Hemorrhagic Cystitis

Treatment with hyperbaric oxygen therapy in patients with acute lymphoblastic leukemia

Lauren M. Botta, RN, BSN, CHPN, and Gregory P. Botta, MD, PhD

BACKGROUND: Hyperbaric oxygen therapy is a rare treatment modality for hemorrhagic cystitis (HC) following BK virus reactivation in the immunosuppressed population. Clinicians need to be aware of the etiology, preventive measures, complications, and various management techniques in HC while treating patients undergoing bone marrow transplantation.

OBJECTIVES: This study details the pathologic progression of HC in a patient with acute lymphoblastic leukemia harboring BK virus after cytotoxic induction chemotherapy and haploidentical marrow transplantation.

METHODS: A search of PubMed for literature published from 1973–2018 was conducted using keywords.

FINDINGS: Hyperbaric oxygen therapy in chemotherapy-induced and BK virus–associated HC is a viable management option in parallel with tapering of immunosuppressives, bladder irrigation, and IV resuscitation within the post-transplantation acute lymphoblastic leukemia population.

KEYWORDS
hemorrhagic cystitis; hyperbaric oxygen; BK virus; acute lymphoblastic leukemia

DIGITAL OBJECT IDENTIFIER
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HEMORRHAGIC CYSTITIS (HC) IS ASSOCIATED WITH BK VIRUS REACTIVATION in the immunosuppressed transplantation population after exposure to various cytotoxic therapies, most commonly the alkylating agents cyclophosphamide and ifosfamide. In addition, the incidence of HC is common with busulfan; rare with thiotepa, fludarabine, and chlorambucil; 20%–30% with doxorubicin; and 17% with cabazitaxel (Moy, Linder, Chao, & Grounder, 2018). The annual incidence post-transplantation ranges from 3%–24% and is associated with renal and hemorrhagic pathology (Gilis et al., 2014). HC is clinically defined as minimal or massive based on either the presence of microscopic hematuria (5–50 red blood cells per high power field) or the necessity of blood transfusion, respectively. For clinical diagnosis of HC, diffuse bladder inflammation, microscopic hematuria (red blood cell per high power field on urinalysis), or significant hematuria requiring red blood cell infusion is required. Massive blood loss with subsequent transfusion disrupts the normal coagulation, fibrinolysis, and platelet mechanism, sometimes leading to disseminated intravascular coagulation (DIC). The combination of malignancy, infection, and bleeding diathesis incites DIC at a higher rate than if a patient had any one cause alone (Russo, 2000). With massive bleeding, mortality from HC increases to about 2%–4%, and subsequent complications (hydronephrosis, anemia, and thrombocytopenia) generally require prolonged hospitalization (Watson & Notley, 1973). These extended institutional stays expose immunosuppressed patients to various opportunistic pathogens during a period of heightened risk. As hematopoietic transplantation rates increase, clinicians should understand these complex complications and their management.

