BCG for Upper-Tract Transitional-Cell Carcinoma: Is It Safe in Patients with Renal Compromise?

SALEH BINSALEH, M.D., FRCSC, 1 KANISHKA SIRCAR, M.D., 2 MOSTAFA ELHILALI, M.D., 1 and MAURICE ANIDJAR, M.D. 1

ABSTRACT

We report three cases of end-stage renal failure necessitating hemodialysis subsequent to BCG administration for the treatment of upper-urinary tract transitional-cell carcinoma in patients with a solitary kidney, one with normal renal function and two with chronic renal failure prior to BCG instillation. We discuss treatment-related issues with pertinent literature review.

INTRODUCTION

Bacillus Calmette-Guerin (BCG) is an attenuated strain of Mycobacterium bovis that has stimulatory effects on immune responses. Since the report by Morales and associates in 1976, 1 several studies have demonstrated the efficacy of this agent for the prophylaxis of tumor recurrences and the therapy of superficial bladder carcinoma, especially carcinoma in situ of the bladder and the upper urinary tract.

Concerns about potential side effects related to the treatment of urinary-tract transitional-cell carcinoma (TCC) initially slowed the use of this agent. Thereafter, deeper insight into the causes and treatment of side effects related to BCG administration increased the interest in its use for urinary TCC. 2 To date, there are only a few reports that address the safety of this agent in patients with renal impairment. We report in three cases subsequently complicated by end-stage renal failure and dialysis after BCG administration for the treatment of superficial renal TCC.

CASE REPORTS

Case 1

A 79-year-old woman with right renal agenesis and a long history of superficial bladder TCC managed with multiple transurethral resections developed a filling defect in the lower calix of her solitary left kidney. Ureteroscopy and tumor biopsy followed by laser fulguration of the tumor was accomplished. The pathology report described a stage Ta grade 3 tumor. She developed a recurrence at the same site, so percutaneous resection of the tumor was done by an access through the lower pole, and simultaneous ureteroscopy and cystoscopy were both normal. The lesion again was Ta grade 3. Her serum creatinine concentration always remained within normal limits. A plan was created to administer BCG (OncoTICE strain; 150 mg in 250 mL of 0.9% saline) for six treatments. Each treatment was given through a 10F percutanous nephrostomy tube. Nephrostograms were obtained prior to each instillation and demonstrated free passage to the bladder. The tube was left closed between perfusions. The BCG perfusion was started only in the absence of microhematuria. The flask was placed 20 cm above the level of the kidney. A continuous flow of approximately 1 mL/min (12–20 drops/min) was maintained for 2 hours. After the perfusion was finished, the catheter was closed. These perfusions were repeated on a weekly basis for 6 weeks. No antibiotics were given at any time. The baseline creatinine value was normal prior to BCG treatment but began rising in slow increments to 364 μmol/L over a few weeks (normal 55–110 μmol/L). There was no obstruction of the upper tract demonstrated by the nephrogram. Nephrology evaluation was obtained, and work-up revealed no obvious prerenal or postrenal etiology. Other than BCG, she received no medications, and a presumption of renal insult likely related to the BCG administration was made.

Treatment was given for 2 months for presumptive BCG infection with isoniazid 300 mg (INH), rifampin 600 mg, and

1Division of Urology, Department of Surgery, Royal Victoria Hospital, McGill University, McGill University, Montréal, Québec, Canada.
2Department of Pathology, Montréal General Hospital, McGill University, Montréal, Quebec, Canada.
ethambutol 800 mg but with little change in the serum creatinine concentration. The patient had a tumor recurrence at the same site, and metastatic work-up (bone scan and CT) was negative. Nephroureterectomy was done, and ultimately patient underwent regular hemodialysis. The pathologist reported a high-grade papillary urothelial carcinoma invading the renal parenchyma (pT3), negative surgical margins, BCG-related changes (BCG granuloma with giant cells), and nonspecific nephritis in the uninvolved parenchyma (Fig. 1).

