A preliminary report assessing the feasibility and effectiveness of amniotic bladder therapy in patients with chronic radiation cystitis

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Introduction: *Chronic radiation cystitis (CRC) can develop between 6 months and 20 years after radiation therapy that presents with symptoms of urinary frequency, urgency, bladder pain, and nocturia. Amniotic membrane (AM) is known to contain pro-regenerative properties and could thereby be a potential therapeutic modality for radiation-induced tissue injury of the bladder.*

Materials and methods: *CRC patients recalcitrant to previous treatments received amniotic bladder therapy (ABT) comprised of intra-detrusor injections of 100 mg micronized AM (Clarix Flo) diluted in 10 mL 0.9% preservative-free sodium chloride. Clinical evaluation and questionnaires (Interstitial Cystitis Symptom Index (ICSI), Interstitial Cystitis Problem Index (ICPI), Bladder Pain/ Interstitial Cystitis Symptom Score (BPIC-SS), Overactive Bladder (OAB) Assessment Tool, and SF-12 Health Survey) were repeated at preop and 2, 4, 8 and 12 weeks post-injection.*

Results: *Five consecutive female patients aged 64.4 ± 20.1 years with a median CRC disease duration of 10 years were included. After ABT, BPIC-SS scores improved from baseline to 12 weeks (36.6 ± 1.1 to 12.6 ± 3.1) and this was associated with an improvement in ICSI, ICPI, OAB, and SF-12 scores. One patient had an acute urinary tract infection at 2 weeks but was successfully treated with oral antibiotics. No other adverse events related to micronized AM injections were observed. Uroflow assessments showed increases in voided volume for all five patients.*

Conclusions: *This data provides additional evidence for the potential benefit of ABT in patients with chronic inflammatory conditions of bladder such as CRC.*

Key Words: amniotic, chronic radiation cystitis, intravesical therapy, lower urinary tract symptoms, radiation cystitis

Introduction

Radiotherapy plays a crucial role as a treatment for malignant pelvic tumors, in which the bladder represents an organ at risk for radiotoxicity. Exposing the bladder wall to ionizing radiation is sometimes unavoidable because of its central position in the pelvic cavity and may lead to urothelial tissue and vascular damage.[1] This subsequently leads to an inflammatory and hypoxic environment and formation of secondary bladder wall fibrosis.[2] Chronic radiation cystitis (CRC) is a term used to describe this sequela that arises 6 months after radiation and can be associated with several bladder storage symptoms such as frequent urination, urinary urgency, nocturia and pelvic pain.[3] Unfortunately, currently no adequate treatment options are available for this condition.[3]

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Amniotic membrane (AM) is known to contain pro-regenerative properties and has been shown effective in managing tissue fibrosis, inflammation, and ischemia,[4,5] which are the hallmarks of CRC. Clinically AM has been used to promote significant vascular granulation tissue formation and complete wound healing in cases of radiation-induced skin ulcers[6] and could thereby be a potential therapeutic approach for radiation-induced tissue injury of the bladder. To further support this notion, we have recently shown that intra-detrusor injections of AM (termed amniotic bladder therapy (ABT)) led to symptomatic improvement in patients with interstitial cystitis/ bladder pain syndrome,[7] which has similar mechanisms of pathologies to CRC and thus favor a potential therapeutic effect of ABT for CRC patients. Based on the data, we explored the role of ABT as a therapeutic alternative for the management of bladder storage dysfunction in CRC patients.

Material and methods

This study was approved by the local institutional review board committee and all patients gave their written informed consent. The patients were eligible to be included in the study if they had CRC that arose at least 6 months after radiation therapy and had failed previous treatment modalities including oral and intra-vesical therapies. We excluded patients with active urinary tract infections, upper tract lesions, gross hematuria, concomitant bladder outlet obstruction, renal dysfunction, hemorrhagic cystitis, and intra-vesical stones. All patients were confirmed to be in remission for at least 5 years. We also excluded the patients who had used intravesical botulinum toxin (Botox) within 6 months before the commencement of study to avoid interference in the results.

