Risk of post-operative intravesical mitomycin C instillation following transurethral bladder tumor resection

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Bladder cancer is the fifth most common cancer in the Western world and is on the rise. Most patients present with superficial disease and are treated by transurethral resection of bladder tumor. More than half of these patients experience recurrence with about 20% progressing to muscle invasive disease. Intravesical chemotherapy has been shown to decrease the risk of recurrence of bladder cancer. Mitomycin C has emerged as a major agent for an immediate post-resection intravesical instillation. This article reviews the literature on the mode of action, rationale for immediate adjuvant treatment with mitomycin C and adverse effects associated with its use.

Key Words: mitomycin C, bladder cancer, adverse effects

Introduction

Transitional cell carcinoma of the bladder is the fifth most common cancer in the Western world. Most patients (70%-80%) with bladder cancer present with superficial disease (stages Ta, T1, carcinoma in situ). Transurethral resection (TURBT) is the treatment of choice for all visible low stage bladder tumors. After treatment with TURBT alone, 50%-70% of patients will recur with about 20% progressing to muscle invasive disease. Intravesical chemotherapy is used to treat recurrent TCC, T1 cancers, multifocal and high-grade tumors and CIS. There is no consensus whether patients with single, low-risk tumor should receive this form of treatment.[1] Multiple agents are available to treat superficial bladder cancer, including thiotepa, doxorubicin, adriamycin, BCG, interferon α, epirubicin, valrubicin, ethoglucid, and mitomycin C (MMC). Some of these agents are also used to decrease the rate of tumor cell implantation after TURBT.[2] Immediate post-operative intravesical instillation of a chemotherapeutic agent has been used to decrease the risk of recurrence.[2] The purpose of this review is to alert the urology community about the potential detrimental side effects of adjuvant MMC intravesical therapy after TUR. Literature is scarce with report of serious complications attributed to MMC. We feel that this is an underreported problem which deserves further study.

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Mode of action of MMC and its therapeutic options

MMC is a tumor antibiotic which also exhibits carcinogenicity in the mouse and rat. It is not known to be a carcinogen in humans.[3] The antitumor and carcinogenic activity appears to be related to its interaction with DNA. MMC is reduced by NADPH cytochrome P-450 reductase, xanthine oxidase, or DT diaphorase to MMC hydroquinone, which is spontaneously converted to leuco-aziridinomitosene,

an alkylator of DNA.[4-7] In vivo treatment with MMC results in the formation of inter- and intrastrand cross-linking of DNA. Activated MMC covalently binds to the N2 of deoxyguanosin residues of DNA.[8] MMC probably cross-links protein by several different mechanisms. MMC hydroquinone is detoxified by glutathione S transferase.[9] Several peroxidases oxidize MMC hydroquinone to MMC and block DNA cross-linking to varying degrees.[7]

The concept of intravesical chemotherapy instillation after transurethral resection is not new, and has been used in many centers in light of reports indicating decreased recurrence rates of bladder cancer. MMC has become the agent of choice for an immediate post-operative instillation.[10] It is usually given in the recovery room through the catheter in 1 of 2 doses (20 mg MMC in 40 ml of water or 40 mg MMC in 40 ml of water). Patient is asked to rotate the position every half hour for a total of 2 hours, after which the bladder is drained. Alternatively, MMC has also been used as a definitive treatment of superficial TCC of the bladder. Like BCG therapy, it is given weekly for a 6-week course. However, studies failed to show the superiority of MMC over BCG therapy.[11]

Rationale for immediate post-TURBT instillation of MMC

In an elegant animal study, Weldon and Soloway demonstrated that an inflamed urothelium is significantly more susceptible to tumor implantation than normal bladder mucosa.[12] They produced an inflammatory response in murine bladder by using N-methyl-N-nitrosourea. Tumor cell suspension was subsequently instilled intravesically. Tumor cell implantation occurred in only 13% of controls versus 60% of mice with inflamed urothelial surface. In the follow-up study, Soloway and Martino, showed that systemic cyclophosphamide and intravesical epipodophyllotoxin significantly reduced the incidence of tumor cell implantation.[13] The authors concluded that intravesical chemotherapy prevents tumor recurrence by inhibiting implantation of free-floating cancer cells following resection.

