CANCER DIAGNOSIS & PROGNOSIS
3: 383-386 (2023) doi: 10.21873/cdp.10228

Successful Phytotherapy for Acute Refractory Radiation Cystitis in a Cervical Cancer Patient: A Case Report

BA X. HOANG[1], BO HAN[1], HUNG Q. TRAN[2], WILLIAM H. FANG[3] and HAU D. TRAN[4]

[1]*Nimni-Cordoba Tissue Engineering and Drug Discovery Laboratory, Department of Surgery, Keck School of Medicine, University of Southern California, Los Angeles, CA, U.S.A.;*
[2]*Department of Oncology, Phenikaa University, Hanoi, Vietnam;*
[3]*Department of Translational Research, Western University of Health Sciences, Pomona, CA, U.S.A.;*
[4]*Department of Oncology, National Children Hospital of Vietnam, Hanoi, Vietnam*

Abstract. *Background/Aim: Radiation cystitis is a frequent complication that can occur after therapeutic irradiation of pelvic cancers. The current treatment for this condition is complex and often ineffective. Case Report: We present a clinical case of a 54-year-old patient diagnosed with small cell cervical cancer FIGO stage IIIC who developed grade 2-3 radiation cystitis following post-operational chemoradiation therapy. The patient exhibited increased urinary urgency and frequency, dysuria, and low abdominal pain, which failed to respond to acupuncture and corticosteroid treatments. A course of Ich Nieu Khang phytotherapy tablets, resulted in significant improvement of symptoms within 24 hours of initiation. The symptoms resolved completely within 10 days, and ultrasonography documented a marked decrease in bladder wall thickening and improved bladder evacuation function. The phytotherapy was well-tolerated, and no side-effects were observed during the 60-day treatment period. Conclusion: These findings suggest that phytotherapy may be viable for managing radiation cystitis. However, further controlled clinical trials are needed to confirm the efficacy of Ich Nieu Khang and promote its broader clinical applications.*

Correspondence to: Ba X. Hoang, MD, Ph.D., Nimni-Cordoba Tissue Engineering and Drug Discovery Lab, Department of Surgery, Keck School of Medicine, University of Southern California, 1333 San Pablo Street, BMT-302, Los Angeles 90033, CA, U.S.A. Tel: +1 3234420762, e-mail: baxuanho@usc.edu

Key Words: Radiation cystitis, phytotherapy, cervical cancer, food supplements, Ich Nieu Khang.

©2023 International Institute of Anticancer Research
www.iiar-anticancer.org

This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY-NC-ND) 4.0 international license (https://creativecommons.org/licenses/by-nc-nd/4.0).

Radiotherapy is an essential component for the treatment of cervical cancer. It has been reported that approximately 60% to 70% of cervical cancer patients receive radiotherapy alone or in combination with chemotherapy (1, 2). Radiotherapy complications on the bladder are mainly radiation cystitis with clinical symptoms of frequent urination, urgency, dysuria, cystalgia with bladder spasms, and hematuria (1). Acute radiation cystitis occurs during or up to three months after the end of radiation therapy. It has been estimated that 50% to 80% of patients will develop radiation cystitis within 3 to 4 weeks at the initiation of pelvic irradiation, which may persist for an extended period of time (2, 3).

The treatment for acute and late radiation cystitis is mainly symptomatic with analgesics and anti-inflammatory drugs. Alpha-blockers, 5-reductase inhibitors, or phosphodiesterase inhibitors may be used to alleviate voiding symptoms (4). Anticholinergic agents, such as oxybutynin, trospium chloride, solifenacin, fesoterodine or flavoxate hydrochloride, can be prescribed to help alleviate urgency and increased daytime frequency (5). Their action is to decrease the contractility of the detrusor and improve symptoms.

Several treatment strategies for radiation cystitis have been proposed for the last two decades. However, the evidence for the efficacy of the investigated therapeutic modalities is anecdotal and presented in case reports or small population case series (6-9). No high-quality evidence exists in randomized control trials, which makes developing evidence-based treatment recommendations difficult. Radiation cystitis remains a significant clinical problem and is difficult to treat.

