Single-dose perioperative mitomycin-C versus thiotepa for low-grade noninvasive bladder cancer

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Introduction: *Mitomycin-C (MMC) and thiotepa are intravesical agents effective in reducing the recurrence of low-grade noninvasive bladder cancer when instilled perioperatively. No studies have compared these agents as a single-dose perioperative instillation. This study tests whether there is a difference in recurrence-free survival in patients with low-grade noninvasive bladder cancer who received intravesical MMC versus thiotepa.*

Materials and methods: *A retrospective review was performed of patients who underwent cystoscopic excision of a bladder mass identified as a small, low-grade, treatment-naïve, noninvasive, wild-type urothelial carcinoma of the bladder and who received either intravesical thiotepa (30 mg/15 cc) or MMC (40 mg/20 cc) between January 1, 2002, and January 1, 2016. Data were collected for demographic characteristics, comorbid conditions, operative information, surveillance, and recurrence. The primary outcome was disease-free survival. Cohorts were compared via the doubly robust estimation approach, which used logistic regression to model the probability of recurrence.*

Results: *Of 154 total patients, 84 received intravesical MMC; 70, thiotepa. No statistical differences were shown between groups for age, sex, race, body mass index, smoking status, or baseline comorbid conditions; mass size, tumor multifocality, or tumor grade; and unadjusted recurrence rates (MMC, 36.0%; thiotepa, 46.0%; p = .33) at similar median follow up (MMC, 20.4; thiotepa, 22.8 months; p = .46). The robust logistic regression analysis yielded no differences in recurrence rates between MMC and thiotepa (OR, 0.65 [95% CI, 0.33-1.31]; p = .23). No episodes of myelosuppression or frozen pelvis were identified.*

Conclusions: *As single-dose perioperative agents, both thiotepa and MMC were associated with similar recurrence-free survival rates.*

Key Words: bladder cancer, bladder drug administration, intravesical instillation, mitomycin-C, thiotepa

Introduction

In patients with low-risk or intermediate-risk nonmuscle-invasive bladder cancer (NMIBC), the American Urological Association guidelines panel recommends a single postoperative instillation of intravesical chemotherapy within 24 hours of complete transurethral resection of a bladder tumor (TURBT). The rationale for intravesical chemotherapy is based on preclinical data showing its beneficial effect in preventing tumor implantation in murine bladder tumor lines.[1,2] Since this critical discovery, numerous clinical trials have confirmed that cytotoxic chemotherapy can reduce the recurrence of bladder cancer when it is administered intravesically immediately after a TURBT.[3-8]

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Historically, thiotepa is one of the most widely used chemotherapeutic agents and is still the only agent with a US Food and Drug Administration (FDA) indication for treatment of noninvasive bladder cancer.[9] Because of inconsistently reported adverse effects associated with thiotepa, including myelosuppression, other drugs are now being used to treat bladder cancer, including gemcitabine and mitomycin-C (MMC). Several randomized trials have shown the superiority of a single perioperative instillation of thiotepa, MMC, and gemcitabine over placebo in preventing cancer recurrence; however, studies directly comparing these agents to each other have not been done.[5,6,10]

Therefore, we performed a retrospective comparative study to determine whether recurrence rates of low-grade, treatment-naïve noninvasive bladder cancer varied after a single perioperative dose of MMC or thiotepa. The results of this study may have implications for guiding urologists in therapeutic decision making for this patient population.

Materials and methods

Data source

For this retrospective study, we reviewed the records of patients who underwent cystoscopic excision of a small (< 5 cm), low-grade, treatment-naïve, noninvasive, urothelial cell carcinoma of the bladder and received either intravesical thiotepa (30 mg/15 cc) or MMC (40 mg/20 cc) between January 1, 2002, and January 1, 2016. The use of both of these agents overlapped in the above time period, with thiotepa more commonly used in the earlier years and MMC in the latter years. The selection of the agent used was based mainly on surgeon preference, as some surgeons preferentially used one agent over the other. Evaluation of gemcitabine, epirubicin, or doxorubicin was not possible because these agents were not commonly used for perioperative chemotherapy during this time.

