Administration of Mycobacterium phlei cell wall-nucleic acid complex in the immediate postoperative period for the treatment of non-muscle-invasive bladder cancer

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Abstract

Introduction: This review sought to investigate the safety of intravesical administration of Mycobacterium phlei cell wall-nucleic acid (MCNA) in the immediate postoperative period after biopsy/resection for non-muscle-invasive bladder cancer (NMIBC).

Methods: Patients with NMIBC who failed bacillus Calmette-Guérin (BCG) therapy and at high risk of recurrence and progression participated in this study. Treatment involved an induction phase of six weeks and maintenance of three weekly instillations every six months for two years. Biopsies were mandatory at six months and resections/biopsies as indicated. Of the 129 patients enrolled, 18 (14%) received one or more instillations of MCNA within 24 hours of an endoscopic procedure for a total of 32 instillations.

Results: Fourteen patients (78%) received MCNA in the immediate postoperative period. Two (11%) received treatment the day after surgery, but a second treatment immediately after a transurethral resection of the bladder tumour (TURBT). The remaining two patients received an instillation each the day after surgery. Adverse events (AEs) occurred in 31.3% of those treated immediately after the procedure; they were mild, limited to the lower urinary tract, and not drug-related. Only one patient experienced systemic symptoms of moderate severity. None of the AEs resulted in postponement of treatment. There were no AEs among those receiving MCNA the day after surgery.

Conclusions: The dual mechanism of action of MCNA suggests that early treatment would take advantage of its chemotherapeutic (pro-apoptotic) activity. Concerns about early administration due to the presence of live bacteria are circumvented with this sterile preparation. These preliminary results warrant further investigation to confirm the safety of perioperative administration of MCNA.

Introduction

Limited progress has occurred in the last three decades in the treatment of high-risk non-muscle invasive bladder cancer (NMIBC). Intravesical administration of cytotoxic drugs (most commonly mitomycin C and epirubicin)[1] or bacillus Calmette-Guérin (BCG)[2] are generally recognized as the most active agents against these neoplasms. Evidence has been presented indicating that the efficacy of chemotherapy is enhanced when the drug is instilled immediately following endoscopic ablation of a bladder tumour. On the other hand, administration of BCG, a live and pathogenic micro-organism, is absolutely contraindicated in the postoperative period in the presence of a disrupted urothelium that may permit systemic spread of the micro-organism and development of sepsis.[3]

Mycobacterium phlei cell wall-nucleic acid complex (MCNA) suspension originates from the non-pathogenic Mycobacterium phlei and contains cell wall fragments composed primarily of carbohydrates, peptides, and lipids, to which nucleic acid oligomeric fragments are complexed. MCNA has been reported to exhibit a dual mechanism of action, displaying both indirect immunomodulatory (BCG-like) activity[4] and direct chemotherapeutic effects (inhibition of proliferation, cell cycle arrest, and apoptosis)[4,5] (Fig. 1). If the administration of MCNA immediately following resection of bladder tumours or biopsies proves to be safe, its perioperative use is worth investigating in order to enhance its anticancer efficacy by exploiting its indirect mode of action.

The efficacy and overall safety of MCNA in patients failing BCG treatment has been recently published.[6] Herein, we report on a retrospective subset analysis focusing exclusively on the tolerance and adverse effects reported in those patients in whom intravesical instillation of MCNA took place during the immediate postoperative period in an effort to make a case for immediate MCNA intravesical administration and not specifically addressed in the original protocol.

MCNA is formulated in water for injection and terminally sterilized, and does not require special handling measures other than usual aseptic techniques during intravesical administration. These characteristics of MCNA indicate

that the specific safety and handling concerns existing with BCG due to its potential for proliferation, dissemination, and sepsis are not a significant concern with MCNA.

Methods

Details of the study, registered on ClinicalTrials.gov (NCT00406068), have been published.[6] Briefly, the trial enrolled patients with NMIBC who had failed prior BCG therapy and were at a high risk of recurrence and progression to muscle-invasive or metastatic disease. Treatment encompassed an induction phase of weekly intravesical administration of MCNA (8 mg [8 mL] in 42 mL of sterile water for injection) for six weeks, followed by a maintenance phase of three weekly instillations at three, six, 12, 18, and 24 months. Cystoscopic examinations and urine cytologies were performed every three months. Biopsies were mandatory at six months and resections/biopsies were carried out when indicated for cause. Therefore, these surgical procedures would coincide with intravesical treatments occurring at three, six, 12, 18, and 24 months, as shown by the grey arrows on Fig. 1.

