigue or dyspnea, chest pain, or heart syncope.
- Class III: Marked limitation of physical activity. Comfortable at rest. Less than ordinary physical activity causes undue fatigue or dyspnea, chest pain, or heart syncope.
- Class IV: Inability to carry on any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present even at rest. Discomfort is increased by physical activity.

MANAGEMENT OF PULMONARY HYPERTENSION

Management of all classes of PH begins with conventional, or primary, therapy. **Primary therapy** is directed at the *underlying cause* of the PH. Note there are no effective primary therapies for most types of group 1 PAH. Consider the risks and benefits of each of the following primary therapies: [3]

- Oxygen (recommended in group 2 PH (LHD) and group 3 PH (chronic lung disease and/or hypoxemia)
- Diuretics
- Anticoagulants (recommended in group 4 PH (chronic thromboembolic))
- Digoxin

Response to therapy as well as disease severity should be reassessed following primary therapy to determine whether advanced therapy is indicated. **Advanced therapy** is directed at the *pulmonary hypertension itself,* producing pulmonary vasodilation, rather than the underlying cause.[3] Medications and available dosage forms include: [4, 5]

- Endothelin receptor antagonists (nonselective): Opsumit® (macitentan) (oral), Tracleer® (bosentan) (oral)
- Endothelin receptor antagonist (selective): Letairis® (ambrisentan) (oral)
- Selective PDE type 5 inhibitors: Adcirca® (tadalafil) (oral), Revatio® (sildenafil) (oral, parenteral)
- Guanylate cyclase simulator: Adempas® (riociguat) (oral)
- Prostacyclin agonists and analogs: Flolan®, Veletri® (epoprostenol) (parenteral), Ventavis® (iloprost) (inhalation), Orenitram® (treprostinil) (oral), Remodulin® (treprostinil) (parenteral)

Tyvaso® (treprostinil) (inhalation), Uptravi® (selexipag) (oral)

- Calcium channel blockers: First-line - Procardia XL® (nifedipine long-acting) or Cardizem® (diltiazem), Alternative - Norvasc® (amlodipine)

Advanced therapy is broadly accepted for group 1 PAH, however must be considered on a case-by-case basis for patients with group 3, 4 or 5 PH, after weighing the risks versus the benefits. Importantly, evidence supporting advanced therapy is resultant from study patients with group 1 PAH, and not with other groups, and should only be prescribed by experienced clinicians. Advanced therapy should be avoided in group 2 as it may be harmful.[3]

ADVANCED THERAPY AGENT SELECTION

There is no best practice method for selecting an appropriate agent. The choice should be based on patient-specific factors, potential drug interactions with medications treating other comorbidities, as well as clinicians' expertise and clinical experience. For patients with group 1 PAH, it is recommended to perform a **vasoreactivity test** to identify those who may respond to calcium channel blockers (CCBs), less expensive options with fewer adverse effects than other advanced therapies. Initiate CCB therapy for patients with positive vasoreactivity. For those with negative vasoreactivity, consider patients for other advanced therapy based on WHO functional class, as discussed below: [3, 6, 7]

- Class I: These patients do not require pharmacotherapy; Treat contributing factors and monitor.

- Class II: Preferred therapy is oral ambrisentan plus oral tadalafil; Alternatives include other endothelin receptor antagonist-PDE type 5 inhibitor combinations OR single agent oral therapy (ambrisentan, bosentan, macitentan, sildenafil, tadalafil, riociguat, or selexipag).

- Class III: Preferred therapy is oral ambrisentan plus oral tadalafil; Alternatives include other endothelin receptor antagonist-PDE type 5 inhibitor combinations OR single agent oral therapy (ambrisentan, bosentan, macitentan, sildenafil, tadalafil, riociguat, or selexipag); Alternatives in patients with rapid or progressive disease include oral selexipag or intravenous epoprostenol, intravenous or subcutaneous treprostinil, or inhaled treprostinil or iloprost.

- Class IV: Preferred therapy is intravenous epoprostenol; Alternative is intravenous treprostinil; with no improvement or deterioration, consider double or triple combination therapy if not trialed yet; Consider atrial septostomy or lung transplantation.

COMBINATION THERAPY [6, 8]

For patients with progressive or refractory disease, combination therapy with a second, and rarely third, agent of a different class is appropriate, with the exception of combining PDE type 5 inhibitors and guanylate cyclase stimulants, which is contraindicated due to an unfavorable safety profile.[3]

PATIENT CASE CONTINUED

The decision to continue therapy with Letairis® (ambrisentan) and Adcirca® (tadalafil) for PM, a patient with PAH on hospice care, is multifactorial. The specific combination of ambrisentan taken with tadalafil is FDA-approved to reduce the risks of disease progression and hospitalization for worsening PAH and to improve exercise ability.[5] During hospice care, therapy that is curative or has long-term outcomes is typically discontinued while therapy that provides symptom management and comfort is continued. PM's PAH therapy, similar to most advanced therapy for PAH, serves both a long-term outcome and short-term symptom management. Other factors to consider are adverse effects associated with therapy, PM's quality of life and most importantly, PM's goals of care. Only when all of these factors are balanced may an informed decision be made on how to manage her therapy.

For additional information on this topic, please review these references:

1. Rubin LJ, Hopkins W. Classification and prognosis of pulmonary hypertension in adults. UpToDate. Updated August 9, 2018. Accessed March 2, 2019.
2. Klings ES. Pulmonary hypertension due to lung disease and/or hypoxemia (group 3 pulmonary hypertension): Epidemiology, pathogenesis, and diagnostic evaluation in adults. UpToDate. Updated February 21, 2019. Accessed March 3, 2019.
3. Hopkins W, Rubin LJ. Treatment of pulmonary hypertension in adults. UpToDate. Updated September 26, 2018. Accessed March 2, 2019.
4. Clinical Resource, Meds for Pulmonary Arterial Hypertension. Pharmacist's Letter/Prescriber's Letter. March 2017.
5. Clinical Pharmacology [database online]. Tampa, FL: Elsevier/Gold Standard, Inc.; 2019. Access 2019 Feb.
6. The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart* J. 2009; 30:2493-2537.
7. Barst RJ, Gibbs US, Ghofrani HA, et al. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol.* 2009; 54: S78.
8. Burks M, Stickel S, Galie N. Pulmonary Arterial Hypertension: Combination Therapy in Practice. *Am J Cardiovasc Drugs*. 2018;18(4):249-257. https://www.medscape.com/viewarticle/899222_1

