

Innovative use of intravesical tacrolimus for hemorrhagic radiation cystitis

Chirag N. Dave¹ · Fahad Chaus¹ · Michael B. Chancellor¹ · Michelle Lajness¹ · Kenneth M. Peters¹

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Abstract Hemorrhagic cystitis is a rare and severe late complication of pelvic radiation, and there is no regulatory-approved drug treatment. We present an 81-year-old man with a history of localized prostate cancer, which was treated with external beam radiation therapy and subsequently developed severe hemorrhagic radiation cystitis for which he has failed several treatments. We present the novel use of intravesical tacrolimus for the treatment of refractory radiation cystitis and gross hematuria. The patient tolerated the treatment well, and it resulted in the resolution of his gross hematuria without further consideration for formalin instillation or cystectomy and diversion. Intravesical tacrolimus is a safe, minimally invasive, and promising treatment option for radiation hemorrhagic cystitis.

Keywords Hemorrhagic cystitis · Radiation cystitis · Tacrolimus · Prostate cancer

Introduction

Radiation is commonly used in the management of pelvic malignancies, including prostate, bladder, uterine, and colon cancer. Along with the antineoplastic effects of radiation, the bladder mucosa becomes edematous and friable, which leads to progressive endarteritis and eventually tissue hypoxia, ischemia, and bleeding. The degree of complications is related to the location, dose, and type of radiation that is used. Despite improved techniques in delivering

ionizing radiation, hemorrhagic cystitis is reported in up to 9 % of patients receiving full-dose radiation therapy. Bleeding can range from mild microhematuria to a life-threatening hemorrhage requiring blood transfusions and even radical surgery. Gorzynska and associates [2] defined hemorrhagic cystitis as the presence of sustained hematuria and lower urinary tract symptoms in the absence of active tumor and other conditions, such as bacterial or fungal urinary tract infection. The incidence of radiation cystitis (RC) has been reported to be <100,000 in the USA [2], and despite vigorous preventive measures, a 2–4 % mortality rate has been reported [1].

Case presentation

We present an 81-year-old man with a history of atrial fibrillation, coronary artery disease, congestive heart failure, obstructive sleep apnea, hypothyroidism, and gastrointestinal bleeding, as well as localized prostate cancer, which was treated with external beam radiation therapy in 2004 and complicated by RC which required hospitalization and ultimately cystoscopy, clot evacuation, and fulguration in 2010. There has been no evidence of prostate cancer recurrence. The patient had developed progressively worsening irritative lower urinary tract symptoms including urinary urgency, frequency, and incontinence. In early May 2015, the patient required several outpatient urology visits for recurrence of hematuria and underwent urodynamics, which demonstrated urge urinary incontinence and reduced bladder capacity. On May 20, 2015, the patient presented to the emergency department with brisk gross hematuria. He again failed conservative measures and was taken to the operating room for cystoscopy, which showed severe RC with focal areas of bleeding near the bladder

✉ Michael B. Chancellor
chancellormb@gmail.com

¹ Department of Urology, William Beaumont Hospital, Royal Oak, MI, USA

neck. His hematuria briefly resolved with clot evacuation and fulguration. Hematuria resumed, and on postoperative day three, hemoglobin dropped from 9.4 to 7.8 requiring 2 units packed red blood cell (PRBC) transfusion. His hematuria persisted despite continuous bladder irrigation. His hematuria resolved gradually, and his catheter was removed on May 28. However, he failed a trial of void, and a catheter was replaced prior to discharge. He re-presented to the emergency department on May 29 with recurrent severe gross hematuria and acute blood loss anemia (Hb 7.8). He was transfused 2 units PRBC and taken to the operating room for repeat cystoscopy, clot evacuation, and fulguration. He was started on phenazopyridine and Bactrim and admitted for further observation. He continued to have gross hematuria requiring additional blood transfusions. Due to the patient's baseline voiding dysfunction, detrusor overactivity, and urinary frequency, intravesical formalin was avoided. On June 4, 2015, the urology department, in consultation with the patient's primary care physician and nephrologist, presented the option of off-label use of a bladder instillation of tacrolimus. After informed consent was obtained, a sterile solution of tacrolimus injection (Prograf) containing 5 mg anhydrous tacrolimus in 1 ml ampule containing polyoxyl 60 hydrogenated castor oil (HCO-60), 200 mg, and dehydrated alcohol, USP, 80.0 % v/v, was diluted in 40 ml sterile saline (0.125 mg/ml tacrolimus) and instilled by urethral catheter into the patient's urinary bladder and held for 30 min. The procedure was performed on June 4, 2015. The instillation was well tolerated, and whole-blood tacrolimus level was 0.8 ng/ml on June 5, 2015 (reference range 5.0–15.0 ng/ml). The patient received a second course of instillation on June 5, 2015, and his whole blood tacrolimus level on June 6, 2015, was 2.3 ng/ml. The patient's gross hematuria diminished and was observed with catheter in place for an additional 48 h. On June 8, 2015, the patient was discharged without gross hematuria. His renal function remained stable at the time of discharge to home. He continues to do well over the next 2 months without needing further irrigation or hospitalization, and his gross hematuria has since resolved. He had elected to undergo hyperbaric oxygen treatment as an outpatient in hopes of preventing future hematuria episodes.

