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COMPARISON OF EFFICACY AND SAFETY BETWEEN POSTOPERATIVE INTRAVESICAL INSTILLATION OF MITOMYCIN-C AND CONTINUOUS SALINE BLADDER IRRIGATION AFTER TURBT IN NON-MUSCLE INVASIVE BLADDER CANCERS

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ABSTRACT

Objective

To critically analyse the efficacy and safety of continuous saline bladder irrigation versus single installation of mitomycin-C (MMC) after transurethral resection of bladder tumour (TURBT) in patients with low to intermediate risk non-muscle invasive bladder cancer.

Materials and Methods

The question in consideration best merits answer by critically reviewing and analyzing the literature and finally to provide the recommendation about the relevance of the conclusions from the literature. A search study identifies the relevant literature from the well-known academic databases in the context of the research question. The particular sets of the key words are used in different formats to search the literature. The literature has been thoroughly reviewed and analyzed for the strengths and limitations. Specific data was critically taken for analysis depending upon the type of literature articles with special reference to their usefulness, knowledge, attitudes, transferability, validity/reliability and strength of conclusions.

Results

A total of 6 papers meeting the inclusion criteria, which compared the results of the efficacy and safety between intravesical chemotherapy and continuous saline bladder irrigation (CSBI) were critically analyzed.

Conclusion

CSBI cannot replace MMC in terms of its efficacy in the prevention of recurrence and progression but because of the better safety profile can be used as an alternative in patients with low to intermediate risk bladder cancers after TURBT.

Keywords: *continuous saline bladder Irrigation, transurethral resection of bladder tumour, mitomycin-C (MMC), non-muscle invasive bladder cancer*

Nearly 75% of bladder cancers are confined to the mucosa (Ta, CIS) or sub-mucosa (T1).[1] Proper transurethral resection of bladder tumour TURBT) can eradicate the low to intermediate risk tumours completely but there is a chance of recurrence and progression to higher grades and muscle-invasive bladder cancer (MIBC). Single intravesical instillation of chemotherapy in the form of MMC after TURBT has been shown to act by destroying the circulating tumour cells and by ablative effect on the residual tumour cells at the resection sites.[2]

Around 40% of Ta/T1 tumours recur within a year possibly due to residual tumour or incomplete resection.[3] In addition the recurrence of NMIBC throughout the life of these patients with requirement of repeated surgical interventions contributes not only to the significant burden on the health care delivery systems from the financial view point but also results in poor patient and physician compliance to the disease.

To predict short- and long-term risks of bladder cancer risk in non-muscle invasive types EORTC (European Organisation for Research and Treatment of Cancer) Genito-urinary Group developed a scoring system and risk tables. MMC was not thought to be effective as a single adjuvant instillation in patients with EORTC score of >5 or more than one recurrence in prior years. The standard adjuvant treatment for NBIBC following TURBT is single intravesical instillation of MMC. The most recent systematic review and individual patient data analysis of 2278 patients has shown reduction in the 5-year recurrence by 14%, down to 45% from 59% and to prevent one recurrence within 5 years the number needed to treat (NNT) is 7 eligible patients.[4]

The postulated mechanism of action of MMC is to prevent the implantation of the floating cancer cells on the TURBT site. The side effect profile of the MMC intravesical instillation is low and considered a safe treatment. Some case studies reported severe complications with MMC and epirubicin after the single instillation and one patient died due to consecutive complications.[5,6] Routinely the complications, though rare MMC is known to cause significant complications in the form of severe lower urinary tract symptoms immediately with chronic bladder pain on long term. Some cases of bladder necrosis have also been reported.[7] Moreover, MMC is contraindicated in patients with gross hematuria and concern of bladder perforation after TURBT. Many alternative strategies to prevent the re-implantation of cancer cells and to reduce the morbidity have been tried considering the limitations of MMC. Conflicting results have been yielded with intravesical Gemcitabine from a Cochrane review in 2012.[8] Phase 3 clinical trial is going on to check the safety and tolerability of apaziquone, a novel intravesical alkylating agent.[9] Recently sterile water and normal saline have been used as an alternative to MMC as the study had shown that water in addition to lysing the tumour cells also causes cytotoxic effect by osmotic cytolysis.[10] About 17% reduction in relative risk of recurrence of bladder cancer has been demonstrated in study following postoperative irrigation of normal saline for 18 hours post operatively after TURBT.[11]

