LUTS LOWER URINARY TRACT SYMPTOMS

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REVIEW ARTICLE

Advances in Therapeutic Development for Radiation Cystitis

Bharathi Raja RAJAGANAPATHY,[1] Nirmal JAYABALAN,[1] Pradeep TYAGI,[2] Jonathan KAUFMAN,[3] and Michael B. CHANCELLOR[1]*

[1]Department of Urology, Centre for Urology Research Excellence, Oakland University William Beaumont School of Medicine, Royal Oak, Michigan, USA, [2]Department of Urology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA, and [3]Lipella Pharmaceuticals, Pittsburgh, Pennsylvania, USA

Radiation treatment for pelvic malignancies is typically associated with radiation injury to urinary bladder that can ultimately lead to radiation cystitis (RC). The late sequelae of radiation therapy may take many years to develop and include bothersome storage symptoms such as hematuria, which may be life-threatening in severe cases of hemorrhagic cystitis. Although no definitive treatment is currently available, various interventions are used for radiation and hemorrhagic cystitis including blood transfusion, bladder irrigation, intravesical instillation of substances such as alum, silver nitrate, prostaglandins or formalin, and fulguration of intravesical bleeding sites and surgery options such as supravesical urinary diversions and cystectomy. Effects of non-surgical treatments for radiation and hemorrhagic cystitis are of modest success and studies are lacking to control the effects caused by RC. When such measures have proven ineffective, use of bladder botulinum toxin injection has been reported. New therapy, such as intravesical immunosuppression with local tacrolimus formulation is being developed for the treatment of radiation hemorrhagic cystitis.

Key words intravesical immunosupression, pelvic malignancies, radiation cystitis, tacrolimus

1. INTRODUCTION

1.1. Radiation therapy

Radiation therapy aims to deliver high doses of radiation to target organs while simultaneously respecting the normal tolerance of surrounding tissues to eradicate the tumor while preserving the structure and function of other organs. External beam irradiation of the pelvis is widely used as a curative treatment for malignancies originating from the bladder, prostate, colon, rectum and cervix or uterus. The EORTC (European Organization for Research and Treatment of Cancer) and RTOG (Radiation Therapy Oncology Group) have produced standardized scoring scales for uniform reporting of radiation toxicity in different target organs. These scales include four elements, representing subjective, objective, management and analytical (SOMA) evaluation of late effects to normal tissues (LENT). Each individual organ or tissue known to be within the target irradiation zone, and hence at risk of being damaged, has its own LENT-SOMA scale, which is based on the original RTOG criteria for radiation morbidity.[1] The LENT-SOMA scale is a comprehensive system and provides much information, but it may be difficult to implement in routine practice outside of clinical studies.[2] Advances in radiation therapy, such as high-energy linear accelerators, conformal radiation therapy and intensity-modulated radiation therapy (IMRT), have allowed higher doses of radiation to be delivered to the tumor while sparing surrounding tissues. Despite these advances, tissue injury to non-target organs does still occur.[3] In this review we have discussed the current and the advanced therapeutic strategy of radiation cystitis management and treatment.

1.2. Epidemiology

Tumors of the pelvic organs are common in men, comprising 35% of expected new cancer diagnoses.[4] In women, cancer such as uterus, ovary, bladder, rectum, and vagina/vulva were expected to make up 14% of new cancer diagnoses in 2009.[5] Radiation therapy is an important management tool for the treatment of these malignancies, creating significant potential for the development of radiation injury to the bladder.

In men, after the treatment of prostate cancer, rectal complications are lower with conformal beam therapy than with small-field therapy (19 vs. 32% grade 2 toxicity); however, the incidence of bladder complications is unchanged, probably because of the proximity of the bladder neck and unavoidable exposure to the urethra. IMRT has also demonstrated an improvement in rectal complications compared with three-dimensional conformal

***Correspondence:** Michael B. Chancellor, MD, Department of Urology, Oakland University William Beaumont School of Medicine, 3535 West 13 Mile Road, Royal Oak, MI 48073, USA. Tel: +1-248-551-8296; Fax: +1-248-551-0486. Email: chancellormb@gmail.com

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radiation therapy. Fewer grade 2 bladder complications occur with IMRT, but the rate of grade 3 complications is similar with both modalities. Gastrointestinal symptoms can be further reduced by using fiducially marker-based position verification in patients with prostate cancer.[6]

1.3. Pathophysiology

The effects of radiation on a cellular level are twofold. A somatic effect is caused by radiolysis of water, resulting in the production of activated free oxygen radicals (hydroxyl and superoxide radicals). These highly reactive radicals cause lipid peroxidation, which induces cell membrane injury. Genetic damage is caused directly by absorption of energy by DNA, as well as indirectly via reaction of DNA with oxygen radicals. This can lead to mutation and/or replication failure.[7]

