Single instillation of mitomycin C reduces 1st year recurrence following transurethral resection of non-muscle invasive bladder cancer

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SINGLE INSTILLATION OF MITOMYCIN C REDUCES 1ST YEAR RECURRENT FOLLOWING TRANSURETHRAL RESECTION OF NON-MUSCLE INVASIVE BLADDER CANCER

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Objective: To study the impact of single instillation of 40 mg Mitomycin C (MMC-40) within first hour of transurethral resection (TUR), on first year recurrence of non-muscle invasive bladder cancer. Methods: In this study of two groups of patients with similar demographics and tumour profile were compared to assess first year tumour recurrence pattern. Group A received MMC-40 within 30 minutes of TUR. Group B patients only had TUR of bladder tumour. Patients’ charts were reviewed for demographic profile, preoperative diagnosis and imaging used, cytological work up, tumour profile both during cystoscopy and imaging used, patients records were also reviewed for all subsequent check cystoscopies for recurrence. Any adjuvant treatments like intravesical chemotherapy etc. were also noted. The results were analysed using a commercially available statistical package, SPSS™. The level of significance was <0.05. Results: There were 29 and 46 patients in group A and B respectively. The demographic profile in terms of age, gender distribution, tumour characteristics (size, site, multiplicity) and pathological evaluation including, tumour grade and presence of carcinoma in situ were similar (p<0.4 and p<0.5) respectively. The first year recurrence rate in group A was 15% whereas it was 37.4% in group B (p<0.04). Conclusions: The first year recurrence rate is significantly decreased if MMC-40 is instilled following TUR. MMC-40 is safe and cost effective. Most low grade, low volume tumours would not require any further treatment if MMC-40 is given immediately following TUR.

Key words: non-muscle invasive bladder cancer, single instillation of chemotherapeutic agent, recurrence

INTRODUCTION
Bladder cancer is the second commonest urological malignancy in the world1 and commonest in Pakistan. In United States in year 2006, estimated 61420 new cases are diagnosed.1 Majority of bladder cancers presents as superficial transitional cell cancers. Superficial tumours have a high rate of recurrence (25-40%) in the first year2 following transurethral resection (TUR). Following TUR intravesical treatment of either immunotherapeutic agent, Bacillus Calmette-Guérin (BCG), or a chemotherapeutic agent like Mitomycin C (MMC) is considered to avoid recurrence. However, in majority of cases it is an over treatment in patients with low risk cancers. Transurethral resection of the tumour is considered as treatment of choice in non-muscle invasive bladder cancer. A number of studies agree with the fact that intravesical instillation of cytotoxic agents within the first hours after operation reduces the risk of tumour recurrence.3 It is assumed that transurethral resections of bladder tumours evoke relevant intravesical tumour cell suspensions. Thus, reimplantation of tumour cells and consequently a cancer recurrence are promoted.4 In this case, early intravesical instillations of chemotherapeutic agents such as Mitomycin or Epirubicin have cytotoxic and preventive effects. Side effects of intravesical instillation are uncommon, and therefore, this therapy is considered to be simple and safe.5 In the current work we have looked at the efficacy, of administration of 40 mg of MMC in the recovery room in prevention of 1st year recurrence of non-muscle invasive bladder cancer.

MATERIAL AND METHODS
This is a comparative study conducted to assess the impact of 40 mg of Mitomycin C (MMC-40) on recurrence in the first year following TUR. Patients were divided in two groups with similar demographic and tumour profile. The difference between first year recurrence pattern, toxicity and safety of SICA was compared in the two groups. Group A received MMC-40 within 60 minutes of transurethral resection, in the recovery room, if the surgeon believes there is no overt perforation and bladder injury during TUR. Group B patients only had TUR of bladder tumour.