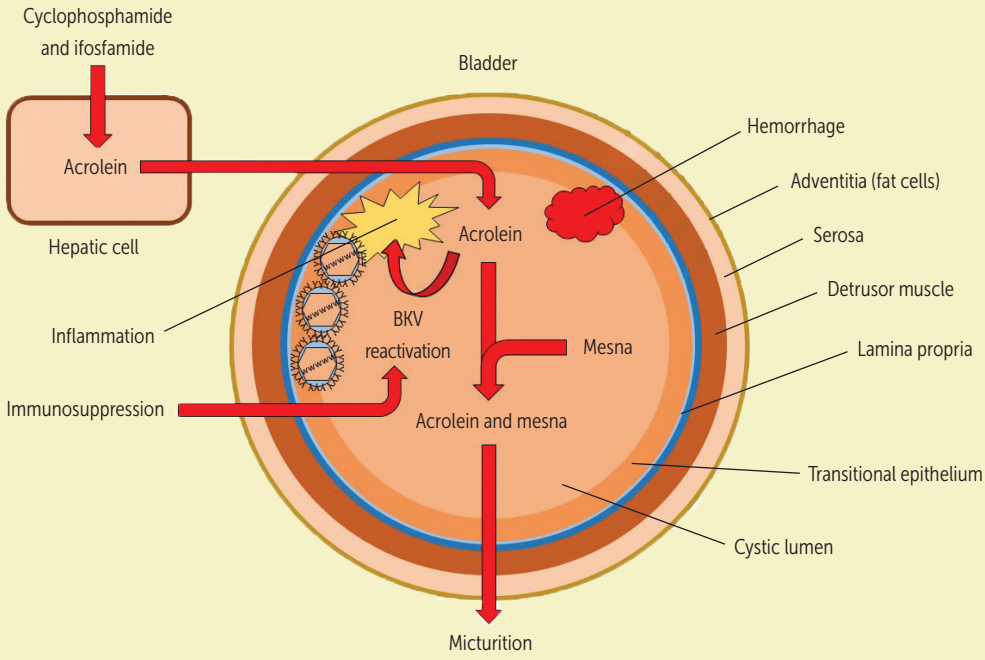
The immunosuppressed are particularly vulnerable to HC because of their immune attenuation and direct urothelial contact with cyclophosphamide or ifosfamide (Arthur, Shah, Baust, Santos, & Saral, 1986) (see Figure 1). Urotoxic acrolein, a liver metabolite of both compounds, is excreted into the renal tubules. The bladder, acting as a storage vessel, has prolonged exposure to its inflammatory effects. Acrolein toxicity disrupts the normal transitional epithelium to induce polyuria, dysuria, urgency, and suprapubic discomfort, in addition to micro- and macroscopic blood loss. Catastrophic events, such as bladder rupture, can occur with chronic inflammation (Imataki, Uchida,

Kushida, & Uemura, 2017). The incidence of HC increases with large and cumulative doses of chemotherapy, as well as with use of ifosfamide versus cyclophosphamide (Wong, Yeo, Chan, & Mok, 2000).

BK virus (named after an unidentified patient's initials) is an opportunistic pathogen acquired in childhood. The virus remains latent in the genitourinary system but is typically reactivated in immunocompromised individuals (Bedi et al., 1995; Leung, Yeun, & Kwong, 2005). Studies have identified a correlation between HC severity and burden of BK viremia (Dropulic & Jones, 2008). Patients who excreted BK virus were four times more likely to develop HC at diagnosis and require a prolonged hospital stay (Dropulic & Jones, 2008). Factors that increase the incidence of BK virus–associated HC include younger age, unrelated donor stem cells, source of stem cells, HLA mismatch, and type of conditioning regimen (Gilis et al., 2014). A study of a large cohort of patients with allogeneic hematopoietic transplantation (n = 1,321) from a single center found that of those who develop HC, 90% have a detectable level of BK viuria (Lunde et al., 2015). In addition, the combination of chemotherapy-induced bladder inflammation, coagulopathies associated with malignancy, and BK viremia create a synergistic bladder pathology that induces the bleeding diathesis (Russo, 2000).

Prevention of HC is of the utmost importance within a susceptible population. Superhydration coupled with mesna (2-mercaptoethanesulfonate sodium), an acrolein binder that helps in urine excretion, has proven to be an effective standard of care. It must be noted that mesna must be infused within the bladder prior to chemotherapeutic dosing to be effective (Siu & Moore, 1998). Treatment for HC is determined by the presence or absence of massive blood loss requiring transfusion (see Figure 2). In patients with minimal hematuria, IV fluid boluses and superhydration assist in diluting the acrolein within the bladder and reducing inflammation within the kidney tubules and transitional epithelium. In addition, continuous bladder irrigation (CBI) is a common modality to assist in flushing the acrolein, as well as any mechanically obstructing blood clots, from the bladder and reducing comorbidities. In the presence of massive blood loss, options include hormonal therapy with oral estrogens (acknowledging a delay in response), intravesicular topical prostaglandins that increase smooth muscle contraction and stave off bleeding, interventional radiologic

FIGURE 1.
PATHOGENESIS OF HEMORRHAGIC CYSTITIS IN THE SETTING OF ACROLEIN AND BKV REACTIVATION



Note. Acrolein, a toxic metabolite of cyclophosphamide and ifosfamide, is transferred to the liver from the bladder for renal clearance. The combination of acrolein and BK virus causes inflammation, leading the transitional epithelium to hemorrhage. Patients are prophylactically given the organosulfur compound mesna to aid in the detoxification and elimination of acrolein through micturition.
Note. Based on information from Moy et al., 2018.

embolization of bleeding vessels, or, ultimately, surgical resection of the bladder (Payne et al., 2013). For centers with access to it, hyperbaric oxygen therapy (HBOT) has been an effective treatment option.

