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Tolerance of *Phellodendron amurense* bark extract (Nexrutine®) in human prostate cancer patients

Gregory P. Swanson^{1,5}, William E. Jones III^{1,5}, Chul S. Ha¹, Carol A. Jenkins¹, Addanki Pratap Kumar^{2,3,4,5}, and Joseph Basler^{2,5}

¹Department of Radiation Oncology, The University of Texas Health Science Center, San Antonio, TX

²Department of Urology, The University of Texas Health Science Center, San Antonio, TX

³Department of Pharmacology, The University of Texas Health Science Center, San Antonio, TX

⁴Department of Molecular Medicine, The University of Texas Health Science Center, San Antonio, TX

⁵South Texas Veterans Health Care System, San Antonio, TX

Abstract

Purpose—*Phellodendron amurense* bark extract (Nexrutine®) has shown a favorable effect on prostate cancer in vivo and in vitro. We evaluated its tolerance in patients undergoing surgery or radiation for prostate cancer.

Materials and Methods—Patients received Nexrutine® orally (500 mg tid) either one to two months pre-operatively or one to two months prior to and with radiation therapy. Common terminology criteria for adverse events (CTCAE) were used to measure tolerance.

Results—In total, 21 patients (9 surgery and 12 radiation) underwent treatment. During the Nexrutine® alone component, there were 2 transient grade 3 toxicities (hypokalemia and urinary incontinence). There was no grade 4 toxicity. For the combined Nexrutine® and radiation component, no additional patients suffered a grade 3 toxicity. All the toxicities were transient. By the end of the neoadjuvant treatment, 81 % of the patients had a decline in PSA.

Conclusion—This is the first report of prostate cancer patients being treated with *Phellodendron amurense* bark extract and it was very well tolerated. Toxicities were minimal and self-limited. This compound can be safely used in further evaluation of a treatment effect on cancer.

Keywords

Nexrutine®; *Phellodendron amurense* extract; prostate cancer; prostatectomy; radiation therapy; combined modality

Corresponding author: Gregory P. Swanson M.D., 7979 Wurzbach Road, San Antonio, TX 78229, swansong@uthscsa.edu, phone: 210-450-1109.

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Introduction

Prostate cancer is a highly treatable disease and while most men survive it, there are still about 30,000 deaths from prostate cancer each year in the United States. A large number of these patients failed primary treatment (usually surgery and/or radiation) for their prostate cancer. Ongoing efforts are attempting to enhance the primary treatment and increase cancer control. Studies have been completed utilizing androgen ablation and/or cytotoxic chemotherapy with mixed, but generally favorable results (Pilepich 2001, Pilepich 2005, Rosenthal 2009). These treatments have toxicity (Rosenthal 2009, Taylor 2009, Kintzel 2008), so there is interest in identifying less toxic agents. To that end, naturally occurring plant based compounds are of interest. Preliminary results have shown favorable effects of Nexrutine®, a *Phellodendron amurense* bark extract, on both in vivo and in vitro prostate cancer models. (Garcia 2006, Ghosh 2007, Muralimanoharan 2009). Specifically, in cell lines (Garcia 2006, Ghosh 2007, Muralimanoharan 2009) it inhibits cellular proliferation through induction of apoptosis. In the transgenic adenocarcinoma of the mouse prostate (TRAMP) model, Nexrutine® administration prevented the development of naturally occurring prostate cancer (Kumar 2007). Nexrutine® has been evaluated in human subjects, primarily for inflammatory processes such as arthritis (Oben 2009). It appears well tolerated, but has never been studied in prostate cancer patients. Given its potential as a therapeutic, we evaluated its tolerability in prostate cancer patients treated with surgery or radiation.

Materials and Methods

Through an Institutional Review Board approved protocol and with informed consent, prostate cancer patients already committed to radical prostatectomy (n=9) or primary radiation therapy (n=12) signed on to the study. Surgery patient were planned to receive a minimum of 30 days and a maximum of 80 days of oral Nexrutine®, followed by surgery. Radiation patients were planned to receive Nexrutine® a minimum of 30 days and a maximum of 60 days in advance of and then during radiation therapy (for a total of 4 months). The compound was given orally 500 mg TID and compliance was monitored via pill counts.

Patients were required to have a histologic diagnosis of prostate cancer (in more than 1 biopsy core) with either/or Gleason > 6, bilateral Gleason 6 or PSA > 10.0 ng/ml. They were required to have an absolute neutrophil count (ANC) of $\geq 1,500$ cells/ μ L, a platelet count $\geq 100,000$ cells/ μ L, a Hemoglobin of ≥ 9 g/dL; and total serum bilirubin of $\leq 1.5 \times$ institutional upper limit of normal (ULN). They were required to have no new, undiagnosed bone pain or have a negative bone scan within 2 months of consent. If there was no bone pain, then a bone scan was not required. Prior chemotherapy, androgen ablation, immunotherapy or similar treatments were not allowed. The diagnosis of congestive heart failure, prior cancer, use of anticoagulation medications or intercurrent illness with a life expectancy of less than 5 years excluded participation. Due to the possibility of Cox-2 inhibitor like activity, patients could not have a baseline QTc > 450 msec, ischemic changes on current EKG, prior history of drug-induced QTc prolongation, or concurrent treatment with medications known to cause/suspected of QT prolongation).

Toxicity was measured using common toxicity criteria 4.0 (CTCAE 2014). Grossly defined, Grade 1 toxicity is mild with asymptomatic or mild symptoms, based on clinical or diagnostic observations and no intervention is indicated. Grade 2 toxicity is considered moderate with only local or non-invasive intervention indicated. Grade 3 toxicity is severe or medically significant (but not immediately life threatening), disabling, potentially requiring hospitalization. Grade 4 is potentially life threatening requiring urgent intervention and Grade 5 is the result of death.