Patient selection

The Mayo Clinic Institutional Review Board approved the study as minimal-risk and waived informed consent for those patients included in the study. Electronic health records were queried for adult patients (> 18 years) with noninvasive bladder cancer, which yielded over 3,000 patients. Patients with low-grade (World Health Organization [WHO] grades 1-2), treatment-naïve, noninvasive bladder cancer were included. Patients with any of the following variables were excluded: high-grade or variant histologic findings, invasion, carcinoma in situ, masses > 5 cm, lymphovascular invasion, history of bladder cancer or upper tract disease, and any adjuvant intravesical therapy other than a single dose of perioperative chemotherapy. To be included, patients also had to have a minimum 6 month follow up with postoperative surveillance cystoscopy.

Variables measured

Data were collected for the following patient characteristics: demographic variables (age, sex, race, body mass index), smoking and alcohol status, and comorbid conditions (history of hypertension, hyperlipidemia, chronic kidney disease, cerebrovascular accident, congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, and acute coronary syndrome). Perioperative information collected included the procedure date, surgeon, procedure approach (ie, excision with resectoscope versus cold-cup forceps), size of tumor resected, multifocality of the tumor, and pathologic findings (histologic characteristics, stage, grade, and presence of lymphovascular invasion). Data were also recorded for surveillance and recurrence. If a tumor recurred, the following information was recorded: recurrence date, tumor size, mulifocality, histologic diagnosis, stage, and grade. If there was no recurrence, the last surveillance date was used to determine a patient's disease-free interval (loss to follow up, end of the study period, or death).

Outcome measure, sample size, and power

The primary outcome was disease-free survival, which was determined by the period between time of diagnosis and recurrence, if there was recurrence. Secondary end points were the incidence of myelosuppression and frozen pelvis. A power calculation was then performed on the basis of the sample size to determine what effect size would achieve an 80% power. Using an alpha level of .05 and assuming equal allocation, a sample size of 55 subjects with recurrence was determined to achieve an 80% power to detect a 53% relative reduction in risk of recurrence (hazard ratio [HR], 0.47).[11] We anticipated that 40% of the patients would have recurrence, and, therefore, at least 138 patients were required for the study. Sample size calculation was performed by PASS 15 software (NCSS).

Statistical analysis

Categorical variables were summarized using frequencies and quartile ranges, and continuous variables were summarized using mean and SD. We conducted a bivariate analysis to determine the unadjusted association between treatment and patient demographic and clinical characteristics. We applied

a doubly robust approach by Funk et al[12] to quantify the effect of treatment on recurrence, using logistic regression to model the probability of recurrence and treatment simultaneously. This approach incorporates both an outcome model (ie, time to recurrence) and a propensity score model (ie, treatment allocation) to provide a robust estimation. The variables in the outcome model included age, sex, body mass index, smoking status (prior or current smoker), Charlson-Deyo comorbidity score, size of tumor resected, tumor grade, and multifocality. The variables to compute the propensity score for treatment allocation included type of insurance, size of tumor resected, tumor grade, and multifocality. The odds ratio (OR) for recurrence and 95% bootstrap CI were reported. We performed a complete case analysis, as there were no missing data in the variables in the model.

Sensitivity analysis

Because the outcome was treated as a binary variable, we performed several sensitivity analyses using recurrence as a time-to-event outcome. We fitted a multivariable Cox proportional hazards model to assess the effect of treatment. The covariates included the same variables as in the doubly robust models. The HR and 95% CI were reported. We also computed and compared the adjusted restricted mean survival time (RMST) for both groups. RMST, the area under the survival curve, is an alternative approach when the assumption in the proportional hazard in the Cox model is violated.[13] In this study, RMST was the mean survival time up to a given time point. The same set of covariates was used in the model, and the treatment effect was expressed as the adjusted difference in the RMST between groups.