The smooth muscle of the urinary bladder is sensitive to radiation. Edema occurs early and may be followed by cellular destruction. Normal smooth muscle may be replaced by fibroblasts, ultimately leading to increased collagen deposition. Such changes lead to decreased bladder compliance and functional changes in bladder capacity. Changes in endothelial cells are seen months to years following radiation therapy. Bladder epithelium has a low proliferative rate, and is thus sensitive to radiation. In general, intermediate and basal urothelial cells show signs of damage within 3 months of radiation exposure. By 6–12 months, a radiation-dose-dependent increase in proliferative activity of the urothelium is usually evident. Vascular endothelial cell edema also occurs early after radiation exposure, with endothelial cell proliferation seen months later. Late endothelial cell damage and perivascular fibrosis occur as a result of vascular occlusion and bladder ischemia.[8,9]

Late radiation tissue injury can take several months to many years to develop, and is largely a function of the total radiation dose and fraction size. The pathological hallmark of late radiation tissue injury is obliterative endarteritis resulting in atrophy and fibrosis.[10] This causes the bladder mucosa to become necrotic and slough off, leading to hematuria. Impaired healing under ischemic conditions can lead to ulcer and fistula formation. Telangiectasia (permanent dilation of blood vessels, usually in the mucous membranes) develops, and can also cause bleeding. Fibrosis forms part of the repair process and, if severe, can lead to a reduction in bladder capacity.

2. DIAGNOSIS

2.1. Clinical presentation

Symptoms experienced on RC include dysuria and increased urinary frequency and urgency. This condition may be self-limiting, and seldom persists for longer than 3 months after radiation therapy. Management is conservative with symptomatic relief with the use of anticholinergic drugs. Late radiation cystitis can develop from 6 months to as long as 20 years after radiation treatment, with a mean latent period of 35 months in one study.[11]

TABLE 1. Potential long-term consequences of radiation on the urinary system

Radiation damaging effects on the urinary tract
Bladder (radiation cystitis)
• Lower urinary tract symptoms
• Hemorrhagic cystitis
• Impaired bladder compliance
• Bladder cancer
• Fistulas
Urethra
• Stricture disease
• Stress urinary incontinence
• Fibrosis
• Fistula
Ureter
• Stricture
• Vesicoureteral reflux
• Fistulas
○ Ureteroenteric
○ Ureterovascular
○ Ureterovaginal

The treatment factors might increase the risk of developing late radiation cystitis. Pre-existing medical conditions, such as diabetes, hypertension and previous unrelated abdominal surgery may put patients at increased risks. Tumor stage determines the volume of tissue irradiated and the overall dose of radiation administered. History of surgery and chemotherapy are also important considerations in evaluating the baseline risk, and may contribute to the development of late radiation hemorrhagic cystitis. Most important are factors related to the radiation treatment, including the volume of tissue treated, total bladder dose and fractionation, mode of delivery (external beam and/or brachytherapy), concurrent treatments and the radio sensitivity of the affected bladder tissue.[8] Hematuria is the main presenting symptom, and can vary from mild hematuria to life-threatening hemorrhage. Hematuria with clot formation can lead to urinary retention. Other lower urinary tract symptoms including pain, increased urinary frequency and urgency and incontinence may also be present. Table 1 lists some of the possible long-term consequences of radiation on the urinary system. Urethral stricture is common in men and rare in women. Depending on the underlying pathology, patients may present with obstructive lower urinary tract symptoms including urinary retention secondary to detrusor dysfunction and urethral stricture. Urinary incontinence can be stress urinary incontinence secondary to intrinsic sphincter deficiency or urgency incontinence due to small bladder capacity and impaired detrusor compliance. Patients may also experience underactive bladder overflow incontinence secondary to chronic retention (www.underactivebladder.org) or continuous incontinence if fistulas develop.

2.2. Patient evaluation

The clinical features of late radiation cystitis are nonspecific, and can overlap with symptoms of bladder infection or malignancy. Thus, diagnosis is focused on the

exclusion of other causes of hematuria. Urinalysis may be used to diagnose microscopic hematuria or urinary tract infection. Dipstick urinalysis and urine culture are important to exclude infection, and urine cytology is valuable to detect high-grade malignancy. Cystoscopy should be done to assess stricture, pipe stem urethra, contracted bladder, fistulas, hemorrhagic cystitis and bladder biopsy if needed. Upper urinary tract evaluation is also recommended. Lower urinary tract evaluation in the form of cystoscopy is required, and may reveal erythema, edema, and telangiectasia, bleeding ulcers, fistulas or fibrosis with reduction in bladder capacity. At the time of cystoscopy, bladder biopsy may be performed if there is suspicion of tumor recurrence, with particular attention to the potential risk of perforation of the irradiated bladder wall.

Radiation treatment details including total dose, daily dose, number of sessions, radiation delivery technique should be recorded. Physical examination should include a detailed pelvic examination to evaluate for possible vaginal fistulas, vaginal scarring and skin changes secondary to urinary incontinence. Post-void residual volume can diagnose urinary retention. A voiding diary provides an objective assessment of the patient's symptoms. Upper tract imaging and renal function assessment should be performed to rule out hydronephrosis secondary to ureteral stricture or vesicoureteral reflux. Videourodynamic may be helpful to assess cystometric capacity, detrusor compliance, sphincter function and vesicoureteral reflux simultaneously.