The decision to administer MCNA in the immediate (same day or day after) postoperative period following biopsy/resection was left at the discretion of the investigator. Incidence of adverse events (AEs), including severity, seriousness, and the possible causal relationship to MCNA administration were recorded. All sites received institutional review board approval and all participants provided written informed consent.

Results

Timing of MCNA after TURBT or biopsy

Of the 129 patients participating in the trial, 18 (14%) received one or more intravesical instillations of MCNA within 24–48 hours of the endoscopic procedure, for a total of 32 instillations. As illustrated in Fig. 2, the large majority (14 or 78%) of patients receive MCNA the same day of the surgery. Two (11%) received one treatment the day after surgery, but a second dose of MCNA was administered immediately after a subsequent transurethral resection of the bladder tumour (TURBT). The remaining two patients were given an instillation each, the day after surgery. Also shown in Fig. 2, six patients (33%) had a single immediate treatment, 10 (56%) had two treatments, and two (11%) had three perioperative instillations. In other words, 16 of 129 patients (12%) received a total of 28 instillations in the immediate postoperative period, while four (3%) were given a total of four instillations the day after the procedure. Included in this latter group are the two patients who had both an instillation the day after surgery, but a subsequent instillation on the same day of the operation.

Safety of MCNA immediately after TURBT or biopsy

Although the purpose of the review was to determine the tolerability of administering a mycobacterial product in the presence of an iatrogenically disrupted bladder mucosa, we recognize that the area of injured epithelium may be relevant in assessing safety. Table 1 shows the breakdown of the number of biopsies/TURs. Interestingly, all the AEs were

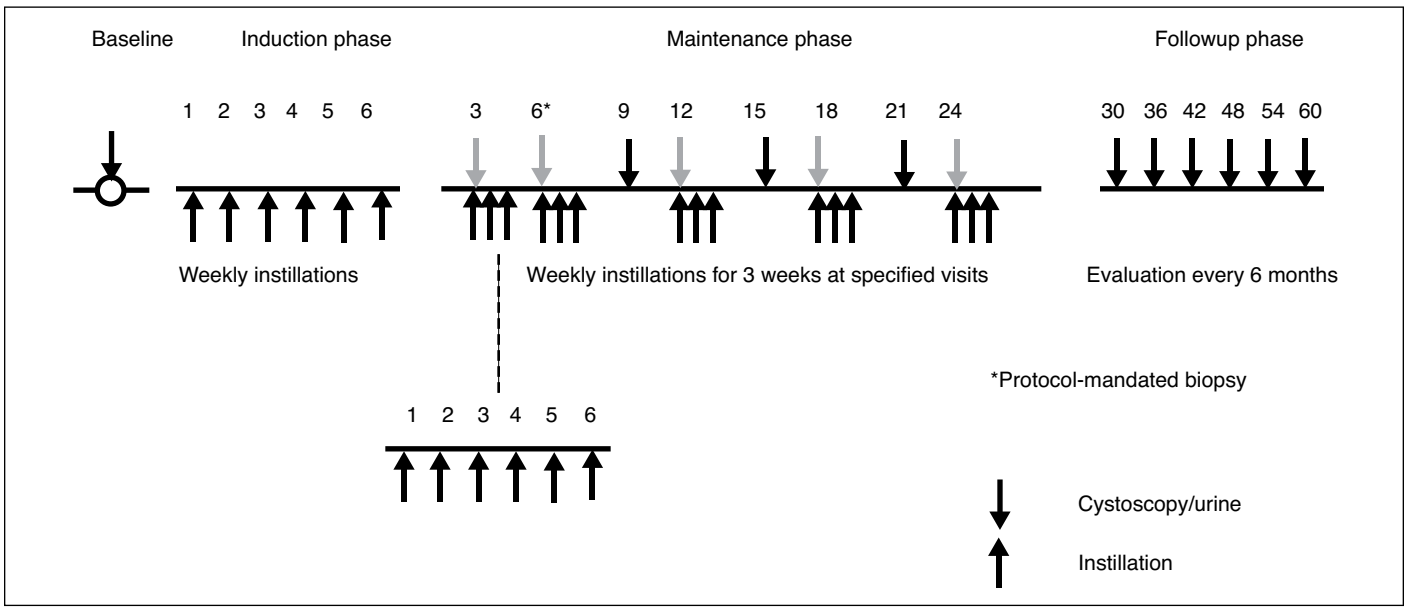

Fig. 1. Treatment and evaluation schedule.

