Early Recognition and Management of Posterior Reversible Encephalopathy Syndrome: A Newly Recognized Complication in Patients Receiving Tyrosine Kinase Inhibitors

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Background: Adult patients with cancer receiving antineoplastic, targeted, and other immunosuppressive therapies are at risk for severe side effects. Studies link posterior reversible encephalopathy syndrome (PRES) with immunosuppressants used for patients undergoing transplantation, as well as select tyrosine kinase inhibitors (TKIs) and other targeted therapies used in patients with cancer. PRES is a reversible condition with early recognition and management; however, permanent neurologic toxicities have been reported.

Objectives: This article aims to educate oncology nurses on signs, symptoms, and management of PRES in patients receiving TKIs.

Methods: The literature was reviewed to develop an educational session about causes, manifestations, pathophysiology, and management of PRES. Using a case study and flipped classroom model, staff participated in an online lecture and concept engagement exercise. Education for nurses included frequent neurologic and mental status assessments, blood pressure monitoring with mean arterial blood pressure goal, and seizure precautions. Nursing knowledge was evaluated with pre- and post-testing.

Findings: Evaluation revealed improved knowledge in recognizing and managing patients with PRES related to TKIs. The flipped classroom approach was perceived as a valuable tool for busy staff nurses.

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Posterior reversible encephalopathy syndrome (PRES) is a neurotoxic disorder with specific neuroimaging findings (Bartynski, 2008). Hinchey et al. (1996) first described PRES as a clinicoradiologic entity based on 15 observed cases. The pathophysiologic etiology for PRES is unknown, but some hypotheses for its cause exist. The syndrome is usually diagnosed by its common symptoms and neuroimaging findings. It can be identified using computed tomography (CT) and magnetic resonance imaging (MRI) findings along with significant clinical changes (Legriel, Pico, & Azoulay, 2011).

Tyrosine kinase inhibitors (TKIs) are one of the known agents that can cause PRES (Neill, 2016). TKIs work in cancer therapy by binding to the adenosine triphosphate binding sites on malignant cells, where they inhibit angiogenesis and proliferation (Yu, Steeghs, Nijenhuis, Schellens, & Huijema, 2014). According to Yu et al. (2014), TKIs are used to treat several disorders, such as acute lymphoblastic leukemia, chronic myelogenous leukemia, renal cell...
carcinoma, HER2-positive breast cancer, ovarian cancer, and non-small cell lung cancer.

Oncology Drugs Associated With Posterior Reversible Encephalopathy Syndrome

Several agents have been known to cause PRES in patients with cancer. One of these agents is immunosuppressive therapy. About 9% of patients using immunosuppressive therapy for stem cell transplantation or bone marrow transplantation have been found to develop PRES (Bartynski, 2008). PRES has also occurred in patients receiving combination chemotherapy regimens. According to Bartynski (2008), common drugs used in cancer therapy that can cause PRES include cyclophosphamide, cytarabine (Depocyt®), cyclosporine (Neoral®), and tacrolimus (Prograf®).

Another drug class that can cause PRES in patients with cancer is TKIs, such as vascular endothelial growth factor receptor inhibitor (Bartynski, 2008). According to Weingart et al. (2011), 25% of antineoplastic agents approved by the U.S. Food and Drug Administration are oral agents. These drugs can be given in inpatient and outpatient settings. Because these therapies are given in both settings, all oncology nurses need to have a greater understanding of this syndrome.

Posterior Reversible Encephalopathy Syndrome

Pathophysiology

The pathophysiology of PRES is unknown, but it is associated with specific clinical and radiologic findings (Legriel et al., 2011). However, several strong hypotheses exist related to the etiology of PRES. The three hypotheses include cerebral autoregulatory failure, endothelial damage, and cerebral ischemia (Neill, 2016).

In cerebral autoregulatory failure, the cerebral arteries constrict and dilate based on blood pressure changes during normal regulation. When normal regulation is exceeded, the brain has excessive perfusion, causing disruption in the blood–brain barrier and increased amounts of fluid and blood to reach the brain. This disruption of the blood–brain barrier can lead to encephalopathy (Neill, 2016). According to Neill (2016), the threshold for disruption in autoregulatory process is different between individuals. Those with chronic hypertension may have a smaller threshold than those without hypertension. According to Legriel et al. (2011), a mean arterial blood pressure (MAP) increase of more than 170 mmHg can cause autoregulatory dysfunction. However, those with chronic hypertension can have an increase in MAP by 50 mmHg, which can lead to autoregulatory failure (Legriel et al., 2011).