In this case report, we describe the clinical presentation and successful phytotherapy for acute refractory radiation cystitis in a 54-year-old patient diagnosed with small cell cervical cancer FIGO stage IIIC.

Table I. *Content and composition of Ich Nieu Khang*.

Content	Composition
Eucommia ulmoides herbal extract (DER: 16:1)	350 mg
L-Carnitine fumarate	150 mg
GO-LESS [Content pumpkin seed extract 87.5% (EFLA®940) and soy isoflavone 12.5% (Soylife®40)]	25 mg
Excipients: Starch, magnesium stearate, talc, PVP K30, microcrystalline cellulose, HPMC	175 mg

Case Report

A 54-year-old patient diagnosed post-surgically with small cell cervical cancer, Federation International of Gynecology and Obstetrics (FIGO) stage IIIC. The patient was treated post-operationally with pelvic radiotherapy, total dose 45 Gy, 4-week fractions, chemotherapy with cisplatin 115 mg and Etoposide 154 mg for 4 cycles.

Three weeks after initiation of radio chemotherapy, the patient developed severe low abdominal pain, increasing dysuria, frequent urination, urgency, and micro-hematuria plus leukocytosis in urine analysis. In addition, the patient also developed hemotoxic side-effects of chemotherapy with a decrease in all blood counts. Standard urine culture was negative. The pelvic ultrasound showed a thickening of the posterior bladder wall (9.8 mm), and the residual urine was 189 ml. The patient was diagnosed with radiation cystitis and underwent therapy with 10 days of oral prednisolone 20 mg daily and acupuncture daily for 12 days. The patient continued and finished radiochemotherapy. The treatment with Prednisolone and acupuncture reduced the patient's pelvic pain, but her symptoms related to radiation cystitis were accelerated with increased urinary urgency (voiding every 15 to 20 min) and frequency, both during the day (17-20 times) and at night (9-11 times). Due to urinary urgency, the patient has experienced multiple falls, resulting in a dislocated left ankle joint. With the worsening of radiation cystitis symptoms, the patient was treated by her husband, a urologist-oncologist, with a 60-day course of phytotherapy. The standardized registered herbal food supplement Ich Nieu Khang was administered 3 tablets 3 times daily on an empty stomach.

The Ich Nieu Khang (INK) dietary supplement tablets were distributed by FOBIC Pharma Co., Ltd. The Food Safety Department of the Vietnamese Health Ministry issued the Certificate of Conformity with Food Safety Regulations No. 5768/2018/DKSP. Acute and chronic toxicity tests of INK on animals were conducted at the Department of Pharmacology, Hanoi Medical University. INK was certified as a safe food supplement [Certification of Conformity (Quacert) No. 3269/19/QC-PTN]. The composition of Ich Nieu Khang is described in Table I.

Results of Ich Nieu Khang phytotherapy for radiation cystitis symptoms. On the initial day (D0), the patient experienced a high frequency of urination, with 20 times during the daytime and 11 times during the nighttime, and urgent voiding every 20 min. Following 24 h of phytotherapy (D1), the patient's frequency of urination decreased to 14 times during the day and 6 times at night, with urgency voiding occurring every 60 min. By day 2 (D2), the patient's frequency of urination further reduced to 8 times during the day and 4 times at night, with urgency voiding every 2 h. On day 3 (D3), the patient's frequency of urination remained at 8 times during the day and reduced to 3 times at night, with urgency voiding every 2 h. By day 5 (D5), the patient's frequency of urination further decreased to 7 times during the day and 2 times at night, with urgency voiding every 2 h. After 10 days of treatment (D10), the patient's frequency of urination reduced to 6 times during the day and 1 time at night, with urgency voiding every 3 h. Following 30 days (D30) and 60 days (D60) of treatment, the patient's frequency of urination remained consistent at 6 times during the day and 1 time at night, with urgency voiding every 3 h (Figure 1).

The changes in the value of red blood cell count, hemoglobin value, white blood cell count, platelet count and biochemistry profile of the patient during 60 days of treatment with Ich Nieu Khang are presented in Table II. There was a vast improvement in bladder evacuation with phytotherapy revealed by pelvic ultrasound examination. The residual urine decreased from 189 ml to 30 ml on day 10 and normalized on day 30. The bladder wall thickening decreased from 9.8 mm to 4.8 mm on day 30 and 4.5 mm on day 60.

