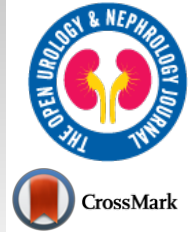




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CASE REPORT

Bacillus Calmette-Guérin Perfusion Treatment *via* Cutaneous Ureterostomy for Carcinoma *in Situ* of the Upper Urinary Tract

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Abstract:

Introduction:

Bacillus Calmette-Guérin instillation is an established therapy for the treatment of carcinoma *in situ* of the upper urinary tract.

Case Presentation:

A 72-year-old woman underwent radical cystectomy with cutaneous ureterostomy for invasive bladder cancer with carcinoma *in situ* of both ureters. For the treatment of upper urinary tract carcinoma *in situ*, an infusion of 40 mg bacillus Calmette-Guérin through each ureterostomy was performed once weekly for 5 times. Urine cytology of the left upper urinary tract became negative, with a recurrence-free survival of 4 months. On the other hand, the right upper urinary tract became temporarily negative but turned positive after 3 months.

Conclusion:

Bacillus Calmette-Guérin perfusion therapy *via* cutaneous ureterostomy is considered as one of the useful therapies for carcinoma *in situ* of the upper urinary tract. Furthermore, there are several factors to be discussed, including the treatment duration, dosage and secondary therapeutic options.

Keywords: Bacillus calmette-Guérin, Carcinoma *in situ*, Cutaneous ureterostomy, Radical cystectomy, Upper urinary tract, Magnetic resonance imaging.

Article History

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1. INTRODUCTION

The intravesical instillation of bacillus Calmette-Guérin (BCG) is an established therapy for carcinoma *in situ* (CIS) of the bladder [1 - 2]. The BCG perfusion therapy for CIS of the upper urinary tract (UUT) has largely been administered in a trial-and-error fashion. The standard treatment of UUT urothelial carcinoma (UC) is radical nephroureterectomy with bladder cuff excision [3]. However, nephron-sparing approaches are desired in patients who have risk factors, such as bilateral tumors, cardiovascular morbidity, and chronic renal failure [4,5]. For these cases and situations, BCG perfusion is expected to have a therapeutic effect on UC of UUT. There are two routes of administration; antegrade perfusion *via* nephrostomy and retrograde perfusion using a ureteric catheter or double-J ureteric stent [6 - 11]. To the best of our knowledge, there is no report of infusion BCG therapy *via* cutaneous ureterostomy. We tried to retrograde BCG perfusion

via cutaneous ureterostomy with a single-J ureteric catheter in patients with CIS of the UUT after radical cystectomy.

2. CASE PRESENTATION

A 72-year-old woman was referred to our department for evaluation and treatment of a bladder tumor detected by cystoscopy. She was diagnosed with muscle-invasive bladder urothelial carcinoma by Magnetic Resonance Imaging (MRI) and pathological examination (clinical classification; T3bN0M0). She underwent radical cystectomy with cutaneous ureterostomy (TOYODA method) reconstruction for the treatment of invasive bladder cancer after neoadjuvant chemotherapy (2 courses, gemcitabine 1000 mg/m² + cisplatin 70 mg/m²). The pathological diagnosis of the bladder specimen was CIS, and ureteral sections submitted twice during the operation were CIS too. This pathological result suggested the possibility of a residual tumor of the ureter. So, we have selected bilateral cutaneous ureterostomy as a urinary diversion for the next treatment of CIS in the UUT, if it remained. As a single course, we planned to inject a 40 mg dose of BCG (Immunobladder, Tokyo strains) with 50 ml saline (154mEq/L

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NaCl) into both sides of the UUT once weekly for a 6-week period. Our procedure was as follows: first, a small incision was made on the cranial side of the stoma pouch. Subsequently, Single-J catheters were pulled out and were connected to the BCG injection route for administration. The incision of the pouch was closed using Pean forceps to prevent contamination and to facilitate the retrieval of overflows through the stoma (Fig. 1). Continuous infusion of the BCG solution was performed in 1 hour through each single-J catheter from a drip-infusion container, which was placed 80 cm above the stoma. The solution which overflowed out of the stoma was collected into the stoma bag. BCG perfusion was started 1 month later after cystectomy. After the 5th administration, the patient complained of the bilateral knee joint pain and high-grade fever above 38°C and was referred to a neighborhood hospital. She was diagnosed with reactive arthritis and received first aid by drainage of the joint capsule; however, the situation did not improve as expected.



Fig. (1). BCG perfusion therapy performed for the treatment of upper urinary tract carcinoma *in situ*.

She was transferred to our hospital for the treatment of reactive arthritis and was initially administered prednisolone 30 mg/day. Her physical and laboratory findings were gradually getting better; therefore, the intake dose of steroids was reduced by 5 mg every week. Her condition was deemed stable, with continuous steroid therapy for over 3 months.

