1. **Protocol Title:** The **B**ladder **I**nstillation **C**omparison (**BIC)** Study: a Prospective, Open-label Randomized Clinical Trial of a Single Bladder Instillation of Mitomycin C vs. Gemcitabine vs. No Additional Treatment Immediately after Transurethral Resection of Bladder Tumor (TURBT)

2. **Investigator(s):** Brian R. Lane M.D., Ph. D. (PI); John E. Humphrey, M.D. (co-PI)

3. **Version Date:** 11.08.2019

4. **Objectives:**
   1. The primary aim of this study is to compare the efficacy of Mitomycin C 40 mg in 40 mL of 0.9% sodium chloride intravesicular vs. Gemcitabine 2 grams in 100 mL of 0.9% sodium chloride intravesicular vs. no adjuvant treatment as a single intraoperative instillation in preventing recurrence of bladder cancer.

   2. The secondary aim is to assess the incidence of dystrophic calcification or bladder calculi in each arm.

5. **Background:**

Bladder cancer is the 6th most common cancer overall (4th in men, 11th in woman). NIH predicts 74,000 new cases in the U.S. in 2015 with 16,000 deaths. About 75% of these tumors first present as non-muscle invasive bladder cancer (NMIBC) which is treated initially with transurethral resection of the bladder tumor (TURBT).[1-3] However, there is a very high recurrence rate. Historically, about 66% will recur within 5 years and 90% within 15 years. The two best predictors of recurrence are:

a) History of recurrence
b) Multiple tumors on presentation:
   - Solitary tumor at presentation has a 51% risk of recurrence
   - Recurrent and/or multiple tumors have a 91% risk of recurrence

The goal of treatment is to try to prevent recurrence by thorough TURBT that removes all of the cancerous cells.[1-3] Adjuvant instillation of chemotherapeutic agents such as Mitomycin C, Gemcitabine, Epirubicin, or Doxorubicin, has been described in literature dating back several decades. Different protocols have evaluated these agents either as a single, immediate instillation performed within 24 hours after surgery or as weekly treatments postoperatively. Nevertheless, no large strides in prevention of cancer recurrence have been made.[1-3]

Current AUA and EAU guidelines list single intraoperative instillation of Mitomycin C or Gemcitabine as options (but not standards).[3] NCCN Guidelines for secondary treatment following TURBT recommend observation or consideration of a single dose instillation.[4] This has been studied since 1975. Most of the literature has been in weekly instillations. The literature is reasonably robust for both Mitomycin C and Gemcitabine. The efficacy of Mitomycin in preventing recurrence in a meta-analysis was only 14%.[5] With techniques to optimize Mitomycin such as alkalizing the urine, dehydrating the patient overnight, emptying the bladder completely before instillation, and maximum concentration of Mitomycin (40 mg in 20cc of sterile water) some report a reduction by half.[6] However, Gemcitabine as a single instillation is poorly studied. A single study comparing Gemcitabine to a saline placebo found it safe, but with no significant difference in preventing recurrence (Gemcitabine 28% vs. Placebo 39%).[7, 8] The rate of progression to invasive disease was actually greater in the Gemcitabine arm 2.4% vs. 0.8% in the placebo arm. A second study comparing Gemcitabine with Mitomycin C showed rates of recurrence (28% vs. 39%) and progression (11 % vs. 18%) were lower with Gemcitabine but did not reach statistical significance. Both of these studies were small and further evidence is needed to add to data already published to allow for more informed treatment decisions.

Since the AUA guidelines have listed instillation as an option, it has increased in usage and indeed is treated more as a recommendation.[9] Evidence suggests that only 0.3% of Medicare patients receive immediate intravesical therapy. Data from the Urological Surgery Quality Collaborative suggest the percentage of patients receiving intravesical therapy ranges from 20-50%. The primary contraindications

to using this therapy are deep resection. Allergic cystitis has been reported in 10% of patients with more severe cases requiring cystectomy. Other barriers include drug shortage, a belief that the therapy is not effective, or that giving the medication presents too great a risk. Anecdotally, increasing observations of formation of bladder calcification and dystrophic calcification have been observed. It is unclear if Gemcitabine and/or Mitomycin C are associated with this. It also has been suggested the technique used for TURBT (bipolar / saline vs. monopolar / water) may be related.[9]

Setting of the Research:

Patients will be consented and have follow up visits in private exam rooms with the doors closed in participating surgeon's offices. Standard of care surgery will be completed in Spectrum Health Butterworth and Blodgett operating suites.