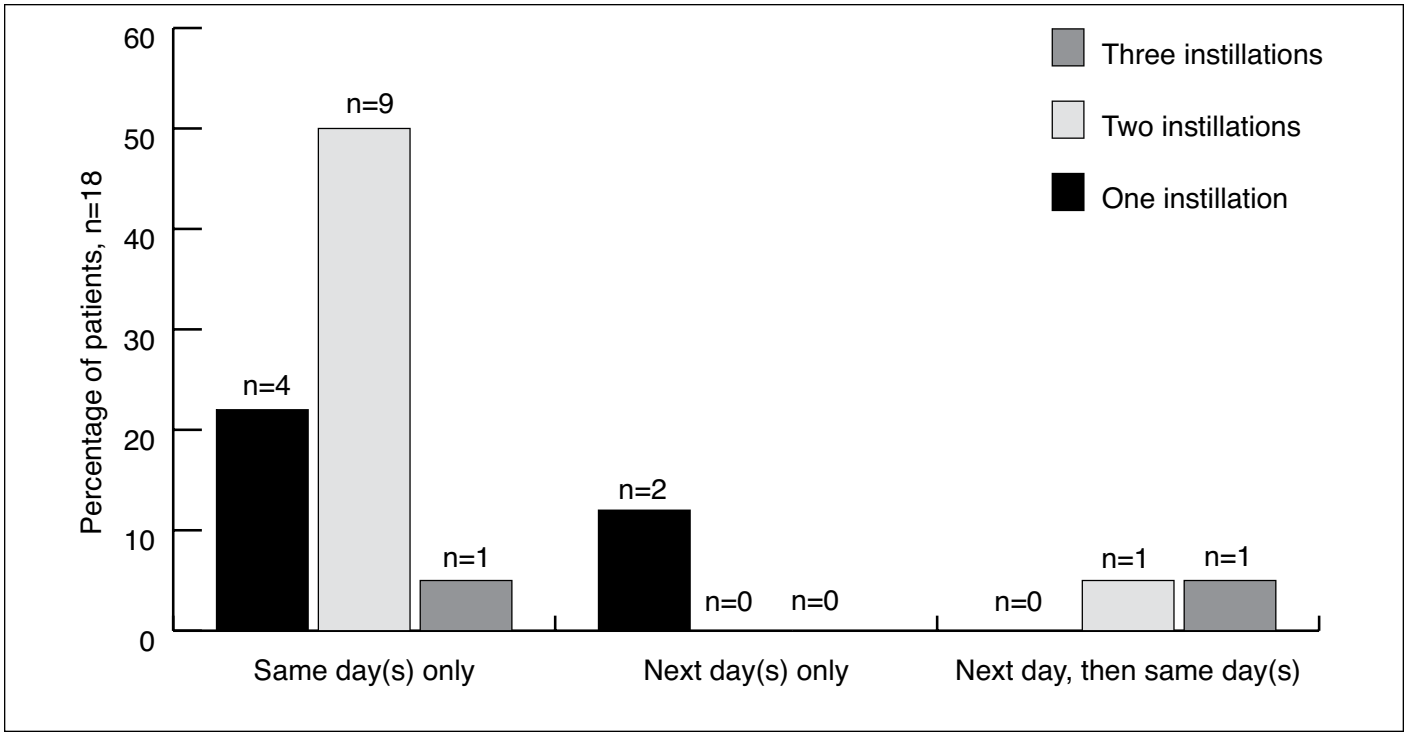

Fig. 2. Timing and number of instillations of Mycobacterium phlei cell wall-nucleic acid following transurethral resection of the bladder tumour or biopsies.

noted in those having biopsies.

Thirty-two MCNA instillations were given to this cohort of 18 patients treated in the perioperative period. Of the 16 patients who received MCNA immediately after surgery, five (31.3%) experienced AEs following five out of 28 (18%) instillations. Four of these experienced lower urinary tract symptoms of mild to moderate severity, but judged not to be related to the drug. The other patient reported systemic symptoms (rigour, headache, nausea) of moderate severity that were possibly related to MCNA. Three of the five patients subsequently received an instillation on the days of surgery without experiencing any AEs. None of the AEs resulted in delays of the scheduled treatments.