Although the majority of patients with bladder cancer present with superficial tumors, 40%-80% recur after TUR.[14,15] After transurethral resection, immediate instillation of mitomycin C into the bladder has been suggested to decrease the rate of recurrence.[1,16-19] Some have recommended immediate instillation of MMC or epirubicin in low risk patients with superficial bladder cancer.[20]

Tolley and coworkers reported the effect of perioperative intravesical MMC on recurrence rates of superficial bladder cancer.[17] After a median follow-up of 7 years, the authors noted a 15% 5-year decrease risk of recurrence with single MMC instillation post-operatively. Interestingly, they also note several patients with delayed healing at the resection site. Similarly, Solsona et al, in a prospective randomized controlled trial, noted a significantly increased recurrence-free interval in the MMC treated group and decreased tumors per year at 24 months.[16] However, long-term follow-up revealed no statistically significant differences between the MMC treated group and controls.

A meta-analysis of seven randomized clinical trials comparing TUR alone to TUR plus an immediate instillation of a chemotherapeutic agent showed a 36.7% recurrence rate in the chemotherapy group compared to 48.4% in the "TUR alone" group (3.4 years median follow-up).[1] In addition, a recurrence rate of 65.2% was noted in patients with multiple tumors treated by TUR plus chemotherapy. In comparison, only 35.8% of patients with single tumor had a recurrence. These data suggest that one instillation of chemotherapy after TUR in patients with multiple tumors may not be sufficient to control the disease. Furthermore, none of the studies have shown a beneficial effect of intravesical chemotherapy on tumor stage progression.

Adverse effects of intravesical MMC

As soon as MMC took on a dominant role as an intravesical chemotherapeutic agent, reports of associated complications started to appear in the literature. Nissenkorn and colleagues reported minor side effects of intravesical MMC definitive therapy in 7 of 29 patients.[21] These included moderate cystitis and palmar desquamation with or without generalized rash. Bracken and coworkers described two patients whose biopsy site failed to heal after weekly intravesical instillations of MMC.[22] Drago et al, reported a patient who developed bladder wall calcification at the resection site after definitive therapy with MMC.[23] Follow-up cystoscopies demonstrated unchanged areas of calcification and urine cytologies remained negative. In an editorial comment following the case report, Soloway pointed out that this is a fairly known complication of the MMC, and urine cytologies are all that is needed to determine if the viable tumor still exists. Resection of the area should be avoided due to the high risk of perforation.[24]

Doherty and associates studied 12 patients who had undergone radical cystectomy for muscle invasive

TCC.[25] Six patients received intravesical chemotherapy (epirubicin in 5, MMC in 1) after TURBT before pathological staging had been completed. Five of six patients had extensive necrosis of the bladder wall and perivesical fat, in at least two patients, necrosis was widespread. None of the six patients who did not receive intravesical chemotherapy experienced such complications. The cystectomies were technically more challenging given the complications of intravesical chemotherapy, and in two cases transmural necrosis may have contributed to the extravesical tumor spread.

Recently, several groups described more serious complications associated with immediate instillation of intravesical MMC following TUR. Cliff and co-authors reported a case of a 62 year old male who received 40 mg MMC instillation 24 hours after TURBT.[26] Over the course of a month he developed severe groin and abdominal pain. Cystoscopy 9 weeks later revealed an ulcer at the resection site. Biopsy revealed necrosis and inflammation. CT scan 19 weeks after surgery showed a persistent defect in the bladder wall with abnormal perivesical enhancement. Complete re-epithilialization of the ulcer was not evident until 18 months post-operatively. Nieuwenhuijzen and colleagues recently reported the case of a 53 year old male who received immediate instillation of 40 mg MMC after TURBT for superficial TCC.[27] This patient developed pelvic pain and a cystogram 2 weeks post-operatively revealed extravasation of contrast. Conservative management with a catheter failed to result in closure of the defect. Biopsies of the area did not reveal malignancy. Open surgical repair of the bladder perforation was done and perivesical and rectal fat necrosis debridement was performed. Cultures of purulent material revealed *E. Coli*. Final pathologic examination showed necrosis and inflammation.

