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EDITORIAL

# Hyperbaric Oxygen Therapy for Hemorrhagic Cystitis Following Chemotherapy

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Hemorrhagic Cystitis (HC), a distressing complication arising after chemotherapy, significantly impairs patients' quality of daily life and can lead to substantial morbidity and mortality.[1] This condition, characterized by inflammation and bleeding of the bladder lining, presents a considerable challenge in clinical management, particularly in cases where conventional treatments prove ineffective.[2] In the search for more effective therapeutic strategies, Hyperbaric Oxygen Therapy (HBOT) has emerged as a promising non-invasive or minimally invasive modality. While HBOT has displayed potential in managing HC, especially that induced by radiation, it's role in treating chemotherapy- induced HC is gaining increasing attention.[3]

Hemorrhagic cystitis is a condition where the lining of the bladder becomes diffusely inflamed and starts to bleed.

Common causes are:

1. Cancer and cancer treatments (Chemotherapy and Radiotherapy)
2. Infections- Bacterial, fungal or parasitic infections
3. Chemical exposure - oxazaphosphorine alkylating agents; busulfan; thiotepa; aniline, and toluidine derivatives such as dyes, insecticides and recreational drugs; turpentine; ether; contraceptive suppositories; methenamine mandelate, and gentian violet.[4]
4. Immunocompromised hosts like bone marrow transplant patients

In the context of chemotherapy, the pathophysiology of HC is often associated with oxazaphosphorine alkylating agents such as cyclophosphamide and ifosfamide.[1] These drugs are metabolized by the liver into acrolein, a toxic metabolite excreted through the Renal system. Prolonged contact of acrolein with the bladder lining epithelium triggers a pyroptotic reaction, leading to gross inflammation and hemorrhage.[1] Preventative measures include using Mesna to neutralize Acrolein, but it is ineffective once cystitis has started.

The frequency of HC development following cyclophosphamide chemotherapy ranges from 20% to 25% in the weeks or months after treatment, with higher individual and cumulative doses increasing the risk.[1] Beyond these alkylating agents, other chemotherapy drugs can also contribute to HC through direct toxicity or immune- mediated hypersensitivity reactions.[2] High-dose chemotherapy drugs used in bonemarrow transplantation further increase the risk of HC.[2] Clinically, HC presents with blood in the urine, ranging from microscopic hematuria to gross hematuria with clots, accompanied by dysuria, increased urinary frequency and urgency, and potentially vague lower abdominal pain.[1] The severity of HC is graded from 0 to IV based on the degree of bleeding and the presence of clots, a classification system crucial for guiding clinical management and standardizing research.[2]

The current treatment aspect for post-chemotherapy HC involves a variety of strategies. Initial management often includes conservative measures such as increasing fluid intake and bladder irrigation with normal saline to evacuate blood clots.[2] If feasible, discontinuing or reducing the dose of the chemotherapy agent responsible for HC is also considered.[2] Pharmacological agents' interventions play a significant role, with intravesical instillations of astringent agents like alum, aminocaproic acid, silver nitrate, and formalin being employed to control bleeding.[2] Systemic agents such as conjugated estrogens and sodium pentosan polysulfate have also been used.[3] Mesna, a compound that protects the

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bladder lining by binding to acrolein, is primarily used prophylactically but may also have some therapeutic benefit .[1] In more severe cases, invasive procedures such as cystoscopy with diathermy fulguration of bleeding vessels or arterial embolization may be necessary.[3] For refractory HC that does not respond to these measures, urinary diversion or cystectomy, the surgical removal of the bladder, may be the last resort.[3] However, these conventional approaches have limitations, including variable efficacy, potential side effects, the need for repeated procedures, and significant morbidity associated with major surgery.[2] The lack of a uniformly effective treatment, especially for severe or chronic HC, underscores the need for exploring alternative therapies like HBOT.