Of the four patients who received MCNA the day after the surgical endoscopic procedure, none experienced any AEs.

Two patients reported multiple AEs on the day of admin-

Table 1. Number of biopsies or TURBTs

No. of cold-cup biopsies	No. of perioperative instillations of MCNA
1	10
2	5
3	1
4	5
6	3
Unknown	1
No. of areas resected (TURBTs)	**No. of perioperative instillations of MCNA**
1	4
2	1
3	2

MCNA: Mycobacterium phlei cell wall-nucleic acid; TURBT: transurethral resection of the bladder tumour.

Table 2. Incidence and type of adverse events recorded when instillation took place the same day as the endoscopic procedure

	Patients with an AE on the day of administration, n (%) (n=16 patients)	Instillations associated with an AE on the day of administration, n (%) (n=28 instillations)
Timing of MCNA administration		
Same day as surgery	5 (31.3)	5 (17.9)
Type of AE	2 (12.5)	2 (7.1)
Hematuria	2 (12.5)	2 (7.1)
Urinary frequency	1 (6.3)	1 (3.6)
Dysuria	1 (6.3)	1 (3.6)
Suprapubic cramps	1 (6.3)	1 (3.6)
Headache	1 (6.3)	1 (3.6)
Nausea	1 (6.3)	1 (3.6)
Rigour	1 (6.3)	1 (3.6)
More than 1 AE reported*	2 (12.5)	2 (7.1)

AE: adverse event; MCNA: Mycobacterium phlei cell wall-nucleic acid.
*2 patients reported multiple AEs on the day of administration (patient 1: rigour, nausea, headache; patient 2: urinary frequency, suprapubic cramps, dysuria) after a single instillation.

istration; one patient experienced rigour, nausea, and headache, while another experienced urinary frequency, suprapubic cramps, and dysuria after a single instillation. The latter patient had received previously an instillation the same day as a TURBT with no AEs reported. A summary of AEs is shown in Table 2.

Discussion

The option to administer MCNA in the immediate postoperative period is attractive not only for the convenience to the patient (to avoid an extra visit and catheterization), but more importantly, because the purported chemotherapeutic-like mechanism of action of the composition would add to its immunological efficacy if given at the time when the tumour load is smallest and the potential for malignant cell-seeding is most likely. The contraindication for use of a mycobacterial product before healing of the bladder mucosa has been rooted among clinicians using BCG for the last few decades. Therefore, it is important to emphasize that MCNA does not have the same potential for severe adverse reactions. This experience supports such a notion. The fact that live Mycobacterium phlei, the source of MCNA, is ubiquitous in nature and non-pathogenic to mammals (including humans) offers a significant contrast with the detrimental potential of BCG. In addition, the absence of whole organisms in the suspension (only cell walls complexed with bacterial nucleic acids) bodes well for its safety.

The MCNA formulation used in this study has evolved from those used in the early studies mentioned above and on experimental observations.[4,7] This product was improved from the emulsion compositions: specifically, growth media is fully synthetic and all animal products and extracts, as well as chemicals (phenol and urea) and enzymes (trypsin and pronase) were eliminated from the manufacturing process. A terminal sterilization step was also introduced in the production of MCNA suspension. All these features would suggest a compound with enhanced safety for use in the presence of a fresh surgical injury to the vesical mucosa.[8]

The importance of early treatment following endoscopic surgery (TURBT or biopsy) for NMIBC is well-recognized with the use of cytotoxic drugs, particularly for low-risk tumours (primary, solitary, low-grade NMIBC). Whether the early administration of BCG may enhance its therapeutic efficacy remains a moot point due to the prohibitive risk of severe complications when the bacterium is administered intravesically in the presence of a recently compromised vesical urothelium. In the case of MCNA, with its postulated dual mechanism of action,[9] it would be relevant to determine whether its early administration exhibits a better antineoplastic activity for intermediate- and high-risk NMIBC.

The American Urological Association[10] and the European Association of Urology[11] indicate that there is high-quality evidence for a single perioperative treatment and it is recommended for all patients following resection of NMIBC. There is also good-quality evidence indicating that the timing of the instillation is important because the efficacy significantly decreases if given beyond 24 hours after TURBT.[12] It should be emphasized that the beneficial effect of perioperative intravesical administration of chemotherapeutic drugs is largely limited to low-grade tumours, while our trial was specifically designed for high-grade and recalcitrant cancers.