Statistical analyses were conducted using SAS 9.4 (SAS Institute Inc.) and R 3.4.4 software (R Project for Statistical Computing). All tests were 2-sided, and a p value of < .05 was considered significant.

Results

A total of 154 patients were enrolled in the study, Figure 1: 84 received intravesical MMC, and 70 received thiotepa. No statistically significant differences between the groups were shown for age, sex, race, body mass index, smoking status, or comorbid conditions, Table 1. Of the patients, 13/67 (19.4%) men in the MMC group and 7/50 (14%) in the thiotepa group had previously been diagnosed with prostate cancer, and 4/67 (6.0%) in the MMC group and 3/50 (6.0%) in the thiotepa group had previously received some form of radiotherapy.

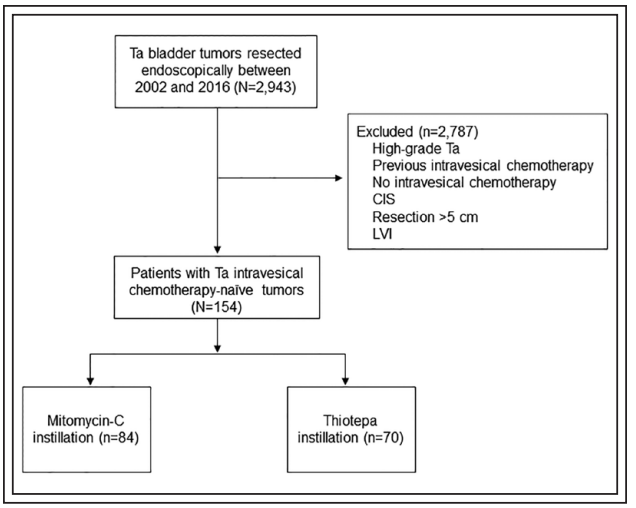

Figure 1. Identification of patients who received perioperative instillation of mitomycin-C or thiotepa after endoscopic resection of a bladder tumor. CIS = carcinoma in situ; LVI = lymphovascular invasion.

Characteristics of the tumors are shown in Table 2. No significant differences were found for surgical approach (cold-cup forceps versus resection), tumor size, or multifocality. No episodes of myelosuppression or frozen pelvis were identified in patients in either cohort.

Table 3 shows descriptive follow up statistics. Approximately 40% of patients had a recurrence by 24

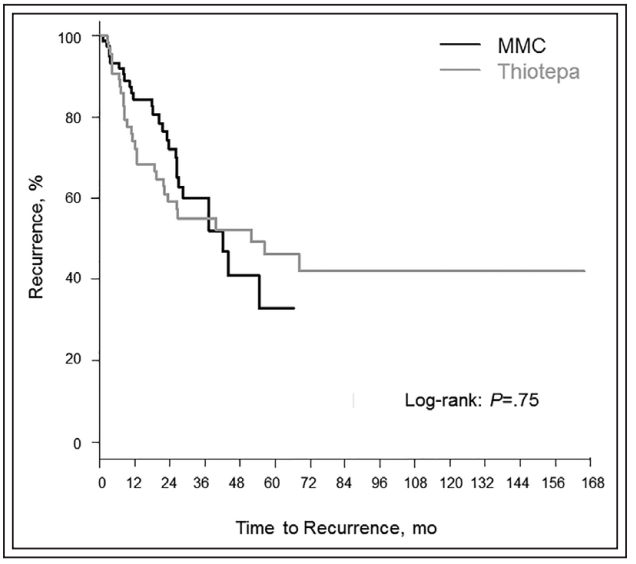

Figure 2. Kaplan-meier time-to-event estimate. No difference was shown in recurrence-free intervals between the 2 cohorts (p = .75). MMC = mitomycin-C.

