Chronic Inflammation and Radiation-Induced Cystitis

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Contributor: Sabine François

Radiation cystitis is a potential complication following the therapeutic irradiation of pelvic cancers.

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1. Introduction

External pelvic radiation therapy is an important tool in the therapeutic arsenal for the treatment of pelvic cancers, such as prostate cancer, cervical cancer, rectal cancer or bladder cancer. Improvements in radiation techniques, such as intensity-modulated radiotherapy (IMRT), stereotactic radiotherapy and image-guided brachytherapy, have made it possible to deliver increasingly effective doses in smaller volumes with a clear improvement in treatment tolerance. However, the bladder is a critical organ thatmay be sensitive to low doses of radiation. Despite improved techniques, pelvic irradiation is still responsible for acute and/or late adverse events affecting the bladder. The term “radiation cystitis” therefore includes all lesions and symptoms of the bladder following the irradiation of the pelvic organs. Its severity is related to the volume of radiation exposure, the total dose delivered as well as the administration schedule and fractionation. This adverse event may have an impact on patients’ quality of life. As cancer patient survival improves, long-term survivorship issues are of increasing importance, and an improved understanding of radiation-induced cystitis mechanisms is essential[1].

2. Current Treatments and Clinical Trials

2.1. Acute and Late Radiation Cystitis with Storage, Voiding Symptoms or Occasional Bleeding

The clinical management of storage symptoms for acute and late radiation cystitis is largely symptomatic with analgesics and anti-inflammatory drugs. Good hydration is recommended for patients in order to increase diuresis, cleanse the bladder, and avoid urinary obstruction resulting from blood clots[16].

Likewise, anticholinergics, like oxybutynin, trospium chloride, solifenacin, fesoterodine or flavoxate hydrochloride, can be prescribed to help alleviate urgency and increased daytime frequency. Their action is to decrease the contractility of the detrusor and improve symptoms[4].

In some cases, antibiotics may be proposed to prevent the condition from worsening in the event of infection.

Alpha-blockers, 5-reductase inhibitors or phosphodiesterase 5 inhibitors may be useful to alleviate voiding symptoms. Their action is to decrease the tone of the posterior urethra, bladder neck and the volume of the prostate [1]. In severe cases, it is sometimes necessary to hospitalize the patient for transfusions or clot evacuation[4]. In fact, bladder irrigations are performed in order to obtain a dilution of hematuria and drain the clots. It is a sterile technique with lubrication for standard catheter insertion with a large three-way catheter. Blood clot evacuation is performed manually by using a large Toomey or catheter syringe until no further clots and output begin to clear. Then, we use normal saline (0.9%) for continuous irrigation[17].

If acute active bleeding does persist and is refractory to irrigations, electrocoagulation should be discussed, as described by Martinez and colleagues[18]. The procedure was performed with a rigid 22 French cystoscope. It was performed to identify the source of bleeding and rule out any other unidentified pathology. The Green Light laser was used to target any active source of bleeding. These areas were coagulated with the laser. Throughout the procedure, saline irrigation was used, and care was taken to ensure that the ureteral orifices were not injured. At the completion of the procedure, the bladder was drained under direct visualization to ensure adequate hemostasis. Very minimal bladder mucosal damage was reported. Then, a large three-way catheter was placed, and continuous irrigation was maintained overnight and stopped the next morning[18].

These treatments are tailored according to the severity of the symptoms (Figure 1).https://www.mdpi.com/2073-4409/10/1/21

2.2. Late Radiation Cystitis with Persistent or Recurrent Hematuria

2.2.1. Intravesical Instillations

Different molecules have been used for this indication, with different mechanisms of action. Their objectives are sterilization, cleansing and arrest of focal bleeding points.

Aluminum salt: Intravesical aluminous salts are considered astringent agents. They exert their action through protein precipitation on the cell surface and in interstitial spaces. They decrease blood vessel diameter and stiffness of capillary endothelium[9][19]. Aluminum salts are typically delivered as a 1% concentration of alum mixed with sterile water. Westerman et al. evaluated the benefit of alum instillations in 40 patients with hematuria, which was linked in 95% of patients to radiation cystitis[20]. These instillations led to a reduction in transfusion requirements (82% before instillation vs. 59% after instillation, $p = 0.05$). Moreover, 32.5% of patients did not require additional treatment after a median follow-up of 17 months. Tolerance was generally good. The main side effect reported was bladder spasm in 35% of patients[20].

