A Comparative Study Between Single Session Versus Six Sessions Mitomycin C instillation in Patients With Low Risk Non-Muscle Invasive Bladder Cancer

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ABSTRACT:

BACKGROUND:

Intra vesicle instillation following trans uretheral resection of low grade and low stage bladder cancer proved its efficacy in reducing recurrence and progression of bladder cancer.

OBJECTIVE:

To compare the efficacy of a single session of mitomycine C versus six sessions mitomycine C following TURBT on recurrence and progression rates in patients with low risk non-muscle invasive bladder cancer.

PATIENTS AND METHODS:

A total of 50 patients with low risk non-invasive bladder cancer were included in a prospective randomized controlled trial. Inclusion criteria include all patients who had a 3cm or less, single, papillary tumor. The tumor was completely resected before were randomized patients into 2 arms; Group one; those who receiving one session mitomycin C instillation of 40 mg (usually within 6 hours) into the urinary bladder. And Group B; Receiving six sessions mitomycin C instillation into the urinary bladder, Median follow up was 24 months. The events studied where the recurrence free rate, the recurrence rate/ year, the number of new tumors developing/year, and progression.

RESULTS:

At 24 months follow up, the recurrence free rate in a single session of mitomycin C instillation (group A) was (70.2%) while in six sessions mitomycin C instillation group was (84.7%) (Group B). Recurrence rate was ; Group A VS Group B : (10% VS 4 %) and recurrence per year rate (5% VS 2%), were decreased in the six sessions mitomycin C instillation (Group B) compared to the single session mitomycin C instillation (Group A). The number of new tumors per year rate (18% VS 11%), were decreased in the six sessions mitomycin C instillation (Group B) compared to the one session mitomycin C instillation, (Group A). A shorter hospital stay, catheterization period, and low level of local symptoms were noted in one session mitomycin C instillation (Group A) compared to six sessions mitomycin C instillation, (Group B).

CONCLUSION:

Single session mitomycin C given immediately after surgery or within 6 hours after resection may be as effective as six session protocol. This regimen may be cost effective and avoid prolonged hospitalization and catheterization with sex sessions regimen.

KEYWORDS: bladder cancer, intra vesicle, chro therapy , mitomycin.

INTRODUCTION:

Bladder cancer (BCa) is the most expensive solid tumor to treat mainly due to the high recurrence rate of its non–muscle-invasive form (confined to the urothelium [Ta] or lamina propria [T1]) [(1)].

Many non–muscle-invasive BCas (NMIBCs) are amenable to treatment with transurethral resection of bladder tumor (TURBT) alone. However, despite the therapeutic impact of TURBT, BCa recurrence rates can be as high as 80% [(2)]. Attempts have been made to decrease these high recurrence rates and consequently their associated costs.

It is hypothesized that one of the mechanisms for early recurrence of NMIBC following TURBT is implantation of floating cancers cells into the bladder urothelium following resection [(3)]. To

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address this so-called seeding phenomenon, many investigators have utilized an immediate postoperative instillation of intravesical chemotherapy (IVC) to eradicate any free-floating cancer cells after a complete TURBT [4]. Evidence supporting such a practice was strengthened in 2004 by Sylvester et al., who performed a meta-analysis incorporating all immediate postoperative chemoprophylaxis trials published to date [5]. They demonstrated a significant improvement in the likelihood of recurrence for NMIBC patients who received IVC after TURBT. The number needed to treat to prevent one NMIBC recurrence was 8.5 [6]. Critics of IVC believe that NMIBC recurrences can be managed with simple office-based fulguration [7]. Some trials suggest that the benefit of IVC may be limited to a select subset of patients with small tumors [8,9]. Both the American Urological Association and the European Association of Urology guidelines continue to recommend immediate post-TURBT IVC for suspected NMIBC [10,11] . The aim of this study is To compare the efficacy of single session of mitomycine C versus six sessions mitomycine C following TURBT on recurrence and progression rates in patient with low risk non-muscle invasive bladder cancer.

MATERIAL AND METHODS:

Between October 2012 and October 2014, we conducted a prospective , double -blind, randomized clinical trial in surgical specialties hospital, Medical city complex, Iraq.

