SINGLE INSTILLATION OF MITOMYCIN C REDUCES 1ST YEAR RECURRENCE 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 chemo/immunotherapy 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 world[1] 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 year[2] 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 indexing[6] (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

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

$p<0.4$

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

	Group A (n=29)	Group B (n=46)
Multiple	33%	16%
Papillary	89%	86%

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.[7] 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.[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.[8] To date, the instillation strategy should be chosen according to risk criteria.[8-10] TUR alone is still the standard treatment for low-risk patients, e.g., patients with a single bladder carcinoma.[11,12] 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.[13,14]

Figure-1: Pathological evaluation of tumour

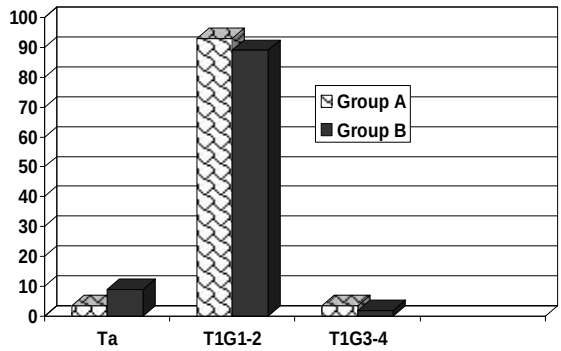
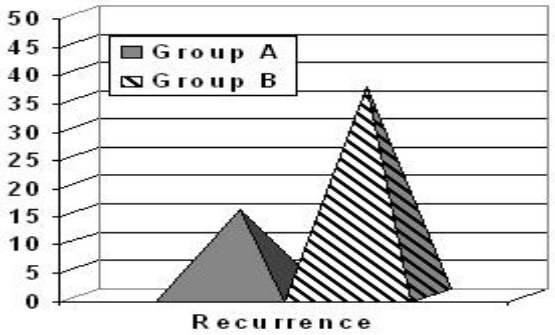


Figure-2: Recurrence at 1st year of follow up ($p<0.04$)



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.[2] For single tumours, the 3-month recurrence varied from 0 to 36%

and for multiple tumours from 7 to 75%. The 3-month recurrence by number of tumours was 8.7% for single tumours, 21% for 2–5 tumours and 32.2% for >5 tumours. The 3-month recurrence by year of entry for single tumours ranged from 21.0 to 43.8% during 1975–1978, from 6.3 to 12.7% during 1984-1986 and from 3 to 5.3% during 1987–1989. For multiple tumours it ranged from 50.0 to 61.5% during 1975–1978, from 20.2 to 27.3% during 1979–1983 and from 14.4 to 24.6% during 1984–1986. The use of more refined instruments probably led to decreasing percentage of the 3-month recurrence in more recent years, the large variation between institutions remains unexplained. The bladder's unique location renders its mucosa accessible to instillation of chemotherapeutic and immunotherapeutic agents. Cytostatics can be instilled into the bladder hours after surgery without severe complications. A single early instillation within 6 hours after transurethral resection (TUR) in patients with a solitary bladder tumour category T(a)/T(1) G(1) to G(3) could reduce the recurrence rate per year by nearly 50%. The superiority of any of the commonly used intravesical drugs has never been demonstrated; the time to initiate therapy is important for treatment outcome. Optimal results can be achieved by initiating treatment early (within 24 hours after TUR) and for a duration of 6 months, and maintenance (>6 months) for patients with a delayed first instillation (>7 days after TUR). Our study also presented the 1st year recurrence rate as 37.4% in the controlled group and 15% in the study group.

Transurethral resection of a bladder tumour alone has been recommended for low risk patients, but the substantial recurrence rates affected even the low-risk patients because they subsequently underwent TUR-Bt again. Recently, some studies have revealed that a single instillation immediately after TUR-Bt prevents recurrences.[13-14] Oosterlinck *et al* first demonstrated that a single instillation clearly prevented recurrence for patients with a single tumor.[13] Tolley *et al* stated that a single instillation can prevent recurrences of patients with either a single or multiple tumours.[14] In this study, we demonstrated the prophylactic effect of THP for patients with a single superficial bladder carcinoma. The net benefit was 25.4% at 1 year, 27.0% at 2 years and 21.5% at 3 years.[14]

CONCLUSION

A single immediate intravesical instillation after TUR prevents recurrences for patients with a 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

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, Thun MJ. Cancer statistics, 2006. CA Cancer J Clin. 2006;56:106–30.
2. Kurth KH, Bouffioux C, Sylvester R, van der Meijden AP, Oosterlinck W, Brausi M. Treatment of superficial bladder tumors: achievements and needs. The EORTC Genitourinary Group. Eur Urol. 2000;37 Suppl 3:1–9.
3. Sylvester RJ, Oosterlinck W, van der Meijden AP. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. J Urol 2004;171:2186–90.
4. Kaasinen E, Rintala E, Hellstrom P, Viitanen J, Juusela H, Rajala P, *et al.* Factors explaining recurrence in patients undergoing chemoimmunotherapy regimens for frequently recurring superficial bladder carcinoma. Eur Urol 2002;42:167–74.
5. Thrasher JB, Crawford ED. Complications of intravesical chemotherapy. Urol Clin North Am 1992;19:529–39.
6. American Medical System. Physicians ICD-9-CM 2007. International classification of disease: Clinical Manual. American Medical Association; 2007-09-29.
7. IARC. GLOBOCAN 2002. Cancer Incidence, Mortality and Prevalence Worldwide (2002 estimates). Accessed 2005
8. Herr HW, Laudone VP, Whitmore WF. An overview of intravesical therapy for superficial bladder tumors. J Urol. 1987;138:1363–8.
9. Lamm DL, Blumenstein BA, Crawford ED, Montie JE, Scardino P, Grossman HB *et al.* A randomized trial of intravesical doxorubicin and immunotherapy with bacille Calmette-Guérin for transitional-cell carcinoma of the bladder. N Engl J Med. 1991;325:1205–9.
10. Witjes JA, Meijden AP, Sylvester LC, Debruyne FM, van Aubel A, Withes WP. Long-term follow-up of an EORTC randomized prospective trial comparing intravesical bacille Calmette-Guerin-RIVM and mitomycin C in non-muscle invasive bladder cancer. Urology. 1998;52:403–10.
11. Kurth KH, Bouffioux C, Sylvester R, van der Meijden, Oosterlinck W, Brausi M. Treatment of superficial bladder tumors: achievements and needs. The EORTC Genitourinary Group. Eur Urol. 2000;37(Suppl 3):1–9.
12. Parmar MKB, Freedman LS, Hargreave TB, Tolley DA. Prognostic factors for recurrence and followup policies in the treatment of non-muscle invasive bladder cancer: report from the British Medical Research Council subgroup on superficial bladder cancer (Urological Cancer Working Party). J Urol. 1989;142:284–8.
13. Oosterlinck W, Kurth KH, Schröder F, Bultinck J, Hammond B, Sylvester R. Randomized trial comparing transurethral resection followed by a single intravesical instillation of epirubicin or water in single stage Ta, T1 papillary carcinoma of the bladder. J Urol. 1993;149:749–52.
14. Tolley DA, Parmar MKB, Grigor KM, Lallemand G. 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 1996;155:1233–8.

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