Formalin: Formalin action consists of precipitating cellular proteins in the mucosa of the bladder. The consequence is to create occlusion within telangiectatic tissue. It appears to be the most effective intravesical agent with complete resolution rates ranging from 70 to 89%. However, the safety profile for this treatment is mediocre. First of all, its instillation is quite painful and must therefore be performed under general anesthesia. In addition, formalin has a high rate of morbidity and mortality (31%), with risks of vesicoureteral reflux complicated by severe bilateral pyelonephritis, ureteral stenosis and fibrosis of the bladder with reduced capacity and increased urinary frequency [21]. To date, its use remains very limited due to its poor safety profile.

Hyaluronic acid: Hyaluronic acid is a mucopolysaccharidethathelps to repair the normal glycosaminoglycan layer of the bladder when administrated through intravesical instillations. It has immunomodulatory properties that enhance connective tissue healing. Shao et al. evaluated the efficacy of intravesical hyaluronic acid (HA) instillation and hyperbaric oxygen (HBO) in the management of hemorrhagic radiation cystitis[22]. The clinical benefit was identical in the 2 groups but was maintained over time significantly in the HA arm. Indeed, complete resolution of hematuria was noted in 88%, 75%, and 50% of HA patients and in 75%, 50%, and 45% of patients in the HBO group, at 6-, 12- and 18-months following therapy, respectively. Hyaluronic acid appears to be an interesting therapeutic alternative, though this must be confirmed in a larger cohort.

Other agents have shown interesting results but have been studied only in small cohorts, like botulinum toxin, chondroitin sulfate, polydeoxyribonucleotides, early placental extract [23][24][25][26].

2.2.2. Hyperbaric Oxygen Therapy (HBOT)

This technique consists of placing the patient in a pressurized chamber (hyperbaric chamber) to administer pure or mixed oxygen at a pressure greater than atmospheric pressure, for 5–7 days a week, for a daily duration of 60–90 min up to approximately 30–45 sessions[27]. The effect of hyperbaric oxygen therapy is to allow better oxygen diffusion in tissues and to disrupt the continuum between hypoxia and fibrosis. Hyperoxia induces primary neovascularization, secondary growth of healthy granulation tissue, and induces short-term vasoconstriction, which may help control active bleeding[28][29]. It is the most widely reported therapeutic technique in the management of hemorrhagic radiation cystitis. Dellis et al. evaluated the benefit of HBOT in 38 patients with severe radiation cystitis. The complete response rate was 86.8%, and the partial response rate was 13.2%. The mean follow-up was 29.3 months. For the thirty-three patients with complete response who received HBO therapy within 6 months of the hematuria onset, the mean time interval was 4.9 months (range 1–6), while in the remaining five patients with partial response, the mean time interval was 22 months (range 8–48) ($p < 0.001$). Thirty-three patients were alive at the end of follow-up[29].

Recently, the randomized phase 2–3 RICH-ART evaluated the benefit of HBOT compared to standard of care for patients with late radiation cystitis and a value of fewerthan 80 points in the urinary domain of the expanded prostate index composite score (EPIC score). Forty-one patients were randomized in the HBOT arm and 38 in the standard of care arm. HBOT significantly alleviated patient-perceived symptoms of late radiation cystitis and improved HRQOL. The mean improvement in EPIC urinary total score was higher (17.8 [SD 18.4]) in the hyperbaric oxygen therapy group compared with patients in the control group (7.7 [SD 15.5]). Seventy patients in HBOT presented a grade 1–2 adverse events. The main adverse events grade 1–2 were ear pain (15%), myopia (12%) and barotrauma (10%). No grade 3–4 or 5 was reported in this group[30]. The HBOT's benefit was maintained in the time. In fact, Pereira et al. reviewed 105 patients diagnosed with RIHC whowere treated with HBOT between 2007 and 2016. After a median follow-up of 63 months, 76.3%