Written informed consent was obtained from all patients. Patients with primary or papillary tumors, single tumors of 3 cm or less in size, and low-grade superficial tumors (Ta G1, Ta G2, and T1 G1) were included. Individuals with muscle-invasive or grade 3 tumors or in situ bladder carcinoma on the pathological examination, non transitional cell carcinoma, invasion to the prostate and the upper urinary tract, and a history of previous TURBT or intravesical chemotherapy were excluded. Using balanced randomization method, we randomly assigned the patients into 2 groups ; group 1; with 24 patients who received a single dose of mitomycin C, 40 mg diluted in 50 mL of distilled water and group 2: with 26 patients who received six weekly sessions of 40mg mitoaycin C. After emptying the bladder, mitomycin C were instilled intravesically within 6 hours after TURBT for group 1 and weekly for six weeks group 2. The instillation was retained for 2 hours by catheter clamping and then the bladder was irrigated using normal saline.

Side effects of mitomycin C such as cystitis, allergic reactions, hematuria, fever, erythema, skin rash, incontinence, chills, nausea and vomiting, fatigue, weakness, and muscle pain were recorded. The two groups were compared using urinary cytology and cystoscopy at 3, 6, 9, 12, 18, and 24 postoperative months. The time of the onset, location, size, stage, and grade of the recurrent tumors were determined. We compared the two groups by chi-square test and unpaired t test. Recurrence-free interval is the period between initial transurethral resection and first recurrence. Recurrence was defined histologically as biopsy confirmed carcinoma. Statistically recurrence represent the percentage of patients with recurrence during the follow up period, recurrence per year represent the number of positive cystoscopies divided by the total years of follow-up.

Tumor per year represent the total number of tumors observed during all positive cystoscopies divided by the total years of follow-up, progression was the percentage of cases of invasive bladder tumor or metastases.

Disease-free interval was calculated using Kaplan-Meier method and the distribution was compared by Breslow test. Values were considered statistically significant at $P < 0.05$.

RESULTS:

Mean follow-up was (24)months. Of the (24) patients in the one session mitomycin C, (Group A); eleven patients experienced at least (l) recurrent tumor compared to four patients of (26) given 6 sessions mitomyicn C. A lower recurrence rate was observed in the six sessions mitomycin C compared to the one session mitomycin C group (table 1). Only (2) patients (4%, 1 in each group) had progression (table1).

Table 1: Recurrence and progression.

	One session MMC Group(Group A)	Six sessions MMC Group(Group B)	P value
Total	24	26	
Recurrence No(%)	11(45.8)	4(15.3)	0.018
Progression No(%)	1(4.1)	1(3.8)	00.951

The recurrence free rates is shown in (table 2) at two years were (70.2%) and (84.7) for groups A&B, respectively. A longer recurrence-free interval was observed in the six sessions mitomycin C compared to the one session mitomycin C group , log-rank test (p=0.012) .

Table 2: Recurrence free rate.

GROUPS	3MOS.	6MOS.	9MOS.	12MOS.	18MOS	24MOS.
(A) One session MMC	91.7%	90.3%	85.1%	82.9%	73.4%	70.2%
(B) Six sessions MMC	100%	100%	100%	96.2%	87.8%	84.7%

A lower recurrence and tumor per year rates were noted in the group B compared to group A (Table 3).

Table 3: Recurrence and tumor per Year rates.

•	One session MMC group A	Six sessions MMC group B	P Value
Recurrence per year	1.10	0.04	0.007
New tumor per year	0.18	0.01	0.038

Recurrence timing was considered using different cutoff points when determining the possible impact of single early instillation of mitomycin C on cell implantation as a mechanism of early recurrence. Early recurrence developed during the first 12 months in (72%) of the one session mitomycin C group but only (25%) of the six sessions mitomycin C group (p = 0.005) , no significant differences were observed in the second year, (Fig.1).

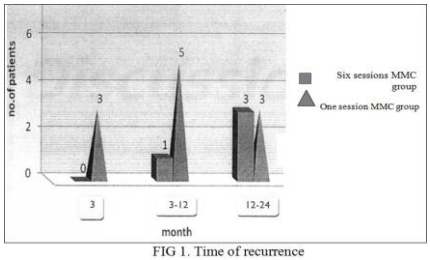

FIG 1. Time of recurrence

At 24-month follow-up a prolonged hospital stay and catheterization period were observed in the six sessions mitomycin C group compared to one session mitomycin C. In the six sessions mitomycin C group (group B); 3 patients (11.5%) had chemical cystitis and slight allergic skin reactions. No hematological changes were recorded.

