Paclitaxel-Hyaluronic Acid for Intravesical Therapy of Bacillus Calmette-Guérin Refractory Carcinoma In Situ of the Bladder: Results of a Phase I Study

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Purpose: Carcinoma in situ represents high grade anaplasia of the bladder mucosa. Intravesical immunotherapy with bacillus Calmette-Guérin is the gold standard treatment for patients with carcinoma in situ. Patients with carcinoma in situ refractory to bacillus Calmette-Guérin are candidates for major surgery such as radical cystectomy. We identified the maximum tolerated dose and the recommended dose, and evaluated the safety profile of paclitaxel-hyaluronic acid bioconjugate given by intravesical instillation to patients with carcinoma in situ refractory to bacillus Calmette-Guérin.

Materials and Methods: A total of 16 patients with carcinoma in situ refractory to bacillus Calmette-Guérin were enrolled in a phase I, open label, single institution study. A minimum of 3 eligible patients were included per dose level. Paclitaxel-hyaluronic acid solution (ONCOFID-P-B™) was administered for 6 consecutive weeks. The primary objective was to identify the maximum tolerated dose and the recommended dose. As secondary objectives the safety profile of ONCOFID-P-B, the pharmacokinetic profile after each instillation and the tumor response were also evaluated.

Results: No dose limiting toxicity occurred at any drug level evaluated. The plasma levels of the study drug were always below the lower limit of quantification at all tested doses after each instillation. A total of 11 adverse events were reported by 7 patients and 9 (60%) showed complete treatment response.

Conclusions: Intravesical instillation of ONCOFID-P-B for carcinoma in situ refractory to bacillus Calmette-Guérin showed minimal toxicity and no systemic absorption in the first human intravesical clinical trial to our knowledge. Finally, satisfactory response rates were observed.

Key Words: paclitaxel; hyaluronic acid; administration, intravesical; carcinoma in situ; urinary bladder

Abbreviations and Acronyms

AEs = adverse events
BCG = bacillus Calmette-Guérin
CIS = carcinoma in situ
CR = complete response
DLT = dose limiting toxicity
HA = hyaluronic acid
NMIBC = nonmuscle invasive bladder cancer
NR = no response

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Study received approval from the Ethical Committee of the Catholic University and the Italian Superior Institute of Health.

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For another article on a related topic see page 693.

Bladder cancer is the 4th most common genitourinary cancer in men and the 7th in women with an incidence of more than 70,000 new cases in the United States in 2010.[1] NMIBC accounts for 70% of newly diagnosed bladder cancers.[2] The primary treatment for NMIBC is transurethral resection.[3] Intravesical instillation has been used to decrease recurrence and progression to muscle invasive bladder cancer since the 1970s.[4] CIS represents high grade anaplasia and is considered a precursor of muscle invasive bladder cancer.[5] BCG is the gold standard treatment for CIS. De-

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spite BCG treatment 42% to 83% of patients with CIS associated with papillary tumors and 20% to 34% with primary CIS experience progression to muscle invasive disease.[5] Radical cystectomy is the subsequent treatment and is considered a major surgical procedure with a 1% to 2.5% mortality rate in major series.[6] Thus, more active drugs are needed to treat NMIBC.

Paclitaxel is a chemotherapeutic agent with a wide spectrum of proven antitumor activity as well as activity against muscle invasive bladder cancer.[7,8] Theoretically these characteristics make paclitaxel an attractive candidate for intravesical therapy for NMIBC. Unfortunately because of its lipophilicity and the higher dose used in the intravesical therapy setting, paclitaxel is considered a poor candidate for intravesical therapy because it penetrates the urothelium, potentially causing systemic toxicity. A previous experimental study demonstrated that the conjugation between paclitaxel and HA reverses the lipophilic properties, and enhances antitumor in vitro activity against bladder cancer and bladder biocompatibility in vivo through acquired hydrophilic characteristics. HA is a linear polysaccharide formed by alternating D-glucuronic acid and N-acetyl-D-glucosamine units. Thus, the chemical conjugation between paclitaxel and HA makes the active ingredient water soluble and easier to handle in a therapeutic context.[9]