Discussion

Radiation cystitis is a known complication of pelvic radiotherapy and presents a range of clinical symptoms for which there are no recommended standard management treatments [1]. Pelvic irradiation may result in damage to multiple bladder cell types including urothelial, neuronal, detrusor, and vascular smooth muscle cells. RC can reduce bladder capacity and compliance. The extent of the injury

can vary depending on several factors including patient tissue sensitivity to radiation, all of which can severely degrade cancer survivors' quality of life and require long-term follow-up and treatment [3]. These cases can be challenging problems to the clinician and a source of substantial morbidity and sometimes mortality for patients.

Current management varies by the degree of RC. Acute RC is most commonly due to the swelling of tissues and generally improves with time. Associated lower urinary symptoms are managed with anticholinergics. Late effects of radiation are marked by fibrosis, which can lead to chronic RC. First-line therapy is conservative management such as oral and intravenous hydration, treatment of concomitant infections, and cessation of anticoagulants. Persistent and problematic hematuria is managed with cystoscopy, clot evacuation, and fulguration with or without intravesical agents such as Amicar, alum, silver nitrate, alcohol, prostaglandins, hyaluronic acid, or formalin. These treatments focus on sterilization, lavage, and arrest of focal bleeding points; however, as doses escalate, intravesical treatments frequently result in increased toxicity [4, 5]. Cystectomy and urinary diversion are sometime necessary as the ultimate solution in cases where bleeding cannot be stopped, but such surgery in acutely ill patients carries high risks [1].

Tacrolimus, a calcineurin inhibitor, hinders the production and release of pro-inflammatory cytokines in T cells. It serves as a potent immunosuppressant that improves barrier function of the skin and mucosa [6]. Systemic administration has a high incidence of adverse events, such as nephrotoxicity and hypertension due to arterioconstriction [7]. However, when used site-specifically to treat dermal inflammatory conditions in an ointment or lotion formulation, minimal adverse events occur [8]. The potential to inhibit inflammation and induce local vasoconstriction prompted studies to investigate intravesical instillation of tacrolimus as a treatment for radiation hemorrhagic cystitis. Rajaganapathy et al. [9] showed in a RC rat model that intravesical liposomal tacrolimus therapy provided a dose-dependent decrease in the intermicturition interval without inducing short-term skin or gastrointestinal damage. The effect of liposomal tacrolimus has also been in cyclophosphamide (200 mg/kg; ip)-induced hemorrhagic cystitis model [10]. That study demonstrated that cyclophosphamide-induced hyperactivity (i.e., decrease in intercontraction interval) was suppressed in rats with intravesical liposomal tacrolimus treatment but not in the rat groups left untreated (sham) or treated with empty liposomes (vehicle control). The reduced urinary frequency in the rat group treated with liposomal tacrolimus is related to the suppressed inflammatory reaction compared to the control groups (edema score and inflammatory cell score, 39.3 and 35.7 % decrease, respectively). Liposomal tacrolimus

treatment also suppressed hemorrhagic cystitis-induced increase in EP4 receptor expression in the nucleus of bladder mucosa and inflammatory cells of submucosa regions. Cyclophosphamide-induced increases in the level of urine PGE2 and bladder tissue PGE2 and IL2 levels were also suppressed by liposomal tacrolimus. Furthermore, blood analysis of several rats indicated that systemic levels of tacrolimus were below the detection limit (<1.5 ng/ml) of the clinically approved assay for tacrolimus [10].

Conclusion

We present a novel approach of using intravesical instillation of tacrolimus as a simple, safe, and effective treatment of hemorrhagic cystitis. Further studies will be needed to determine the safety and efficacy of intravesical tacrolimus for the rare but severe disease of hemorrhagic cystitis.

Compliance with ethical standards

Conflict of interest Michael B. Chancellor has financial interest with Lipella Pharmaceuticals, Inc. There are no other conflicts of interests related to this publication to report.

Ethical standard This letter does not contain any studies with human participants or animals performed by any of the authors.

References

1. Rajaganapathy BR, Jayabalan N, Tyagi P et al (2014) Advances in therapeutic development for radiation cystitis. *Lower Urin Tract Symptoms* 6:1–10
2. Gorczynska E, Turkiewicz D, Rybka K (2005) Incidence, clinical outcome, and management of virus-induced hemorrhagic cystitis in children and adolescents after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 11:797–804
3. Manikandan R, Kumar S, Dorairajan LN (2010) Hemorrhagic cystitis: a challenge to the urologist. *Indian J Urol* 26:159–166
4. Chong KT, Hampson NB, Corman JM (2005) Early hyperbaric oxygen therapy improves outcome for radiation-induced hemorrhagic cystitis. *Urology* 65:649–653
5. Smit SG, Heyns CF (2010) Management of radiation cystitis. *Nat Rev Urol* 7:206–214
6. Rico MJ, Lawrence I (2002) Tacrolimus ointment for the treatment of atopic dermatitis: clinical and pharmacologic effects. *Allergy Asthma Proc* 23:191–197
7. Naesens M, Kuypers DR, Sarwal M (2009) Calcineurin inhibitor nephrotoxicity. *Clin J Am Soc Nephrol* 4:481–508
8. Ebert AK, Rosch WH, Vogt T (2008) Safety and tolerability of adjuvant topical tacrolimus treatment in boys with lichen sclerosus: a prospective phase 2 study. *Eur Urol* 54:932–937
9. Rajaganapathy BR, Janicki JJ, Levanovich P et al (2015) Intravesical liposomal tacrolimus protects against radiation cystitis induced by 3-beam targeted bladder radiation. *J Urol* 194:578–584
10. Chuang Y, Tyagi P, Huang H et al (2011) Intravesical immune suppression by liposomal tacrolimus in cyclophosphamide-induced inflammatory cystitis. *Neurourol Urodyn* 30:421–427