The second and third hypotheses include endothelial damage and cerebral ischemia. Endothelial damage is thought to occur because of the direct damage of the cerebral arteries, causing capillary leakage and disruption of the blood–brain barrier (Neill, 2016). Endothelial damage and autoregulatory dysfunction are hyperperfusion-related issues. In contrast, the final hypothesis of cerebral ischemia is thought to be a hypoperfusion problem. According to Neill (2016), cerebral arteries vasoconstrict in the presence of systemic hypertension. This causes a hypoperfusion of blood to the brain, subsequent cerebral ischemia, and, in severe cases, infarction.

Clinical Manifestations

Although dispute exists regarding the pathophysiologic etiology of PRES, the management, clinical manifestations, and risk factors are less debated. Clinical manifestations of PRES include headaches, altered consciousness, seizures, and visual disturbances (Mishra et al., 2008; Neill, 2016; Yoon et al., 2013).

As many as 92% of people who have a diagnosis of PRES have seizure activity (Legriel et al., 2011). Seizures are typically tonic-clonic seizures, and can cause status epileptics in severe cases (Neill, 2016). Acute hypertension is another common clinical manifestation in PRES, and it occurs as much as 80% of the time (Legriel et al., 2011).

Risk Factors

Although anyone can develop PRES, several risk factors put patients at higher risk. Three specific risk factors include fluid overload, elevated blood pressure, and decreased kidney function. Fluid overload is defined by a 10% or greater increase in baseline weight (Neill, 2016). The second risk factor is a MAP greater than 25% of baseline. The last risk factor is elevated creatinine greater than 1.8 mg/dL (Neill, 2016). Patients are at higher risk of developing PRES if they have one or more of these three risk factors.

Diagnosis

Diagnosis of PRES is completed by clinical manifestations and radiologic findings. Diagnosis can be made by MRI or CT...
Which of the following is a risk factor for PRES while receiving cytotoxic therapy?
- Hypotension
- Tachycardia
- Fluid overload
- Creatinine 1.4 mg/dl

Which of the following is not a symptom indicative of PRES?
- Seizures
- Hypertension
- Mental status changes
- Tachypnea

Give one way PRES can be diagnosed.

What should the goal MAP be when managing a patient with PRES?
- Increase MAP by at least 50%.
- Lower MAP by at least 50%.
- Lower MAP by at least 10%.
- Increase MAP by at least 10%.

PRES is always reversible.
- True
- False

Which medications have been shown to cause PRES? Choose all that apply.
- Tacrolimus (Prograf®)
- Cyclosporine (Neoral®)
- Cytarabine (DepoCyt®)
- Imatinib (Gleevec®)

Note. Bolded responses are correct.

MAP—mean arterial blood pressure; PRES—posterior reversible encephalopathy syndrome

FIGURE 1. Pre- and Post-Test Questions and Responses

scan. MRI has been shown to be superior to CT scan (Legriel et al., 2011). Four radiologic features are found on imaging associated with PRES: holohemispheric watershed pattern, superior frontal sulcus pattern, dominant parietal-occipital pattern, and partial expression of the three primary patterns (Legriel et al., 2011).

All four features have fluid-attenuated inversion recovery (FLAIR). The four features are determined based on the pattern of the FLAIR on imaging (Legriel et al., 2011). Twenty-three percent of patients have holohemispheric watershed pattern, which is a linear pattern (Legriel et al., 2011). Twenty-seven percent of patients have superior frontal sulcus pattern, which is a nonconfluent pattern (Legriel et al., 2011). Dominant parietal-occipital pattern occurs in 22% of patients, and it is solely in the parietal and occipital lobes (Legriel et al., 2011). Lastly, 28% of patients have the fourth pattern, which is an asymmetrical form of all other three patterns. Any of these findings can be diagnostic for PRES (Legriel et al., 2011).

