Phase II Trial of Intravesical Nanoparticle Albumin Bound Paclitaxel for the Treatment of Nonmuscle Invasive Urothelial Carcinoma of the Bladder after bacillus Calmette-Guérin Treatment Failure

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Purpose: Response rates to current second line intravesical therapies for recurrent nonmuscle invasive bladder cancer range between 10% and 30%. Nanoparticle albumin bound (nab-)paclitaxel has increased solubility and lower toxicity compared to other taxanes. Results of the phase I intravesical trial of this compound demonstrated minimal toxicity during dose escalation. We now report the results of a phase II trial to assess efficacy.

Materials and Methods: This study was an investigator initiated, single center, single arm, phase II trial investigating the use of nab-paclitaxel in patients with recurrent Tis, T1 and Ta urothelial carcinoma in whom at least 1 prior regimen of intravesical bacillus Calmette-Guérin failed. Patients received 500 mg/100 ml nab-paclitaxel administered in 6 weekly intravesical instillations. Efficacy was evaluated with cystoscopy, biopsy, cytology and imaging. If complete response was achieved, patients were treated with full dose monthly maintenance treatments for 6 months.

Results: A total of 28 patients were enrolled in the study. Of these patients 10 (35.7%) exhibited a complete response after initial treatment. At 1 year all of these responses remained durable after maintenance therapy. At a mean followup of 21 months (range 5 to 47) 19 of 28 (67.8%) patients retained their bladders without progression or distant metastases. A single patient had progression to muscle invasive disease at radical cystectomy. Treatment related adverse events were noted in 9 of 28 (32.1%) patients and were limited to grade 1 or 2.

Conclusions: Intravesical nab-paclitaxel has minimal toxicity and a 35.7% response rate in patients with nonmuscle invasive bladder cancer and previous bacillus Calmette-Guérin failure. Complete response remained durable at 1 year followup in this heavily pretreated patient population.

Key Words: urinary bladder neoplasms; intravesical administration; therapies, investigational; paclitaxel; nanotechnology

Abbreviations and Acronyms

BCG = bacillus Calmette-Guérin
CFS = cystectomy-free survival
CIS = carcinoma in situ
CR = complete response
MDD = maximal deliverable dose
nab = nanoparticle albumin bound
NMIBC = nonmuscle invasive bladder cancer
RC = radical cystectomy
RFS = recurrence-free survival

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In 2013 the incidence of bladder cancer in the United States was 72,500 with approximately 15,000 deaths.[1] Urothelial carcinoma constitutes more than 90% of cases and approximately 70% present initially with NMIBC.[2]

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In 1976 Morales reported the therapeutic efficacy of BCG in high grade NMIBC.[3] Subsequently BCG has become the gold standard treatment.

Currently the American Urological Association and European Association of Urology recommend intravesical BCG as first line treatment after transurethral resection of high grade NMIBC.[4,5] Five-year recurrence rates after BCG induction with maintenance range from 30% to 60% depending on stage, grade, multiplicity and length of followup.[3,6,7] Recurrent NMIBC is a heterogeneous disease state, and can be defined and characterized using terms such as refractory, resistant and relapsing. With a progression risk of 20% to 30% in this setting, radical cystectomy is currently the standard of care.[4–8] Second line novel agents have been an area of active investigation. To date, valrubicin is the only FDA (Food and Drug Administration) approved intravesical therapy for BCG refractory NMIBC and has been associated with an 18% to 21% CR rate in studies limited exclusively to patients with CIS.[9,10] Multiple other agents have been investigated, including BCG combined with alpha-interferon, mitomycin C with or without electromotive and hyperthermic techniques, gemcitabine, docetaxel and combination intravesical chemotherapy in preclinical studies.[11–13]