The main objective of this review was to assess the safety of MCNA when administered in the presence of a disrupted bladder epithelium. The AEs were all mild to moderate in severity, easily manageable, self-limiting, and did not require interruption of treatment. Studies to conclusively determine the safety of immediate postoperative intravesical delivery of MCNA would be required, as well as determination of a better outcome with the use of this agent as it has been shown for cytotoxic drugs.

The retrospective nature of the study represents a shortcoming in the interpretation of our results. A more significant drawback resides in the limited number of immediate postoperative instillations (32) that constitutes an encouraging, but still inconclusive experience. However, the excellent tolerance of MCNA under these circumstances provides comfort as to its safety and the basis for further investigation to determine whether MCNA can be administered in the perioperative setting to prevent re-implantation of tumour cells and, potentially, reduce the rate of recurrences.

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References

1. Brausi MA. Challenging the EAU guidelines on non-muscle-invasive bladder cancer (NMIBC): Single instillation of chemotherapy after transurethral resection of NMIBC and chemotherapy vs. bacillus Calmette-Guérin in the treatment of intermediate-risk tumours. *Eur Urol* 2010;Suppl.9:406-10. http://dx.doi.org/10.1016/j.eursup.2010.02.002
2. Sylvester R, van der Meijden APM, Lamm DL. Intravesical bacillus Calmette-Guérin reduces the risk of progression in patients with superficial bladder cancer: A meta-analysis of the published results of randomized clinical trials. *J Urol* 2002;168:1964-70. http://dx.doi.org/10.1016/S0022-5347(05)64273-5
3. Lamm D L, van der Meijden AP, Morales A, et al. Incidence and treatment of complications of bacillus Calmette-Guérin intravesical therapy in superficial bladder cancer. *J Urol* 1992;147:596.
4. Reader S, Ménard S, Filion B, et al. Pro-apoptotic and immunomodulatory activity of a mycobacterial cell wall-DNA complex towards LNCaP prostate cancer cells. *Prostate* 2001;49:155-65. http://dx.doi.org/10.1002/pros.1130
5. Filion MC, Lépicier P, Morales A, et al. Mycobaterium phlei cell wall complex directly induces apoptosis in human bladder cancer cells. *Brit J Cancer* 1999;79:229-35. http://dx.doi.org/10.1038/sj.bjc.6690038
6. Morales A, Herr H, Steinberg G, et al. Efficacy and safety of MCNA in patients with non-muscle-invasive bladder cancer at high risk for recurrence and progression after failed treatment with bacillus Calmette-Guérin. *J Urol* 2015;193:1135-43. http://dx.doi.org/10.1016/j.juro.2014.09.109

7. Filion MC, Lepecier P, Morales A, et al. Mycobacterium phlei cell wall complex directly induces apoptosis in human bladder cancer cells. *Brit J Cancer* 1999:79:229-35. http://dx.doi.org/10.1038/sj.bjc.6690038
8. Morales A, Cohen Z. Mycobacterium phlei cell wall-nucleic acid complex in the treatment of non-muscle-invasive bladder cancer unresponsive to bacillus Calmette-Guérin. *Exp Op Biol Ther* 2016;18:273-83 http://dx.doi.org/10.1517/14712598.2016.1134483
9. Fillon MC, Phillips NC. Therapeutic potential of mycobacterial cell wall-DNA complexes. *Expert Opin Investig Drugs* 2001;10:2157-65. http://dx.doi.org/10.1517/13543784.10.12.2157
10. Hall HM, Chang SS, Dalbagni G, et al. Guideline for the management of non-muscle-invasive bladder cancer (stages Ta, T1, and TIS): 2007 update. *J Urol* 2007;178:2314-30. http://dx.doi.org/10.1016/j.juro.2007.09.003
11. Oosterlinck W, Lobel B, Jackse G, et al for the EAU Working Group on Oncological Urology: Guidelines on bladder cancer. *Eur Urol* 2002;41:105-12. http://dx.doi.org/10.1016/S0302-2838(01)00026-4
12. Oosterlinck W, Solsona E, Akaza H, et al. Low-grade Ta (non-invasive) urothelial carcinoma of the bladder. *Urology* 2005;66:75-89.

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