

A Phase III, Double-Blind, Randomized Study Comparing Intravesical Instillations of BCG Plus Docetaxel and BCG Plus Interferon- α 2B in BCG-Refractory Superficial Bladder Cancer

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A. Introduction

In 2002, it is estimated that 56,500 new cases of bladder cancer will be diagnosed in the United States and 12,600 people will die from the disease. This makes bladder cancer the fourth leading cause of cancer in men and the eighth leading cause of cancer in women in the United States. (Jemal et al, 2002). Bladder cancer is the second most common genitourinary cancer and its etiological factors include smoking, occupational exposure in the form of aniline dyes, and bacterial and parasitic infections. Transitional cell carcinoma is the most common histological type.

Superficial bladder cancer accounts for 70 to 80 percent of these cases and the natural history can vary widely with recurrence being common. Superficial bladder cancer includes tumors limited to the mucosa (Ta and Tis) and those tumors limited to the lamina propria (T1). Transurethral resection of bladder tumor represents the cornerstone of treatment for bladder cancer with the goal to excise all visible tumor and obtain tissue for pathological assessment. Tis and high grade Ta and T1 tumors (Grade 2 & 3) have greater recurrence rates and malignant potential. Recurrence rates after transurethral resection in this subset of the patient population have ranged from 50-80 percent. In patients with these high-risk pathological features, the use of adjuvant (after transurethral resection) intravesical therapy to prevent adverse outcomes has become the standard of care. The goal of adjuvant intravesical therapy is to reduce recurrence as well as progression to muscle invasion.

Bacillus Calmette-Guerin (BCG) has been shown to be the most effective agent for delaying recurrent CIS and high grade stage T1 bladder cancer. BCG attaches to the bladder urothelium and subsequently causes a local immunological response. The host's immunological response attacks aberrant cells and has been shown to delay and prevent recurrence. The recent AUA Bladder Cancer Clinical Guidelines Panel (Smith et. al, 1999) noted that BCG after TURBT decreases recurrence rate 30 percent compared with TURBT alone. Yet, 50 percent of patients will recur after treatment with BCG within 5 years, with most relapsing in less than 2 years (Nadler et. al, 1994). Other chemotherapeutic agents including Mitomycin C, thiotepa, doxorubicin have also been minimally effective in prophylaxis for superficial bladder cancer.

In patients who fail at least one course of BCG (i.e. have a recurrence), the majority of urologists advocate cystectomy with some type of urinary diversion. Cystectomy, especially for those patients with high-risk pathological features, is the option most likely to improve patient survival. Cystectomy is usually advocated for patients who fail single or multiple courses of BCG. Major surgery, however, in many bladder cancer patients is contraindicated given the presence of several comorbid conditions, including serious underlying cardiac and respiratory disease. Many patients for quality of life reasons simply refuse cystectomy.

In patients who refuse cystectomy or who do not medically qualify for cystectomy, there are a paucity of effective options once they fail a prior course of BCG. Repeat BCG courses have limited effectiveness (Catalona et al., 1987). Invasive or metastatic disease occurred in 25 percent of patients with a second course of BCG. Invasive or metastatic disease occurred in 80 percent of patients after a third course of BCG. Chemotherapy after BCG failure has been shown to be minimally effective as well. Only 23 percent of patients were disease-free at 2 years with mitomycin C (Malmstrom et al, 1999). In

patients with recurrent Tis, only 8 percent were disease-free at 2 years with Valrubicin (Steinberg et al, 2000).

Additional immunotherapy, however, has shown early promise and in combination with BCG seems to be the most effective. A combined regimen of intravesical low-dose BCG plus interferon- α 2B resulted in 53 percent of patients showing no evidence of recurrence at 2 years (O'Donnell et al., 2001). This regimen, although in its earlier stages, seems to warrant further studies in randomized clinical trials.

In this proposed clinical trial involving patients with BCG-refractory superficial bladder cancer, we will evaluate the effectiveness of the low-dose BCG/Interferon combination in comparison with a low dose BCG/Taxotere combination. The primary outcome of this study will be percentage of patients in both groups who are recurrence-free at 24 months.