3. MANAGEMENT

Initial management of patients with radiation and hemorrhagic cystitis includes intravenous fluid replacement and blood transfusion if required, followed by transurethral catheterization with bladder washout and irrigation. Most patients will respond to these measures; however, if conservative management fails, the following managements should be attempted.

3.1. Procedural intervention

3.1.1. Cystoscopy with fulguration

Cystoscopy with fulguration of bleeding points is an effective method of treating hemorrhagic cystitis that is unresponsive to conservative measures.[11] This procedure can be performed under local anesthesia, especially in females. Methods of fulguration include the use of electro coagulation, diathermy, and argon or neodymium-doped yttrium–aluminum–garnet laser.[12,13] Potential morbidity following cystoscopy and cystoscopy and fulguration includes bladder perforation with subsequent fistula formation.[14] Reports state that more-severe cases of hemorrhagic cystitis often do not respond to this treatment modality.[15]

Neodymium: YAG laser has been used to successfully treat 42 patients[13] with no recurrence at a mean follow-up period of 14 months. Argon laser achieved hemostasis in all seven patients with severe radiation-induced hematuria.[12] Patients were discharged the following day with clear urine and there was only one treatment failure, which required retreatment at a mean follow-up of 15 months. Nine-hundred and eighty nanometers diode laser achieved a mean hematuria-free time of 11 months in four patients with severe hemorrhage due to chronic radiation cystitis refractory to conservative treatment and standard electro cautery.[16] Green light achieved hemostasis in 10 patients with intractable hematuria with only one requiring re-treatment at 7 months because of recurrence of significant bleeding.[17]

3.1.2. Surgical interventions

More-aggressive treatment options include selective embolization or ligation of the iliac or bladder arteries.[18] Surgical options include urinary diversion with or without cystectomy, which should be considered a last resort. Reports suggest that a transverse colon conduit is the preferred method of urinary diversion, which has the advantage of using the no irradiated bowel and ureters for creating the diversion. Alternative options for urinary diversion include percutaneous nephrostomy and cutaneous ureterostomy.[19]

Complications related to the defunctionalized bladder occur in more than 50% of patients who undergo urinary diversion, and include pyocystis, hemorrhage, pain and neoplastic transformation;[20] therefore, cystectomy is recommended at the time of urinary diversion. Preoperative high-dose radiation therapy contributes to increased postoperative morbidity rates, particularly enteroenteric fistulas, urointestinal fistulas and stenosis of the ureterointestinal anastomosis.[19] Any alternative treatment options that are associated with less morbidity should be considered first before embarking on such debilitating surgery.

3.2. Intravesical instillation

A number of agents have been administered intravesically for the purpose of alleviating symptoms associated with late radiation cystitis. Although the mechanisms of action of these agents vary, the principles essentially include sterilization, lavage and arrest of focal bleeding points. Table 2 describes different agents for intravesical instillation with dosing, interactions and contraindications.

3.3. Formaldehyde (formalin)

Reserved for severe and intractable hemorrhagic cystitis, formaldehyde instillation hydrolyzes protein and coagulates superficial bladder mucosal tissue. Most critical factor is the administration of proper solution (2.5–4% for 10–30 min). One formulation for 4% solution is by mixing buffered formalin 10% 200 mL with sterile water for irrigation 300 mL (total volume, 500 mL).[21]

3.3.1. Precautions

Before instillation, monitor with intraoperative cystography and if ureteral reflux is present rule out

TABLE 2. Intravesical instillation treatment of radiation cystitis with dosing, interactions and contraindications

Agent	Dosing	Interactions	Contraindications
Formaldehyde (formalin)	Adult: Bladder irrigation: 4% solution; manually fill bladder to capacity under gravity (catheter < 15 cm above symphysis pubis); contact time 10–30 min; painful procedure, and general anesthetic needed. Pediatric: Administer as in adults Pregnancy: C – Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus	None reported	Documented hypersensitivity
Alum	Adult: Bladder irrigation: Extemporaneously prepared as 1% solution; administer as continuous bladder irrigant until bleeding stops Pediatric: Administer as in adults Pregnancy: C – fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus	None reported	Documented hypersensitivity
Silver nitrate	Adult: Bladder irrigation: instill 0.5–1.0% solution in sterile water into bladder with dwell time of 10–20 min Pediatric: Administer as in adults Pregnancy: C – fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus	None reported	Documented hypersensitivity; broken skin
Carboprost	Adult: Bladder irrigation: instill 0.1–0.4% solution; contact 45–60 min Pediatric: Not established, suggested to administer as in adults Pregnancy: C – fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus	Limited data exist; no interactions reported	Documented hypersensitivity; active cardiac, pulmonary, renal or hepatic disease

through placing occlusive balloon catheters in each ureter and special care must be taken to avoid bladder rupture which causes ureteral necrosis, obstruction and fibrosis.

Formalin has been used in patients with severe radiation cystitis refractory to other treatment options.[22–24] Intravesical formalin instillation is performed under general or regional anesthesia once vesicoureteral reflux has been excluded. It causes precipitation of cellular proteins in the mucosa, producing an occlusive and fixative action on telangiectasia tissue and small capillaries. However, fixation of the bladder musculature may result in a small, contracted bladder, and fixation of the intramural ureter can also lead to obstruction with subsequent hydronephrosis and renal failure. Formalin is toxic even in very diluted (1%) solution, and a recognized adverse effect is reflux leading to bilateral pylonephrosis with fatal sepsis.[23] Thus, it is recommended that intravesical formalin only be used when the bladder has been defunctioned by means of urinary diversion.

