

Prospective Phase II Trial of intravesical Taxotere in conjunction with Bacillus Calmette Guérin-Interferon Alpha IIB in the Treatment of Recurrent Superficial Transitional Cell Carcinoma of the Urinary Bladder

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A. Study Purpose and Rationale

This is a phase II study to determine the efficacy and toxicity of intravesical Taxotere in conjunction with Bacillus Calmette-Guérin (BCG)-Interferon Alpha IIB (IFN) in the treatment of recurrent superficial transitional cell carcinoma (TCC) of the urinary bladder. The purpose of this trial is to see whether the addition of intravesical Taxotere to BCG-INF increases disease-free survival by a clinically important parameter for patients with refractory TCC. As many patients failing intravesical treatment are left with cystectomy as their only option, there is a need for the development of alternative nonsurgical options for refractory TCC.

a. Background

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). Superficial bladder cancer accounts for 70 to 80 percent of these cases and the natural history can vary widely with recurrence being common. In individual cases with high-risk clinical and pathological features (Ta, T1 and Tis), the use of intravesical therapy to prevent adverse outcomes has become the standard of care. However up to 50 percent of patients treated with intravesical therapy for high-risk superficial bladder cancer or carcinoma in situ will recur (Kim & Steinberg, 2001). Response rates to second-line intravesical therapy are 20 percent or less in this population. When currently available intravesical agents fail to control the disease, the option most likely to improve patient survival is radical cystectomy (the surgical removal of the bladder) with urinary diversion. Cystectomy is performed in patients with high-risk superficial bladder tumors in order to prevent death from metastatic bladder cancer. Many patients, however, are not candidates for cystectomy because either they possess several comorbid conditions or because they simply refuse to undergo the major procedure (Crawford 2002). For these patients, there are currently no active chemotherapeutic alternatives, and thus there is a definite need to investigate other intravesical options.

Intravesical BCG installation has been proven to be the most effective agent in reducing the rate of recurrence and progression of bladder cancer; however, it is associated with significant toxicity (Brosman 1992). Intravesical instillation of recombinant interferon- α -IIB, though less effective than BCG as a monotherapy, has demonstrated higher efficacy when combined with reduced dose BCG than either agent alone (Stricker et al, 1996). Additionally, combination therapy using both agents has been shown to rescue patients refractory to BCG alone and reduce BCG-associated toxicity (O'Donnell et al, 2001). In a larger multi-institutional study among 3 medical centers, it was found that BCG plus IFN had an efficacy of 66% with 21 out of 32 patients remaining disease free after a median follow up of 22 months. Of 20 patients previously treated with BCG, 12 patients (60%) remained disease free from the combination therapy. Additionally, patients tolerating BCG in prior studies received a one-third dose of standard BCG + 50 million units (MU) of IFN α -IIB administered intravesically over 6 weeks, and were found to tolerate this dose (Lam et al, 2003). Because of these results low-dose combination BCG-IFN is becoming a popular treatment for individuals seeking alternatives to cystectomy.

In 1960, the National Cancer Institute screening program introduced paclitaxel (Taxol), an extract from the bark of the Pacific Yew, namely *Taxus brevifolia* L. (Wani et al, 1971). Wani et al, isolated and characterized the extracts in 1971. Paclitaxel was found to have properties that interfere with the mitotic spindle which stabilizes microtubules and inhibits depolymerization to free tubules. Paclitaxel, however, was in limited supply.

In 1981, docetaxel (Taxotere) [(2R,3S)-N-carboxy-3-phenylisoserine, N-tert-butyl ester,13-ester with 5 β ,20-epoxy-1, 2 α ,4, 7 β ,10 β ,13 α -hexahydroxytax-11-en-9-one 4-acetate2 benzoate, trihydrate] was discovered. Docetaxel was obtained from the needles of *Taxus baccata*, a European yew which was a renewable resource. 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.