Baseline evaluation included history, physical examination, serum chemistries, urinalyses, urine culture, urine cytology, cystoscopy, uroflow, post-void residuals, computed tomography urography and symptom assessments as measured by questionnaires of Bladder Pain/ Interstitial Cystitis Symptom Score (BPIC-SS), Overactive Bladder (OAB) Assessment Tool, O'Leary/ Sant Voiding and Pain Indices (Interstitial Cystitis Symptoms Index and Interstitial Cystitis Problem Index) and SF-12 Health Survey. The uroflow assessments were maximum flow rate (mL/sec), average flow rate (mL/sec), voiding time (sec), time to Q max (sec), voided volume (mL) and post-void urine volume (mL) (PVR) via bladder scan.

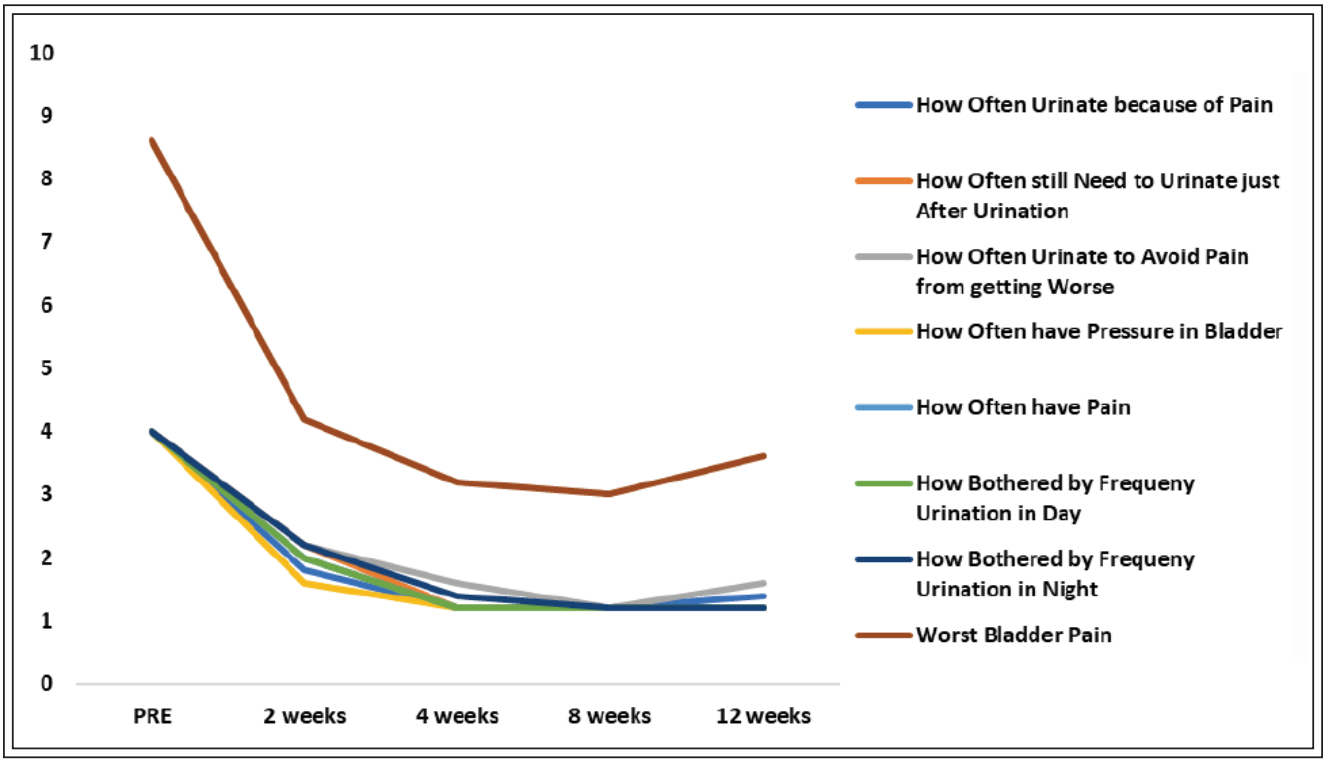

Figure 1. BPIC-SS scores on individual questions before and after ABT.