Management

According to Legriel et al. (2011), management of PRES is symptom management through reduction of hypertension, seizures, and removing the causative agents. According to Mishra et al. (2008), PRES can be reversible if managed within seven days through blood pressure control, removal of the causative agent, and resolution of seizures. Delayed diagnosis and treatment can result in permanent brain damage (Mishra et al., 2008).

Hypertension can be managed with several different agents, including IV labatelol (Trandate®), sodium nitroprusside (Nitropress®), and diuretics (Mishra et al., 2008). Initial lowering of the diastolic blood pressure to 100 or 105 mmHg is suggested (Neill, 2016). After initial lowering, the goal is to decrease the MAP by 10%–25% (Legriel et al., 2011).

Seizure management is another important part of management of PRES. Benzodiazepines should be used for persistent seizure activity (Legriel et al., 2011). According to Legriel et al. (2011), complementary IV anticonvulsants, such as phenytoin (Dilantin®) or phenobarbital, can be used for refractory seizures. Valproate (Depakote®) and levetiracetam (Keppra®) have also been used to manage seizures related to PRES (Yoon et al., 2013). Long-term therapy is typically not required and can be titrated off after three to six months (Neill, 2016).

Recognition and Management of Evaluation

In an effort to educate oncology nurses at a large comprehensive cancer center, an education intervention was developed regarding PRES and TKIs. A flipped classroom model was adapted for busy staff nurses to improve knowledge and practice. The flipped classroom model is not a new model, but it has increased in popularity. The flipped classroom model is an asynchronous model that provides for advanced preparation using technology prior to classroom time (Hawks, 2014). Classroom time is spent discussing topics and reinforcing information through peer learning activities (Hawks, 2014). According to Hawks (2014), the resurgence of the flipped classroom has occurred because of the need for improved education models to increase provider competencies. Hawks (2014) found that the flipped classroom model...
improved engagement, which directly correlated with an increase in knowledge.

Thirty-two staff members working in inpatient and outpatient oncology settings participated in the education session. Using a case study and flipped classroom model, staff listened to an online pre-recorded lecture with a Microsoft® PowerPoint® presentation, followed by an in-person session with personal concept engagement with peers and the instructor. Educational technology and active learning are key components of the flipped classroom model. Nursing knowledge about pathophysiology, causes, and clinical manifestations of PRES was evaluated with pre- and post-testing (see Figure 1). Participants completed the pretest before the online session. Post-testing was completed after the online and in-person sessions. The pre- and post-test questions were exactly the same (see Figure 2).

Evaluation before and after the education revealed improved knowledge in recognizing and managing patients with PRES. Only 25 of 32 staff members participated in the post-test. Participants perceived the flipped classroom approach to be a valuable tool for busy staff nurses.

Discussion

PRES is well documented in populations of patients undergoing transplantsations. However, other agents are known to cause PRES in patients with cancer. Early recognition, assessment, and management are essential to prevent long-term damage or death. Inpatient and outpatient oncology nurses are integral in identifying the signs and symptoms of PRES when caring for patients at risk. Patients at risk should receive specific education, including specific symptoms to report.

The educational intervention described in this article involved 32 nurses at a large comprehensive cancer center. Of those nurses, several worked in both outpatient and inpatient settings. Only a few were solely inpatient oncology nurses. In this small sample size, improved education showed an increase in knowledge for these particular nurses. Improved knowledge was found with improvement from pre- to post-test scores. Limitations include that only one specific group of nurses were involved, that it was limited to one comprehensive cancer center, and that only 25 of 32 nurses completed both the pre- and post-tests.

Most information found in reviewing the current literature on PRES was limited to general side effects and management. No information was found that specifically showed differences in manifestations regarding causative agents. Minimal data were found regarding the relationship between TKIs and PRES and specific management strategies. However, in the reviewed articles about PRES, a substantial number discussed the correlation between TKIs and PRES.

Implications for Practice

- Identify agents and risk factors that can put patients at higher risk of developing posterior reversible encephalopathy syndrome (PRES).
- Increase early detection of signs and symptoms related to PRES in patients with cancer.
- Improve knowledge related to early treatment and management of PRES in patients with cancer.

and management of PRES related to TKI therapy in the population of patients with cancer. Inpatient and outpatient oncology nurses are at the forefront of patient care, and they need specialized knowledge to identify potential life-threatening side effects in a timely manner.

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References