TABLE 1. **Patient demographic and preoperative characteristics**

Characteristic	No. (%)[a] MMC (n = 84)	Thiotepa (n = 70)	Total (n = 154)	p value
Age at surgery, y				.49
Mean (SD)	74.3 (9.1)	73.3 (8.3)	73.9 (8.7)	
Median Q1-Q3	75.5	75.6	75.6	
Range	68.2-80.3	67.1-79.8	67.9-80.0	
Sex, female	17 (20.2)	20 (28.6)	37 (24.0)	.31
Race, white	75 (89.3)	66 (94.3)	141 (91.6)	.41
Primary insurance				.39
None	2 (2.4)	3 (4.3)	5 (3.2)	
Medicare/Medicaid/ other government	74 (88.1)	56 (80.0)	130 (84.4)	
Private	8 (9.5)	11 (15.7)	19 (12.3)	
Marital status				.80
Single	5 (6.0)	4 (5.7)	9 (5.8)	
Married	67 (79.8)	54 (77.1)	121 (78.6)	
Widowed	8 (9.5)	10 (14.3)	18 (11.7)	
Divorced/separated	3 (3.6)	2 (2.9)	5 (3.2)	
Did not answer	1 (1.2)	0 (0.0)	1 (0.6)	
Body mass index				.76
Mean (SD)	27.1 (4.3)	27.4 (4.8)	27.2 (4.5)	
Median Q1-Q3	27.0	26.7	26.8	
Range	24.1-29.8	24.0-29.7	24.1-29.8	
Current smoker	10 (11.9)	8 (11.4)	18 (11.7)	> .99
Former smoker	50 (59.4)	45 (64.2)	95 (62.3)	.66
Total pack-years				.75
No.	60	53	113	
Mean (SD)	34.1 (22.8)	32.1 (30.4)	33.4 (26.5)	
Median Q1-Q3	25.0	25.0	25.0	
Range	20.0-50.0	10.0-40.0	15.0-45.0	
Alcohol use	28 (33.3)	23 (32.9)	51 (33.1)	>.99
Drinks per week				.88
No.	28	23	51	
Mean (SD)	8.4 (6.4)	8.0 (7.3)	8.3 (6.7)	
Median Q1-Q3	7.0	7.0	7.0	
Range	3.5-14.0	2.5-14.0	2.5-14.0	
Weighted Charlson comorbidity score				.47
Mean (SD)	6.0 (1.7)	5.7 (1.5)	5.8 (1.7)	
Median Q1-Q3	6	6	6	
Range	5.0-7.0	5.0-6.0	5.0-7.0	
Medical history				
Hypertension	41 (48.8)	30 (42.9)	71 (46.1)	.57
Hyperlipidemia	48 (57.1)	32 (45.7)	80 (51.9)	.21
COPD	9 (10.7)	6 (8.6)	15 (9.7)	.86
Coronary artery disease	23 (27.4)	12 (17.1)	35 (22.7)	.19

TABLE 1 (cont.). **Patient demographic and preoperative characteristics**

Characteristic	No. (%)[a] MMC (n = 84)	Thiotepa (n = 70)	Total (n = 154)	p value
Diabetes mellitus	13 (15.5)	10 (14.3)	23 (14.9)	> .99
Chronic kidney disease	10 (11.9)	9 (12.9)	19 (12.3)	> .99
Aortic stenosis	5 (6.0)	2 (2.9)	7 (4.5)	.60
Asthma	4 (4.8)	2 (2.9)	6 (3.9)	.85
Atrial fibrillation	4 (4.8)	6 (8.6)	10 (6.5)	.53
Cerebrovascular accident	1 (1.2)	2 (2.9)	3 (1.9)	.87
Congestive heart failure	0 (0.0)	1 (1.4)	1 (0.6)	.93
Hepatitis C	1 (1.2)	1 (1.4)	2 (1.3)	>.99
Cirrhosis	0 (0.0)	0 (0.0)	0 (0.0)	
None	8 (9.5)	17 (24.3)	25 (16.2)	.02
Subgroup: men	n = 67	n = 50	n = 117	
Prior prostate cancer treatment	13 (19.4)	7 (14.0)	20 (17.1)	.44
T stage, prostate cancer				> .99
T1	3/13 (23.1)	1/7 (14.3)	4/20 (20.0)	
T2	2/13 (15.4)	1/7 (14.3)	3/20 (15.5)	
Unknown	8/13 (61.5)	5/7 (71.4)	13/20 (565.0)	
Prostate radiotherapy before TUR	4 (6.0)	3 (6.0)	7 (6.0)	> .99
Radical prostatectomy before TUR	2 (3.0)	5 (10.0)	7 (6.0)	.14