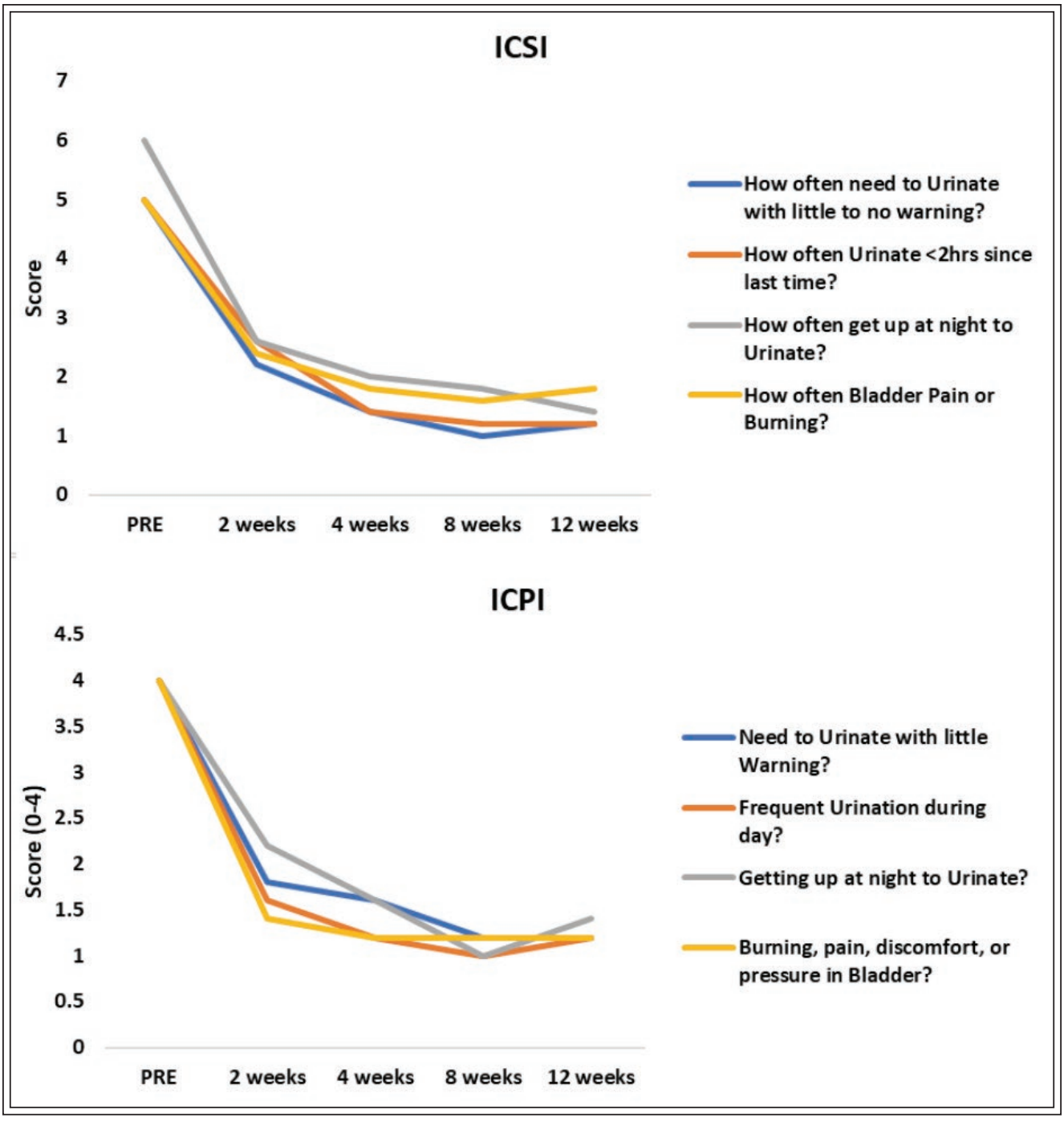

Figure 2. ICSI and ICPI scores on individual questions before and after ABT.