Due to severe reactive arthritis, she could not be subjected to BCG perfusion therapy anymore.

Urine cytology of the right and left UUT was class 3 and 2, respectively, at 3 weeks after the last BCG perfusion. After 6 weeks, both sides were negative.

After the confirmation of negative results, urine cytology of each UUT was checked every 4 weeks, with computed tomography conducted every 3 months. Three months later, the

cytology of the right UUT was positive. It was considered that there was CIS recurrence in the right UUT. Informed consent was obtained from the patient regarding this therapy and the report.

3. DISCUSSION

The BCG perfusion therapy for CIS of the bladder, which was first reported by Morales et al.² in 1976, has been widely performed as a standard treatment. For UUT CIS, BCG perfusion treatment was first reported by Herr¹ in 1985. Recently, several authors have mentioned the use of BCG for UUT CIS and drawn attention [12 - 17]. The response rate of this treatment for UUT CIS was reported to be 60%;⁵ Hayashida et al. described that the response rate after 1 course was 100% and the progression-free survival was 22.2 months [18]. Even though the long-term effect cannot be expected, BCG perfusion therapy is suggested for the patients who have risk factors for operation, such as single kidney, bilateral tumors, and cardiovascular morbidity.

As for perfusion methods, two types were considered: an antegrade approach through percutaneous nephrostomy and retrograde approach using single-J (ureteral catheter) or double-J stent. The antegrade approach is supposed to be effective because BCG attachment to cancer cells in the UUT is certain. Additionally, it can reduce bladder irritation symptoms. However, this approach is thought to be invasive and might cause the dissemination of cancer cells along the nephrostomy path [18]. The retrograde perfusion with a single-J stent can deliver BCG solution up to the renal pelvis but has a possibility of increased renal pelvic pressure. A similar method of using a double-J stent for creating vesicoureteral reflex is not certain for the BCG delivery into the UUT. Each of these methods has merits and demerits, and it is necessary to determine the method for each case. In our case, the patient underwent radical cystectomy with cutaneous ureterostomy due to invasive bladder cancer. Therefore, for the treatment of bilateral UUT CIS, retrograde perfusion was performed spontaneously, with a single-J stent for each UUT. Since the BCG injection was performed directly into the UUT, the dose was 40 mg in consideration of the appearance of side effects, and the administration schedule was set at weekly intervals according to BCG intravesical injection therapy. Our method of drip injection with catheters and a small-sized stoma pouch was developed by the medical staff in our hospital with some discussions. This method was thought to be feasible for the treatment and was considered safe from the viewpoint of infection prevention. BCG infusion therapy into the UUT is popularly known, that is why superior progression-free survival has not been shown for CIS treatment. However, it is considered to be an alternative because this therapy has been found to be effective for some patients. Of course, surgical treatment is considered if the above treatments have not been successful.

More investigation is needed on the optimal dose, injection speed, suitable pressure to obtain better clinical outcomes.

CONCLUSION

BCG perfusion therapy *via* cutaneous ureterostomy is

useful for UUT CIS, especially for bilateral cases. However, its therapeutic effect on CIS is thought to be limited; a strict follow-up of several years is needed.

LIST OF ABBREVIATIONS

BCG	=	Bacillus Calmette-Guérin
CIS	=	Carcinoma <i>In Situ</i>
MRI	=	Magnetic Resonance Imaging
UC	=	Urothelial Carcinoma
UUT	=	Upper Urinary Tract

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication of this case report.

STANDARDS OF REPORTING

CARE guidelines and methodology have been followed.

FUNDING

None.

CONFLICTS OF INTEREST

None of the authors has any conflicts of interest to disclose.

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None.