COPD = chronic obstructive pulmonary disease; MMC = mitomycin-C; TUR = transurethral resection
[a]unless otherwise indicated

months. No differences in unadjusted recurrence rates were found between MMC and thiotepa (36.0% versus 46.0%; p = .33) at median follow up (20.4 versus 22.8 months; p = .46). Kaplan-Meier disease-free estimates also did not differ between groups, Figure 2 (p = .75).

The analysis for the doubly robust estimation, performed to assess the adjusted effect of treatment on recurrence, yielded no difference in recurrence between the groups (MMC versus thiotepa: OR, 0.65 [95% CI, 0.33-1.31]; p = .23), Table 4.

TABLE 2. **Operative and pathologic characteristics**

Characteristic	No. (%) MMC (n = 84)	Thiotepa (n = 70)	Total (n = 154)	p value
Surgical approach				.73
CBF	49 (58.3)	38 (54.3)	87 (56.5)	
TURBT	35 (41.7)	32 (45.7)	67 (43.5)	
Size of resection, cm				.08
< 0.5	22 (26.2)	10 (14.3)	32 (20.8)	
0.5-2.0	45 (53.6)	37 (52.9)	82 (53.2)	
2.0-5.0	17 (20.2)	23 (32.9)	40 (26.0)	
WHO biopsy				< .001
Grade 1	75 (89.3)	46 (65.7)	121 (78.6)	
Grade 2	9 (10.7)	24 (34.3)	33 (21.4)	
Multifocality	11 (13.1)	15 (21.4)	26 (16.9)	.25

CBF = cystoscopy with biopsy and fulguration of bladder lesion; MMC = mitomycin-C; TURBT = transurethral resection of bladder tumor; WHO = World Health Organization

TABLE 3. **Descriptive follow up data**

Characteristic	No. (%) MMC (n = 84)	Thiotepa (n = 70)	Total (n = 154)	p value
Follow up, median (IQR), mo	20 (10-35)	22 (8-50)	20 (8-39)	.58
Lost to follow up	20 (23.8)	25 (35.7)	45 (29.2)	.15
Recurrence	30 (35.7)	30 (42.8)	60 (39.0)	.37
Resection, cm				.94
< 0.5	15 (53.6)	16 (51.6)	31 (52.5)	
0.5-2.0	11 (39.3)	12 (38.7)	23 (39.0)	
2.0-5.0	2 (7.1)	3 (9.7)	5 (8.5)	
> 5	0 (0.0)	0 (0.0)	0 (0.0)	
Pathologic findings				.22
Ta	25 (86.2)	30 (100.0)	55 (93.2)	
T1	2 (6.9)	0 (0.0)	2 (3.4)	
CIS only	1 (3.4)	0 (0.0)	1 (1.7)	
T2 or higher	1 (3.4)	0 (0.0)	1 (1.7)	
CIS	4 (13.3)	1 (3.3)	5 (8.3)	.31
Histologic findings				.48
Urothelial	26 (89.7)	29 (96.7)	55 (93.2)	
Adenocarcinoma	1 (3.4)	0 (0.0)	1 (1.7)	
CIS	2 (6.9)	1 (3.3)	3 (5.1)	
WHO biopsy				
Grade 1	17 (56.7)	25 (83.3)	42 (73.7)	.07
Grade 2	6 (20.0)	3 (10.0)	9 (15.8)	
Grade 3	4 (13.3)	2 (6.7)	4 (7.0)	
Grade 4	4 (13.3)	0 (0.0)	2 (3.5)	
LVI	5 (16.7)	0 (0.0)	5 (8.8)	.05
Multifocality	7 (23.3)	6 (20.0)	13 (22.0)	.95