Under general anesthesia, patients were given intra-detrusor injections of 100 mg of commercially available micronized AM (Clarix Flo; BioTissue, Miami, FL, USA) diluted in 10 mL 0.9% preservative free sodium chloride using a 23-gauge Williams needle through a cystoscope. Injections were made into the lateral and posterior bladder wall sparing the dome and trigone. A standardized procedure was followed for all patients, with twenty injections of 0.5 mL delivered into two rows of ten throughout the lateral and posterior bladder wall. Clarix Flo is a sterile, micronized human AM product derived from placenta and umbilical cord that is aseptically processed and manufactured from donated human birth tissue according to regulations

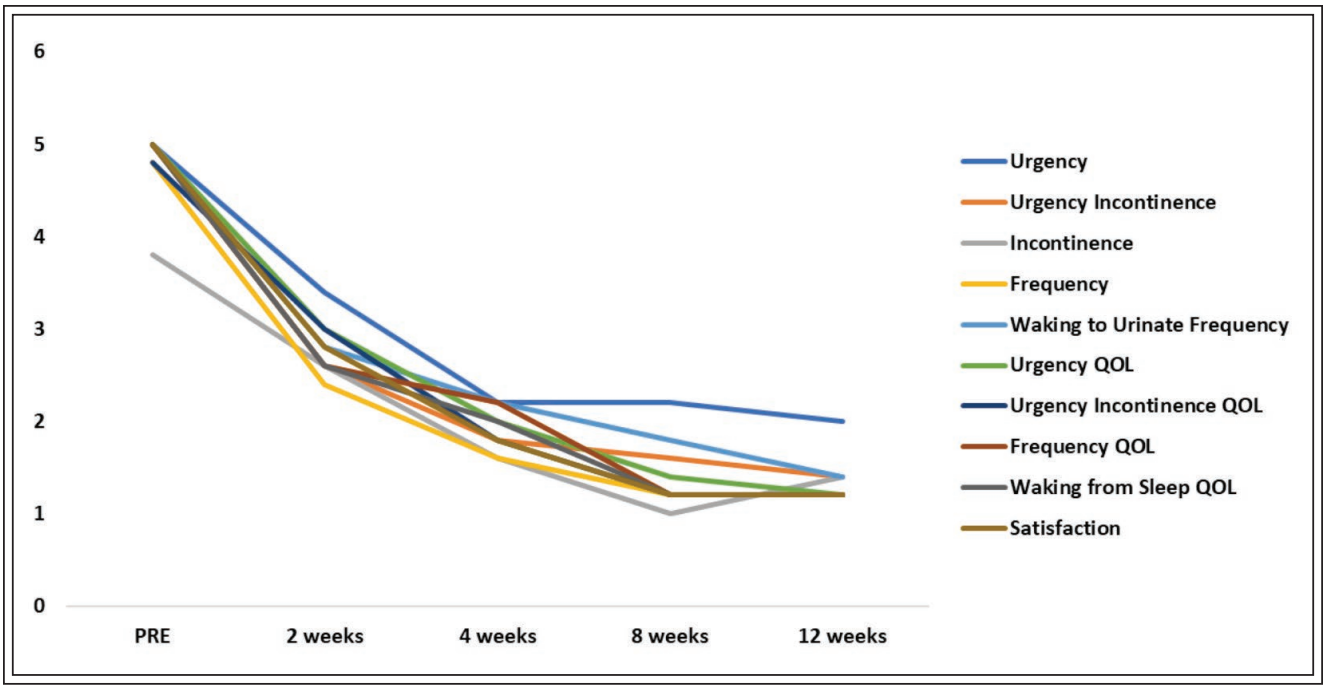

Figure 3. OAB scores on individual questions before and after ABT.

established by the US Food & Drug Administration. There are no live cells within the micronized AM, however it retains the natural extracellular matrix components innate to the AM.