In addition to the above-mentioned paraclinical investigations, the patient's urinalysis showed significant improvement after 60 days of phytotherapy. The results showed microhematuria, and urine leukocytosis disappeared on day 30. The pH, protein, glucose, nitrite, ketone, bilirubin, urobilinogen, white blood cell, and red blood cell counts were within normal ranges on day 60. The patient tolerated the phytotherapy well, with no complaints or clinically meaningful side-effects reported during the 60 days of treatment.

Ethics and consent statement. Appropriate consent was obtained from the patients to write up and publish the case.

Discussion

Radiation cystitis is one of the most common complications of radiation therapy and significantly affects patients' quality

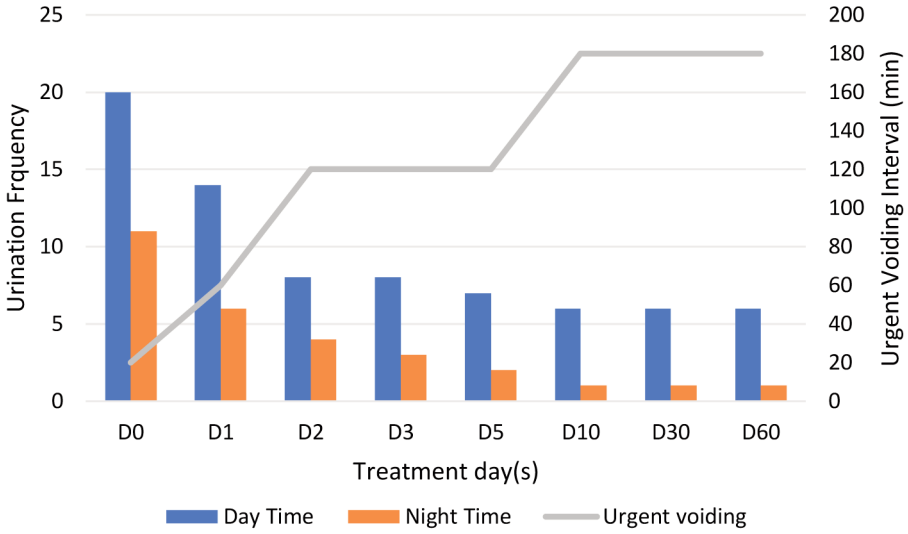

Figure 1. *Changes in urination frequency and urgent voiding intervals in a radiation-induced cystitis patient following phytotherapy with Ich Nieu Khang.*

of life and can lead to life-threatening situations (10-12). The combination of surgery and post-surgical radiochemotherapy may increase the incidence and severity of radiation-induced cystitis compared to radiotherapy alone, suggesting that bladder dysfunction due to the surgical procedure may increase the frequency and severity of radiation cystitis as it was seen in the reported patient (13). Surgical procedures may partially destroy the autonomic bladder nerve, causing the decrease of the bladder wall's elastic muscle fibers, leading to neurogenic bladder dysfunction resulting in frequent urination, urgency, and urinary incontinence (14).

Our clinical observation reported that Ich Nieu Khang, a phytomedicine that was previously used to successfully treat patients with neurogenic bladder dysfunction and overactive bladder syndrome, demonstrated a fast and dramatic therapeutic efficacy for a patient with radiation cystitis. The various biological activities of phytomedicines can be credited to their effectiveness. The components of Ich Nieu Khang specifically target bladder neurogenic dysfunction, inflammatory reactions, and fibrotic transformation and promote epithelial and muscle regeneration – these being the primary pathogenic events in radiation cystitis (15-18). Managing radiation complications is challenging and costly due to impaired tissue healing. Most current treatment options are complex and provide only short-term relief, with no therapy available to reverse the progression of the disease. The available therapeutic methods include hyperbaric oxygen therapy, clot evacuation, fulguration, intravesical instillation of astringent agents, and surgery. Innovative investigative strategies such as Botulinum Toxin injections and liposomal-tacrolimus instillations are also being explored (6).

