

Phase III randomized controlled trial comparing an immediate intravesical instillation of electromotive mitomycin-C before trans-urethral resection of bladder tumours with an immediate intravesical instillation of passive diffusion mitomycin after transurethral resection of bladder tumour and with transurethral resection of bladder tumour alone in patients with primary urothelial non-muscle invasive bladder cancer.

TRIAL DESIGN: Multicentre randomised phase III trial

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BACKGROUND

Bladder cancer is the 7th most common cancer in men. In 2008 an estimated 386,300 cases were diagnosed and 150,200 patients died of the disease worldwide.¹ Of newly diagnosed bladder cancer cases, 75%-85% present as non-muscle invasive disease, including papillary lesions confined to the urothelium (stage Ta), or invading the lamina propria (stage T1), and carcinoma in situ (stage Tis).² Despite adjuvant intravesical therapy after transurethral resection of bladder tumour (TURBT), 31%-78% of patients relapse and 0.8%-45% progress to muscle-invasive disease within 5 years.³ Repeating TURBT and intravesical instillations of immunotherapeutic and chemotherapeutic agents cause considerable inconvenience and morbidity, making cost per patient from diagnosis to death the highest of all cancers.⁴

One commonly accepted mechanism for tumour recurrence is re-implantation of floating tumour cells that are released at resection sites during TURBT.⁵ To kill exfoliated tumour cells that could implant and thus reduce recurrence, researchers tested intravesical chemotherapy instillation immediately after TURBT.² Meta-analyses by the European Organisation for Research and Treatment of Cancer,⁶ and the American Urological Association (AUA),⁷ reported that intravesical chemotherapy instillation immediately post-TURBT reduced recurrence in patients with low- and intermediate- risk NMIBC by 11.7% and 17% respectively (*vs* TURBT alone), with negligible side effects. The European Association of Urology (EAU),² and to a lesser extent, the AUA,⁷ guidelines consequently recommended this strategy be included in treatment plans for all patients with NMIBC. However, despite level I evidence supporting its use, disagreement persists,⁸⁻¹² and it is rarely administered by urologists.¹³

In laboratory,¹⁴ and clinical studies,¹⁵ intravesical electromotive drug administration (EMDA) increased MMC bladder uptake, improving clinical efficacy in high-risk NMIBC. Intravesical EMDA/MMC instillation is not recommended immediately post-TURBT because catheter electrode rigidity may cause additional mechanical trauma and urothelial injury, leading to bladder spasm

and drug solution leakage. Furthermore, hematuria and bladder perforation are contraindications to intravesical EMDA/MMC.

This study compares the effects of intravesical EMDA/MMC instillation immediately pre-TURBT vs intravesical passive diffusion (PD) MMC instillation immediately post-TURBT vs TURBT alone in patients with primary urothelial NMIBC.

METHODS

Trial design

This is a multi-centre, randomised, parallel-group study conducted in Italy.

The institutional review boards (IRB) of each participating centre approved the study design. All enrolled patients are requested to undersign an IRB-approved informed-consent form which provides details of treatments.

All patients undergo: abdominal ultrasound, urinary cytology, and cystoscopy with cold-cup biopsy of the bladder tumours. All tumour biopsy samples are graded using the 1973 WHO classifications.¹⁶ Risk categories for recurrence and progression are assessed according to Guidelines of the European Association of Urology for NMIBC.²

Participants

Diagnostic criteria for admission: histologically proven primary pTa and pT1 urothelial carcinoma of the bladder.