Dewan et al. (1993) reported on a retrospective series of 35 women with hemorrhagic radiation cystitis following radiation therapy for cervical cancer who were treated with 1% ($n=22$), 2% ($n=10$) or 4% ($n=4$) intravesical formalin. After a single instillation, 31 patients (89%) achieved complete responses and three (8%) achieved partial responses. Most patients responded within 48 h, and the response was durable for a mean of 3–4 months. Five percent and 10% formalin solutions were associated with increased morbidity and mortality.

3.4. Alum

Indicated for bladder hemorrhage and consists aluminum potassium sulfate or aluminum ammonium sulfate and works as astringent that causes protein precipitation in interstitial spaces and cell membranes. Systemic absorption is minimal.[21]

3.4.1. Precautions

Encephalopathy or acidosis may occur with increased ammonia levels in blood so monitoring blood pH and ammonia is advised.

Aluminum salts, such as alum, are classified pharmacologically as astringents, and act by precipitating proteins on the cell surface and in interstitial spaces. This mechanism arrests capillary bleeding in mild cases, but in heavy bleeding the precipitant tends to clot, leading to clot retention, distension and more bleeding.[25] Local adverse effects include suprapubic pain and vesical tenesmus, which can be controlled with antispasmodic and/or analgesic drugs.[26] Encephalopathy has been reported in patients with renal failure, indicating that adequate renal function is essential for clearing a parenteral aluminum load.[27] Complete response rates range from 50 to 100%. In a retrospective series of seven patients reports with radiation cystitis and hematuria treated with 1% aluminum sulfate

as an intravesical lavage had good control of bleeding in all cases.[28]

3.5. Silver nitrate

Used because of caustic, antiseptic, and astringent qualities with mixed results observed.[21]

3.5.1. Precautions

Renal failure and anuria reported.

3.6. Carboprost (Hemabate)

In various studies, carboprost elicited cytoprotective, anti-inflammatory, and vasoconstriction properties and produced no coagulum. Three case studies have been reported in which patients were successfully treated with intravesical prostaglandins; but whether the treatment results in these isolated reports were durable is not known. The protective mechanism of prostaglandins is probably mediated by increased cyclic AMP levels and stimulation of active sodium transport, with subsequent reductions in edema and the inflammation.[21,29]

4. SYSTEMIC THERAPY

4.1. Hyperbaric oxygen

HBO therapy – Reported response rate is 27–92%, and recurrence rate is 8–63%.[21]

The hyperbaric chamber provides conditions under which hemoglobin is fully saturated and oxygen is dissolved at very high concentrations in the blood plasma, which on circulation provides therapeutic benefits such as increased angiogenesis and fibroblast activity in damaged tissues.[30] Thus, it can be considered as an alternative treatment for patients with an underlying ischemic process that is unresponsive to conventional therapy. An advantage of HBO in these patients is the absence of adverse effects on the bladder structure or function that may be seen with other therapies, such as formalin or silver nitrate instillations, while avoiding the need for surgery. Various HBO regimens have been used: in general, 100% oxygen is administered at pressures of 1.5–2.5 atm for 45–120 min, allowing extra time for compression and decompression (Table 3). In addition, 5 min "air-breaks" can be introduced each half-hour to reduce the risk of oxygen toxicity. Sessions are administered once daily for a pre-determined length of time ([usually 20–30 sessions) (Barometric Research Foundation 2010).

4.1.1. Precautions

Adverse effects are oxygen toxicity, which is rare and cause alveolar membrane damage, confinement anxiety, ear pain and digitalis toxicity (if taking drugs). Severe emphysematous changes can lead to spontaneous pneumothorax or congenital spherocytosis. HBO may increase red blood cells fragility in pregnancy so use only in life-threatening situations. Patients with epilepsy must be sedated because oxygen is a CNS stimulant and in fever of unknown origin, etiology must be known before treatment.

5. RESULTS

In a retrospective analysis for the efficacy of HBO for treating hemorrhagic cystitis and proctitis secondary to pelvic and prostate radiotherapy, 19 patients were treated with HBO for radiation-induced hemorrhagic cystitis and proctitis. The median age at treatment was 66 years (range, 15–84 years). The range of external-beam radiation delivered was 50.0–75.6 Gy. Bleeding was refractory to other therapies. Patients received 100% oxygen at 2.0 atm absolute pressure for 90–120 min per treatment in a monoplace chamber. Symptoms were retrospectively scored according to the Late Effects of Normal Tissues Subjective, Objective, Management, Analytic (LENT-SOMA) scale to evaluate short-term efficacy. Recurrence of hematuria/hematochezia was used to assess long-term efficacy. Four of the 19 patients were lost to follow-up but 15 patients were evaluated and received a mean of 29.8 dives: 11 developed hemorrhagic cystitis and four proctitis. All patients experienced a reduction in their LENT-SOMA score. After completion of HBO, the mean LENT-SOMA score was reduced from 0.78 to 0.20 in patients with hemorrhagic cystitis and from 0.66 to 0.26 in patients with proctitis. Median follow-up was 39 months (range, 7–70 months). None of the cases of hematuria were refractory to HBO. Complete resolution of hematuria was seen in 81% and partial response in 18%. Recurrence of hematuria occurred in 36% after a median of 10 months.[31]