Table II. *Blood count and biochemistry profile of the patient during phytotherapy.*

Tests	Time			
	Day 0	Day 10	Day 30	Day 60
RBC	3.15	3.26	3.95	4.69
Hemoglobin	83	91	105	119
WBC	3.25	3.58	5.03	5.27
Platelets count	115	132	215	297
AST	75.21	66.14	60.13	51.32
ALT	83.27	71.64	62.75	54.07
BUN	8.12	7.84	5.73	5.21
Creatinine	67.52	63.47	61.83	52.38

RBC: Red blood cell count; WBC: white blood cell count; AST: aspartate aminotransferase; ALT: alanine transaminase; BUN: blood urea nitrogen.

Current radiation cystitis management mainly involves symptomatic and supportive measures due to the lack of a reliable, evidence-based, and uncomplicated therapeutic approach. Most patients require personalized multimodal treatment to alleviate symptoms and improve their quality of life. Moving forward, it is essential to conduct large, randomized trials to explore emerging phytotherapeutic and nutraceutical strategies that could lead to safe, cost-effective, and efficient modalities for preventing and treating radiation cystitis.

Conclusion

Our study suggests that a 60-day treatment of phytotherapy using the standardized food supplement Ich Nieu Khang may

be a safe and effective treatment option for patients with radiation cystitis. However, further extensive controlled clinical trials are necessary to validate our results and encourage the broader adoption of phytotherapy for managing urological complications associated with radiation therapy.

Conflicts of Interest

The Authors report no conflicts of interest.

Authors' Contributions

Ba X. Hoang: Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft. Bo Han: Conceptualization; Data curation; Formal analysis; Methodology. Hung Q. Tran: Investigation; Methodology; Data curation; Formal analysis. William H. Fang: Writing – review & editing. Hau D. Tran: Investigation; Methodology; Data curation.

References

1 Rehailia-Blanchard A, He MY, Rancoule C, Guillaume É, Guy JB, Vial N, Nivet A, Orliac H, Chargari C and Magné N: Medical prevention and treatment of radiation-induced urological and nephrological complications. Cancer Radiother *23(2)*: 151-160, 2019. PMID: 30898418. DOI: 10.1016/j.canrad.2018.05.007

2 Martin SE, Begun EM, Samir E, Azaiza MT, Allegro S and Abdelhady M: Incidence and morbidity of radiation-induced hemorrhagic cystitis in prostate cancer. Urology *131*: 190-195, 2019. PMID: 31201826. DOI: 10.1016/j.urology.2019.05.034

3 Kolla SB and Dash A: Radiation cystitis: Acute and chronic. *In*: Radiation Therapy for Pelvic Malignancy and Its Consequences. Ehrenpreis ED, Marsh RDW, Small Jr. W (eds.). New York City, NY, USA, Springer, pp. 111-118, 2015. DOI: 10.1007/978-1-4939-2217-8_7

4 D'Ancona C, Haylen B, Oelke M, Abranches-Monteiro L, Arnold E, Goldman H, Hamid R, Homma Y, Marcelissen T, Rademakers K, Schizas A, Singla A, Soto I, Tse V, de Wachter S, Herschorn S and Standardisation Steering Committee ICS and the ICS Working Group on Terminology for Male Lower Urinary Tract & Pelvic Floor Symptoms and Dysfunction: The International Continence Society (ICS) report on the terminology for adult male lower urinary tract and pelvic floor symptoms and dysfunction. Neurourol Urodyn *38(2)*: 433-477, 2019. PMID: 30681183. DOI: 10.1002/nau.23897

5 Helissey C, Cavallero S, Brossard C, Dusaud M, Chargari C and François S: Chronic inflammation and radiation-induced cystitis: Molecular background and therapeutic perspectives. Cells *10(1)*: 21, 2020. PMID: 33374374. DOI: 10.3390/cells10010021

6 Zwaans BMM, Lamb LE, Bartolone S, Nicolai HE, Chancellor MB and Klaudia SW: Cancer survivorship issues with radiation and hemorrhagic cystitis in gynecological malignancies. Int Urol Nephrol *50(10)*: 1745-1751, 2018. PMID: 30132277. DOI: 10.1007/s11255-018-1970-2