CIS = carcinoma in situ; LVI = lymphovascular invasion; MMC = mitomycin-C; WHO = World Health Organization

TABLE 4. **Survival and sensitivity analyses**

Analysis	MMC vs. thiotepa adjusted values	95% CI	p value
Doubly robust estimation	OR: 0.65	0.33-1.31	.23
Cox proportional hazards model	HR: 0.81	0.46-1.44	.48
Restricted mean survival time, mo	Difference		
12	0.37	–0.49 to 1.22	.40
24	1.86	–0.68 to 4.41	.15
36	3.00	–1.31 to 7.32	.17
48	3.21	–3.25 to 9.67	.33
60	–1.75	–9.74 to 6.24	.67

HR = hazard ratio; MMC = mitomycin-C; OR = odds ratio

Sensitivity analysis

When using the Cox proportional hazards model to assess the effect of treatment, we found that the adjusted HR of recurrence, comparing MMC versus thiotepa, was not significant (HR, 0.81 [95% CI, 0.46-1.45]). In the model using RMST, patients who received MMC had a longer recurrence-free period than patients who received thiotepa, but after adjustment, the difference was not significant at each time point, Table 3. The results from both sensitivity analyses were consistent with the results from the doubly robust approach.

Discussion

In this study of patients with newly diagnosed, small, low-grade, treatment-naïve, noninvasive, wild-type urothelial carcinoma of the bladder, we did not find any significant difference in recurrence-free interval according to the type of chemotherapy patients received. Approximately 40% of patients had a cancer recurrence by 24 months whether they received MMC or thiotepa.

Thiotepa was the first agent to show effectiveness in reducing recurrence of NMIBC.[10] Different concentrations of the drug have been used, although results have not been consistent for the various concentrations. For instance, in an early prospective randomized controlled trial that included 51 patients, Burnand et al[10] reported a 39% greater recurrence-free rate for patients who received 90 mg/100 cc of intravesical thiotepa after transurethral resection than for control patients. Koontz et al[14] reported a 27% recurrence-free benefit with 30 mg/30 cc and 60 mg/60 cc intravesical thiotepa instilled as a maintenance regimen versus control groups in this randomized controlled trial of 93 patients. A subsequent randomized controlled trial of 417 patients by the Medical Research Council found no benefit over controls for patients who received single or long term (5 doses in 1 year) instillation of 30 mg/50 cc intravesical thiotepa.[15] The authors hypothesized that the concentration of 0.6 mg/cc used for their study may have been too low to be effective because results from previous studies had shown a benefit with higher concentrations of the drug. Masters et al[16] investigated different concentrations of intravesical thiotepa and found that, although a dose of 60 mg of thiotepa increased plasma concentrations of the drug by a factor of 2, the concentration in the bladder was 70% higher when the drug was instilled in a lower volume of 30 cc (2 mg/cc) rather than 60 cc (1 mg/cc). This result suggests that lower doses of the drug at higher concentrations can provide both a safe and effective regimen. As a result, the dose of 30 mg/15 cc (2 mg/cc) has been used in the modern era and in the present study.[17]

Several randomized controlled trials have shown the efficacy of a single perioperative instillation of MMC and thiotepa, but no direct comparison studies exist.[4,10,14,18] However, comparative trials in different disease contexts do exist. For instance, in a prospective, randomized crossover study, Zincke et al[19] compared 40 mg/40 cc MMC and 60 mg/60 cc thiotepa for NMIBC in 83 patients with stage Ta or Tis urothelial carcinoma who received one instillation of each drug after transurethral resection, followed by an instillation biweekly for a total of five treatments. The study showed no significant difference in recurrence-free rates between thiotepa and MMC at 1 year (78% versus 67.1%, respectively). In addition to its effectiveness in reducing bladder cancer recurrence, thiotepa can be instilled in the bladder if a perforation occurs, because, unlike other chemotherapeutic agents, it does not cause a caustic reaction.[17,20,21] Thiotepa is also less likely to cause dystrophic calcifications than agents such as MMC.[17,22]