Some studies believe the use of MMC in view of its complications is not a popular option with the urologist and its use is on decline. Only 18% European urologists responded that they chose MMC post TURBT while 28% never use it. Regarding American Urologists only 2% use it and 66% would not use MMC.[12,13]

MATERIALS AND METHODS

Relevant research papers which met the set inclusion criteria are identified for discussion in this critical review through a systematic approach from the appropriate academic databases involved in providing the data regarding medical research. All the literature on the Medline, Embase and Cochrane Register was searched between year 1980 till 2019 which investigated the use of MMC and CSBI following TURBT. The references of the related articles were also browsed to obtain more information on the usefulness of the data. The search formula used the following words saline, irrigation, mitomycin-C, intravesical chemotherapy, bladder cancer, bladder tumour and non-muscle invasive bladder cancer. The set inclusion criteria included were: (1) intravesical chemotherapy and CSBI were investigated in the article after TURBT, (2) full content and associated data could be obtained and (3) the data contained the valid and worthy information. Five articles which met

all the criteria, comparing CSBI versus MMC were included for analysis and discussion.

RESULTS

In a study by Onishi et al between April 2009 to Dec 2014 in a prospective, single-centre unblinded randomized study 250 consecutive were taken for TURBT following the diagnosis of bladder cancer on cystoscopy were included in the study.[14] Bladder irrigation was carried manually using a 50 ml bladder syringe immediately after TURBT and then randomly allocated to receive a single instillation of 30 mg in 30 ml saline of MMC or CSBI 2 litres/h for first hour, then one litre/hour for 2 hours and 500 mL/hour for another 15 hours. MMC was kept in the bladder for one hour to obtain a high concentration in the bladder. Patient age more than 85 years, CIS, high grade or muscle invasive TCC, history of upper tract TCC or any other neoplasm were excluded from the study.

Recurrence was determined by lesions seen on flexible cystoscopy and confirmed pathologically after TURBT. An increase in the tumour grade or stage on pathology was deemed as progression. CSBI group comprised of 124 patients and MMC group of 126 patients. Patients who had T2 tumour (6) and G3 or high Grade G2 or Carcinoma in situ (17) patients were excluded from the study. Ultimately 114 patients were allocated to CSBI and 113 to the MMC groups.

The median follow-up in both groups was 37 months. In the CSBI group the recurrence-free rates at at1, 3 and 5 years was 78.6%, 70.2%, and 62.6% respectively. At 1, 3, and 5 years it was 81%, 70.7%, and 70 % respectively for the MMC group. No statistically significant difference in terms of recurrence-free survival was seen between the groups by Kaplan-Meier analysis (Log rank test p=0.53). The median period of first recurrence was 8.5 months in MMC while it was 8 months in CSBI group. Tumour progression was seen in 6.2% in CSBI and 4.4% in MMC groups. Rates of local toxicities were seen in 27.4% of patients in MMC group and in 6.1% in CSBI groups.

Recent study by Onishi et al evaluated the role of CSBI after TURBT in high grade NMIBC against MMC in 250 patients in prospective randomized trial. World Health Organisation (WHO) 2004/2016 classification was used to review the histopathology which found 151 patients with high grade NMIBC (73 in MMC group and 78 in CSBI group) who were evaluated according to the recurrence and progression rates and adverse events. No statistically significant differences were found in a median follow-up of 58 months between the 2 groups in terms of recurrence rates at 12, 18, and 24 months (25.6% vs 23.3%, 28.5% vs 23.3%, and 32.1% vs 28.8% respectively), time to initial recurrence (12.6±11 vs 12.4±10.1 months) and a progression rate (8.9% vs 8.2 %). CSBI group had a significantly lower incidence of adverse events.[15]