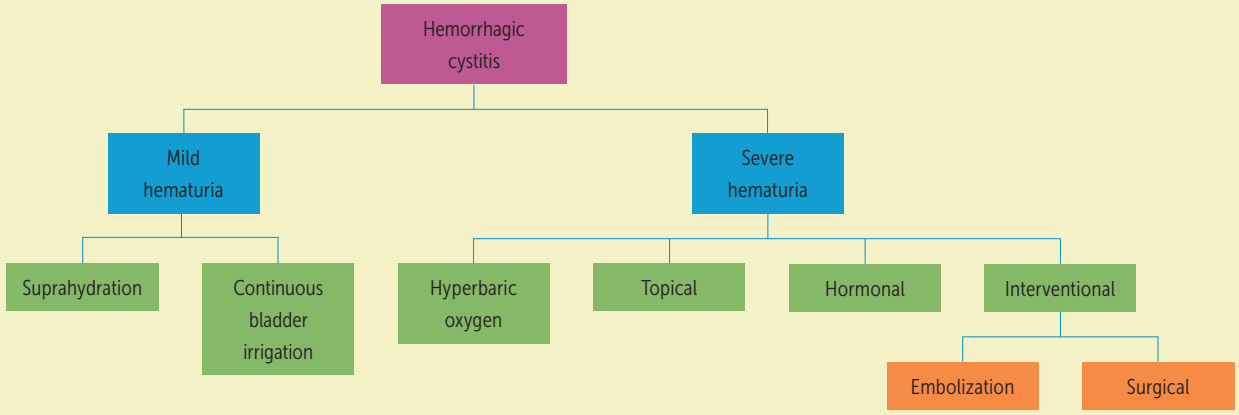
HBOT heals patients with BK virus–associated HC after hematopoietic stem cell transplantation (HSCT) by promoting fibroblast proliferation and capillary angiogenesis while decreasing edema within the urothelium (see Figure 3). Mechanistically, it appears that the molecular oxygen of HBOT is capable of deeper diffusion within the transitional epithelium to regulate hypoxia-inducible factor 1 and vascular endothelial growth factor, reducing leaky capillaries and bleeding (Cianci & Sato, 1994). A randomized, controlled trial of 338 patients with HC treated with allogeneic HSCT and undergoing HBOT found that 94% of patients who received therapy immediately after HC diagnosis had faster clinical resolution of symptoms after 13 90-minute sessions. Longer delay in initiation of HBOT resulted in longer courses of symptomatology (Dropulic & Jones, 2008). Cystitis, hematuria, and urine BK viral loads greater than 7^10 copies assist in the diagnosis of BK virus HC (Cesaro et al., 2018). Complications of HBOT include myopia, pulmonary oxygen toxicity, decompression illnesses, and claustrophobia-induced anxiety, which is attenuated with anxiolytics (Savva-Bordalo et al., 2012). Most of the relevant HBOT literature stems from radiation-induced cystitis, where complete resolution of hematuria can be achieved in 81% of the HC population (Oliai et al., 2012). However, HBOT access is limited to facilities that own the appropriate chamber. Appropriately stable patients must be able to be disconnected from IV medications and health monitors unless a customized chamber or appropriate pump is available to support these functions (Bell, Weaver, & Deru, 2016).

"The incidence of hemorrhagic cystitis increases with large and cumulative doses of chemotherapy."