6. Resources Available to Conduct this Research:

Anticipated enrollment is 200-300 patients. The number of TURBT's performed among participating surgeons is approximately 400 annually. Enrollment is anticipated to be completed in one year with two years of follow-up for each patient.

Brian R. Lane, M.D., Ph.D. (PI), is a urologist with over 15 years' experience treating patients with bladder cancer and other genitourinary cancers who serves as the chair for cancer research at Spectrum Health. John E. Humphrey, M.D., is a urologist with 9 years of experience treating patients with bladder cancer and participating in clinical research. Treatment of these patients in this study is considered standard of care. Drs. Lane and Humphrey will provide approximately 10% FTE of research time to this project.

The research coordinator is a registered nurse. The research coordinator will provide approximately 25% of her time to this project.

Standard of care follow-up and surgery will take place in participating surgeon's offices in Grand Rapids, Michigan and in the operating suites at Spectrum Health Butterworth and Blodgett campuses.

7. Study Design:

a. Recruitment Methods

Potential subjects will be recruited during consultation for bladder tumors, either in participating physician offices or during a hospital consult. All patients requiring a TURBT will be presented with this stated research for potential participation.

Approximately 200-300 subjects will be enrolled. Subjects will not be reimbursed for participation in this study. No advertising materials will be used to recruit subjects.

b. Inclusion and Exclusion Criteria

Inclusion Criteria:

To be eligible for this study, patients must:

1. Be over 18 years old
2. Sign an Informed Consent Form for the study
3. Be scheduled for a TURBT for suspected non-muscle invasive bladder tumor (Stage cTa, cT1 or Tis).

Exclusion Criteria:

1. Patients unable to consent for themselves
2. Individuals under 18 years old
3. Pregnant women
4. Prisoners

5. Patients with known allergy or intolerance to the Mitomycin C or Gemcitabine
6. Any other sound medical, psychiatric and/or social reason as determined by the investigator

c. Study Endpoints

- To compare the efficacy of Mitomycin C 40 mg in 40 mL of 0.9% sodium chloride intravesicular versus Gemcitabine 2 grams in 100 mL of 0.9% sodium chloride versus no adjuvant treatment as a single intraoperative instillation immediately after TURBT in preventing NMIBC recurrence. Efficacy will be measured by the number of patients with Grade 3 through Grade 5 Adverse Events that are related to study treatment, graded according to NCI CTCAE Version 4.03.

- The secondary endpoint for this study will the incidence of dystrophic calcification or bladder stones measured by the number of patients with Grade 3 through Grade 5 Adverse Events that are related to study arm, graded according to NCI CTCAE Version 4.03.

d. Procedures Involved in the Research

This is a Phase III, prospective, randomized, open label clinical trial comparing two different FDA approved medications for bladder cancer and no medication given as a single dose immediately following TURBT.

All tests and visits the patient will participate in involve standard of care treatment. No tests or visits will be completed only for research purposes. At the time the surgeon identifies that a patient needs to have a TURBT the patient will be presented with the study materials. The patient will then have the opportunity to read the ICF and ask questions about the study. Patients may consent while in office or may take home for consideration and complete their ICF at a later date if they chose to participate.

Standard of care cystoscopies will be performed on a regular schedule to assess patients for toxicity and tumor recurrence.

Data for the study will be extracted from the patient's electronic health records (EHR), EPIC at SHMG, Cerner at Spectrum Health Hospitals, and the EHR at Urologic Consultants P. C.

The overall duration of the research is three years. One year to complete enrollment and two years of standard of care follow up for all patients.

