Therapies in bladder cancer: intravesical mitomycin-C

Naureen Iqbal[2], Iqbal Shergill[1,2,3†], Faruquz Zaman[2], Khurshid Alam[2], Hemali Trivedi[3] & Sandy Gujral[3]

†Author for correspondence
[1]Department of Urology, 7th Floor John Harrison House, Royal London Hospital Whitechapel, London E1 1BB, UK
Tel.: +44 797 694 6282; Fax: +44 207 377 7292; E-mail: super_iqi@yahoo.co.uk
[2]Barts and The London NHS Trust, London, UK
[3]Harold Wood Hospital, Essex, UK

'Various studies have found intravesical chemotherapy with mitomycin-C to be an effective treatment in preventing the recurrence rate of superficial bladder cancer.'

The use of intravesical therapy for the treatment of superficial bladder cancer aims to reduce morbidity and mortality by eradicating existing disease, preventing tumor recurrence and attempting to halt tumor progression.

Mitomycin-C is a commonly used intravesical treatment option for superficial bladder cancer and was used for the first time by Shida and colleagues in 1967 [1]. It is an antitumor antibiotic with a molecular weight of 334.3 and is soluble in water and organic solvents. Mitomycin-C is usually minimally absorbed on intravesical instillation due to its high molecular weight and hydrophobic nature. The use of an instillate at the lowest achievable osmotic strength appears to be optimal for the intravesical instillation of the drug and, hence, sterile water is preferred over saline. Its dose is typically 40 mg per instillation – this regimen has been shown to exhibit a longer time-to-recurrence and less recurrence compared with the standard regimen (20 mg) in patients with Stage Ta and grade 1–2 bladder cancer [2].

Various studies have found intravesical chemotherapy with mitomycin-C to be an effective treatment in preventing the recurrence rate of superficial bladder cancer [3–6]. Clinically, it increases the recurrence-free interval and therefore avoids the morbidity of repeated operative tumor resection. None of the studies comparing a single, immediate dose of mitomycin-C with delayed multidose regimen have found any significant difference between the two groups [4–6]. The Medical Research Council has shown that a single dose of mitomycin-C administered within 1 h of transurethral resection (TUR) significantly decreases the recurrence rate, although subsequent instillations provide a nonsignificant benefit.

Intravesical chemotherapy with mitomycin-C appears to have a negligible effect on disease progression in high-risk superficial bladder cancer (grade 3, Stage T1, *in situ* carcinoma) and various studies have failed to find any significant decrease in disease progression with single- or multiple-dose mitomycin-C regimens [5,6] or when given in combination therapy [7]. However, Minervini and colleagues have found significantly higher progression in the control group compared with mitomycin-C (only 3% with grade 1 and 4% with Stage Ta tumors had progression in the mitomycin-C group compared with 31 and 28% with grade II and Stage T1, respectively, in the control group) [8].

The guidelines from the European Urological Association recommend one single instillation of mitomycin-C to all patients immediately after transurethral resection; an additional course of intravescial chemotherapy over 4–8 weeks is advocated in intermediate-risk groups [9]. The patients that form these groups include those with Stage Ta, grade 1–2 tumors refractory to resection and primary intravesical therapy as assessed at first follow-up cystoscopy.

'...virus-based gene therapy in combination with mitomycin-C is showing some promise as a treatment modality in bladder cancer cell lines.'

More recently, McLarty and colleagues have described the use of a new device, MITO-IN (Physion S.R.I., Medolla, Italy), for reconstitution and delivery of intravesical mitomycin-C [10]. A 50-ml leur-lock syringe with 50 ml of sterile water/normal saline (0.9%) and 40-mg vial of mitomycin-C are attached to the device through a connector. By a system of releasing clamps, the drug is mixed and reconstituted and withdrawn back into the syringe and then administered directly into the bladder via a catheter attached to the same device. It is a closed system, safe for administration and easy to use in the theatre, ward

10.2217/14750708.4.2.115 © 2007 ISSN 1475-0708

or in an out-patient setting without the need for specialist pharmacy technicians and equipment. The waste of reconstituted drug is prevented if it is ordered in advance but not used later and decreases the chance of a patient missing the dose after TUR. No significant complications associated with the delivery system have been reported thus far.

Combinations of anticancer drugs have not been used consistently as intravesical agents to treat superficial bladder cancer. Patients assigned sequential Bacillus Calmette–Guèrin (BCG) and electromotive mitomycin-C (*vide infra*) had a higher disease-free interval (69 vs 21 months) and lower recurrence (41.9 vs 57.9%), disease progression (9.3 vs 21.9%), overall mortality (21.5 vs 32.4%; $p = 0.045$) and disease-specific mortality (5.6 vs 16.2%; $p = 0.01$) than those assigned BCG alone [11]. However, other studies have not shown such improvement in survival rate with single- or multiple-dose mitomycin-C [6] or combination therapy [7]. In their series of 242 patients with superficial bladder cancer with high risk of recurrence, treated with intravesical mitomycin-C, Hurle and colleagues demonstrated a crude survival rate of 86.4%, disease-specific mortality of 2.5% and nondisease-specific mortality of 6.6% [12].