Case Presentation, Management, and Outcome

A middle-aged woman presented to the oncology service with pancytopenia. White blood cells were noted to be 72,000 cells/mcl with 80% circulating leukemic blasts, and a bone marrow biopsy showed 90% involvement of precursor Philadelphia chromosome–negative acute lymphoblastic leukemia. Following a lumbar puncture for altered cognition, cerebrospinal fluid analysis was negative for disseminated leukemia. Complaints of dyspnea prompted a chest computed tomography scan, revealing retrosternal lymphadenopathy causing superior vena cava syndrome followed by pulmonary edema. Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine induction was completed. Prophylactic intrathecal methotrexate and cytarabine was also initiated for eight

FIGURE 2.
DECISION TREE FOR THE CLINICAL MANAGEMENT OF HEMORRHAGIC CYSTITIS



Note. Based on information from Moy et al., 2018.

treatments because of a lactate dehydrogenase of over 600 U/L. Complete remission was attained, and mercaptopurine, vincristine, methotrexate, and prednisone maintenance was tolerated until the patient's sibling was able to provide a haploidentical HSCT on day 0.

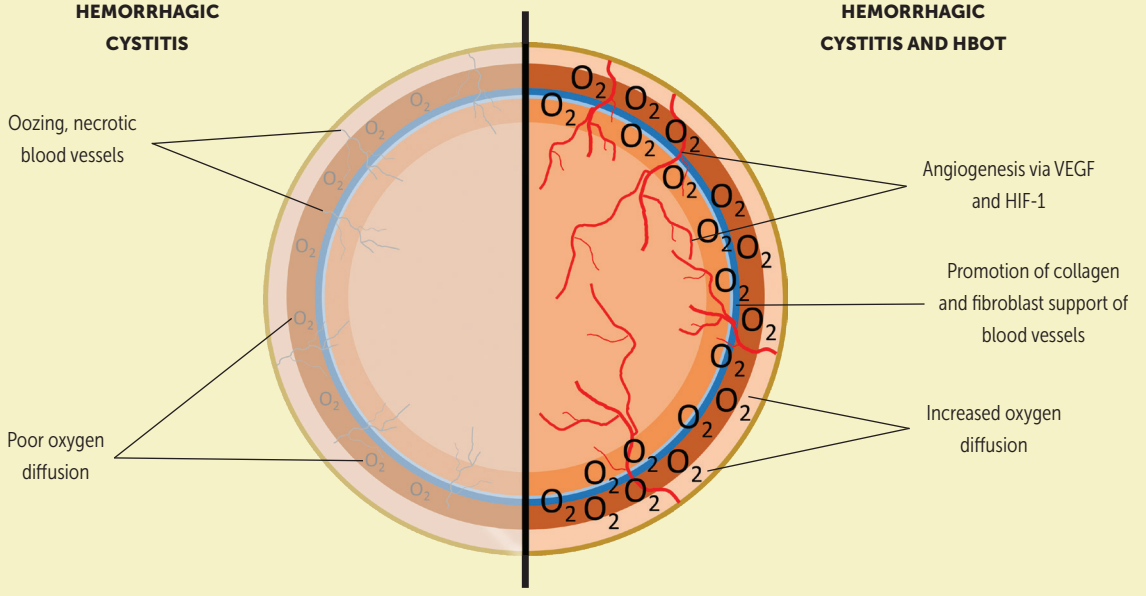
On day 4 post-transplantation, a bone marrow biopsy showed no evidence of disease and 100% donor DNA chimerism. Prior to discharge, the patient was placed on blood and marrow transplantation protocol prophylaxis and cyclosporine to inhibit graft-versus-host disease (Kanakry et al., 2013). Prior to discharge, the physician and nursing team educated her on red-flag symptoms to be aware of. She and her family were told to call the provider or present to the emergency department for any signs of infection (fever, chills, sore throat), bleeding diathesis (ecchymosis, hemorrhage, hematuria, hematochezia), abdominal pain or jaundice (relating to liver failure), or mucositis.

On day 10 post-transplantation, the patient was readmitted for an acute overgrowth of *Rothia mucilaginosa*, a gram-positive opportunistic coccus, within her oropharynx. Subsequent blood cultures returned positive for *Rothia* bacteremia, and two weeks of IV vancomycin was initiated. On day 15, while the patient was on antibiotics, profuse diarrheal stool cultures revealed *Clostridium difficile*, which was treated with IV metronidazole and vancomycin.