In a prospective study on HBO of 40 patients at a single center over an 8-year period, all patients received

TABLE 3. Describes the dosing, interactions and contraindications of hyperbaric oxygen therapy

Therapy	Dosing	Interactions	Contraindications
HBO therapy	Adult: Administer as 100% oxygen at 2.0–2.5 atm; each lasts from 90 to 120 min administered 5 day/week for a total of 40–60 sessions	None reported	Viral infection, absolute contraindication (can cause widespread viremia); partial pressure of carbon dioxide (pCO_2) > 60 mmHg and pneumothorax, relative contraindications; history of ear surgery with inability to decompress the middle ear space; vitamin E deficiency; massive doses of ASA, vitamin C, or steroids (enhances likelihood of CNS oxygen toxicity); vitamin E deficiency, massive doses of ASA, vitamin C, or steroids (enhances likelihood of CNS oxygen toxicity)
	Pregnancy – A: Fetal risk not revealed in controlled studies in humans		

HBO for refractory radiation-induced hemorrhagic cystitis, defined as persistent or recurrent symptoms despite one or more conventional treatments. The success rate was 92%: 30 patients had no recurrent bleeding within 3 months, seven had a partial response with minimal bleeding, and three had recurrent bleeding after a mean of 13.3 months.[32] Chong et al. (2005) reported from a retrospective study on HBO in 60 patients over a 13-year period. The results showed an 80% overall success rate.[33]

Patients who had undergone primary, adjuvant or salvage radiation therapy showed equivalent response rates (81, 83 and 78%, respectively). Report states, poor long-term results, with 8 of 11 patients ultimately requiring urinary diversion to achieve definitive control of their hematuria. At a median follow-up of 2.5 years, eight patients were asymptomatic and three required urinary diversion; however, at a median of 5.1 years, five of the eight initially asymptomatic patients had episodes of delayed recurrent hematuria, which ultimately required urinary diversion as definitive therapy.[34]

6. EXPERIMENTAL MODALITIES

6.1. Hyaluronic acid

Hyaluronic acid (HA) is a major mucopolysaccharide found widely in the connective, epithelial and neural tissues and has been used in patients with interstitial cystitis/painful bladder syndrome. It is one of the main components of the extracellular matrix that contributes to cell proliferation and migration. It also constitutes a protective barrier against irritating agents that can potentially cause damage to epithelium. A damaged glycosaminoglycan layer may lead to direct exposure of epithelial cells to components of urine.

HBO was compared with intravesical hyaluronic acid instillation in the treatment of radiation-induced hemorrhagic cystitis. Forty milligrams of HA was instilled into the bladder for a minimum of 20 min. All patients received intravesical instillation weekly in the first month and then monthly in the following 2 months. Intravesical HA and HBO noted sustained amelioration of hematuria of HC. Reduction of voiding frequency was significant at 6 and 12 months after HA instillation, while this effect in HBO could only last for 6 months. The improvement of bladder pain was maintained for 18 months in both groups. Despite HA's slightly higher incidence of urinary tract infection, intravesical instillation of HA was reported to be more convenient and less costly than HBO treatment. The main limitation of this study was that it was not a randomized control study.[35]

6.2. Chondroitin sulfate

A comparative pilot study in 20 patients planned for primary or adjuvant radiotherapy for endometrial or cervical cancer examined the feasibility and efficacy of intravesical instillations with 40 mL chondroitin sulfate (0.2%) solution in preventing or reducing acute radiation cystitis.[36] Ten patients consented for weekly bladder instillations for the duration of radiation therapy while the remaining 10 did not opt for intravesical treatment and served as controls. Although there were improvements with the chondroitin group, the lack of randomization resulting in younger, more eager to prevent radiation cystitis and less likely to have voiding symptoms patients to consent for the instillation group, limited the interpretation of the study.

6.3. Botulinum toxin

The endoscopic bladder injection with botulinum toxin blocks acetylcholine release at neuromuscular junctions is now an approved therapy for neurogenic and idiopathic detrusor overactivity.[37] Recent research has shown that it also blocks release of neurotransmitters, inhibits vanilloid and P2X receptors, cyclooxygenase-2 expression and suppresses inflammatory reactions,[38] that drive the inflammation cascade of RC.