Data being collected will include age, sex, race, height, weight, BMI, smoking history, operative time, estimated blood loss, number of blood transfusions (if applicable), size of turmor(s), number of tumors, grade of tumors, and pathological stage of tumors. Post-operative data being collected will include time to recurrence of bladder tumors including size of tumor(s), number of tumors, grade of tumor(s), pathological stage of tumors and any further standard of care treatment the patient may receive.

e. Data Management

Data being collected will include age, sex, race, height, weight, BMI, smoking history, operative time, estimated blood loss, number of blood transfusions (if applicable), size of tumor(s), number of tumors, grade of tumors, and pathological stage of tumors. Post-operative data being collected will include length of hospital stay, time to recurrence of bladder tumors including size of tumor(s), number of tumors, grade of tumor(s), pathological stage of tumors, pain scale, and pain medications used following the procedure, unplanned office visits, readmissions, and any further standard of care treatment the patient may receive.

There are no specimens for this study. Data will be extracted by dedicated study personnel from Cerner, EPIC, and other EHR platforms. Information transmitted by Urologic Consultants P. C. will be sent via facsimile to the dedicated research fax machine in the locked research coordinator's office.

The data will be used to compare the efficacy of Mitomycin C vs. Gemcitabine vs. no adjuvant treatment after TURBT as well as assessing the safety and toxicity of the different treatments arms by comparing incidence of dystrophic calcification or bladder calculi in each arm.

This data will be combined into a secure spreadsheet on the Spectrum Health network and accessed only by study personnel. The data will be quantified to determine the total number of incidences resulting in safety and toxicity concerns (i.e., readmissions, unplanned office visits, etc.) as well as number of recurrences of bladder cancer across all arms.

Data Management: Power Analysis

Power Analysis was performed using SAS 9.4 for the log rank test to test solely for pair-wise differences between survival curves of patients in each treatment (Mitomycin C, Gemcitabine alone, or no adjuvant treatment). Since we will be doing three log rank tests to test for pair-wise differences (i.e. Mitomycin C vs. no treatment, Gemcitabine vs. no treatment, and Mitomycin C vs. Gemcitabine), we use a Bonferroni correction on the assumed two-tailed significance level of .05 to get a significance level of .05/3=.016. The analysis further assumes a 1 year accrual period followed by a 2 year follow-up period with 3 month follow-up intervals, and that the survival curves for each of the pair-wise tests are of exponential form with recurrence probability of 66% at 5 years (for no adjuvant treatment) versus an estimated 43% at 5 years (for both Mitomycin C and Gemcitabine). Given a sample of 80, 100, 120, or 140 patients per treatment group, the estimated power levels are, respectively, 0 .480, 0.590, 0.684, and 0.762. Note that these figures assume no loss to follow-up and; therefore, to maintain power, an increase in sample size may be desired in order to compensate for patient withdrawal from the study.

The POWER Procedure
Log-Rank Test for Two Survival Curves

Fixed Scenario Elements	
Method	Lakatos normal approximation
Number of Sides	2
Accrual Time	1
Follow-up Time	2
Number of Time Sub-Intervals	4
Alpha	0.016
Group 1 Survival Curve	Standard
Form of Survival Curve 1	Exponential
Group 2 Survival Curve	Proposed
Form of Survival Curve 2	Exponential
Group 1 Loss Exponential Hazard	0
Group 2 Loss Exponential Hazard	0

Computed Power		
Index	N per Group	Power
1	80	0.480
2	100	0.590
3	120	0.684
4	140	0.762
5	160	0.823

Provisions to Monitor the Data for the Safety of Subjects

Patients will have standard of care cystoscopies performed at regular intervals to assess for tumor recurrence or drug toxicity.

f. Withdrawal of Subjects

Patients will be discontinued (prematurely) from the study if they withdraw consent or if the study is closed early by the investigator.

If a patient withdraws from the study at any time the reason for withdrawal will be recorded by the Investigator in the patient's EHR. If a patient withdraws prematurely from the study, data that has been collected cannot be removed from the study however, no further data will be collected.