Research has shown that this taxane derivative has antitumor activity in a wide range of cancers. In bladder cancer, as a single agent, Taxotere has demonstrated safety and efficacy in patients with metastatic disease. DeWit et al, observed an overall response rate of 31% in a phase II study among 30 patients with metastatic urothelial cancer. Fourteen percent of these patients achieved a complete response (deWit et al, 1998). In a smaller published preliminary study by Dimopoulos et al in metastatic patients with renal insufficiency, 5 of 11 patients (45%) achieved a partial response (Dimopoulos et al, 1998). Experience with Taxotere combined with other chemotherapeutic agents has shown response rates ranging from 43% to 67% (Taxotere Bladder Monograph, 2002).

Both Taxol and Taxotere exhibit the same chemotherapeutic mechanism owing to their similar molecular composition. In preclinical studies these agents have proven both safe and effective with excellent cytotoxicity in cell culture and for Taxol, minimal systemic absorption in intravesical animal models (Rangel et al, 1994 and Song et al., 1997). Furthermore, in order to be maximally effective as intravesical agents, it is essential that both Taxol and Taxotere be stable inside the bladder while urine production is occurring simultaneously. It has been shown that both Taxol and Taxotere are stable within the normal narrow pH range (pH 5-7) of human urine. Rangel et. al were able to recover 85 percent of both Taxol and Taxotere 4 hours after incubation in urine samples with pH values of 5, 6 and 7 (Rangel et. al, 1994). Taxotere has been 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). In a study involving beagle dogs, Song et al. instilled 500 micrograms of Taxol in 20 mL water into the bladder of each dog (Song et al., 1997). Song et al. found that the plasma concentration of Taxol after intravesical instillation was <0.05 percent of the maximally tolerated plasma concentration of Taxol in humans (1 microgram/mL) (Song et al., 1997). Song et al. also found that intravesical Taxol produces a substantial chemotherapeutic targeting advantage with a 6000-fold higher average bladder tissue concentration of the drug compared to the steady-state plasma concentration (Song et al, 1997).

The systemic efficacy of Taxotere and the preclinical safety data available for its close molecular relative, Taxol, in the animal model made it an excellent candidate for a Phase I trial in patients with refractory superficial bladder cancer. This in conjunction with the lack of effective nonsurgical treatment for superficial transitional cell carcinoma (TCC) provides the rationale for a Phase I study.

We are currently completing this Phase I study at Columbia, where we have not shown any systemic absorption nor toxicity associated with intravesical Taxotere. We anticipate our maximum tolerated dose (MTD) to be 75mg of Taxotere, diluted in 90mL of normal saline. We have enrolled 24 patients, with groups of 3 patients receiving escalating doses of Taxotere starting at 5mg and continuing to 75mg. All of these patients have failed intravesical BCG treatment and have recurrent TCC of the bladder with a diagnosis of stage Ta, T1, or Tis, and are either refusing cystectomy or are inoperable candidates. Our data revealing the safety of intravesical Taxotere in this Phase I study sets the stage for a Phase II protocol investigating the safety and efficacy of intravesical Taxotere in conjunction with a BCG-IFN regimen.

Patients eligible for this study will either have refused a recommended cystectomy or will not be candidates for surgery due to medical comorbidities. In patients without significant medical

comorbidities, the standard of care in this population is radical cystectomy. The study duration is 12 weeks of treatment, with a 22 month follow-up. Patients who are eligible for surgery may at any time withdraw consent and proceed with a cystectomy. In a high-risk superficial bladder cancer population, a 12-week delay in cystectomy is unlikely to alter disease-free survival.

b. Hypothesis

Intravesical Taxotere in conjunction with combination BCG-INF will be clinically efficacious compared to combination BCG-INF alone for refractory TCC resistant to standard intravesical treatment. Our study is designed to look for a 10% increase in disease-free survival when intravesical Taxotere is added to combination BCG-INF. Additionally, intravesical Taxotere will also exhibit minimal toxicity when added to the BCG-INF regimen, making it a safe alternative for individuals refusing or incapable of having cystectomy.