REFERENCES

- Herr HW, Pinsky CM, Whitmore WF Jr, Oettgen HF, Melamed MR. Effect of intravesical Bacillus Calmette-Guérin (BCG) on carcinoma *in situ* of the bladder. *Cancer* 1983; 51(7): 1323-6. [http://dx.doi.org/10.1002/1097-0142(19830401)51:7<1323::AID-CNCR2820510724>3.0.CO;2-2] [PMID: 6337700]
- Morales A, Eiding D, Bruce AW. Intracavitary Bacillus Calmette-Guérin in the treatment of superficial bladder tumors. *J Urol* 1976; 116(2): 180-3. [http://dx.doi.org/10.1016/S0022-5347(17)58737-6] [PMID: 820877]
- Rouprêt M, Babjuk M, Compérat E, *et al.* European guidelines on upper tract urothelial carcinomas: 2013 update. *Eur Urol* 2013; 63(6): 1059-71. [http://dx.doi.org/10.1016/j.eururo.2013.03.032] [PMID: 23540953]
- Giannarini G, Kessler TM, Birkhäuser FD, Thalmann GN, Studer UE. Antegrade perfusion with bacillus Calmette-Guérin in patients with non-muscle-invasive urothelial carcinoma of the upper urinary tract: who may benefit? *Eur Urol* 2011; 60(5): 955-60. [http://dx.doi.org/10.1016/j.eururo.2011.07.051] [PMID: 21807456]
- Balasubramanian A, Metcalfe MJ, Wagenheim G, *et al.* Salvage topical therapy for upper tract urothelial carcinoma. *World J Urol* 2018; 36(12): 2027-34. [http://dx.doi.org/10.1007/s00345-018-2349-9] [PMID: 29804202]
- Studer UE, Casanova G, Kraft R, Zingg EJ. Percutaneous bacillus Calmette-Guérin perfusion of the upper urinary tract for carcinoma *in situ*. *J Urol* 1989; 142(4): 975-7. [http://dx.doi.org/10.1016/S0022-5347(17)38957-7] [PMID: 2795755]
- Sharpe JR, Duffy G, Chin JL. Intrarenal bacillus Calmette-Guérin therapy for upper urinary tract carcinoma *in situ*. *J Urol* 1993; 149(3): 457-9. [http://dx.doi.org/10.1016/S0022-5347(17)36117-7] [PMID: 8437246]
- Schoenberg MP, van Arsdalen KN, Wein AJ. The management of transitional carcinoma in solitary renal units. *J Urol* 1987; 146: 700-3.
- Ramsey JC, Soloway MS. Instillation of bacillus Calmette-Guérin into the renal pelvis of a solitary kidney for the treatment of transitional cell carcinoma. *J Urol* 1990; 143(6): 1220-2. [http://dx.doi.org/10.1016/S0022-5347(17)40230-8] [PMID: 2342185]
- Herr HW. Durable response of a carcinoma *in situ* of the renal pelvis to topical bacillus Calmette-Guérin. *J Urol* 1985; 134: 531-2.
- Smith AD, Orihuella E, Crowley AR. Percutaneous management of renal pelvic tumors: A treatment option in selected cases. *J Urol* 1987; 137: 852-6.
- Nonomura N, Ono Y, Nozawa M, *et al.* Bacillus Calmette-Guérin perfusion therapy for the treatment of transitional cell carcinoma *in situ* of the upper urinary tract. *Eur Urol* 2000; 38(6): 701-4. [http://dx.doi.org/10.1159/000020365] [PMID: 11111187]
- Nishino Y, Yamamoto N, Kameda H, Takahashi Y, Deguchi T. Bacillus Calmette-Guérin instillation treatment for carcinoma *in situ* of the upper urinary tract. *BJU Int* 2000; 85(7): 799-801. [http://dx.doi.org/10.1046/j.1464-410x.2000.00610.x] [PMID: 10792155]
- Okubo K, Ichioka K, Terada N, Matsuta Y, Yoshimura K, Arai Y. Intrarenal bacillus Calmette-Guérin therapy for carcinoma *in situ* of the upper urinary tract: long-term follow-up and natural course in cases of failure. *BJU Int* 2001; 88(4): 343-7. [http://dx.doi.org/10.1046/j.1464-410x.2001.02297.x] [PMID: 11564018]
- Horiguchi H, Yoneyama T, Hatakeyama S, *et al.* Impact of bacillus Calmette-Guérin therapy of upper urinary tract carcinoma *in situ*: Comparison of oncological outcomes with radical nephroureterectomy. *Med Oncol* 2018; 35(4): 41. [http://dx.doi.org/10.1007/s12032-018-1102-y] [PMID: 29480348]
- Tomisaki I, Kubo T, Minato A, Fujimoto N. Efficacy and tolerability of bacillus calmette-guérin therapy as the first-line therapy for upper urinary tract carcinoma *in situ*. *Cancer Invest* 2018; 36(2): 152-7. [http://dx.doi.org/10.1080/07357907.2018.1430815] [PMID: 29393701]
- Foerster B, D'Andrea D, Abufaraj M, *et al.* Endocavitary treatment for upper tract urothelial carcinoma: A meta-analysis of the current literature. *Urol Oncol* 2019; 37(7): 430-6. [http://dx.doi.org/10.1016/j.urolonc.2019.02.004] [PMID: 30846387]
- Hayashida Y, Nomata K, Noguchi M, *et al.* Long-term effects of bacille Calmette-Guérin perfusion therapy for treatment of transitional cell carcinoma *in situ* of upper urinary tract. *Urology* 2004; 63(6): 1084-8. [http://dx.doi.org/10.1016/j.urology.2004.01.046] [PMID: 15183955]