7 Veerasarn V, Khorprasert C, Lorvidhaya V, Sangruchi S, Tantivatana T, Narkwong L, Kongthanarat Y, Chitapanarux I, Tesavibul C, Panichevaluk A, Puribhat S, Sangkittipaiboon S, Sookpreedee L, Lertsanguansinchai P, Phromratanapongse P, Rungpoka P, Trithratipvikul S, Lojanapiwat B, Ruangdilokrat S and Ngampanprasert P: Reduced recurrence of late hemorrhagic radiation cystitis by WF10 therapy in cervical cancer patients: a multicenter, randomized, two-arm, open-label trial. Radiother Oncol *73(2)*: 179-185, 2004. PMID: 15542165. DOI: 10.1016/j.radonc.2004.05.007

8 Lowe BA and Stamey TA: Endoscopic topical placement of formalin soaked pledgets to control localized hemorrhage due to radiation cystitis. J Urol *158(2)*: 528-529, 1997. PMID: 9224340.

9 Miura M, Sasagawa I, Kubota Y, Iijima Y, Sawamura T and Nakada T: Effective hyperbaric oxygenation with prostaglandin E1 for radiation cystitis and colitis after pelvic radiotherapy. Int Urol Nephrol *28(5)*: 643-647, 1996. PMID: 9061423. DOI: 10.1007/BF02552159

10 Ma JL, Hennessey DB, Newell BP, Bolton DM and Lawrentschuk N: Radiotherapy-related complications presenting to a urology department: a more common problem than previously thought? BJU Int *121(Suppl 3)*: 28-32, 2018. PMID: 29360286. DOI: 10.1111/bju.14145

11 Wit EM and Horenblas S: Urological complications after treatment of cervical cancer. Nat Rev Urol *11(2)*: 110-117, 2014. PMID: 24473416. DOI: 10.1038/nrurol.2013.323

12 Dautruche A and Delouya G: A contemporary review about the management of radiation-induced hemorrhagic cystitis. Curr Opin Support Palliat Care *12(3)*: 344-350, 2018. PMID: 30015689. DOI: 10.1097/SPC.0000000000000375

13 He L, Wang Z, Chen J, Chen L, Chen P and Cai W: Analysis of clinicopathological factors associated with radiation-induced cystitis in patients with cervical cancer. J Healthc Eng *2022*: 6216072, 2022. PMID: 35911584. DOI: 10.1155/2022/6216072

14 Pellatt GC and Geddis T: Neurogenic continence. Part 2: Neurogenic bladder management. Br J Nurs *17(14)*: 904, 906,908-904,906,913, 2008. PMID: 18935843. DOI: 10.12968/bjon.2008.17.14.30658

15 Huang L, Lyu Q, Zheng W, Yang Q and Cao G: Traditional application and modern pharmacological research of *Eucommia ulmoides* Oliv. Chin Med *16(1)*: 73, 2021. PMID: 34362420. DOI: 10.1186/s13020-021-00482-7

16 Szymański M, Wandtke T, Wasilow K, Andryszczyk M, Janicki R and Domaracki P: Comparison of 3- and 6-month outcomes of combined oral L-carnitine fumarate and acetyl-L-carnitine therapy, included in an antioxidant formulation, in patients with idiopathic infertility. Am J Mens Health *15(5)*: 15579883211036790, 2021. PMID: 34515581. DOI: 10.1177/15579883211036790

17 Shim B, Jeong H, Lee S, Hwang S, Moon B and Storni C: A randomized double-blind placebo-controlled clinical trial of a product containing pumpkin seed extract and soy germ extract to improve overactive bladder-related voiding dysfunction and quality of life. Journal of Functional Foods *8*: 111-117, 2019. DOI: 10.1016/j.jff.2014.03.010

18 Gažová A, Valášková S, Žufková V, Castejon AM and Kyselovič J: Clinical study of effectiveness and safety of CELcomplex(®) containing Cucurbita Pepo Seed extract and Flax and Casuarina on stress urinary incontinence in women. J Tradit Complement Med *9(2)*: 138-142, 2018. PMID: 30963048. DOI: 10.1016/j.jtcme.2017.10.005

Received February 16, 2023
Revised February 28, 2023
Accepted March 15, 2023