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A Phase II clinical trial of intravesical Cabazitaxel, Gemcitabine, and Cisplatin (CGC) in the Treatment of BCG-Refractory Non-muscle invasive Transitional Cell Bladder Cancer

Study Purpose and Rationale

In 2010, it is estimated that 70,530 new cases of bladder cancer will be diagnosed in the United States and 14,680 people will die from the disease. This makes bladder cancer the fourth leading cause of cancer in men and the ninth leading cause of cancer in women in the United States (American Cancer Society, 2010. Bladder cancer is a heterogeneous disease with 70% of patients initially presenting with non-muscle invasive disease (i.e. stages Ta, T1, or carcinoma in situ {CIS}). The majority of these patients (50-70%) will recur after initial treatment and 10-20% will eventually progress to muscle invasive disease. In cases with high-risk clinical and pathological features (high grade Ta, T1 and Tis) the use of intravesical therapy to prevent adverse outcomes has become the standard of care. Efforts to improve recurrence free survival and the potential for progression include the use of intravesical (*i.e.,* delivery of agents directly into the bladder lumen) immunomodulators such as BCG (Bacillus Calmette Guerin) and interferon alpha, and chemotherapeutics agents such as mitomycin C, doxorubicin, thiotepa, docetaxal, and gemcitabine. However up to 50 percent of patients treated with intravesical therapy for high-risk non-muscle invasive 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. Additionally, patients with high-risk non-muscle invasive disease (i.e. high grade Ta, T1, or CIS) who are refractory to BCG treatment are at a high risk of progression and disease specific mortality. Preemptive early radical cystectomy prior to the development of muscle invasive disease has been offered in these patients to obviate this risk, however this subjects patients who may never have gone on to progress to invasive disease, to life altering radical surgery. As such there is a clear need for further therapeutic options which would improve chances for bladder preservation without sacrificing cancer control and survival.

Thus far, attempts to discover alternatives to BCG have primarily rested on studies involving single agent intravesical chemotherapy instillations. Intravesical gemcitabine and cisplatin take their intellectual justifications from their use as the 1st line systemic agents in advanced bladder cancer (1). Similarly, taxane therapy has been used in combination with gemcitabine and cisplatin systemically for metastatic disease (2). As these three drugs are currently employed in combination for systemic disease, and each has been previously tested intravesically in prior human trials, there is a strong rationale for a multimodal regimen of intravesical gemcitabine, cisplatin, and an active taxane agent. Few if any single drug systemic therapy protocols have demonstrated durable disease free survival and for this reason the use of a multidrug regimen in this intravesical trial design has the potential for significant improvement in survival.

Study Design and Statistical Analysis

This study is a single arm, non-randomized Phase II trial investigating the efficacy of multimodal intravesical chemotherapy in the treatment of non-muscle invasive BCG refractory bladder cancer.

Hypothesis

We hypothesize that 60% of patients will have a complete response at 6 months on our treatment, an improvement over the 30% of patients have a complete response experienced with intravesical paclitaxel at 6 months.

Power Analysis

In order to adequately assess the proportion of patients who respond to treatment we use the chi square test. In order for out trial to be powered at 80% with a 5% significance level, the number needed in the treatment arm=25.

Outcomes of Interest:

In addition to examining the proportion of complete responders to our treatment regimen, we will also examine:

- Time to recurrence or progression defined as ' The Time from 1st intravesical treatment to cystoscopically confirmed disease
    - This data will be compared against the norms for patients on standard intravesical therapy using Kaplan Meir curves and log rank model.
- Factors associated with complete response to the multimodal intravesical treatment
    - This will be analyzed using the Cox Proportional Hazard Model

Study Procedure

In this study, patients will visit the doctor's office six to eight times during the study.

During the first visit, your doctor will check to see if you fulfill the requirements for the trial as outlined below. A blood sample will be taken to evaluate the patient's CBC and LFTs, a urine specimen collected for analysis and culture.

During the second visit, it will be decided if the patient is suitable for inclusion in the trial. Participants will complete a baseline validated quality of life questionnaires. They will then undergo cystoscopy and removal of any visible tumor within the bladder at CPMC. With the patient's permission, blood, urine and tissue samples may be stored for future analysis to determine the biologic factors that may predict response to this therapy.