**Case 2**

A 71-year-old nonsmoking man with hypertension and chronic renal failure (baseline creatinine 200 μmol/L) had a long history of superficial urothelial tumor of the bladder and the upper tracts. He had undergone multiple transurethral resections of bladder tumors (stage T1 grade 2/3) over a 10-year period and at one stage received adjuvant BCG intravesical immunotherapy instillation with no reported side effects.

Three years prior to the current presentation, the patient had undergone laparoscopic right nephroureterectomy for renal pelvic tumor (pT2 grade 2/3). On subsequent follow-up, he was found to have left upper-tract high-grade urine cytology and a tumor in the left renal pelvis. This tumor was resected percutaneously (pT1 grade 1). The tumor recurred again <6 months later, so the decision was made to instill BCG through a left nephrostomy tube beginning 6 weeks after the last resection. His serum creatinine concentration at this time was 400 μmol/L. The same BCG protocol was used as in Case 1. Unblocked flow through the nephrostomy tube was ascertained before each instillation, and the tube was kept clamped after each instillation until the next dose was given. Three instillations were accomplished with no complications, but before the fourth one, the patient complained of increasing weakness, low appetite, and low urine output. Serum creatinine was assayed and found to be 770 μmol/L. At this point, a left nephrograms showed no obstruction to urine flow. The only medications he was taking were antihypertensive drugs, which he had used long term; the patient was on neither nephrotoxic medications nor drugs that increase BCG toxicity. A nephrology evaluation was performed, and a presumptive diagnosis of BCG-related nephritis was made. Anti-tuberculosis treatment was started (INH 300 mg, rifampin 600 mg, and pyridoxine 25 mg once daily). Hemodialysis was started. There was no improvement in urine output or serum creatinine noticed between dialysis sessions after 3 months of therapy. No recurrence of the upper-tract tumor has been seen.

**Case 3**

An 80-year-old hypertensive man presented initially with gross hematuria. Investigations confirmed bladder tumor for which a transurethral resection was done, yielding stage pTa grade 3 tumor. His creatinine concentration at this time was normal. Left nephroureterectomy was done a year later for a stage pTa grade 1 tumor in the left renal pelvis and upper ureter. Further superficial low-grade recurrences in the bladder were resected transurethrally.

Three years later, he developed recurrence of his disease in the solitary right kidney, and tumor resection done through an antegrade access. Pathologic examination of the resected tumor confirmed pT1 grade 3 disease. The serum creatinine concentration was stable around 250 μmol/L, since the time of nephroureterectomy. Further recurrences at the same site were managed by resections and antegrade BCG instillation through the right nephrostomy tube 2 weeks after the last resection (same BCG protocol as above). The patient tolerated three instillations before presenting with acute renal failure (serum creatinine 815 μmol/L) necessitating hemodialysis.

**FIG. 1.** Hematoxylin and eosin-stained sections of kidney in Case 1. (A) BCG granulomas in renal interstitium. (B) Higher magnification showing BCG granuloma with giant cells. (C) Chronic pyelonephritis changes.
There were no constitutional signs or symptoms other than weakness. Imaging studies confirmed residual tumor in the renal pelvis, with no evidence of obstruction to explain his renal failure. As the patient was quite sick, antituberculous treatment was not considered, and renal replacement therapy through hemodialysis was instituted. No improvement in renal function was achieved over 4 months of renal support. No surgery was attempted to treat the upper-tract tumor, as the patient’s clinical condition was not acceptable for surgery.