Clinical evaluation and questionnaires were repeated at 2, 4, 8 and 12 weeks, and additional urine culture and post-void residuals were repeated at 2 and 4 weeks. Cystoscopy and uroflow assessment were repeated at 12 weeks. Local or systemic side effects were noted during and after treatment.

Descriptive statistics for continuous variables are reported as the mean ± SD and statistical analysis was performed using MiniTab (Minitab Inc., State College, PA, USA). Differences between parameters before and after treatment were analyzed with non-parametric, Wilcoxon signed rank test. A p value < 0.05 was considered statistically significant.

Results

Five consecutive patients fulfilling all criteria were selected and included in this study. All patients had been in clinical remission for at least 5 years and had previously received external beam radiation for cervical cancer (n = 3), colon cancer (n = 1), and vaginal rhabdomyosarcoma (n = 1). The five women had an average age of 64.4 ± 20.1 years (range: 29-75 years) and median CRC disease duration of 10 years (7-12 years) that was recalcitrant to multiple therapies including anticholinergics (n = 5), beta-3 adrenergic agonist (n = 5), tricyclic antidepressant (n = 4), hydro-distension (n = 3), botulinum toxin injection (n = 5) and vaginal valium (n = 4).

Prior to treatment, patients had severe symptoms of RC as suggested by ICSI score of 21.0 ± 0.0, ICPI score of 16.0 ± 0.0, BPIC-SS of 36.6 ± 1.1, and OAB score of 23.6 ± 1.1. One patient had an acute urinary tract infection 2 weeks post injection and was successfully treated with oral antibiotics. No other adverse events related to micronized AM injections that occurred throughout the study.

After micronized AM treatment, the ICSI score decreased from 21.0 ± 0.0 at baseline to 9.8 ± 2.7 at 2 weeks, 6.6 ± 3.0 at 4 weeks, 5.6 ± 1.1 at 8 weeks, and 5.6 ± 1.5 at 3 months and the ICPI score significantly decreased from 16.0 ± 0.0 at baseline to 7.0 ± 2.5 at 2 weeks, 5.6 ± 2.5 at 4 weeks, 4.4 ± 0.9 at 8 weeks, and 5.0 ± 1.7 at 3 months, Figure 1. Similarly, the BPIC-SS decreased from 36.6 ± 1.1 at baseline to 17.8 ± 5.1 at 2 weeks, 12.0 ± 4.5 at 4 weeks, 11.4 ± 3.7 at 8 weeks, and 12.6 ± 3.1 at 3 months. As noted in Figure 2, there was a reduction in the score of each individual question of the BPIC-SS. This corresponded to an improvement in their overall physical and mental quality of life as measured by the SF-12 PCS and SF-12 MCS. The SF-12 PCS score decreased from 26.6 ± 4.5 at baseline to

TABLE 1. **Uroflow parameters at baseline and 3 months post injection**

Patient number	Maximum flow rate (mL/sec)		Average flow rate (mL/sec)		Voiding time (sec)		Time to Q max (sec)		Voided volume (mL)	
	Baseline	3 months	Baseline	3 months	Baseline	3 months	Baseline	3 months	Baseline	3 months
#1	20.2	21.8	11.8	12.3	24	35	5	7	120	300
#2	21.4	19.9	11.4	12.7	22	42	7	10	140	345
#3	23	24.5	10.9	12.2	25	41	7	11	125	360
#4	21	23.6	11	13.4	22	40	5	9	90	230
#5	22.2	25.5	13	12.8	29	45	8	12	145	380

44.1 ± 6.8 at 2 weeks, 52.2 ± 1.1 at 4 weeks, 52.8 ± 0.9 at 8 weeks, and 53.1 ± 1.0 at 3 months. The SF-12 MCS score decreased from 34.8 ± 2.0 at baseline to 50.6 ± 3.4 at 2 weeks, 49.9 ± 2.5 at 4 weeks, 51.3 ± 2.5 at 8 weeks, and 50.8 ± 4.5 at 3 months.