B. Study Purpose and Rationale

The purpose of this study is to evaluate the effectiveness of two different treatments for recurrence prophylaxis of patients with superficial bladder carcinoma who have failed a prior treatment of BCG. One randomized group of patients will receive a low-dose BCG/Interferon combination and the other randomized group will receive a low-dose BCG/Taxotere combination. The hypothesis of the study is that we will find a difference in clinical outcomes between the two groups. The outcomes to be determined will be percentage of patients in both groups who are recurrence-free at 24 months, median time difference in the two groups to first recurrence, evidence of disease progression in the two groups as determined by biopsy, and side effects in the two groups as determined by the National Cancer Institute common toxicity criteria version 2.0.

The rationale for undertaking this Phase III trial is that there are presently few options for patients with recurrent superficial bladder carcinoma who fail a prior treatment of BCG. Many patients who medically qualify go on to have a cystectomy. Cystectomy, however, may be over-treatment for a superficial bladder tumor with low-risk pathological features. In addition, many patients, because they have both significant cardiac and pulmonary co-morbidities, are not candidates for a major surgery such as a cystectomy with urinary diversion. Furthermore, many patients fearful of an adverse quality of life and the prospect of undergoing a major surgery, simply refuse to have cystectomy performed. For these groups of patients, it is necessary to continue to explore other intravesical options.

C. Study Design and Statistical Analysis

This study will be a Phase III prospective, randomized, double-blinded study comparing a BCG/Interferon combination and BCG/Taxotere combination in patients with BCG-refractory superficial bladder cancer. The primary outcome of the study will be the percentage of patients who are recurrence-free at 24 months. Recurrence in this study will be defined as pathological evidence of bladder carcinoma of any stage or positive cytology on 2 consecutive evaluations with a negative biopsy result. All patients in this study will have a diagnosis of superficial bladder carcinoma confirmed at the study site. All patients will have previously failed at least one course of BCG alone or one course of BCG in combination with another standard intravesical therapy. The patient's recurrence will be treated by transurethral resection of the bladder tumor or tumors. At the time of study initiation, patients will have no evidence of bladder tumor by cystoscopy. The medications in this study will solely be given for prophylaxis.

After subjects meet the inclusion and exclusion criteria and after giving proper informed consent, they will be randomized into two groups. Both randomized groups will have similar median ages. Each randomized group will have similar numbers of equivalent stage (Ta, T1, Tis) patients. Both subjects and their primary urologists will be blinded in all aspects of the trial. After the medications are received from the respective pharmaceutical companies, the medications will be prepared by pharmacists at each study site. After preparation, the pharmacists will deliver the blinded drug to the patient's urologists. Patients in both groups will initially receive induction therapy weekly for six weeks. During this induction period,

the patients randomized to receive weekly BCG/Interferon will get 27 mg BCG in 50 cc saline and 50 million units of interferon. The BCG dose consists of 1/3 the regular amount (81 mg) that patients usually receive. During the induction period, the patients randomized to receive weekly BCG/Taxotere will get 27 mg BCG in 50 cc saline and 40 mg of Taxotere. Patients disease-free after induction will be given maintenance therapy consisting of a 3 weekly mini-series at 5, 11 and 17 months after the start of induction. The maintenance therapy during week 1 will consist of 27 mg BCG in 50 cc saline and 50 million units of interferon. The week 2 and week 3 dose of BCG will be lowered to 8 mg. During all three weekly maintenance treatments, both the Taxotere and Interferon dose will be constant, 40 mg and 50 million units respectively.