In a study by Lenis et al, 205 patients were included in the study who met all the inclusion criteria and underwent TURBT for NMIBC.[16] About 82% of the patients were males with the mean age 71.9 (SD 11.4) with low-grade bladder cancer in 105(51.2%0) and high-grade bladder cancer in 100 (48.2%). Tumour sizes varied in different patients with <0.5 cm in 20 (9.8%), 0.5–2.0 cm in 90(43.9%), 2–5 cm in 45(21.9%) and >5 cm in 50(24.4%). Stage Ta without CIS in 126(61.5%), Ta with Cis in 12 (5.9%), T1 only in 36 (17.6%), T1 with CIS 13(6.3%) and CIS only in 18 (8.8%) patients. Using modified AUA risk stratification 23 (11.2%) had low risk, 80 (39%) had intermediate risk and 102 (49.8%) had high-risk disease on TURBT. An immediate postoperative treatment to prevent recurrence 71(34.6%) patients had single instillation of MMC, 45 (22%) had CSBI and 89 (43.4%) had no postoperative treatment. MMC 40 mg in 20 mL saline was instilled for 60–90 minutes and CSBI was performed by putting 3-way Foley catheter and running saline at maximum flow for 2 hours.

The entire cohort had a median follow-up of 16 months and 74 (36.1%) had recurrence at a median of 9.5 months and 16 (7.8%) progressed at a median of 16 months. The median disease-free survival (DFS) was 55 months for those who received MMC, 16 months for those receiving CSBI and 25 months for those receiving no treatment. The Kaplan-Meier survival curve demonstrated a significant DFS advantage of MMC as compared to either CSBI or no treatment options (log rank test: p<0.01)

In a retrospective study by of 332 patients by Do et al. diagnosed with NMIBC had TURBT between January 2010 to May 2015 and also had overnight continuous saline irrigation (OCSI).[17] Patients with

MIBC, lymph nodes or distant metastasis on CT scan or the ones who had MMC, epirubicin instillation following transurethral resection were excluded from the study. Patients were followed up with cystoscopies every 12 weeks for one year.

After TURBT a three-way Foley catheter was inserted and continuous irrigation with 3000 cc bag of normal saline used in OCSI (120 patients) group and a total of 9000 cc is used. In non OCSI (212 patients) two-way Foley catheter was used and no irrigation used. In terms of age, gender, co-morbidities, smokers, tumour grade, stage, size and number of tumour, or prior Bacillus Calmette Guerin treatment no significant differences were found.

Initial recurrence in no irrigation group was 277.19 +/- 7.39 days (95% CI) and in OCSI group 302.85+/- 8.11 days (95% CI). In no irrigation group 38.2% patients had recurrence and in OCSI group only 26.4%. the recurrence-free survival rate following surgery was significantly higher in OCSI group (log rank test p=0.032).

A meta-analysis by Zhou et al included 4 randomized studies amounting to 861 patients with 433 patients in CSBI group and 428 in MMC group.[18] The RCTs were included after the search on Medline, Embase and Cochrane Registry with a main aim of checking the efficacy and safety of the 2 groups after transurethral resection of bladder tumours. The studies included comparing the instillation protocol of epirubicin solution(40 mg/mL for 20 hour following surgery with CSBI in same manner , Gemcitabine (2000 mg/100mL) or placebo (100 mL of saline) followed by CSBI for more than 20 hours, MMC (4 weekly instillation starting the week after surgery followed monthly instillations till 12 months, CSBI 2 litre for one hour, then 1 L/hour for 3 hours, and then 250 mL/hour for 14–18 hours and the last one with single 30 mg MMC in 30 mL saline instillation versus CSBI 2 L/hour first hour, then 1 L/hour for 2 hours and the 500 mL/hour for 15 hours)

In terms of the efficacy no statistically significant differences were found regarding one-year recurrence-free survival, Two-year recurrence-free survival, median period of first recurrence, the number of tumour progression and the number of recurrences during follow-up in the 2 groups. Regarding the safety profile in the 2 groups micro-hematuria was seen more in chemotherapy group, frequency of micturition was similar and bladder irritation symptoms showed smaller incidence in bladder irrigation group.