had a complete response[31] Cardinal et al. evaluated the benefits of HBOT through a meta-analysis of data from 602 patients treated with HBOT for hemorrhagic radiation cystitis. They determined that 84% of patients achieved partial or complete resolution, while 75% saw an improvement in hematuria. In their analysis of 499 patients with documented follow-up, authors observed a recurrence rate of 14%, with a median time to recurrence of 10 months (6 to 16.5 months). To summarize, this treatment is well-tolerated, the most common side effects being pressure-related, most notably ear and sinus barotrauma. HBOT is offered to patients for whom bladder washings and instillations are ineffective[32]. In a systemic review, Villeirs et al. emphasized HBOT benefit in radiation cystitis. In a cohort of 815 patients, an overall and complete response rate varied from 64.8% to 100% and 20% to 100%, respectively. Blood transfusion before HBOT, other treatment modalities before HBOT, use of anticoagulant therapy, along the interval between the onset of hematuria and start of HBOT were possible factors associated with lower efficacy of HBOT[27]. It is important to start HBOT in the onset of late radiation cystitis symptoms[33][34]. However, the availability and cost-effectiveness of high-pressure oxygen tanks is a critical factor in the success of HBOT[27].

2.3. Late Radiation Cystitis with Refractory or Life-Threatening Hematuria

In late radiation cystitis with refractory or life-threatening hematuria, the treatments aim at achieving volume expansion and at limiting the need for frequent transfusions due to active bleeding[35].

2.3.1. Arterial Embolization

Improvements in interventional radiological techniques have led to improvements in morbidity and mortality compared with surgery in patients with refractory hemorrhagic radiation cystitis. The technical success rate reported is 88–100%. The main adverse events were Brown–Sequard's syndrome, bladder necrosis, and gluteal paresis or skin necrosis. Thanks to improved techniques, the incidence of adverse events has decreased from 65% to 9–31% [36][37]. The follow-up of these studies is brief.

2.3.2. Cystectomy and Urinary Diversion

In some patients, treatment by means of cystectomy with urinary diversion is unfortunately inevitable when clot evacuation, bladder fulguration and bladder irrigation have failed. This therapeutic option should be reserved for patients for whom local and conservative treatments have proven unsuccessful, given its high rate of morbidity and mortality. Linder et al. reported a postoperative complication rate of 42% and a 90-day mortality rate of 16%[38].

References

1. Rehailia-Blanchard, A.; He, M.Y.; Rancoule, C.; Guillaume, É.; Guy, J.-B.; Vial, N.; Nivet, A.; Orliac, H.; Chargari, C.; Magné, N. Medical prevention and treatment of radiation-induced urological and nephrological complications. Cancer Radiother. J. Soc. Fr. Radiother. Oncol. 2019, 23, 151–160.
2. Martin, S.E.; Begun, E.M.; Samir, E.; Azaiza, M.T.; Allegro, S.; Abdelhady, M. Incidence and Morbidity of Radiation-Induced Hemorrhagic Cystitis in Prostate Cancer. Urology 2019, 131, 190–195.
3. Freites-Martinez, A.; Santana, N.; Arias-Santiago, S.; Viera, A. CTCAE versión 5.0. Evaluación de la gravedad de los eventos adversos dermatológicos de las terapias antineoplásicas. Actas Dermo-Sifiliográficas 2020.
4. Rigaud, J.; Hetet, J.-F.; Bouchot, O. Management of radiation cystitis. Progres. En. Urol. J. Assoc. Fr. Urol. Soc. Fr. Urol. 2004, 14, 568–572.
5. Smit, S.G.; Heyns, C.F. Management of radiation cystitis. Nat. Rev. Urol. 2010, 7, 206–214.
6. Mazeron, R.; Castelnau-Marchand, P.; Dumas, I.; Del Campo, E.R.; Kom, L.K.; Martinetti, F.; Farha, G.; Tailleur, A.; Morice, P.; Chargari, C.; et al. Impact of treatment time and dose escalation on local control in locally advanced cervical cancer treated by chemoradiation and image-guided pulsed-dose rate adaptive brachytherapy. Radiother. Oncol. 2015, 114, 257–263.
7. Zwaans, B.M.M.; Chancellor, M.B.; Lamb, L.E. Modeling and Treatment of Radiation Cystitis. Urology 2016, 88, 14–21.
8. Cox, J.D.; Stetz, J.; Pajak, T.F. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int. J. Radiat. Oncol. Biol. Phys. 1995, 31, 1341–1346.
9. Denton, A.S.; Clarke, N.W.; Maher, E.J. Non-surgical interventions for late radiation cystitis in patients who have received radical radiotherapy to the pelvis. Cochrane Database Syst. Rev. 2002, CD001773.
10. Pavlidakey, P.G.; MacLennan, G.T. Radiation cystitis. J. Urol. 2009, 182, 1172–1173.