Inclusion criteria: age 18 years or over; adequate bone-marrow reserve (i.e. white-blood-cell count $\geq 4000 \times 10^6$ cells/L; platelet count $\geq 120 \times 10^9$ /L); normal renal function (ie, serum creatinine ≤ 123.76 $\mu\text{mol/L}$); normal liver function (ie, serum glutamic-oxaloacetic transaminase ≤ 42 U/L, serum glutamic-pyruvic transaminase ≤ 48 U/L, and total bilirubin ≤ 22 mol/L); ECOG performance status between 0 and 2.¹⁷

Exclusion criteria: non-urothelial carcinomas of the bladder; previous bladder cancer; previous intravesical treatment with chemotherapeutic and immunotherapeutic agents; known allergy to

MMC; prior or concomitant urinary tract carcinoma in situ and/or urothelial carcinoma of the upper urinary tract and urethra; bladder capacity under 200 ml; untreated urinary-tract infection; severe systemic infection (ie, sepsis); therapy with immunosuppressive agents; urethral strictures that would prevent endoscopic procedures and catheterisation; previous radiotherapy to the pelvis; other concurrent chemotherapy, radiotherapy and treatment with biological-response modifiers; other malignant diseases within 5 years of trial registration (except for adequately treated basal-cell or squamous cell skin cancer, in situ cervical cancer); pregnancy; and any factors that would preclude study participation.

Study Settings

The Department of Surgery/Urology of Tor Vergata University of Rome, Italy (coordinating centre). Participants recruitment from: the Operative Unit of Urologic Oncology, Policlinico Casilino, Rome, Italy and the Operative Unit of Urology, “A. Perrino” Hospital, Brindisi, Italy.

Randomisation

Within 7 days of cystoscopy, cold-cup bladder tumour biopsy and urinary cytology.

Strata: tumour number and histology.

Random allocation to one of three treatment arms by means of stratified blocked randomization across 6 (2×3) strata derived from two prognostic criteria: 1) unifocal versus multifocal tumours, and 2) grade 1 versus grade 2 versus grade 3 urothelial carcinoma. This method ensures prognostic parity among the 3 treatment groups (Figure 1).

Blinding

Participants and physicians in each intervention group: aware of allocation.

Outcome assessors and data analysts: blinded.

Interventions (Treatment schedules)

About 2 weeks after randomization:

- a. TURBT alone: TURBT of all bladder tumour visible on endoscopy, including muscle in resected samples.

- b. Intravesical PD/MMC instillation immediately post-TURBT: Within 6 hours of TURBT, 40 mg MMC (Mitomycin, Kyowa Italiana Farmaceutici, Srl, Milan, Italy) dissolved in 50 ml bacteriostatic-free solution of 0.9% sodium chloride. After bladder draining, the MMC solution is infused intravesically through a Foley catheter, retained in the bladder for 60 minutes with catheter clamping and then drained. Bladder draining is followed by continuous intravesical irrigation with saline for 8 (day surgery admission) to 18 (elective admission) hours. When persistent macroscopic hematuria is present and/or bladder perforation suspected or noticed during TURBT, post-TURBT intravesical PD/MMC instillation is avoided, but patients are followed-up and included in the analysis.
- c. Immediately pre-TURBT intravesical EMDA/MMC instillation: ~30 minutes before spinal or general anaesthesia TURBT, 40 mg MMC dissolved in 100 ml sterile water, infused intravesically through the Foley catheter by gravity and retained in the bladder for 30 min, while 20 mA pulsed electric current for 30 minutes is given externally. The MMC solution was drained and followed by continuous intravesical irrigation with saline for 8 to 18 hours. As previous described,¹⁸ intravesical EMDA is administered by a battery powered generator delivering a controlled electric current which passes between the active intravesical electrode (integrated into a specific transurethral catheter) and dispersive ground electrodes (on the lower abdomen skin). Operators set active electrode polarity and current intensity on the generator.

Patients in the MMC arms are placed on fluid restriction without urine alkalization to prevent changes in acid-base balance during and after anaesthesia.

Tumours are staged according to the 1997 TNM classification of the International Union Against Cancer.¹⁹

About 1 month after TURBT, patients without muscle in resected samples, positive or suspect cytology, carcinoma in situ, stage T1, or grade 3 tumours undergo re-staging TUR, random cold-cup bladder and prostatic urethra biopsies (i.e. sampling of seemingly healthy urothelium and

suspicious areas) and upper urinary tract imaging. All tumour and bladder biopsy samples are reviewed by a reference pathologist (AR) for histology, grade and stage.

