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Therapeutic Utilization of Mitomycin C in Urological Conditions: Systematic Review of the Literature

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Abstract

Introduction: Mitomycin C offers a wide range of potential clinical uses in various disciplines, including urological diseases. As experimentally proven the effect of mitomycin C can be partly explained by its antifibrotic properties exerted on different target organs as well as its anticarcinogenic properties. We systematically reviewed the clinical applications of mitomycin C in the urological literature and comment on its safety, efficacy and long-term outcomes.

Methods: We searched the MEDLINE® database, Cochrane Library® Central Search and Web of Science™ using the search terms mitomycin C and clinical applications. Peer reviewed clinical, experimental and review articles published in the English language that included mitomycin C and urological conditions were identified and screened between 2000 and 2014.

Results: Our search resulted in 13 peer reviewed published articles that fit our criteria, including 2 randomized, controlled trials, 2 prospective studies, 3 retrospective studies, 1 meta-analysis, 3 reviews and 2 in vitro studies. The majority of studies detailed the clinical use of mitomycin C in various urological conditions. Information was extracted from studies that discussed the safety, efficacy and long-term outcomes of mitomycin C across each urological disease.

Conclusions: This systematic review details the different therapeutic applications of mitomycin C and comments on its safety, efficacy and long-term outcomes in urological diseases and conditions. This review also provides a useful guide for urologists to become familiar with the potential therapeutic roles of mitomycin C in the treatment of different urological diseases.

Key Words: urethra, urinary bladder neoplasms, mitomycin, anticarcinogenic agents, urological agents

Abbreviations and Acronyms

BNC = bladder neck contracture

MMC = mitomycin C

NMIBC = nonmuscle invasive bladder cancer

TUR = transurethral resection

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Traditionally it is well known that MMC, an antibiotic isolated from the broth of Streptomyces caespitosus, acts as a noncell cycle specific DNA alkylating agent that engages in cross-linking guanine-guanine nucleotides to prevent DNA synthesis and subsequent cell death.[1,2] In particular, MMC inhibits the synthesis of certain extracellular matrix proteins, especially collagen and fibronectin. Additionally, MMC has the important function of inhibiting fibroblast proliferation when treated tissue is exposed to MMC at concentration of 0.04 mg/ml for 4 minutes, resulting in decreased fibroblast proliferation.[2] MMC has a relatively large molecular weight (334 kDa), which prevents relevant systemic uptake. Nevertheless, side effects can also manifest, such as anemia, contact dermatitis, hair loss, fatigue, mouth sores and chemical cystitis as well as certain carcinogenic effects.

MMC was first approved to treat a wide spectrum of oncologic conditions, including bladder carcinoma in 1974.[3] The contemporary literature shows the important role of MMC in the treatment of nonmalignant conditions such as urethral stricture and recurrent or recalcitrant BNC.[4,5] In this systematic review we analyzed and summarized the various therapeutic uses of MMC in malignant and nonmalignant urological conditions, and comment on the safety, efficacy and long-term outcomes of MMC.

Methods

A detailed, comprehensive literature review was performed to identify all published peer reviewed articles in the English language describing the use of MMC as treatments for various conditions of urological diseases during the 14-year period 2000 to 2014. The search was done via the MEDLINE database, Cochrane Library Central Search and Web of Science. Initial search terms were MMC and therapeutic applications. Search results were screened for appropriate studies with particular emphasis placed on clinical and experimental studies as well as review articles. Referenced articles were screened to maximize review and inclusion of pertinent data. While English language text was not a specific search parameter, only English language publications were considered. All collected relevant studies were carefully examined to extract relevant data pertaining to the proposed therapeutic application of MMC for urological diseases.

Results

Systematic Review Evidence Synthesis

Our search resulted in 13 peer reviewed published articles that fit our criteria. There were 2 randomized controlled trials, 2 prospective studies, 3 retrospective studies, 1 meta-analysis, 3 review articles and 2 in vitro studies. The majority of studies detailed the perioperative and therapeutic use of MMC for various urological conditions. Information extracted from these studies discussed the safety, efficacy and long-term outcomes of MMC across each urological disease. The table (http://urologypracticejournal.com/) shows the main published studies of MMC for urological diseases, therapeutic applications, followups and complications.

MMC for Malignant Urological Disease in Perioperative Setting

Off label use of MMC to treat low risk (TaG1, primary, solitary and/or less than 3 cm tumors) to intermediate risk (Ta/T1, G1-2, multifocal and/or recurrent tumors) bladder carcinoma was first suggested in 1985 by Doll et al.[6] NMIBC represents about 75% of all bladder carcinomas. Cancer can recur within 2 years in 53% of patients with superficial urothelial bladder cancer who undergo TUR of bladder tumors. Studies have shown that intravesical MMC treatment can reduce overall bladder tumor recurrence by about 30% in certain patients with recurrent NIMBC.[7,8] In summary, the clinical indications for MMC in the treatment of bladder carcinoma are to 1) eradicate residual papillary bladder tumor after incomplete surgical resection and 2) decrease bladder tumor recurrence in completely resected tumors.

Recent randomized studies have demonstrated efficacious methods to administer MMC intravesically during the treatment of NMIBC, such as chemohyperthermia or EMDA (electromotive drug administration).[9,10] Additionally, different pharmacokinetic optimization regimens have been previously proposed and found to potentially increase the efficacy of MMC as treatment of NMIBC, including an increased MMC concentration (40 mg in 20cc), urine alkalization (pH greater than 6.0) with 1.3 gm sodium bicarbonate, dehydration and an increased intravesical dwell time of up to 2 hours.[3,11]

Different intravesical MMC regimens have been investigated to treat recurrent bladder carcinoma. Colombo et al studied 2 induction preoperative MMC regimens in a randomized, controlled trial in patients with low risk urothelial bladder carcinoma, including once weekly MMC for 6 weeks vs 3 times weekly for 2 weeks, each before TUR. The group concluded that complete responses were significantly more frequent in the triweekly MMC group compared with the once weekly MMC group (70% vs 44%, $p = 0.04$).[7]

A single postoperative intravesical MMC regimen was extensively examined by Sylvester et al.[12] In this meta-analysis a total of 1,476 patients were included from 7 large clinical trials with a median followup of 3.4 years. The study shows that the bladder tumor recurrence rate was