Retrospective review of our institutional experience identified three patients incurring complications due to immediate instillation and 6-week adjuvant MMC treatment. Two patients developed non-healing ulcers at the site of resection. One patient, a 71 year old male, was diagnosed with grade 3 non-invasive TCC of the bladder. The tumor was resected and the bladder treated with a definitive MMC therapy. Patient developed a recurrence for which another TURBT was performed with immediate adjuvant MMC instillation and subsequent 6-week course of MMC. Shortly thereafter, patient complained of lower abdominal pain and was discovered to have a bladder perforation which failed conservative management. Cystoscopy demonstrated inflamed urothelium and widespread bladder wall calcifications. Repeat biopsies revealed necrosis and inflammation, but no evidence of residual carcinoma. This patient eventually underwent radical cystectomy which revealed extensive necrosis and chronic inflammation without a residual transitional cell carcinoma.

Histology and proposed mechanisms of the adverse effect of MMC on the bladder

The histological examination reveals morphology which is marked by features suggesting a chronic inflammatory process which overlaps interstitial cystitis, probably representing a nonspecific stereotypic pattern of injury and response, Figure 1a-d. These features include necrosis, edema, acute and subacute inflammation with prominence of eosinophils, granulation tissue and fibrosis, chronic inflammatory elements including lymphocytes and plasma cells, and calcification.

Histological resemblance to chronic cystitis may suggest a common mechanism of injury to the bladder by the MMC and the inflammatory disease. The presence of numerous lymphocytes, plasma cells and other factors of inflammatory response support this theory.

Immune complexes are likely formed by MMC cross-linking DNA and proteins. Therefore, a severe

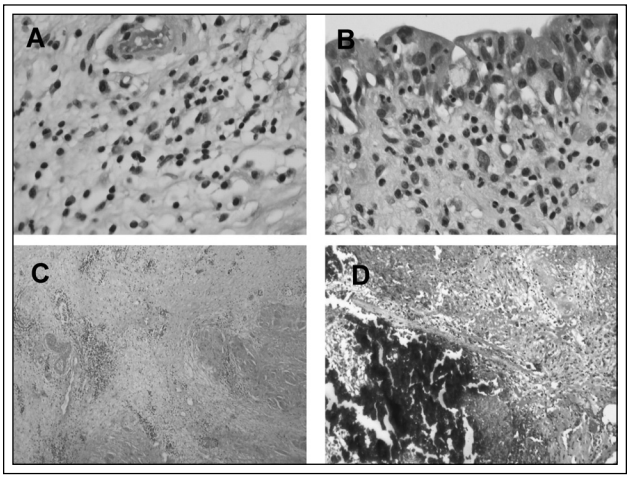

Figure 1. (a) Lymphocytes, plasma cells and eosinophils seen within bladder wall (40x magnification); (b) Intense inflammation with numerous eosinophils (40x magnification); (c) Muscle with fibrosis and interspersed pockets of inflammation, as well as edema and collagenization in the bladder wall (10x magnification); (d) Intense inflammation of the detrusor muscle, with areas of marked fibrosis, necrosis, and calcification (10x magnification).

autoimmune reaction may be responsible for the clinical picture of a non-healing ulcer in the bladder after tumor resection and immediate MMC instillation. The isolation of bacteria from the perivesical tissue in one report further complicates the picture.[27] It is not known whether the presence of microbial elements is a cause or a consequence of the clinical scenario described.

Conclusion

MMC is a useful agent for preventing a recurrence of TCC, however, it has a potential to produce a severe adverse reaction, albeit in a relatively small number of patients. MMC in the post-operative period may impede wound healing, resulting in chronic ulceration and perforation in severe cases. The urologic community should be aware of this side effect of MMC and factor this in the decision to proceed with chemotherapeutic option. Mechanisms responsible for the failure of the bladder to heal appropriately after a tumor resection have not been studied. Further research should identify the causes and possible preventative strategies to avoid this serious complication of MMC. □

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