Patients will be evaluated by cystoscopy, cytology and biopsy beginning 3 months after start of induction therapy in order to evaluate response to treatment. Cystoscopy will be performed every 3 months thereafter with cytology and biopsy if necessary. Cystoscopy will be performed at the study site by the patient's blinded urologist. Biopsies and cytology will be evaluated at the study site by a blinded pathologist. During treatment, subjects will have a weekly CBC and CMP drawn in order to monitor for any hematologic and electrolyte abnormalities. During the weekly visit, patients will be asked about any local symptomatology including gross hematuria, dysuria, urinary urgency or urinary frequency. The patients will be scored using the National Cancer Institute common toxicity criteria version 2.0 (see appendix 1). If any grade 3 or 4 symptoms occur, the patient will be immediately removed from the trial and offered immediate care. If patient develops any grade 2 symptoms, treatment may be delayed one week. If symptoms resolve, patient will continue on the trial as scheduled. If they do not resolve, patient will be immediately be withdrawn from the trial. There will be no planned crossover. Patients will be withdrawn from the study if tumor shows muscle invasion (T2) on biopsy. If medically feasible, these patients will be offered cystectomy.

Patients will have cystoscopy performed every three months. The primary outcome will be recurrence rate at 24 months. If a patient recurs, he or she will be taken off the trial and if medically feasible, offered cystectomy. If the patient refuses cystectomy or is not a candidate for a cystectomy, they will have a transurethral resection of their bladder tumor performed with biopsy. They will then be counseled on all of their options and a informed decision will be made about further intravesical treatment.

This study calculated a sample size using an α of 0.05, a power of 80 percent, and a two-sided test. The BCG/Interferon combination has a 2-year recurrence-free rate of 50 percent, according to the literature. The assumption is that Taxotere may have a 2-year recurrence-free rate of 70 percent, which would be clinically significant. We therefore wish to detect an improvement in cure rate of 20 percent. Using chi-square calculation, we thus would need 93 subjects in each of the study groups. Kaplan-Meier method will be used to assess the percentage of patients who are free from recurrence (Y-axis) at a specified monthly interval (X-axis) after treatment initiation.

D. Study Procedures

There will be no procedures performed in these subjects which are not part of routine care and follow-up in patients with bladder cancer. All patients will have a cystoscopy performed in the office. This consists of inserting a telescope into the bladder and observing the bladder mucosa for any abnormalities. Topical anesthetic solutions will be used for patient comfort. Cytology will be obtained by washing the bladder through a catheter and collecting bladder cells for pathologic evaluation. If patients require a bladder biopsy, they will be taken under general anesthesia. Suspicious areas will be biopsied with cup biopsy forceps and the areas cauterized with an electrode. Every patient will have a biopsy performed at three months, but then only if cystoscopic exam requires one to be performed. Patients will have cystoscopic exam every three months while they are on the study. This is the normal standard of care for patients with superficial bladder tumors. Patients will be enrolled indefinitely with close follow-up until they develop a recurrence of bladder cancer.

E. Study Drugs

Bacillus Calmette Guerin (BCG) is an approved intravesical agent for the treatment of bladder cancer. BCG is an attenuated strain of *Mycobacterium bovis*. BCG works by establishing a local immunological response in the bladder. The release of cytokines and the activation of helper T lymphocytes create an immunological response against any tumor cells present after transurethral resection. AUA Bladder Cancer Clinical Guidelines Panel (Smith et. al, 1999) noted that BCG after TURBT decreases recurrence rate 30 percent compared with TURBT alone. The most commonly recommended induction regimen is BCG weekly for 6 weeks followed by 6 weeks without BCG. At 12 weeks, if no cancer is present, BCG is given weekly for three weeks. Side effects of BCG include urgency, frequency, and occasionally hemorrhagic cystitis.

Interferon- α 2b is given intravesically and is an immunostimulant which works by creating a sufficient immunological response against residual tumor cells. Interferon has been shown to induce a complete response in up to 40 percent of patients with superficial bladder cancer, but most have a relapse within 1 year. Previous studies have shown interferon to be effective when combined with BCG weekly for 6 weeks and then a maintenance dose three months after end of induction. The dose of interferon was 50 million units.