Results

A total of 21 patients were consented and were monitored for toxicity. One surgery patient completed the neoadjuvant study drug, but then elected to proceed with radiation rather than surgery. He was monitored for toxicity. One surgery patient completed the neoadjuvant study drug, but cancelled surgery. He was also monitored for toxicity. Another surgery patient was taken off the compound early (<30 days) due to gastrointestinal toxicity (grade I, but lead to fluid avoidance with the risk of dehydration and he was taken off as a precaution not to preclude surgery) and was followed with the cohort as planned. One surgery patient and one radiation patient were poorly compliant with taking the compound (<50%), but were monitored with the cohort. Another radiation patient terminated participation at 3 weeks to go on active surveillance, but was compliant to that time and monitored for toxicity. Patient characteristics are shown in Table 1.

In this older population, mild baseline somatic complaints (grade 1) and findings were common. Reported prestudy grade 2 toxicity included: erectile dysfunction (10), gastroesophageal reflux (4), hypertension (4), back pain (4), arthralgia (4), neck pain (3), allergic rhinitis (3), anxiety (3), urinary frequency (2), hypothyroidism (2), sleep apnea (2), constipation (1), cataract (1), hyperglycemia (1), neuropathy (1), depression (1), glucose intolerance (1), hypertriglyceridemia (1), foot pain (1) and presyncope (1). Reported prestudy grade 3 toxicity included: hypertension (4), hearing impaired (1), obesity (1), hyponatremia (1), and cataract (1).

With the use of the extract, additional grade 3 toxicity was rare- There were one patient with urinary incontinence (occurring after surgery) and one with hypokalemia (occurring two months after stopping Nexrutine®), both in the preoperative cohort. Grade 2 toxicities were more common, but also diffuse and non-specific (Table 2). The most common (3 patients) were anemia and cystitis (3 patients, but also receiving radiation).

Since the extract has been evaluated as an anti-inflammatory with the potential (although undefined) for COX-2 inhibitor like characteristics, we specifically monitored EKGs for changes in the QTc interval. Three patients had mild (grade 1) changes.

Although the ability to measure response is limited in this small phase II study, we recorded PSA response during the neoadjuvant portion of the extract. Of the 16 evaluable patients, 13 (81%) had a drop in PSA levels (average 17%, range 2–42%).

Discussion

Phellodenron Amurense (Amur cork-tree or Huang Bai) bark is an established component of traditional Chinese medicine and has been used for hundreds of years to treat a variety of ailments. Nexrutine® is the registered trademark of Next Pharmaceuticals for their bark extract. It is reported to contain the alkaloids berberine, palmatine, and phellodendrine. In published studies, it has been used for the treatment of osteoarthritis and stress with some modest benefit.(Oben 2009, Talbott 2013, Kalman 2008)

Across the published studies, the compound appeared to be well tolerated. Detailed toxicity assessment via a defined model such as the common toxicity criteria has not been reported. In the most recent study (Talbott 2013), they report that there were no adverse events or side effects after 4 weeks on a combined *Magnolia officinalis* and *Phellodenron amurense* compound (250 mg of phellodendron amurense bid). In an earlier study of the same combination (Oben 2009) at a little higher dose (with 370 mg of phellodendron amurense bid), there was a high dropout rate. Of 80 subjects, 35 dropped out. For 15, there was no reason given, 10 dropped out because of minimal or no improvement in their weight loss, 2 moved, 2 got malaria, 3 changed treatment approaches and 3 developed nausea. The nausea would be the only clearly identifiable potential toxic event. Also, in earlier study (Kalman 2008) the magnolia and philodendron combination (250 mg tid) was used and three patients dropped out for toxicity. Two (10%) of the compound cohort dropped out for diffuse causes- one with heartburn, shaking hands, perilabial numbness, sexual dysfunction, and thyroid dysfunction, the second due to fatigue and headache. A patient in the placebo cohort dropped out due to fatigue, irritability, and abdominal bloating.

On detailed analysis, even though we used an aggressive dose (500 mg tid) we found very little toxicity attributable to the Phellodenron amurense compound. This is consistent with the studies reported above. Although not definitive, our observation of a PSA response in most patients is encouraging. Certainly this is a compound in which further research can be safely conducted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Patient Characteristics

	Mean	Range
Age	63.5	50–83
Pretreatment PSA	6.01 ng/ml	2.12–10.28 ng/ml
Compliance	85%	44–100%
Pathology		
Gleason score	Percent	
6	33% (N=7)	
7	57% (N=12)	
8	10% (N=2)	
Cores Positive		
2	14% (N=3)	
> 2	86% (N=18)	
bilateral	48% (N=10)	

Table 2

Gr 2 toxicity (CTCAE terminology) with Nexrutine® alone (pre-surgery or radiation, n=21) and with Nexrutine® concurrent with radiation (n=12)

Nexrutine® Alone	Number of Patients	Nexrutine® with Radiation	Number of Patients
Arthralgia	1	Cystitis	3
Dizziness	1	Diarrhea	2
Hypotension	1	WBC decreased	2
Nausea	1	Proctitis	2
Anorexia	1	Bone pain	1
Blood bilirubin increased	1	Weight gain	1
Depression	1	Hemorrhoid hemorrhage	1
		Erectile dysfunction	1
Post Surgery:			
Anemia	3		
Constipation	2		
Hypoalbuminemia	1		
Hypocalcemia	1		
Hiccups	1		
Urinary urgency	1		