Report suggests the use of 200U onabotulinumtoxinA injections in six patients with refractory radiation cystitis. Under sedation or local anesthesia, onabotulinumtoxinA was submucosally injected through a cystoscope into 20 sites in the trigone and floor of the bladder. A moderate to significant improvement was achieved in five of the six patients, with mean bladder capacity increasing from 105 to 250 mL and mean urinary frequency decreasing from 14 to 11 episodes per day. The study concluded that results of this first use of onabotulinumtoxinA in the treatment of radiation cystitis are promising but need to be further investigated.[38]

6.4. Conjugated estrogen

Estrogens have been noted to have a beneficial effect in controlling hemorrhage in patients with late radiation cystitis by stabilizing vascular fragility. In only one study conjugated estrogen was used in five patients unresponsive to other treatment options.[39] Two patients received conjugated estrogen intravenously (1 mg/kg twice daily) for 2 days, and orally (5 mg once daily) thereafter. The other three patients received only conjugated estrogen orally (5 mg once daily). Four of the five patients experienced resolution of their symptoms for 12–22 months without adverse effects.

6.5. WF10

WF10 is a 1:10 dilution of tetrachlorodecaoxide formulated for intravenous delivery. Its pharmacologic actions include promotion of immune functions and tissue repair via the activation of macrophages. A multi-center, randomized, two-arm, open-label trial conducted and evaluated the efficacy and safety of WF10 as an adjunct to standard treatment in the management of late radiation cystitis compared with standard treatment alone. In the WF10 group, 37 of 50 patients showed complete resolution of objective hematuria, compared with 32 of 50 patients in the standard therapy group ($P = 0.28$). Significantly fewer responders in the WF10 group experienced recurrence of hematuria compared to the standard therapy arm (17 of 37 patients vs. 24 of 32 patients, $P = 0.01$).

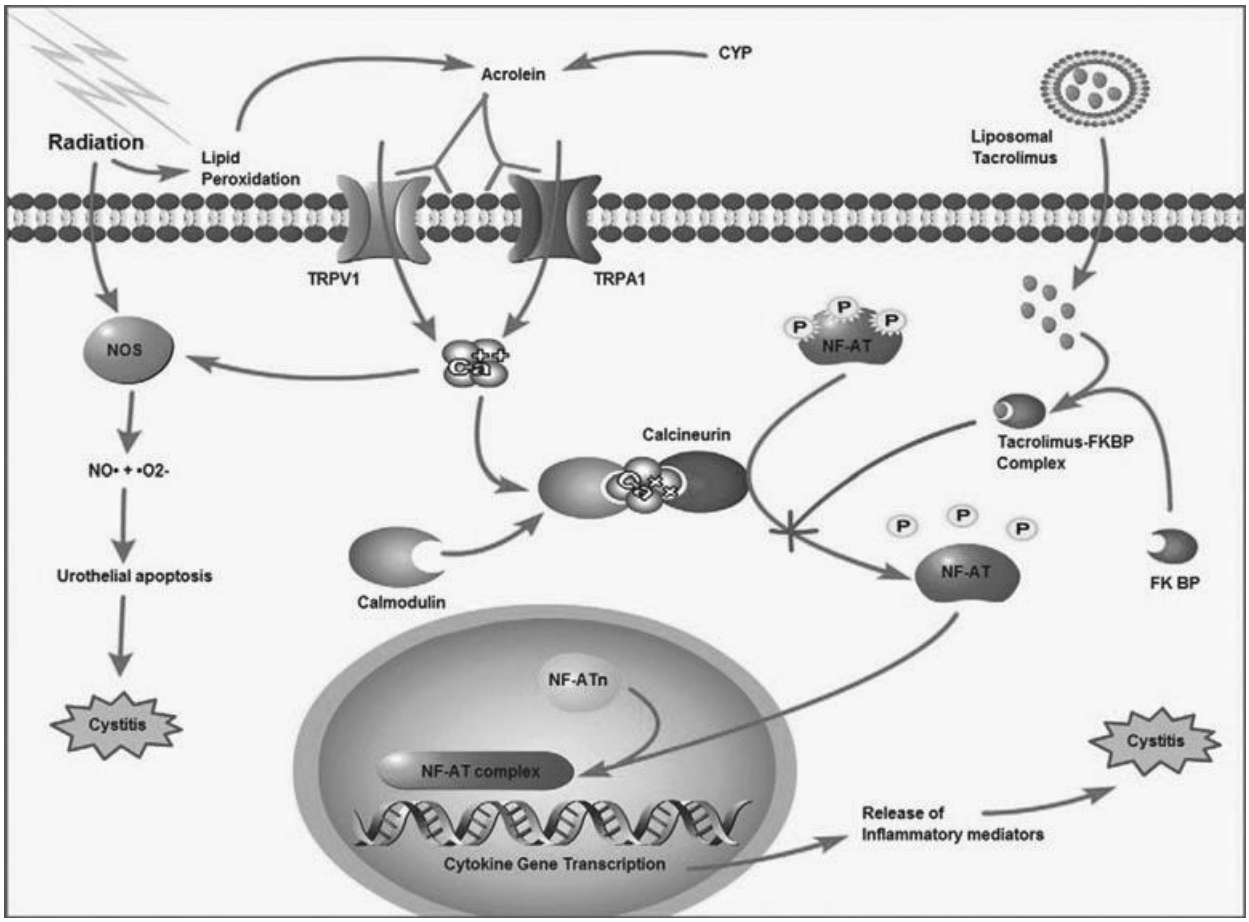

Fig. 1 Schematic illustration of radiation cystitis following irradiation. Irradiation generates free radicals, which injure lipids in cell membrane to generate toxic products like acrolein. Tacrolimus delivered from liposomes can disrupt the signaling events mediated by calcineurin, including nuclear factor of activated T-cell (NFAT)-dependent gene transcription of cytokines produced via NF-κB pathways leading to suppression of cystitis (reproduced from Nirmal et al.,[52] with permission.)