Taxotere is in the planning stages for a phase I trial evaluating its safety in the intravesical form. Taxotere exerts its chemotherapeutic effect through its ability to promote the intracellular bundling of microtubules. The subsequent inhibition of microtubule depolymerization to tubulin results in M-phase-cell-cycle arrest. This eventually leads to cell death. Taxotere was shown to be one of the most effective agents in inhibiting growth in human bladder tumor cell lines (HBTCL) at concentrations as low as 0.1 micromolar. This agent suppressed clonal growth in 100 percent of cell lines tested at this concentration (Rangel et al., 1994). Taxotere has been shown to be effective intravenously for a wide range of solid tumors, including metastatic bladder cancer.

F. Medical Devices

There will be no medical devices used in this study.

G. Study Questionnaires

There will be no study questionnaires used in this study.

H. Study Subjects

All patients will be identified by staff urologists at CPMC Urology Clinic or other study institution. Patients will be counseled about all of their options including cystectomy provided that they obtain medical clearance.

Inclusion Criteria

- a. Men and women >18 years of age with superficial bladder carcinoma
- b. Patient must have Ta, T1 or Tis disease.
- c. Patients must exhibit recurrence after receiving some form of standard intravesical therapy (BCG or combination using BCG)
- d. All grossly visible disease must be fully resected
- e. Normal upper tract study (IVP, CT) within 3 months of enrollment
- f. Hematologic-Inclusion within 2 weeks of treatment:

Absolute neutrophil count $\geq 1,500/\text{mm}^3$

Hemoglobin ≥ 8.0 g/dl

- Platelet count $\geq 100,000/\text{mm}^3$
- g. Hepatic-Inclusion within 2 weeks of entry:
Total Bilirubin must be within normal limits.
Transaminases (SGOT and/or SGPT) may be up to 2.5 x institutional upper limit of normal (ULN) if alkaline phosphatase is \leq ULN, or alkaline phosphatase may be up to 4 x ULN if transaminases are \leq ULN.
- h. Women of childbearing potential must have a negative pregnancy test. Men and women of childbearing potential must be willing to consent to using effective contraception, i.e., IUD, Birth control pills, Depo-Provera while on treatment and for a reasonable period thereafter
- i. No intravesical therapy within 6 weeks of study entry

Exclusion Criteria

- a. Patients with muscle invasion (T2)
- b. Previous systemic or radiation therapy for bladder cancer
- c. Any newly diagnosed cancer (except non-melanoma skin cancer) diagnosed within 2 years of study entry
- d. Concurrent treatment with any chemotherapeutic agent
- e. Women who are pregnant or lactating, or not willing to use birth control

I. Recruitment of Subjects

Potential subjects will be identified through the private physician practices in the Urology Department at CPMC as well as in other urology departments at the other study sites. Each patient's participation in the study will be agreed upon by the patient's urologist, primary care physician (if one exists) and the patient.

J. Confidentiality of Study Data

Any information obtained during the study will remain confidential and will be stored in a secure, locked location in the Urology departments at the various study sites. This information will be accessible only to the study staff. All patients will be assigned a unique code number and will be identified during the trial by only this code number.

K. Potential Conflict of Interest

None of the investigators in this study have a proprietary interest in BCG, Interferon, Schering-Plough, Taxotere or Aventis Pharmaceuticals. None of the investigators will stand to benefit financially in any way from the results of this investigation.

L. Location of the Study

Participants will be evaluated and followed at the Department of Urology located on the 11th floor of the Herbert Irving Pavilion at Columbia-Presbyterian Medical Center as well as in various urology departments at other study sites, including MD Anderson Cancer Center and Memorial Sloan-Kettering Cancer Center.

M. Potential Risks

The main risk of this protocol is that the patient's bladder tumor may progress to muscle invasive disease. We are confident that given the rigorous follow-up, including routine cystoscopy, that this event will be rare. If a patient progresses to muscle invasive disease and is medically fit, they will immediately be pulled out of the study and a prompt cystectomy will be arranged. Since most patients will not be eligible for cystectomy or will have previously refused it, we feel that this risk is outweighed by the potential for benefit.

