

Intravesical Ozone Therapy for Refractory Hemorrhagic Cystitis Following Allogeneic Hematopoietic Stem Cell Transplantation: Report of Two Pediatric Cases

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Hemorrhagic cystitis(HC) is a well-recognized and potentially severe complication after allogeneic hematopoietic stem cell transplantation(HSCT), particularly in pediatric patients. HC may occur early, typically within 48–72 hours following conditioning therapy due to alkylating agents(such as cyclophosphamide/ifosfamide), or later in the post-transplant period due to viral reactivation, most notably BK polyomavirus(BKPyV), adenovirus(ADV), or cytomegalovirus(CMV) [1]. Clinical manifestations range from microscopic hematuria to life-threatening hemorrhage requiring transfusion, bladder irrigation, and even surgical interventions. Standard management includes hyperhydration, diuretics, bladder irrigation, analgesia, and targeted antiviral therapy such as cidofovir or ganciclovir and hyperbaric oxygen therapy. However, in some patients, hematuria persists despite optimal supportive and pharmacological treatment, necessitating alternative interventions [2]. Here, we report two cases of HC post-HSCT that were successfully treated with intravesical ozone therapy after failing conventional options.

Case 1: A 5-year-old male with acute myeloid leukemia received a 9/10 HLA-matched unrelated donor peripheral blood HSCT, conditioning regimen included busulfan and cyclophosphamide. On day +64 post-transplant, he developed macroscopic hematuria. Blood and urine BKV, CMV PCRs were negative, while blood ADV PCR was positive. Platelet count was within normal range, coagulation parameters were unremarkable. Urinary ultrasound showed bladder wall thickening and clots. Despite four weeks of bladder irrigation, hyperhydration, diuretics, ganciclovir, and six weekly doses of cidofovir(intravenously at 1mg/kg/week 4 times), symptoms persisted. Intravesical hyaluronic acid instillations provided no improvement. Therefore, intravesical ozone therapy using 25 µg/ml ozonated saline was initiated weekly for four sessions. Complete remission of hematuria was achieved, with no recurrence during follow-up.

Case 2: An 11-year-old male with relapsed acute lymphoblastic leukemia underwent HSCT from a 9/10 HLA-matched unrelated donor. conditioning regimen included total body irradiation therapy(TBI) and etoposide. On day +20 post-transplant, he developed gross hematuria. Viral PCRs in urine and blood were negative. After failure of conventional measures including hyaluronic acid and supportive care, two sessions of intravesical ozone therapy were administered. Gross hematuria resolved rapidly. However, microscopic hematuria persisted until intravenous foscarnet was initiated for CMV colitis confirmed by colonoscopy. Complete resolution was observed thereafter.

Ozone (O₃) is a triatomic molecule with potent antimicrobial, anti-inflammatory, immunomodulatory, and tissue-regenerative effects [2]. It has been used in urological practice, particularly in chronic cystitis and radiation-induced hemorrhagic cystitis, as well as in limited pediatric indications such as anal fissures, stomatitis, and urinary tract infections [2,3]. Intravesical ozone therapy is believed to act by increasing tissue oxygenation, enhancing epithelial repair, and modulating local oxidative stress. In comparison to hyperbaric oxygen therapy, ozone therapy is more accessible, cost-effective, and less invasive, making it suitable for pediatric patients [4]. Although generally well tolerated, ozone therapy is contraindicated in patients with G6PD deficiency, active hemorrhage, or severe coagulopathies. Possible side effects include transient bladder irritation, dysuria, and

urgency. Nonetheless, in carefully selected patients, it offers a promising adjunctive treatment [2,5]. In conclusion, intravesical ozone therapy may be an effective and safe option in the management of refractory HC following HSCT in children. Larger prospective studies are needed to establish optimal dosing, duration, and long-term outcomes of this novel therapeutic modality.

References

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