B. Study Design and Statistical Analysis

This is a longitudinal prospective randomized study to evaluate the efficacy and toxicity of intravesical Taxotere following combination therapy with intravesical BCG-INF. Eligible patients with Ta, T1, or Tis TCC of the bladder refractory to previous BCG therapy will be randomized into two groups, one receiving combination therapy of BCG-INF for 6 weeks and the other receiving combination therapy of BCG-INF for 6 weeks, followed by intravesical Taxotere for 6 weeks. Physicians conducting post-infusion cystoscopies and biopsies will be aware to the type of treatment program the patient is undergoing.

All patients will receive one-third dose of standard BCG + 50 MU IFN administered intravesically once a week for 6 weeks, as determined by the Lam 2003 protocol. Patients randomized to the Taxotere group will receive Taxotere 75mg intravesically once a week for 6 weeks following the cycle of BCG-INF. Patients will receive weekly instillations of Taxotere prepared in polysorbate 80 in saline diluent initially at an approximate pH of 4.6; the Taxotere will be delivered by sterile urethral catheterization. Patients will be instructed to keep the drug in the bladder for 2 hours before voiding. Their blood will be drawn 4 hours after the infusion to check for systemic absorption.

If treatment intolerance occurs during induction of the BCG dose, the patient will receive a 2-week rest followed by re-initiation of the BCG-INF treatment at one-third of that of the prior dose. This design is based upon prior studies, which shows improved response with lower dose BCG therapy in patients previously sensitized with BCG. Because of the dose-limiting toxicity of BCG therapy, the Lam study also adhered to this protocol design and showed improved tolerance and efficacy of BCG once the dose is de-escalated. BCG intolerance was defined by fever greater than 102°F less than 24 hours in duration, moderate to severe cystitis symptoms persisting beyond 3 days, or irritability to retain treatment at least 1 hour despite urinary antispasmodics. All patients will be monitored for their clinical symptoms weekly during treatment and at 3 and 6 months post-treatment.

This Phase II study will also assess for the toxicity of Taxotere at the 75mg dose. Evidence of systemic absorption will be measured by high performance liquid chromatography (HPLC), and we will be using the Irving Center Clinical Research (ICCR) Lab as used in the Phase I study. The ICCR Lab is part of the Columbia University General Clinical Research Center (GCRC), one of 76 NIH-supported centers in the United States. Blood will be drawn from the patients approximately four hours after the start of the intravesical instillation of Taxotere, and the plasma will be subsequently analyzed for Taxotere. Ardiel et al found that a Taxotere plasma level of 10 ng/ml up to 24 hours after intravenous infusion can be measured chromatographically with an acceptable coefficient of variation (Ardiel et al, 1999). In our Phase I trial, we used a plasma Taxotere value of greater than 10 ng/ml as evidence of systemic absorption and found that none of our patients experienced any dose-related toxicity. We will continue to use a plasma Taxotere value of greater than 10 ng/ml as evidence of systemic absorption. Systemic dose-limiting toxicity will be defined as plasma Taxotere values found to be greater than 10 ng/ml or any grade 2, 3, or 4 systemic toxicity using the National Cancer Institute common toxicity

criteria version 2.0. If a patient exhibits evidence of systemic toxicity, the patient will be removed from the trial and treated appropriately.

a. Outcome & Power Analysis

The primary outcome measure will be through cystoscopy, biopsy of previous tumor sites, and cytology. These will be performed at 6 weeks for the group receiving the combination BCG-IFN treatment, and at 6 and 12 weeks for the group receiving the Taxotere supplement, and also at 3 month intervals following the treatment. Treatment success will be defined as no evidence of disease (normal cystoscopic findings, negative cytology, and negative biopsies). Treatment failure will be defined as a positive biopsy or positive cytology. Progression will be defined as recurrence with a higher pathological stage and/or grade of disease, or the development of muscle-invasive disease or metastasis. The study will conclude after 22 months for patients with treatment success.

The Lam 2003 study indicated that 12 of 20 (60%) patients previously treated with BCG remained disease free at a median follow-up of 22 months. We estimate that the intravesical Taxotere supplement will result in a clinical significant 10% increase in treatment success after 22 months. Based on this data, one-sample chi-square analysis based on these proportions will be used to determine the efficacy of intravesical Taxotere supplement to the BCG-IFN treatment for an alpha of 0.05 and a power of 80%. We will need a total of 376 subjects in each group, for a total of 752 subjects in the study.