Despite its effectiveness in preventing recurrence of bladder cancer and its comparable costs to conventionally used intravesical chemotherapeutic agents, thiotepa has characteristics that make it a less desirable agent for use in patients with bladder cancer. First, its low molecular weight makes it more readily absorbed, which may result in substantial systemic adverse effects.[23] For example, the incidence of leukopenia in patients who received intravesical thiotepa has ranged from 8% to 54% in various studies.[14,22,24-26] The risk of myelosuppressive adverse effects in single-instillation, low-dose thiotepa therapy is difficult to quantify because previous reports have used either higher doses of the drug or more frequent dosage regimens. For instance, in a study by Soloway and Ford,[26] 72 patients received 30 mg-60 mg perioperative doses of thiotepa followed by 3 weekly doses, then 11 monthly doses. In 3.9% of instillations, the patients' white blood cell or platelet counts decreased to below normal. Similarly, most other studies that reported myelosuppression in patients after thiotepa had more intense, frequent dosage regimens with cumulative doses of thiotepa greater than 80 mg per month, which were considered more likely to be associated with myelosuppression.[14,27,28] However, other series in which patients received intense regimens showed little evidence of systemic toxicity.[29-32] Very little data is available regarding any significant incidence of myelosuppression after a single perioperative instillation. Burnand et al[10] reported a

transient postoperative reduction in white blood cell count that did not prove to be significant. In an earlier study by the Medical Research Council, no systemic adverse effects were reported.[33]

The present study has several limitations. It is a relatively small, retrospective, single-institution study. Another limitation was the inability to compare the agents when they were solely being used during the same time period. For instance, there were periods when either agent was used exclusively because of various factors (ie, surgeon preference, availability). To obtain adequate power for this analysis, these patients were included, and robust estimation was used to correct for any potential biases that may have been present. Loss to follow up, residual confounding, and confounding by indication are issues that frequently prevent the estimation of valid treatment effects. For instance, surgeons may be more inclined to use thiotepa when the bladder wall is thin after a TURBT, and this usage may correlate with tumors that are more likely to recur. To mitigate the impact of this potential bias, we used a doubly robust estimation method that models outcome and treatment simultaneously. Theoretically, only 1 of the 2 models needed to be specified correctly to obtain valid estimates of treatment effects. Furthermore, we used conventional time-to-event models and models using RMST to test departures from various assumptions made in both the primary and sensitivity analyses. All 3 models revealed a null association. Finally, even with internally valid estimates, whether these observations are generalizable remains to be determined.

Despite the above limitations, this study has important implications for helping urologists determine treatment for this patient population because it evaluates a previously unasked question that has increasing relevance, particularly with the publication of results from the SWOG-S0337 randomized clinical trial.[5] Gemcitabine was shown to be effective in preventing recurrence of low-grade NMIBC by up to 20% through 4 years of follow up compared with controls, and it is substantially less expensive than the two agents evaluated in the current study.[34] As a result, gemcitabine may eventually become the preferred agent for managing low-grade NMIBC. A population-level comparative study across all types of perioperative chemotherapy agents is needed to determine the most effective agent, as several agents are used throughout the world that demonstrate clinical efficacy, but evaluating various components to each agent (ie, cost, adverse events, availability) may allow for consensus regarding the agent of choice for this clinical setting.

Conclusions

After resection of low-grade bladder cancer, there was no difference in disease-free recurrence when patients received a single perioperative instillation of intravesical MMC or thiotepa. Thiotepa is an acceptable alternative to MMC when MMC is not available, when the tumor resection is large, and when perforation is suspected and an intravesical agent desired.

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