In the subsequent six visits, the patient will be given the trial medications- 6 weeks of weekly treatment with cisplatin, cabaztixel and gemcitabine in the doses outlined below. The study medication will be instilled into the patient's empty bladder using a urinary catheter. All participants are required to maintain the fluid inside the bladder for 2 hours before urinating. In addition to receiving the treatment medications- during each treatment visit, a blood sample will be drawn) to assess **specific lab values**. Treatment medications may be discontinued based on the results of these laboratory tests.

Six weeks after the completion of the weekly instillations of the trial medication, participants will undergo a cystoscopic examination and bladder biopsy. The procedure requires that a cystoscope (telescope) be placed into the urinary channel to examine the bladder while you are under anesthesia and biopsies will be taken at that time.

Study Drugs

Gemcitabine, a deoxycytidine analogue, inhibits DNA synthesis and is a commonly used drug in systemic bladder cancer. Intravesical gemcitabine has been studied in multiple Phase I and II trials. It appears to

have very little systemic absorption, with plasma levels immeasurable or quite low, and metabolite difluorodeoxyuridine levels that reach at most 5 μM in the blood, suggesting that low levels of the drug reach systemic circulation (3). Thus, although myelosuppression is a serious side effect when gemcitabine is used intravenously, it has a very favorable toxicity profile when administered intravesically. In a Phase II study of 30 patients, 15 (50%) had complete responses after 19 months of follow-up. (4) Due to the reported efficacy and low toxicity profile, gemcitabine has been favorably compared to other intravesical agents such as Mytomicin (5). Furthermore the feasibility of intravesical delivery of gemcitabine has recently been confirmed by the completion of the largest multicenter trial of intravesical gemcitabine in the United States last year by the Southwest Oncology Group.

Cisplatin based chemotherapeutic regimens comprise the backbone of any 1st line systemic treatment for advanced urothelial carcinoma. In-vitro studies also demonstrate that it has potent anti-tumor activity when administered intravesically for non-muscle invasive bladder cancer. (6) In a study that reviewed one institution's experience with a combined regimen of intravesical cisplatin, mytomicin, and doxorubicin, the cisplatin regimen was found to have fewer major adverse events (5.6%) compared with BCG, the standard of care (15%). (7) In the cisplatin-treated group, all of the adverse events were lower urinary tract symptoms (LUTS). There were no systemic symptoms that would suggest absorption of the drug into the circulation.

Cabazitaxel is a microtubule inhibitor similar to commonly used docetaxel- a member of the taxane family. While taxanes have long been a cornerstone of intravesical therapy, one important limitation is the development of resistance. Docetaxel has a high substrate affinity for multidrug-resistance proteins, in particular the ATP-dependent drug efflux pump P-glycoprotein (P-gp; also known as ABCB1) (10, 11). Expression of P-gp by cancer cells can be responsible for both constitutive and acquired resistance to taxanes. P-gp expression is high in NMIBC, and its expression has been found to be correlated with shorter progression-free survival, suggesting that P-gp may play a role in the development of chemotherapy resistance in bladder cancer (12). Cabazitaxel is a semisynthetic taxane that was selected for development on the basis of its poor affinity for P-gp compared with docetaxel and paclitaxel. We hypothesize that intravesical cabazitaxel will achieve the same initial response as docetaxel, while extending the drugs durability and long term efficacy by avoiding resistance and subsequent recurrence.

Medical Device

N/A

Study Questionnaire

American Urological Association bladder cancer questionnaire

Study Subjects

Participants must meet all inclusion and exclusion criteria outlined below.

Inclusion Criteria

I. Patients must have a CPMC confirmed diagnosis of non-muscle invasive recurrent urothelial carcinoma of the bladder- which was resistant to standard intravesical therapy defined as a minimum of one induction course of BCG and may also include prior exposure to mitomycin, interferon, single agent gemcitabine or taxane therapy or maintenance with BCG.
   a. This will include Ta, T1, Tis disease.
   b. Patients with Ta disease must have documentations high-grade histology.