The patients were identified from the medical records coding and indexing6 (ICD 9 Cm) using bladder cancer, TUR and MMC as key words. Patients’ charts were reviewed for demographic profile, preoperative diagnosis and imaging used, cytological work up, tumour profile both during cystoscopy and pre-operative imaging used, patients records were also reviewed for all subsequent check cystoscopies for recurrence. Any complications related to the SICA were also noted. To assess the cost effectiveness of SICA, the additional cost of SICA need for over stay in recovery room was analysed and compared with the maintenance dose of 6 cycles in out
patient set up. The resected tumour, along with cold
cup biopsies from the tumour base and random
biopsies, if taken were sent for histopathology. The
tumour staging was done using the 1997 TNM
classification of bladder cancer. The tumour grading
was done according to the WHO/ISUP system.

Any adjuvant treatments like intravesical
chemo/immunotherapy etc. were also noted. Results
were analysed using a commercially available
statistical package, SPSS™.

RESULTS
There were 29 patients in group A and 46 in group B
(Table 1). The mean age of patient in the group A
was 55.5 ±13.7 and 53.5 ±15.8 years. There were 90%
males in group A and 89% in group B. The clinical
presentation in the two groups was similar.

Table 1. Demographic profile and presentation

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=29)</th>
<th>Group B (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years) Mean±SD</td>
<td>55.5±13.7</td>
<td>53.5±15.8</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>27:2</td>
<td>41:5</td>
</tr>
<tr>
<td>Gross haematuria (%)</td>
<td>78</td>
<td>89</td>
</tr>
<tr>
<td>Microscopic haematuria (%)</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>LUTS %</td>
<td>42</td>
<td>37</td>
</tr>
</tbody>
</table>

p<0.4

The cystoscopic findings (Table 2) in the two
groups showed that in group A, two third of patients
had multiple tumours whereas in group B 81% had
multiple tumours. Eighty-nine percent and 86%
tumours had papillary configuration in group A and B
respectively. Seven percent were sessile in both groups
and 4% in group A and 7% in group B had both sessile
and papillary tumours. The mean size in group A was
3.3±1.7 Cm and in group B it was 3.4±2.1 Cm. random
biopsies were taken in 22% cases in group A
and in 40% in group B.

Table 2: Cystoscopic findings

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=29)</th>
<th>Group B (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple</td>
<td>33%</td>
<td>16%</td>
</tr>
<tr>
<td>Papillary</td>
<td>89%</td>
<td>86%</td>
</tr>
</tbody>
</table>

Pathological evaluation (Figure 1) indicated
that 96.5% and 91% respectively were T1 cancers in
group A and B respectively. The recurrence at 1st
year follow up showed a significant difference (p<0.04) in
the two groups (Figure 2).

The cost of single instillation of 40 mg.
MMC in the recovery room is PKR 3,000 (~50 US $)
compared to 6 cycles of MMC 20 mg in the clinic
PKR ~12,000 (~200 US $) (p<0.001).

DISCUSSION
Worldwide an estimated 356,600 new cases of bladder
cancer occur each year and, in terms of overall cancer
frequency, it is ranked as ninth. The highest incidence
rates are generally found in industrially developed
countries, particularly in North America and Western
Europe, and in areas associated with endemic schistosomiasis in Africa and Middle East. Bladder
cancer is more common in men than women, with a
worldwide male/female ratio of 10:3.

Patients with superficial bladder carcinoma can be expected to have recurrences after TUR. Recurrence rates were reported as 30–90% according to
prognostic factors. Chemotherapeutic agents or BCG
often were administered into the bladder to prevent or
delay the recurrences. To date, the instillation strategy
should be chosen according to risk criteria. TUR
alone is still the standard treatment for low-risk patients,
e.g., patients with a single bladder carcinoma. However, the immediate instillation of a
chemotherapeutic agent after TUR has become an
alternative option since Oostelinck et al and Tolley et al
reported on its validity.

The therapeutic objectives in initial treatment
of superficial tumours are to remove completely the
tumour, to assess the need for further therapy and to
plan the follow-up. The EORTC Genitourinary Group
assessed the percentage of patients with recurrence at 3
months after complete resection of all visible lesions
taking into account the institution, number of tumours
at presentation and the year of treatment. For single
tumours, the 3-month recurrence varied from 0 to 36%
A randomized trial of single superficial bladder carcinoma, without serious complications. We believe that a single immediate instillation of MMC-40 should become the standard, which might have the advantage of excellent cost effectiveness.

REFERENCES