A phase II study by the same authors (2006) evaluated 16 patients with late radiation cystitis (grade 2–3) treated with WF10. After completion of therapy, 14 patients had improvement to grade 0–1 hematuria. At a median follow-up of 51 months, 4 of 14 patients had developed recurrent symptoms.[40]

6.6. Orgotein

Orgotein is an analog of the naturally occurring superoxide dismutase, and has been used in the treatment of radiation cystitis The mechanism of late radiation-induced changes relates to the generation of free radicals, particularly the superoxide radical, which has a primary role in initiating and sustaining biologic damage and the growth of fibrotic tissue, and is responsible for the production of other free radicals and lipoperoxidases. Superoxide dismutase catalyzes the destruction of these superoxide radicals.[41] Marberger and Hubert (1981) reported on a retrospective series of 30 patients with late radiation cystitis treated with intramural orgotein injections. Clinical improvement in symptoms and cystoscopy findings were noted in 25 of the 30 patients. Its use cannot be recommended as no further studies have been reported in the literature.[3]

6.7. Vascular endothelial growth factor

Preclinical study of vascular endothelial growth factor (VEGF) neovascular-promoting therapy in adult female rats after a single dose of 20 Gy directed at their bladder and assessed 4 weeks after injection of VEGF.[42] Follow-up at 1.5 or 3 months to assess potential reduction of the pathological changes in bladder wall associated with pelvic radiation. Blood vessel counts in bladder wall were maintained to no-irradiated controls. It remains to be investigated if increased neovascularity may lead to further bleeding or tumor recurrence with time.

6.8. Stem cells

Mesenchymal stem cells therapy may be a promising therapeutic approach for improving radiation-induced skin and muscle damage. Pre-clinical and clinical benefits of mesenchymal stem cell injection for ulcerated skin and muscle restoration after high dose radiation exposure has been successfully demonstrated. Three patients