The OAB score decreased from 23.6 ± 1.1 at baseline to 13.8 ± 2.8 at 2 weeks, 9.2 ± 3.9 at 4 weeks, 7.8 ± 1.9 at 8 weeks, and 7.4 ± 2.1 at 3 months, Figure 3.

No acute urinary retention was observed in the five patients. PVR values were 27.6 ± 14.2 ml at baseline and 28.8 ± 6.3 mL at 4 weeks. Uroflow assessments showed increases in voided volume for all five patients at 3 months post injection compared to baseline, Table 1.

Discussion

CRC can develop between 6 months and 20 years after radiation therapy that is characterized by symptoms of urinary frequency, urgency, bladder pain, and nocturia based on impairment of the storage function of the bladder.[3,8] These symptoms are caused by the loss of impermeability of the urothelium, severe bladder fibrosis, vascular damage and chronic inflammation.[9,10] These processes potentiate each other, allowing the progressive worsening of CRC.[11] CRC is often diagnosed at a late stage when damage may be irreversible, making symptomatic treatment of CRC challenging for clinicians.

During the last decades, multiple therapeutic modalities, including pharmacological agents and surgical interventions have been extensively applied for CRC, however there is still a lack of an effective therapeutic method for this disease entity.[12-14] Most therapies aim to provide symptomatic relief while not addressing the pathologic process. The bladder wall experiences inflammation and undergoes remodeling and fibrosis after radiation; hence it is important to provide CRC patients with new therapeutic solutions that will act simultaneously and progressively on multiple different mechanisms to reduce inflammation and bladder fibrosis as well as ameliorate urothelial and vascular damage.

Previous studies have shown AM is able to simultaneously provide a multi-modality effect including reducing inflammation, reverting scar formation, and promoting epithelialization.[4,5] More specifically, AM and its key extracellular matrix component HC-HA/PTX3 has been shown to promote cell death of pro-inflammatory neutrophil, promotes polarization of M2 macrophages, promotes phagocytosis of apoptotic cells, and suppresses activation of $CD4^+$ T cells.[4,5] This ultimately resolves the chronic inflammation, reduces further tissue injury, and sets the stage for progressive healing characterized by cell proliferation and tissue remodeling. Similar benefits are seen in use of AM for dermal and ocular surface wound healing, wherein a single application reduced inflammation and promoted regenerative healing with a lasting clinical benefit.[15,16]

Preliminary clinical studies have also documented the efficacy of ABT to improve the lower urinary tract and pelvic pain symptoms associated with interstitial cystitis and overactive bladder (OAB).[7,17] In OAB patients, ABT was shown to significantly decrease the OAB score from 23.5 ± 1.2 at baseline to 7.1 ± 1.4 at 3 months ($p < 0.01$) and this was associated with a significant increase in mean volume of first involuntary detrusor contraction and maximum cystometric capacity. In this investigative pilot study, we report improvement in our CRC patients with predominantly bladder storage symptoms despite them having a median disease duration of 10 years and failing multiple prior treatments. Patients presented with severe symptoms of frequency (4.8 ± 0.4 of 5), urinary urgency (5.0 of 5), nocturia and pelvic pain (8.6 ± 1.14 of 10) that significantly improved at 2 weeks and progressively improved up to 12 weeks after ABT. Such results are similar to another study which showed intravesical instillation of placental cytosol extract led

to cystoscopically proven healing of radiation-induced bladder injury with neo-vascularization of the injured bladder mucosa and symptomatic improvement in all 21 treated patients.[18] Collectively these studies provide additional evidence for the potential benefit of ABT in patients with chronic inflammatory conditions of bladder.