11. Sun, R.; Koubaa, I.; Limkin, E.J.; Dumas, I.; Bentivegna, E.; Castanon, E.; Gouy, S.; Baratiny, C.; Monnot, F.; Maroun, P.; et al. Locally advanced cervical cancer with bladder invasion: Clinical outcomes and predictive factors for vesicovaginal fistulae. Oncotarget 2018, 9, 9299–9310.
12. Marks, L.B.; Carroll, P.R.; Dugan, T.C.; Anscher, M.S. The response of the urinary bladder, urethra, and ureter to radiation and chemotherapy. Int. J. Radiat. Oncol. Biol. Phys. 1995, 31, 1257–1280.
13. Manea, E.; Escande, A.; Bockel, S.; Khettab, M.; Dumas, I.; Lazarescu, I.; Fumagalli, I.; Morice, P.; Deutsch, E.; Haie-Meder, C.; et al. Risk of Late Urinary Complications Following Image Guided Adaptive Brachytherapy for Locally Advanced Cervical Cancer: Refining Bladder Dose-Volume Parameters. Int. J. Radiat. Oncol. 2018, 101, 411–420.
14. Mendenhall, W.M.; Henderson, R.H.; Costa, J.A.; Hoppe, B.S.; Dagan, R.; Bryant, C.M.; Nichols, R.C.; Williams, C.R.; Harris, S.E.; Mendenhall, N.P. Hemorrhagic Radiation Cystitis. Am. J. Clin. Oncol. 2015, 38, 331–336.
15. Muruve, N.A. Radiation Cystitis. 2017. Available online: https://emedicine.medscape.com/article/2055124-overview (accessed on 23 December 2020).
16. D'Ancona, C.; Haylen, B.; Oelke, M.; Abranches-Monteiro, L.; Arnold, E.; Goldman, H.; Hamid, R.; Homma, Y.; Marcelissen, T.; Rademakers, K.; et al. The International Continence Society (ICS) report on the terminology for adult male lower urinary tract and pelvic floor symptoms and dysfunction. Neurourol. Urodynam. 2019, 38, 433–477.
17. Pascoe, C.; Duncan, C.; Lamb, B.W.; Davis, N.F.; Lynch, T.H.; Murphy, D.G.; Lawrentschuk, N. Current management of radiation cystitis: A review and practical guide to clinical management. BJU Int. 2019, 123, 585–594.
18. Martinez, D.R.; Ercole, C.E.; Lopez, J.G.; Parker, J.; Hall, M.K. A Novel Approach for the Treatment of Radiation-Induced Hemorrhagic Cystitis with the GreenLightTM XPS Laser. Int. Braz. J. Urol. 2015, 41, 584–587.
19. Arrizabalaga, M.; Extramina, J.; Parra, J.L.; Ramos, C.; Gonzàlez, R.D.; Leiva, O. Treatment of Massive Haematuria with Aluminous Salts. BJU Int. 1987, 60, 223–226.
20. Westerman, M.E.; Boorjian, S.A.; Linder, B.J. Safety and efficacy of intravesical alum for intractable hemorrhagic cystitis: A contemporary evaluation. Int. Braz. J. Urol. 2016, 42, 1144–1149.
21. Donahue, L.A.; Frank, I.N. Intravesical formalin for hemorrhagic cystitis: Analysis of therapy. J. Urol. 1989, 141, 809–812.
22. Shao, Y.; Lu, G.; Shen, Z. Comparison of intravesical hyaluronic acid instillation and hyperbaric oxygen in the treatment of radiation-induced hemorrhagic cystitis. BJU Int. 2012, 109, 691–694.
23. Chuang, Y.-C.; Kim, D.K.; Chiang, P.-H.; Chancellor, M.B. Bladder botulinum toxin A injection can benefit patients with radiation and chemical cystitis. BJU Int. 2008, 102, 704–706.
24. Hazewinkel, M.H.; Stalpers, L.J.A.; Dijkgraaf, M.G.; Roovers, J.-P.W.R. Prophylactic vesical instillations with 0.2% chondroitin sulfate may reduce symptoms of acute radiation cystitis in patients undergoing radiotherapy for gynecological malignancies. Int. Urogynecol. J. 2011, 22, 725–730.
25. Bonfili, P.; Franzese, P.; Marampon, F.; La Verghetta, M.E.; Parente, S.; Cerasani, M.; Di Genova, D.; Mancini, M.; Vittorini, F.; Gravina, G.L.; et al. Intravesical instillations with polydeoxyribonucleotides reduce symptoms of radiation-induced cystitis in patients treated with radiotherapy for pelvic cancer: A pilot study. Support. Care Cancer 2013, 22, 1155–1159.
26. Mićić, S.; Genbacev, O. Post-irradiation cystitis improved by instillation of early placental extract in saline. Eur. Urol. 1988, 14, 291–293.
27. Villeirs, L.; Tailly, T.; Ost, P.; Waterloos, M.; Decaestecker, K.; Fonteyne, V.; Van Praet, C.; Lumen, N. Hyperbaric oxygen therapy for radiation cystitis after pelvic radiotherapy: Systematic review of the recent literature. Int. J. Urol. 2019, 27, 98–107.
28. Capelli-Schellpfeffer, M.; Gerber, G.S. The use of hyperbaric oxygen in urology. J. Urol. 1999, 162, 647–654.
29. Dellis, A.; Deliveliotis, C.; Kalentzos, V.; Vavasis, P.; Skolarikos, A. Is there a role for hyberbaric oxygen as primary treatment for grade IV radiation-induced haemorrhagic cystitis? A prospective pilot-feasibility study and review of literature. Int. Braz J. Urol. 2014, 40, 296–305.
30. Oscarsson, N.; Müller, B.; Rosén, A.; Lodding, P.; Mölne, J.; Giglio, D.; Hjelle, K.M.; Vaagbø, G.; Hyldegaard, O.; Vangedal, M.; et al. Radiation-induced cystitis treated with hyperbaric oxygen therapy (RICH-ART): A randomised, controlled, phase 2–3 trial. Lancet Oncol. 2019, 20, 1602–1614.
31. Pereira, D.; Ferreira, C.; Catarino, R.; Correia, T.; Cardoso, A.; Reis, F.; Cerqueira, M.; Prisco, R.; Camacho, O. Hyperbaric oxygen for radiation-induced cystitis: A long-term follow-up. Actas Urológicas Españolas (English Edition) 2020, 44, 561–567.