Hyperbaric Oxygen Therapy presents a new approach to treating chemotherapy-induced HC by addressing the underlying tissue damage and promoting healing. The primary mechanism of action involves increasing the level of oxygen in the body's tissues by administering 100% oxygen in a pressurized chamber.[3] This high oxygen can reverse tissue hypoxia, a common consequence of chemotherapy-induced damage, and stimulate new angiogenesis, the formation of new blood vessels.[3] The growth of new blood vessels is crucial for restoring blood flow and delivering essential nutrients to the damaged bladder mucosa, thereby facilitating healing 3. Furthermore, HBOT enhances the function of key cells involved in wound healing, such as macrophages, fibroblasts, and granulocytes, which are essential for tissue regeneration and repair[3] It has also been suggested that HBOT can decrease inflammation and edema in the affected bladder tissue, contributing to symptom relief and promoting a healing environment.[7]

Our retrospective, observational study conducted at the HBOT center of the National Institute of Burn & Plastic Surgery (NIBPS) between January 2022 and June 2024 investigated the effectiveness of Hyperbaric Oxygen Therapy (HBOT) for hemorrhagic cystitis following chemotherapy. The study population consisted of 12 patients with this condition, excluding those with hemorrhagic cystitis due to radiotherapy, UTI, coagulative disorders, active bladder cancer or trauma.

The patient had various underlying conditions: 4 immunocompromised bone marrow transplant patients, 4 bladder tumor patients, 2 breast cancer patients, and 2 lymphoma patients, with a male to female ratio of 7:5. The mean number of HBOT cycles administered was 40.9, ranging from 15 to 65 cycles.

The study found that HBOT was largely effective, achieving complete resolution of hematuria in 9 out of the 12 patients (75%). During the maximum follow-up period of 12 months after HBOT completion, none of the patients who achieved resolution experienced a recurrence of hematuria.

However, treatment was discontinued in three patients. One patient with primary bladder cancer experienced increasing hematuria and suspected recurrence. The other two patients discontinued due to coexisting health issues, and in these cases, the hematuria had only lessened or not completely stopped. Notably, no patients reported experiencing claustrophobia during their HBOT sessions.

The evidence base supporting the use of HBOT for post-chemotherapy Hemorrhagic Cystitis is growing, primarily consisting of retrospective studies and case series.[3] These studies often focus on patients with refractory HC who have not responded to conventional treatments, including those who have undergone chemotherapy and/or hematopoietic stem cell transplantation (HSCT).[5] The reported success rates of HBOT in these studies vary, but a significant proportion of patients experience substantial improvement or complete resolution of hematuria.[3] For instance, a retrospective analysis of 25 patients with HC following chemotherapy and HSCT showed complete healing in 44% and improvement in an additional 28% after a median of 12 HBOT sessions.[5] Another study reported complete resolution of hematuria in 80% of 15 patients (including two with chemotherapy-induced HC) after a median of 34 HBOT treatments.[6] The typical HBOT treatment protocols used in these studies involve pressures ranging from 2.0 to 2.5 atmospheres absolute (ATA), with sessions lasting between 60 and 120 minutes, administered once daily, five days a week, for a total of 10 to 40 or more sessions.[3] Some studies have indicated a correlation between the number of HBOT sessions and improved outcomes, suggesting a potential dose-response relationship.[5] Patients undergoing seven or more HBOT sessions appeared to benefit the most in one study.[5]

In conclusion, the current evidence suggests a promising role for Hyperbaric Oxygen Therapy in the management of Hemorrhagic Cystitis following

chemotherapy, particularly in refractory cases. The ability of HBOT to enhance tissue oxygenation and promote angiogenesis offers a biologically thinkable mechanism for its therapeutic effects. While the existing clinical studies, primarily retrospective in nature, indicate significant improvement in many patients, further high-quality research, including prospective, randomized controlled trials, is essential to definitively establish its efficacy and optimize treatment protocols. Addressing the practical challenges of accessibility and cost will also be crucial for the broader adoption of HBOT. Despite these limitations, HBOT holds considerable potential as a valuable therapeutic option for patients suffering from this complication of cancer treatment.

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