In 2006 we reported the results of 18 patients in a phase I clinical trial of intravesical docetaxel for the treatment of recurrent NMIBC after BCG therapy.[14] Docetaxel showed no systemic absorption and minimal toxicity, and a 56% CR at initial assessment in that trial, with a 4-year recurrence-free survival of 22%. In that phase I trial the maximal tolerated dose and safety profile were the primary end points.[12,15] Paclitaxel, another taxane and microtubule depolymerization inhibitor, is used for systemic treatment of multiple cancers and, in its nanoparticle albumin bound (nab-) form, is currently an FDA approved systemic therapy for breast and pancreatic cancer.[16,17]

Nab-paclitaxel has a fivefold higher solubility in aqueous environments compared to docetaxel and a facilitated drug delivery mechanism into tumor cells via albumin receptor mediated transport across epithelial cells.[17,18] A third mechanism of improved action is through the newly described SPARC tumor interstitium protein, which mediates transcytosis into tumor cells.[19] The first human phase I trial of intravesical nab-paclitaxel was published in 2011, with an encouraging safety profile and acceptable secondary end points of efficacy.[20] The current phase II study used the MDD of nab-paclitaxel to further explore the activity of this agent in the treatment of high risk NMIBC that has relapsed or persisted after BCG therapy.

MATERIALS AND METHODS

Study Design

This study was a single center, prospective, institutional review board approved (IRB-AAAC1114), investigator initiated and industry sponsored phase II nonrandomized trial. The MDD was 500 mg in 100 ml normal saline in the previously published phase I study.[20] A Simon 2-stage design was used. There were 10 patients enrolled in the first stage, and only when 2 or more of those patients responded, 18 additional patients were evaluated in the second stage. The probability of correctly concluding the therapy is worthy of further study was calculated to be 80% if the true underlying response rate was 30%. The probability of incorrectly concluding the therapy is promising was 5% if the true response rate was approximately 10%.[21–23] The expected sample size for this study design was a minimum of 15 and a maximum of 28 patients.

Patient Eligibility

Patients eligible for this study all had high risk NMIBC with pathologically proven stage T1, Ta or Tis. Patients had high grade disease except 1 who had multifocal recurrent low grade stage Ta disease. All patients were subject to a minimum of 1 prior intravesical BCG induction course. Prior use of intravesical mitomycin C, interferon, gemcitabine, docetaxel or other experimental clinical agents was allowed. If a patient was treated in a prior clinical trial, a minimum of 3 months after completion of the prior protocol was required with documented disease recurrence before enrollment in this study. All patients had grossly visible disease fully resected with pathological confirmation of histology before enrollment. They were offered RC as the gold standard option and refused, or were at unacceptable surgical risk. Patients underwent pretreatment assessment including physical examination, cystoscopy and cross-sectional imaging, as well as complete blood count, basic metabolic panel, hepatic function panel and coagulation profile before study enrollment.

Additional inclusion criteria were age 18 years or older, ability to provide informed consent, Eastern Cooperative Oncology Group performance status 0 or 1, mild or no peripheral neuropathy, no hematological disturbances as defined by neutrophil count 1,500/mm^3 or less, hemoglobin 9 gm/dl or less, or platelet count 100,000/mm^3 or less, no hepatic dysfunction as defined by abnormal bilirubin or liver function tests 2.5 or greater than upper normal limit, no renal dysfunction as defined by serum creatinine 2.0 mg/dl or greater, negative pregnancy test in women of childbearing age and no intravesical therapy within 6 weeks before enrollment. Exclusion criteria were prior systemic taxane therapy, any other malignancy diagnosed within 2 years of study entry (except nonmelanoma skin cancer, chronic lymphocytic leukemia or noninvasive cervical cancer), concurrent treatment with any chemotherapeutic agent, pregnant or lactating women, history of vesicoureteral reflux or an indwelling urinary stent, or administration of any investigational agent within 3 months before study.

Drug Preparation and Administration

The dose of nab-paclitaxel was the MDD of 500 mg/100 ml 0.9% NaCl. The dose was instilled intravesically on a

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