DISCUSSION:

Although earlier reports suggested that the beneficial effects of adjuvant intravesical chemotherapy are temporary, several studies have demonstrated durable effects. A trial comparing one and five instillations of MMC after TUR versus TUR alone demonstrated a decrease in the recurrence rate for patients with adjuvant intra vesical chemotherapy after a median follow-up of seven years [12].

Similarly, a phase III trial comparing a standard versus an optimized dose of MMC showed a decreased recurrence rate at five years for the optimized dose[13]. The role of maintenance chemotherapy and sequential chemo-immunotherapy, however, remains unclear.

The common indications of adjuvant intravesical chemotherapy instillations are directly related to the risk of tumor recurrence and progression. Despite that there is no clear evidence of reducing progression rates with chemotherapy, classifying the patients according to their risk is essential to improve the outcomes. Both intermediate- and high-risk groups, defined by multiple tumors, tumor size > 3 cm, prior recurrence rate, T1, CIS, and grade (EORTC risk tables), are eligible for intravesical chemotherapy. However, patients at high-risk of progression should certainly consider intravesical immunotherapy, due to the lack of evidence supporting the efficacy of chemotherapy in this setting [13,14].

Although single instillations are the focus of this study, there is some evidence that shows the immediate single post-operative instillation of chemotherapy reduces the recurrence rate when compared to TUR alone. In one study had shown a recurrence risk reduction by half at 2 years of follow-up and over 15% reduction at 5 years, rendering a routine recommendation for single post-operative instillation of MMC in Ta low-risk patients [15].

The timing of the instillation has previously been evaluated by a large meta-analysis of randomized clinical trials, which showed to be sufficient if performed within the first 24 hours after the TUR. The results are best in patients with a single small tumor that was entirely resected [16, 17].

This study tried to evaluate the efficacy of single dose instillation versus six doses instillation for the treatment of low grade non muscle invasive bladder cancer, the study showed that although multiple sessions instillations of mitomycine is effective in reducing recurrence and progression, comparable results also were obtained from single dose instillation of mitomycine giving immediately or within 6 hours after TURBT.

In this study : Multiple instillation of mitomycin C however, are associated with prolonged hospital stay and catheterization period were observed in the six sessions mitomycin C group compared to one session mitomycin C ,This explained by multiple hospital admissions.

The selection of mitomycin-C in this study was made because it avoids the risk of sepsis and myelosuppression associated with BCG and thiotepa ([18]. And avoids the tissue destruction from extravasation associated with doxorubicin [19] , in addition to that the response rate after intravesical mitomycin C seems to be relatively higher than those achieved by other chemotherapeutic drugs [20-22].

At 24-month follow-up a prolonged hospital stay and catheterization period were observed in the six sessions Mitomycin C to group **c**ompared One session mitomycin C group .The incidence of side effect in this study was extremely low. On the other hand, a six sessions mitomycin C instillation is an expensive approach with local and systemic side effects.

The other advantage of one session instillation of mitomycine C is that nearly all patients already had a catheter after TUR and if local regional anesthesia is used, patients will not suffer from any additional discomfort.

The significant reduction in early recurrence with one immediate session of mitomycine instillation strongly supports the hypothesis of cell implantation as a recurrence mechanism. This finding suggests that in controls early recurrences mostly correspond to a cell implantation process, which would not be related to the natural history of the tumors.[23]. In one study comparing immediate mitomycine instillation before BCG instillations for high grade tumors showed that immediate post-TUR MMC instillation significantly reduced

recurrence in high risk non-muscle-invasive bladder cancer patients treated by BCG. But it did not influence the stage and grade at recurrence [24]. Microwave-induced local hyperthermia combined with MMC appears to be a safe and efficient new treatment modality for prophylactic and adjuvant treatment, This technology has a potential additional value for the prevention of recurrence of superficial bladder cancer, particularly when other treatments have failed. [25].

CONCLUSION:

In patients with low risk non-muscle invasive bladder cancer an immediate one session mitomycin C instillation as comparable to six sessions mitomycin C instillations in increasing the disease free interval and significantly decreased recurrence, progression and recurrence tumor per year rates.

This safe approach spares a significant number of transurethral resections in these patients, decrease hospitalization and prolong catheterization with minimal or no associated symptoms associated with multiple mitomycine instillations. Consequently, this approach can be considered an alternative for observation only or to six session mitomycin C instillations in patients with low risk non-muscle invasive bladder cancer.

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