8. Statistical Plan

a. Sample Size Determination

Anticipated enrollment is 200-300 patients. The number of TURBT's performed among participating surgeons is approximately 400 annually.

b. Statistical Methods

Data will be summarized as medians and interquartile ranges. Outcomes will be presented as risk ratios with 95% confidence intervals. The distribution of continuous variables will be compared using t-tests for independent samples and Wilcoxon rank sum tests with continuity correction when the data appear to violate normality assumptions. The distribution of categorical variables will be compared using Pearson chi-square tests with Yates' continuity correction and exact Fisher tests when the proportion of patients in one or more categories is less than 5%. Kaplan-Meier analyses are used to evaluate survival; differences between cohorts are tested with the log rank test. Statistical significance will be assessed based on a two sided significance level of 0.05.

9. Risks to Subjects

The risks of the TURBT and potential medication administration will occur regardless of if the patient participates in the protocol and will be explained to the patient in a separate surgical consent form.

10. Potential Benefits to Subjects

No anticipated direct benefits can be promised to patients for taking part in the research.

The primary benefit of the study is that it will provide information to the scientific community to help better understand how to best treat non-muscle invasive bladder cancer.

11. Provisions to Protect the Privacy Interests of Subjects

All study patients will be assigned a de-identified study number. No personal identifiable information will be shared with those performing data analysis. Only the primary research coordinator will have access to the list of patients and their de-identified numbers.

No personal information will be used in any potential publications.

12. Provisions to Maintain the Confidentiality of Data

Only study personnel will have access to personal health information. All study records will be kept in locked files in the locked research coordinators office. Electronic data will be stored on pass word protected Spectrum Health HIPAA compliant computers.

Data being transmitted from Urologic Consultants P. C. will be done via facsimile and sent to the dedicated research fax machine in the research coordinators locked office.

Data will be stored in accordance with the Spectrum Health System Policy# Sh-Admin-RES-019 that states "to maintain all required research records, including original signed consent forms and IRB submissions and approvals, during the study and for 10 years from the date of the submission of the final expenditure report to the funding agency, or per contracted agreement with the study sponsor, or for 3 years post study closure with the Spectrum Health IRB, whichever is longer, per the IRB Investigator Manual, available on the IRB website".

13. Medical Care and Compensation for Injury

All procedures in this study are standard of care. There are no research related activities that pose a physical risk to the patient. The risks of TURBT and medications will be described in a separate surgical consent form.

If a patient is injured or made sick from taking part in this research study, medical care will be provided. Patients will be responsible to report to the Investigator as soon as possible any possible injuries, illnesses, or conditions that they believe occurred or worsened as a result of their participation in this study.

No funds have been provided for injury care so the patient or his insurance company would be responsible for the cost of injury care.

14. Cost to Subjects

There are no research costs to the patient or their insurance company to participate in this study. The surgery and medications in this study are all standard of care. The patient's insurance company will be billed for all standard of care items and the patient will be responsible for standard of care co-pays.

15. Consent Process

The consent process will take place in the Investigator's office in a private exam room or in the research nurse's office with the doors closed. If the patient is consented in the hospital, the process will occur in a private room or office with the door closed.

Only personnel listed on the IRB study paperwork will be allowed to consent patients. Patients will be given the Informed Consent Form (ICF) at their appointment. They will be given adequate time to read the consent and have all of their questions answered.

Patients will be encouraged to take the consent home to read and discuss with their families. If the patient is in the hospital and needs more time to think about it, the study personnel will return at a later time to complete the discussion.

Patients will demonstrate understanding of the research study through open dialogue with the research nurse and/or Investigator. No patients will be coerced or influenced to participate in the study as this is completely voluntary.

16. Vulnerable Populations

No vulnerable populations will be included in this research.

17. Sharing of Results with Subjects

Research results may be presented in an abstract at a research conference; however, we will not directly share the research results with patients whose charts have been reviewed for the purpose of the study. A manuscript of the study is tentatively scheduled for submission as well.

18. References

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19. Attachments