The other risk is local toxicity as manifested by gross hematuria, urgency, frequency, or nocturia. These are standard risks involved in any intravesical therapy. Patients will be closely monitored for these side effects. Treatment can be postponed for one week if patients develop grade 2 or 3 toxicity. If grade 4 toxicity develops, patients will be taken out of the study and offered the standard of care.

The intravesical therapy procedure may also cause discomfort when the catheter is inserted into the urethra. There is a slight risk of infection that may result from insertion of the catheters. Antibiotic treatment of the infection will be provided if necessary.

Because of possible dangers to an unborn fetus, all women capable of having children must have a negative pregnancy test at screening. During the study you must use either oral contraceptive pills (and have used them for at least three cycles), use a double barrier method of contraception (use of a diaphragm and a condom together), or use Depo-Provera[®] (having completed at least one month of treatment). If you are not post-menopausal for at least two years, you must agree to use a method of contraception.

The risks of drawing blood from a vein include pain at the site of collection, possible bruising around the collection site, rarely an infection or inflammation of the vein, and uncommonly, faintness from the procedure. Care will be taken to minimize these complications.

N. Potential Benefits

There is no guarantee that the patient's disease process will improve. The potential benefit to the patient is the possibility of a chemotherapeutic or immunotherapeutic response and thus the avoidance of radical surgery (cystectomy).

O. Alternative Therapies

When currently available intravesical agents fail to control the disease the only option is radical cystectomy with urinary diversion. This still remains an option for those patients who choose it and who are medically fit to have the procedure performed.

P. Compensation to Subjects

No compensation will be offered to study subjects.

Q. Costs to Subjects

Any procedures or tests that are done solely for research will be paid for by the study supporter, Aventis. The study supporter will not pay for any expenses that are part of normal medical care. The costs of necessary medical treatment will be charged to the subject or their insurance company.

All forms of medical diagnoses and treatment, whether routine or experimental, involve some risk of injury. In spite of all precautions, the subject might develop medical complications from participating in the study. If such complications arise, the researchers will assist in receiving appropriate medical treatment.

R. Minors as Research Subjects

This study will not include minor subjects.

S. Radiation

There is no exposure to radiation other than routine imaging studies. CT and plain radiographs are the standard of care in bladder cancer management and will be used in this study.

T. References

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APPENDIX 1

Bladder toxicity as defined by the National Cancer Institute common toxicity criteria version 2.0

Gross Hematuria (in the absence of vaginal bleeding)

Grade 1: microscopic only

Grade 2: intermittent gross bleeding, no clots

Grade 3: persistent gross bleeding or clots; may require catheterization or instrumentation, or transfusion

Grade 4: open surgery or necrosis or deep bladder ulceration

Grade 5: death related to toxicity

Dysuria (painful urination)

Grade 1: mild symptoms requiring no intervention

Grade 2: symptoms relieved with therapy

Grade 3: symptoms not relieved despite therapy

Grade 4: N/A

Grade 5: death related to toxicity

Urinary retention

Grade 1: hesitancy or dribbling, but no significant residual urine; retention occurring during the immediate postoperative period

Grade 2: hesitancy requiring medication or occasional in/out catheterization (<4 x per week), or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for <6 weeks

Grade 3: requiring frequent in/out catheterization (>= 4 x per week) or urological intervention (e.g., TURP, suprapubic tube, urethrotomy)

Grade 4: bladder rupture

Grade 5: death related to toxicity

Urinary frequency/urgency

Grade 1: increase in frequency or nocturia up to 2 x normal

Grade 2: increase > 2 x normal but < hourly

Grade 3: hourly or more with urgency, or requiring catheter

Grade 4: N/A

Grade 5: death related to toxicity

Bladder spasms

Grade 1: mild symptoms, not requiring intervention

Grade 2: symptoms requiring antispasmodic

Grade 3: severe symptoms requiring narcotic

Grade 4: N/A

Grade 5: death related to toxicity