In a prospective, randomized, open-label, single-centre, two-arm pilot study between an immediate MMC instillation after TURBT and sterile water irrigation (CSWI) was undertaken between December 2013 and September 2015 with 19 patients in CSWI group and 15 patients in MMC group.[19] After 12 months, recurrence-free rates were 52% for CSWI group and 47.1% in MMC group. The mean recurrence-free period for CSWI group was 9.8 months and for MMC group 10.9 months. The difference between the 2 groups in terms of recurrence-free interval and recurrence-free rates was not statistically significant but the complications of MMC were significantly higher in MMC than CSWI group (P=0.047).

DISCUSSION

NMIBC not only incurs a financial burden on the health care delivery system but also necessitates a long-term surveillance to check for recurrence. In high risk patients there is also uncertainty about the possible progression and a need for radical treatments in future. Multiple effective strategies to prevent the risk of recurrence and progression have been tried which include intravesical chemotherapy and immunotherapy.[20] A good TURBT being both diagnostic and therapeutic should theoretically be curative as well but the research shows a substantial number of recurrences are because of residual tumours though particularly in intermediate and high risk T1 cancers.[21,22] The risk of residual tumour after TURBT for T1 tumours is between 33% and 55% and 41.4% for G3Ta cancer. EAU (European Association of Urology) and AUA (American Association of Urology), in order to prevent the recurrence and progression recommend the intravesical chemotherapy.[23]

As the main objective of this review is to analyse the efficacy and safety profiles MMC postoperatively against CBSI in low to intermediate risk bladder cancers the 6 papers matched the important criteria. In a study by Onishi et al the recurrence-free rates between the 2 groups at 1, 3, and 5 years did not show a statistically significant difference, but the progression was slightly more in CSBI patients. The local toxicities were seen in more patients in the MMC group. This

paper recommends CSBI as an alternative to MMC in view of low toxicity, low costs and easier to handle properties. The results of this study have to be assessed with a caution as it was not a multi-centre study.

In another study Onishi et al, in high grade NMIBCs, it was concluded that though no major statistically significant differences were noted regarding recurrence and progression but a larger study is necessary to prove the equivalence or non-inferiority of CSBI.[15] Being easier to administer following TURBT with a reduced risk of adverse events CSBI may be the treatment of choice in patients with high grade NMIBC.

In the study by Lenis et al. a significant improvement was seen in the DFS in MMC group compared to CSBI and no treatment groups and in fact there was barely any difference in the outcomes between CSBI and no treatment groups.[24] The absolute risk reduction was 12.3% in the MMC group which is almost similar to what has been referred in the literature.[24] The important argument regarding the reduced efficacy of CSBI in this study could be its use only for 2 hours postoperatively rather than 18 hours in the study by Onishi et al.[14] This study is underpowered and requires a long term follow-up to effusively appreciate the difference between the 2 postoperative treatment modalities. This study only focused on the efficacy aspects of the 2 groups and not the safety profiles.

The study by Do et al is only a retrospective study in which the efficacy of overnight continuous bladder irrigation was compared with no irrigation rather than with MMC.[17] The results if compared with the results of MMC after TURBT, in the literature, in either groups are far lower to MMC.

The study comparing MMC and sterile water irrigation is limited by a very small sample size and short follow-up though shows the comparable results between the 2 groups in terms of efficacy.

The metanalysis by Zhou et al recommends that either intravesical chemotherapy or CSBI could reduce the recurrence and progression and also improve the prognosis of the patients.[18] The 4 studies quoted that no serious complications were noted in either group however in the areas of local toxic effects CSBI was much safer to use as the incidence of macrohematuria, frequency of micturition and other irritative symptoms were much lower. CSBI in addition has no contraindication to its use as MMC cannot be used in patients with bladder perforation and gross hematuria. This study concluded that CSBI provided better balance between the prevention of recurrence and local toxicities particularly as an alternative. This study due to the short cohort of studies and relatively brief assessment of the efficacy of modalities stand out as its shortcomings. Higher quality-controlled trials with appropriate data could have added to the weight of the results and recommendations of this study.

CONCLUSIONS

In order to establish the role of CSBI as strong option as a replacement for MMC more higher quality studies with long term follow-up need to re-searched. CSBI cannot replace MMC in terms of its efficacy in the prevention of recurrence and progression but because of the better safety profile can be used as an alternative in patients with low to intermediate risk bladder cancers after TURBT.

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No funding was required during this research and authors declare no conflict of interest in preparation of this study.

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