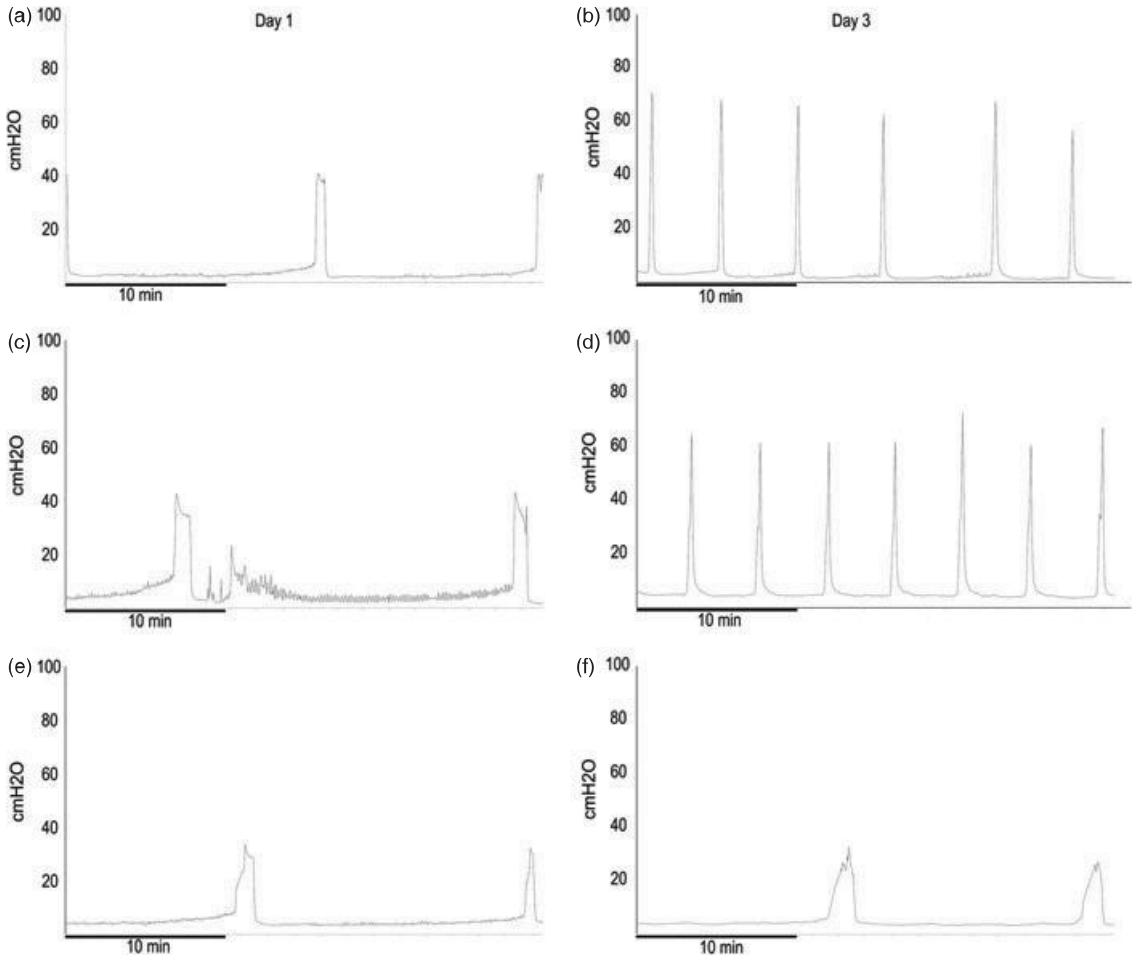

Fig. 2 Effect of intravesical immune suppression on bladder contractions. Increased urinary frequency associated with hemorrhagic cystitis induced by cyclophosphamide (CYP) injection is visible in (b,d) representing control and rat group treated with empty liposomes, respectively. Increased urinary frequency is suppressed in rat group instilled with liposomal tacrolimus (f) but not in control groups not treated with tacrolimus (a–d). Figures (a,c,e) are baseline cystometry (CMG) in the absence of CYP and (b,d,f) is CMG traces after CYP (reproduced from Chuang et al.,[53] with permission.)

suffering from severe radiological syndrome were successfully treated in France based on autologous human grade mesenchymal stem cell injection combined with plastic surgery or skin graft. Stem cell therapy has to be improved to the point that hospitals can put safe, efficient, and reliable clinical protocols into practice. The use of stem cells to treat radiation cystitis remains to be explored and we are currently seeking the Food and Drug Administration (FDA) approval for compassionate use of Investigational New Drug Study for this rare but severe indication.[43]

6.9. Novel approach of local immune suppression

Recent studies have highlighted the overexpression of genes related to immune and inflammatory responses including activation of CD^{4+} T-helper type-1-related chemokines in cystitis.[44] Expression of chemokines precedes infiltration of immune cells and elevation of chemokines is an established signature of the inflammatory phenotype in the bladder pain. In a previous study, the kinetics of cytokines/chemokine secretion into urine in a rat model of inflammatory and hemorrhagic cystitis was correlated with the abnormal voiding and histology of rats.[45] The results with cystoscope guided injection of botulinum toxin in RC patients encouraged, Chuang et al. (2008) to demonstrate that hindering the release of paracrine messengers including neurotransmitters is an option to treat RC. Therefore, an immunosuppression approach that seeks to block the signaling responsible for release of cytokines and inflammatory mediators could be a reasonable approach to halt the inflammation of RC. Furthermore, urothelium is the primary site of tissue damage in the pathophysiology of non-infectious hemorrhagic cystitis.[46,47] The pre-clinical efficacy of this approach was tested in a rodent model of chemically induced HC using tacrolimus.

6.10. Tacrolimus

Tacrolimus is a macro-cyclic lactone derived from the actinomycete *Streptomyces Tsukubaensis*. Tacrolimus binds in the cytoplasm with FK binding proteins and interferes with the calcineurin mediated signal transduction (Fig. 1).

Tacrolimus has proven as an effective immunosuppressive agent for organ transplantation as well as to provide targeted immune suppression via topical use – without the systemic side-effects.[48] Systemic administration of tacrolimus is less attractive for RC as it compromises the immune system, and is also associated with the risk of drug-related side-effects, such as hypertension, renal failure and neurotoxicity.[49] The lipophilic nature of tacrolimus makes it poorly water soluble[50] and has traditionally compelled the use of solubilizing agents, such as polyoxyethylated castor oil (which has been reported to be toxic), for making its injectable formulation. Liposomes are a potential delivery option for such drugs and recent studies have reported development of a liposomal formulation for effective intravesical delivery to the bladder urothelium.[51] We observed that liposomal tacrolimus was able to restrict the systemic exposure of tacrolimus after intravesical administration.[52]

We noted in vivo evidence that supports the viability of liposomal tacrolimus as a treatment for hemorrhagic cystitis. The effect of intravesical immunosuppression produced by tacrolimus liposomal formulation on bladder function was measured by cystometry (CMG) in the rat model of hemorrhagic cystitis induced by intraperitoneal injection of cyclophosphamide (CYP) or treated with empty liposomes (Fig. 2). The reduced urinary frequency in the rat group treated with liposomal tacrolimus is presumably related to the suppressed inflammatory reaction, since CYP associated inflammatory responses were not suppressed in control groups without tacrolimus treatment. Liposomal intravesical delivery method is a critical development, since it achieves high local concentration needed for efficacy while avoiding unwanted systemic exposure. Tissue pharmacokinetics revealed that tacrolimus was retained in bladder tissue[52] and the intravesical administration of liposomal tacrolimus was shown to improve bladder function and effectively attenuated tissue injury and inflammation.

7. CONCLUSIONS

Time is of the essence for patients with radiation cystitis, since there are currently no adequate treatment options. New therapy, such as intravesical immunomodulation with local tacrolimus formulation is being investigated for the treatment of radiation cystitis.

Disclosure

The authors declare no conflicts of interest except Dr Kaufman is the CEO of and Dr Chancellor is the founder of Lipella Pharmaceuticals, Inc.

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