**DISCUSSION**

The treatment for noninvasive urothelial upper-urinary tract TCC is still controversial. Conservative treatment for such disease based on nephron-sparing surgery or endourologic treatment has gained more popularity over the last decade. This conservative approach is generally adopted for the treatment of well-differentiated monofocal tumors or patients with a solitary functioning kidney, bilateral disease, or significant renal impairment. Lee and colleagues evaluated their experience over 13 years with percutanous and open nephroureterectomy approaches for the management of TCC of the renal collecting system and concluded that the tumor grade is the most important prognostic indicator regardless of the surgical approach. Grade 3 tumors are more aggressive, so nephroureterectomy is warranted if the patient is a surgical candidate. The percutaneous approach for grade 1 and 2 disease has a disease-specific survival rate equivalent to that of nephroureterectomy and may be extended to patients with normal contralateral kidneys who are willing to abide by a strict and lengthy follow-up.

Recently, chemotherapeutic or immunotherapeutic intracavitary treatment of upper-tract superficial TCC has been proposed to prevent recurrence after tumor ablation (prophylaxis) or as an adjunct to an ablative procedure (therapy).

Fear of systemic toxicity was a major concern in the past limiting BCG use for this purpose, but better understanding of the side effects and the favorable results reported in the literature have led to wider application of this therapeutic approach. Mukamel and coworkers were the first to investigate this therapeutic approach experimentally. In pigs, they used the same infusion protocol employed for intracavitary BCG in humans, the right kidney receiving BCG and the left one being the control. Renal scan and histology comparison was performed during and at the end of the study. No damage to the structure or function of the kidney or the upper urinary tract was evident after 1 to 3 months. These findings were confirmed in a subsequent study in 14 patients with vesicoureteral reflux who were treated for bladder cancer with BCG instillation.

Bassi et al. reviewed 14 published studies up to 2001 covering BCG treatment of 119 renal units and found the most common side effect to be granulomatous renal involvement (7 patients). Irritative bladder symptoms were minimal and short lived. Other side effects include sepsis, gross hematuria, and ureteral stenosis. No renal failure or treatment-related death was reported. Thalmann and colleagues reported their long-term experience with BCG for upper-tract TCC in 37 patients (41 renal units) who were not eligible for surgery. Patients were followed for a median of 42 months. At the beginning of the trial, 19% of those patients had renal insufficiency. No alteration in renal function was reported except in one patient with established severe renal insufficiency, who subsequently required dialysis, and the conclusion was in favor of BCG for patients not amenable to conventional radical surgery to prevent them from requiring dialysis.

In our current series, two patients with a history of renal insufficiency and one with normal renal function but in a solitary kidney eventually suffered end-stage renal failure necessitating dialysis after treatment with BCG for their superficial upper-tract TCC. Their renal function has not improved on dialysis or discontinuation of BCG. They were using neither nephrotoxic medications nor medications that potentiate the toxicity of BCG. There was no evidence of renal obstruction, as demonstrated by serial nephrograms. The kidney pathology in the patient who underwent later nephroureterectomy demonstrated granulomatous and chronic pyelonephritis changes evidencing a BCG effect.

The presumptive mechanism for renal failure in these cases is the intense inflammatory changes in response to BCG, namely, interstitial nephritis, as reported in the one patient in whom histologic examination was possible. These changes require pathology confirmation, as signs and symptoms are not specific, and radiologic evaluation usually is normal.

Although only a few cases such as these have been reported, they should alert physicians dealing with this situation to consider other treatment modalities for patients with renal insufficiency or patients at risk of renal failure (e.g., those with a solitary kidney).

**CONCLUSIONS**

Although BCG is an effective agent for the prophylaxis and treatment of noninvasive TCC, especially carcinoma in situ, care should be taken in choosing this agent for intracavitary instillation in patients with compromised renal function or at risk of renal failure. The use of BCG with its potential advantages and dangers should be discussed with such patients and be evaluated carefully. This series is a limited observation and needs further large-scale study to confirm BCG safety in patients with impaired or compromised renal function.

**REFERENCES**


Abbreviations Used

BCG = Bacillus Calmette-Guerin; CT = computed tomography; TCC = transitional-cell carcinoma.