C. Subjects Selection

Subjects will be patients with a diagnosis of stage Ta, T1, or Tis TCC of the bladder confirmed at the study institution. They will be either inoperable candidates or operable candidates refusing cystectomy. Additionally, their bladder cancer must be recurrent and refractory to BCG intravesical therapy. All grossly visible disease must be fully resected prior to enrollment. Subjects should also not have gotten any intravesical therapy within 6 weeks of study entry and no prior radiation to the pelvis. A baseline degree of fair health is necessary for patients to enroll in this study and the minimal criteria for this includes:

- Hematologic inclusion: within 2 weeks of start of treatment
 - absolute neutrophil count $\geq 1,500/\text{mm}^3$
 - hemoglobin ≥ 8.0 g/dL
 - platelet count $\geq 100,000/\text{mm}^3$
- Hepatic Inclusion: within 2 weeks of start of treatment
 - Total bilirubin within normal limits
 - Transaminases may be up to 2.5X upper limit of normal (ULN) *if* alkaline phosphatase is \leq ULN, **OR** alkaline phosphatase may be up to 4X ULN *if* transaminases are \leq ULN
- Peripheral neuropathy \leq grade 1

Subjects must be 18 years of age or older and must be able to read, understand, and sign the informed consent. Women of childbearing potential must have a negative pregnancy test and be willing to consent to using effective contraception, i.e., IUD, birth control pills, Depo-Provera while on treatment and for three months after their participation in the study ends. Men must also be willing to take appropriate measures (i.e. prophylaxis) to prevent pregnancy of their partner while on treatment and for three months after their participation in the study ends.

Patients with muscle invasion (T2-4), a history of hypersensitivity to Taxotere or other drugs formulated with polysorbate 80, and having received prior Taxotere therapy are excluded from the study. Any other malignancy diagnosed within 2 years of study entry (except basal or squamous cell skin cancers or non-invasive cancer of the cervix) excludes one from the study. Additionally, patients receiving concurrent treatment with any chemotherapeutic agent or those with a history of vesicoureteral reflux or an indwelling urinary stent will also be excluded.

Because of the large sample of patients required, this Phase II trial will have to be a multi-institutional study with several large-volume urologic oncology centers and Columbia-Presbyterian Medical Center as the lead institution. Subjects will be identified and referred by the patient's primary urologist after a diagnosis of TCC and discussion of treatments alternative to cystectomy. Patients will then be appropriately screened by the study urologist and/or study personnel. Flyers and other IRB-approved advertisements will also be generated and posted for patients to contact screening personnel themselves.

D. Confidentiality of Study Data

All patients will sign a HIPPA consent and their information will be coded, with a unique identifier assigned to each patient. Study data will be stored in the Urological Research office and will be made accessible only to the investigators of the study.

E. Potential Conflict of Interest

None. No compensation in any form will be provided to participating physicians or patients.

F. Potential Risks and Benefits

Patients enrolled in this study are individuals currently either refusing cystectomy or for whom cystectomy is not an option. They will be at risk for significant toxicities secondary to BCG-IFN or to Taxotere, as outlined earlier. Additionally, there is the possibility that their bladder cancer may progress, despite the investigational treatment. Furthermore, there are the risks associated with bladder biopsies, which usually involve minimal risk of bleeding and infection. All of these potential risks will be outlined for patients before their informed consent is attained.

Potential benefits involve longer disease-free survival if the study arm is effective than would have been obtained with conventional treatment. Moreover, these patients will have the opportunity to participate in a study that may refine treatment decisions for future patients with TCC who seek an alternative to cystectomy.

G. Alternative Therapies

Other potential approaches to treating these patients include cystectomy. However, all of our study subjects are either refusing cystectomy at this time or are inoperable candidates.

H. Compensation to Subjects

None. Patients will not incur any additional costs due to their participation in this study.

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