Patients with intermediate- and high-risk NMIBC receive adjuvant long-term intravesical chemotherapy (MMC) or immunotherapy (BCG), respectively, according to standard protocols. No adjuvant intravesical therapy is given to patient with low-risk NMIBC.

Outcomes (Efficacy endpoints)

Primary endpoints are recurrence rate and disease-free interval for patients who are disease-free after treatment—ie, time from randomisation to first cystoscopy noting recurrence. Secondary endpoints are time to progression (i.e. time from randomisation until onset of muscle-invasive disease as recorded by pathological assessment of transurethral-resection samples or biopsy samples), overall survival (i.e. time from randomisation until death from any cause), and disease-specific survival (i.e. time from randomisation until death from bladder cancer). Patients without recurrence or progression are accounted as censored at the last cystoscopy. Drop-outs are accounted as censored on the last known day of survival.

Sample size

Given previous reports,²⁰ and our own experience, the 5-year recurrence-free probability is assumed to be about 60% in patients with NMIBC treated with intravesical therapy; a 20% increase in time to recurrence is assumed to be clinically relevant.

The sample size has to be 297— with power $1-\beta=0.80$ and type I error $\alpha=0.05$ - to detect if the 3 treatments differ by the difference between the arcsin square-root transformations of both expected and known recurrence-free proportions,. Allowance for 15% potential withdrawal increases the sample to about 342, i.e. 114 patients per treatment arm. Recurrences needs to exceed 120 in number to ensure at least 80% power to detect a hazard ratio between any two treatments that may exceed 2.0, using a log-rank test at $\alpha=0.05$, .

Stopping guidelines (Safety analysis)

Response to treatment is assessed with abdominal ultrasonography, cystoscopy, and urinary cytology. Patients who are disease-free 3 months after treatment are assessed every 3 months for the first 2 years, twice during the third year, and yearly thereafter. At cystoscopy any tumour or abnormal looking urothelium is resected and tissue sent to the reference pathologist to confirm recurrence.

All patients are evaluated for safety. Symptoms and side effects, classified as local, systemic, or allergic, are recorded during and after each treatment. The severity of symptoms and side-effects is classified by the attending physician as those that needed “to stop” or “not stop” intravesical treatment.

Statistical methods

All analyses are intention to treat. Times to first recurrence and progression, overall survival and disease-specific survival are estimated using a generalized k-sample log-rank test. All tests are two-sided with $p < 0.05$ significant. Hazard ratios with 95% confidence intervals (CI) are calculated by proportional-hazards regression.

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Appendix 1. ECOG Performace Status [17]

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Appendix 2. 2002 TNM classification of urinary bladder cancer [19].***T – Primary tumour***

- TX Primary tumour cannot be assessed
- T0 No evidence of primary tumour
- Ta Non-invasive papillary carcinoma
- Tis Carcinoma in situ: ‘flat tumour’
- T1 Tumour invades subepithelial connective tissue
- T2 Tumour invades muscle
- T2a Tumour invades superficial muscle (inner half)
- T2b Tumour invades deep muscle (outer half)
- T3 Tumour invades perivesical tissue:
 - T3a Microscopically
 - T3b Macroscopically (extravesical mass)
- T4 Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
 - T4a Tumour invades prostate, uterus, or vagina
 - T4b Tumour invades pelvic wall or abdominal wall

N – Lymph nodes

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in a single lymph node 2 cm or less in greatest dimension
- N2 Metastasis in a single lymph node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension
- N3 Metastasis in a lymph node more than 5 cm in greatest dimension

M – Distant metastasis

- MX Distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis

Appendix 3. WHO grading in 1973 and in 2004

1973 WHO grading [16]

Urothelial papilloma

Grade 1 well differentiated

Grade 2 moderately differentiated

Grade 3 poorly differentiated

2004 WHO grading [21]

Urothelial papilloma

Papillary urothelial neoplasm of low malignant potential (PUNLMP)

Low-grade papillary urothelial carcinoma

High-grade papillary urothelial carcinoma