II. All grossly visible disease must be fully resected and pathologic stage will be confirmed at CPMC.

III. Age ≥ 18 and must be able to read, understand and sign informed consent
IV. Performance Status: ECOG 0,1 (See Appendix II)
V. Peripheral neuropathy: must be ≤ grade 1
VI. Hematologic-Inclusion within 2 weeks of start of treatment
   a. *Absolute neutrophil count ≥ 1,500/mm^3*
   b. *Hemoglobin ≥8.0 g/dl*
   c. *Platelet count ≥ 80,000/mm^3*
VII. Hepatic-Inclusion within 2 weeks of entry
   a. *Total Bilirubin < 2.0 ULN for the institution.*
   b. *Adequate renal function with serum creatinine ≤ 2.4 mg/dL*
      i. *Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5 x ULN for the institution, Alkaline phosphatase ≤ 2.5 x ULN for the institution, unless bone metastasis is present in the absence of liver metastasis*
VIII. Women of childbearing potential must have a negative pregnancy test.
IX. All patients of childbearing potential must consent to using effective contraception, i.e., IUD, Birth control pills, Depo-Provera, and condoms while on treatment and for 3 months after their participation in the study ends.
X. No experimental intravesical therapy within 6 weeks of study entry

Exclusion Criteria

I. Another active ongoing malignancy diagnosed within 6 months of entry to the study
II. Concurrent treatment with any systemic chemotherapeutic agent.
III. Women who are pregnant or lactating.
IV. Documented history of vesicoureteral reflux or an indwelling urinary stent.
V. Participation in any other research protocol involving administration of an investigational agent within 6 weeks prior to study entry.

Recruitment of Subjects

Patients will be recruited from the general urology practice at CPMC. They will first be informed of the study by their primary urologist, at which time their interest will be gauged. They will then be contacted by research staff who will describe the study in its entirety, answer all study related questions and if the patient chooses to participate- consent and coordinate future visits

Confidentiality of Study Data

Any information obtained during this study and identified with you will remain confidential. Study staff at Columbia-University Medical Center, Sanofi- Aventis and the Food and Drug Administration (FDA) will have access to medical records related to the study. Levels of confidentiality will be maintained to the extent permitted by the applicable laws and regulations. Possible identifying material will be kept confidential and will not be made public when the results are published.

Potential Conflict of Interest

N/A

Location of the Study

This trial will be conducted as a phase I trial led by the Columbia University Comprehensive Cancer Center, Herbert Irving Pavilion, 161 Fort Washington Ave, New York, NY 10032.

Potential Risks

Potential Risk of this study includes:

- Absorption of the drug into your bloodstream. Intravesical administration of these drugs reduces the risk of this significantly. In the event that there is significant absorption into the bloodstream this will be detected and treated immediately
- Recurrence or progression of your cancer after completion of therapy.
- Urinary tract infection as a result of the insertion of the catheter into the bladder for drug administration
- Irritation of the lining of the bladder resulting in sensation of increase need to urinate or pain on urination.
- Unknown risk to potential fetuses. As a result, all women of childbearing age must have a negative pregnancy test at screening and agree to use effective birth control for at least three months after their participation in the trial ends.
- Risks associated with venipuncture including the risks of drawing blood from a vein include pain at the site pain at the site of collection, bruising about 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.

Potential Benefits

You or may not benefit personally from this trial. Potential benefits to you may include avoiding radical cystectomy (surgical removal of the bladder) and subsequent creation of another way for urine to leave the body- and the associated risk of morbidity or mortality. You will be providing valuable information to the medical community which will be of benefit to other men and women who suffer from this disease.

Alternative Therapies

Treatment options, in the event of failure of the experimental regimen to control your disease, consist of observation without further treatment, repetition of previously administered treatments, other experimental systemic and intravesical treatments and surgical removing your bladder. Surgery still remains an option at any time if you so desire. You can always choose not to participate in the study.

Compensation to Subjects

You will receive no compensation for your participation.

Costs to Subjects:

Patients will incur no additional costs as a result of participating in this study

Minors as Research Subjects

N/A

Radiation or Radioactive Substances

N/A

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