Electrokinetic forces make the drug delivery faster into and across biological membranes. Mitomycin-C is nonionic within physiological range and its electromotive mode of delivery is by electro-osmosis. Thus, application of appropriate charge makes the electromotive mode the dominant and controllable transport mechanism [13]. Di Staci and colleagues have explored this phenomenon by applying a 20-mA pulsed electric current, through two dispersive cathode electrodes placed on lower abdominal skin, for 30 min in the electromotive arm compared with the passive mitomycin-C arm, where retaining time was 60 min [13]. In their study, intravesical electromotive administration increased the bladder uptake of mitomycin-C by more than fivefold (peak plasma mitomycin-C 43 vs 8 ng/ml) than passive diffusion, resulting in improved response rate in cases of high-risk superficial bladder cancer, and median time-to-recurrence was longer with electromotive mitomycin-C compared with passive mitomycin-C or BCG alone (35 vs 19.5 and 26 months, respectively) [13]. It was observed in the same study that almost all mitomycin-C uptake for each technique was complete after 15 min of residence time and also that local and systemic side effects were more prominent with the BCG group compared with mitomycin-C, and a trend of more side effects was seen in electromotive mitomycin-C compared with passive mitomycin-C [13].

'Mitomycin-C has stood the test of time as an effective intravesical agent for the treatment of superficial bladder cancer, both as a single agent and in combination therapy.'

Finally, virus-based gene therapy in combination with mitomycin-C is showing some promise as a treatment modality in bladder cancer cell lines [14].

Mitomycin-C has stood the test of time as an effective intravesical agent for the treatment of superficial bladder cancer, both as a single agent and in combination therapy. It is anticipated that as a result of further research in delivery modes, as well as new combinations, its efficacy will be further increased.

Bibliography

1. Shida K, Tatani M, Kato N *et al.*: Treatment of the bladder cancer with instillation of mitomycin C. *Jpn. J. Clin. Urol.* 21, 1075–1079 (1967).
2. Au JL, Badalament RA, Wientjes MG *et al.*: Methods to improve efficacy of intravesical mitomycin C: results of a randomized Phase III trial. *J. Natl Cancer Inst.* 93(8), 597–604 (2001).
3. Bouffioux C, Kurth KH, Bono A *et al.*: Intravesical adjuvant chemotherapy for superficial transitional cell bladder carcinoma: results of 2 European Organization for Research and Treatment of Cancer randomized trials with mitomycin C and doxorubicin comparing early versus delayed instillations and short-term versus long-term treatment. European Organization for Research and Treatment of Cancer Genitourinary Group. *J. Urol.* 153(3 Pt 2), 934–941 (1995).
4. Islam MA, Bhuiyan ZH, Shameem IA: Intravesical adjuvant therapy using mitomycin C. *Mymensingh Med. J.* 15(1), 40–44 (2006).
5. Krege S, Giani G, Meyer R, Otto T, Rubben H: A randomized multicenter trial of adjuvant therapy in superficial bladder cancer: transurethral resection only versus transurethral resection plus mitomycin C versus transurethral resection plus bacillus Calmette-Guerin. Participating clinics. *J. Urol.* 156(3), 962–966 (1996).
6. Tolley DA, Parmar MK, Grigor KM *et al.*: The effect of intravesical mitomycin C on recurrence of newly diagnosed superficial bladder cancer: a further report with 7 years of follow up. *J. Urol.* 155(4), 1233–1238 (1996).
7. Serretta V, Pavone C, Ingargiola GB, Daricello G, Allegro R, Pavone-Macaluso M: TUR and adjuvant intravesical chemotherapy in T1G3 bladder tumors: recurrence, progression

and survival in 137 selected patients followed up to 20 years. *Eur. Urol.* 45(6), 730–736 (2004).

8. Minervini R, Felipetto R, Vigano L, Pampaloni S, Fiorentini L: Recurrences and progression of superficial bladder cancer following long-term intravesical prophylactic therapy with mitomycin C: 48-month follow-up. *Urologia internationalis* 56(4), 234–237 (1996).
9. Oosterlinck W, Lobel B, Jakse G, Malmstrom PU, Stockle M, Sternberg C: Guidelines on bladder cancer. *Eur. Urol.* 41(2), 105–112 (2002).
10. McLarty E, Coker CB: A novel device for reconstituting and delivering intravesical chemotherapy. *BJU int.* 91(6), 575–576 (2003).
11. Di Stasi SM, Giannantoni A, Giurioli A *et al.*: Sequential BCG and electromotive mitomycin versus BCG alone for high-risk superficial bladder cancer: a randomised controlled trial. *Lancet Oncol.* 7(1), 43–51 (2006).
12. Hurle R, Manzetti A, Losa A *et al.*: Intravesical instillation of mitomycin-C in 242 patients with superficial bladder cancer at high risk of recurrence: long-term results. *Urologia Internationalis* 61(4), 220–226 (1998).
13. Di Stasi SM, Giannantoni A, Stephen RL *et al.*: Intravesical electromotive mitomycin C versus passive transport mitomycin C for high risk superficial bladder cancer: a prospective randomized study. *J. Urol.* 170, 777–782 (2003).
14. Mullerad M, Bochner BH, Adusumilli PS *et al.*: Herpes simplex virus based gene therapy enhances the efficacy of mitomycin C for the treatment of human bladder transitional cell carcinoma. *J. Urol.* 174(2), 741–746 (2005).