The chemical conjugation was obtained in several steps. Paclitaxel (1 gm) was dissolved in CH2Cl2, and 591 mg N-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrogen chloride and 796 mg 4-bromobutyric acid were then added to the solution. Subsequently the solution was partitioned in water. After eliminating the carbodiimide and bromide residues, the reaction solvent was dried with anhydrous sodium sulfate and eliminated with a rotary evaporator. The intermediate product (1.11 gm) was added to a solution of 4.38 gm HA-thiobarbituric acid dissolved in 220 ml anhydrous N-methyl-2-pyrrolidone. After a 7-day reaction at room temperature the solution was supplemented with 8 ml saturated NaCl solution. After 1 hour 750 ml ethanol were slowly added drop by drop. The resulting product was filtered, dissolved in water and dialyzed. When the conductivity of the dialyzed solution was less than 10 microseconds, it was frozen and subsequently freeze-dried. Paclitaxel loading was analyzed by high performance liquid chromatography analysis. The new conjugate had high solubility in a glucose aqueous solution of 14.6 mg HA-paclitaxel product obtained by esterification with a substitution of 16.3% wt/wt dissolved in 1 ml 5% glucose in water. The solution, with a paclitaxel concentration of 2.38 mg/ml, was filtered through a 0.20 μm filter. In addition, the maximum solubility of product in a 5% glucose aqueous solution was identified. At a concentration of 32.8 mg HA-paclitaxel, a viscous solution was obtained with an equivalent paclitaxel concentration of 5.35 mg/ml.

Thus, paclitaxel-HA bioconjugate (ONCOFID-P-B) could be considered a newer anticancer agent. As a primary objective in this phase I study we identified the maximum tolerated dose and the recommended dose, and evaluated the safety and the toxicity profile of intravesical ONCOFID-P-B (supplied by Fidia Farmaceutici S.p.A., Italy). Tumor response was a secondary objective.

PATIENTS AND METHODS

Eligibility Criteria

All patients enrolled in the study had a histologically and cytologically confirmed diagnosis of bladder CIS. Proven evidence of BCG refractory CIS was required. Other eligibility criteria included age between 18 and 80 years old, women with menopause and performance status 0 to 1 according to the Eastern Cooperative Oncology Group. Specific exclusion criteria were known hypersensitivity to paclitaxel or 1 of its constituents, concomitant papillary tumors (Ta–T1), previous systemic chemotherapy or radiotherapy, previous intravesical immunotherapy less than 3 months before study entry, renal and hepatic function values exceeding 2 times the upper normal value, significant cardiovascular diseases, and pregnant, lactating or any other malignancy within 5 years of study entry. The Ethical Committee of the Catholic University and the Italian Superior Institute of Health approved the study protocol and consent, and all patients provided informed consent before trial enrollment. The study was performed in accordance with the Declaration of Helsinki with the applicable regulatory requirements and Good Clinical Practice.

Intravesical Instillation

The product was supplied in 100 ml glass vials containing 50 ml sterile aqueous isotonic solution in which 750 mg paclitaxel-HA bioconjugate and 2.5 gm glucose were dissolved. The concentration resulted in 15 mg/ml in glucosate solution 5%, which represents the highest concentration achievable because of the viscosity of the drug.

Drug Administration and Dose Escalation

ONCOFID-P-B solution was administered weekly in a 6-week course. The final solution was infused by a 16Ch Foley catheter during a 5-minute infusion and the dwelling time was 2 hours. The phase I trial started with the first dose level of 150 mg, equivalent to 30 mg paclitaxel as a single intravesical instillation. The next dose levels were 300, 450, 600 and 750 mg. Dose levels were planned according to the Eisenhauer scheme. A minimum of 3 eligible patients were treated at each dose level. Before escalating to the next dose level all 3 patients of the evaluated level completed the 6 administrations and no intrapatient dose escalation was allowed. A minimum of 15 patients was required to complete the 5 planned levels. Three patients were treated at each dose level, and between the