32. Cardinal, J.; Slade, A.; McFarland, M.; Keihani, S.; Hotaling, J.N.; Myers, J.B. Scoping Review and Meta-analysis of Hyperbaric Oxygen Therapy for Radiation-Induced Hemorrhagic Cystitis. Curr. Urol. Rep. 2018, 19, 38.
33. Chong, K.T.; Hampson, N.B.; Corman, J.M. Early hyperbaric oxygen therapy improves outcome for radiation-induced hemorrhagic cystitis. Urology 2005, 65, 649–653.
34. Nakada, T.; Nakada, H.; Yoshida, Y.; Nakashima, Y.; Banya, Y.; Fujihira, T.; Karasawa, K. Hyperbaric Oxygen Therapy for Radiation Cystitis in Patients with Prostate Cancer: A Long-Term Follow-Up Study. Urol. Int. 2012, 89, 208–214.
35. Choong, S.K.; Walkden, M.; Kirby, R. The management of intractable haematuria. BJU Int. 2000, 86, 951–959.
36. Loffroy, R.; Pottecher, P.; Cherblanc, V.; Favelier, S.; Estivalet, L.; Koutlidis, N.; Moulin, M.; Cercueil, J.; Cormier, L.; Krausé, D. Current role of transcatheter arterial embolization for bladder and prostate hemorrhage. Diagn. Interv. Imaging 2014, 95, 1027–1034.
37. Gowda, G.G.; Vijayakumar, R.; Tigga, M.P. Endovascular Management of Radiation-Induced Hemorrhagic Cystitis. Indian J. Palliat. Care 2019, 25, 471–473.
38. Linder, B.J.; Tarrell, R.F.; Boorjian, S.A. Cystectomy for refractory hemorrhagic cystitis: Contemporary etiology, presentation and outcomes. J. Urol. 2014, 192, 1687–1692.