On day 20, gross hematuria started, and a clot obstructed the urethra secondary to HC, which was likely caused by injured transitional epithelium and vasculature. The patient was in extreme discomfort and pain during this time, secondary to bladder overdistension. Her oral narcotic pain regimen accordingly increased during these periods. Preventive measures, including IV hydration, blood and platelet transfusions (because of hemorrhagic anemia and thrombocytopenia, respectively), and mesna (acrolein binder), were recommended and given to the patient (Thompson et al., 2014).

On day 25, serum and urine polymerase chain reaction returned positive for BK virus. BK virus is acquired in childhood and reactivated in immunosuppressed patients, so it was the most likely cause for the degree of HC seen in this patient. On day 29, a three-way Foley catheter was placed for CBI (Thompson et al., 2014). Urology was consulted for bladder fulguration with a neodymium-doped yttrium aluminum garnet laser, as well as clot evacuation (Thompson et al., 2014). Gross hemorrhagic bleeding diminished to trace hematuria, which aided in the patient's

FIGURE 3.
MECHANISM OF ACTION OF HBOT



HBOT—hyperbaric oxygen therapy; HIF-1—hypoxia-inducible factor 1; VEGF—vascular endothelial growth factor
Note. The left side of the figure illustrates the pathologic causes of hemorrhagic cystitis, which consists of poor oxygen diffusion related to inflammation of the interstitium, causing necrosing and oozing of blood vessels. The right side of the figure demonstrates how HBOT increases oxygen concentration, stabilizing angiogenesis and promoting collagen and fibroblast vessel support. Neovascularization is accomplished through HBOT, stimulating VEGF and HIF-1.
Note. Based on information from Moy et al., 2018.

overall well-being during recovery. She was discharged 10 days later (day 39) with close follow-up.

Unfortunately, by day 45, the patient was readmitted with continued gross hematuria, clots, and acute renal failure secondary to obstructive hydronephrosis. Cystoscopy, clot evacuation, and fulguration of bladder with biopsies of suspicious areas were performed (Leung et al., 2005; Thompson et al., 2014). CBI aided in preventing additional clots, and HBOT was started on 2.4 atmospheres of 100% oxygen for 90 minutes for 30 days (Savva-Bordalo et al., 2012). During this time, the patient would leave the floor with a dedicated team of nursing staff to the hyperbaric chamber located at the University of California, San Diego, Hillcrest Hyperbaric Oxygen Chamber. CBI and IV hydration would be stopped during this period within the chamber and restarted immediately afterward. This transport required coordination of care among physicians, treatment teams, and nursing management to provide excellent care on the floor, in transport, and during HBOT.

This patient completed HBOT by day 75 with CBI and continuous IV hydration without complication. Transfusions continued for anemia and thrombocytopenia while hematopoietic counts improved in parallel with hematuria resolution. During her overarching care, her immunosuppressive medications were tapered and at times altogether stopped, depending on the degree of cystitis. Ultimately, with control of HC, she was slowly tapered back onto cyclosporine as an outpatient. The patient remained closely followed without hematuria and continued bone marrow chimerism.

Conclusion

Reactivation of senescent viruses and opportunistic infections in an immunocompromised population cause a sequelae of management complications. HC related to reactivation of BK virus is a particularly difficult pathology requiring interprofessional cooperation. In this case, oncology, infectious disease, urology, hyperbaric oxygen, and advanced nursing care services coordinated care in a patient with ALL post-transplantation and ultimately stabilized the acute blood loss anemia. Important considerations for HBOT include access to the chamber, transportation of the patient, management of IV medications during HBOT, and patient hemorrhagic and pain complications of HC. HBOT in chemotherapy-induced and BK virus–associated HC is a viable management option in parallel with tapering of immunosuppressives, bladder irrigation, and IV resuscitation within the post-transplantation ALL population.

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IMPLICATIONS FOR PRACTICE

- Understand mechanisms of BK virus pathogenesis in immunosuppressed patients, including the correlation between hemorrhagic cystitis severity and burden of BK viremia.
- Learn the urothelial toxicities associated with induction chemotherapy, such as diffuse bladder inflammation, microscopic or significant hematuria and polyuria, dysuria, urgency, and suprapubic discomfort.
- Manage hyperbaric oxygen therapy for hemorrhagic cystitis while coordinating patient care.

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