Although we have reported promising findings, our study has several limitations. First, the sample size of five patients is relatively small and is gathered from one institution. Furthermore, there was no control group and there could be a potential placebo effect that patients perceive a potential benefit from. Nonetheless, our study was conducted on consecutive patients who were treated using a standardized method and was shown to have similar benefit in patients with IC/BPS and OAB. Future randomized placebo controlled multicenter studies are warranted with adequate patient population to better clarify the role and durability of ABT in the treatment CRC. □

References

1. Brossard C, Lefranc AC, Pouliet AL et al. Molecular mechanisms and key processes in interstitial, hemorrhagic and radiation cystitis. *Biology* 2022;11(7):972.
2. Basic Clinical Radiobiology. 5 ed.:CRC Press, 2018.
3. Pascoe C, Duncan C, Lamb BW et al. Current management of radiation cystitis: a review and practical guide to clinical management. *BJU Int* 2019;123(4):585-594.
4. Tseng SC. HC-HA/PTX3 purified from amniotic membrane as novel regenerative matrix: insight into relationship between inflammation and regeneration. *Invest Ophthalmol Vis Sci* 2016;57(5):ORSFh1-8.
5. Tighe S, Mead OG, Lee A, Tseng SCG. Basic science review of birth tissue uses in ophthalmology. *Taiwan J Ophthalmol* 2020; 10(1):3-12.
6. Fernandez D. Cryopreserved amniotic membrane and umbilical cord for a radiation-induced wound with exposed dura: a case report. *J Wound Care* 2019;28(Sup 2):S4-S8.
7. Madan R, Radoiu C, Liaw A, Lucas S, Hamada A, Dhar N. Early three-month report of amniotic bladder therapy in patients with interstitial cystitis/bladder pain syndrome. *Int Urol Nephrol* 2023;55(8):1937-1942.
8. Pavlidakey PG, MacLennan GT. Radiation cystitis. *J Urol* 2009; 182(3):1172-1173.
9. Stewart FA. Mechanism of bladder damage and repair after treatment with radiation and cytostatic drugs. *Br J Cancer Suppl* 1986;7:280-291.
10. El-Benhawy SA, Sadek NA, Kamel MM et al. Study the relationship of endothelial damage / dysfunction due to occupational exposure to low dose ionizing radiation versus high dose exposure during radiotherapy. *Cancer Treat Res Commun* 2020;25:100215.
11. Brossard C, Lefranc AC, Simon JM, Benderitter M, Milliat F, Chapel A. Understanding molecular mechanisms and identifying key processes in chronic radiation cystitis. *Int J Mol Sci* 2022;23(3):1836.
12. Bonfili P, Franzese P, Marampon F 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* 2014;22(5):1155-1159.
13. Rajaganapathy BR, Jayabalan N, Tyagi P, Kaufman J, Chancellor MB. Advances in therapeutic development for radiation cystitis. *Low Urin Tract Symptoms* 2014;6(1):1-10.
14. Sommariva ML, Lazzeri M, Abrate A, Guazzoni G, Sandri S, Montorsi F. Intravesical hyaluronic acid and chondroitin sulphate improve symptoms and quality of life in patients with late radiation tissue cystitis: an investigative pilot study. *Eur J Inflamm* 2014;12(1):177-185.
15. Caputo WJ, Vaquero C, Monterosa A et al. A retrospective study of cryopreserved umbilical cord as an adjunctive therapy to promote the healing of chronic, complex foot ulcers with underlying osteomyelitis. *Wound Repair Regen* 2016;24(5): 885-893.
16. John T, Tighe S, Sheha H et al. Corneal nerve regeneration after self-retained cryopreserved amniotic membrane in dry eye disease. *J Ophthalmol* 2017;2017:6404918.
17. Hudson C, Madan R, Ross E et al. A preliminary report assessing the feasibility and effectiveness of amniotic bladder therapy in patients with idiopathic detrusor overactivity. *Curr Urol* Epub 2023.
18. Mićić S, Genbacev O. Post-irradiation cystitis improved by instillation of early placental extract in saline. *Eur Urol* 1988; 14(4):291-293.