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Phase II Study of Docetaxel with Radiation Therapy for Post Prostatectomy Rising PSA

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Authors' contributions

This work was carried out in collaboration between all authors. Authors GPS, ABK and CAJ, designed the study, and wrote the protocol. Authors GPS, ABK, CAJ, CSH and JWB recruited and treated patients on the study. Author GPS wrote the first draft, all authors edited the manuscript. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aims: To determine the tolerability of adding docetaxel to radiation therapy in patients with a rising PSA post prostatectomy for prostate cancer.
Study design: Phase II study of the combination of docetaxel and radiation therapy.
Place and duration of study: University and Veterans Association Hospital from 2007-2009.
Methodology: Patients eligible to receive "salvage" radiation therapy were enrolled in a prospective study to receive concomitant weekly docetaxel (20 mg/m^2) and then 4 cycles of full dose (75 mg/m^2) docetaxel.
Results: All 19 patients were able to complete the concomitant therapy, with just one patient not receiving all 7 cycles of weekly chemotherapy (missing one). Sixteen of 19 completed all four cycles, 2 completed 3 cycles and 1 completed 1 cycle of full dose docetaxel. During combined treatment, there were 3 transient grade 3 toxicities (diarrhea, hemoglobin decline, and hyperglycemia). There was no grade 4 toxicity. During full dose docetaxel, 3 patients suffered a grade 3 decline in WBC count and 2 went on to grade 4. Other single incidents of grade 3 toxicity were anxiety, fatigue, hyperglycemia, diarrhea, febrile neutropenia, port infection and abscess. All the toxicities were transient. By the end of treatment, 89% had a decline in PSA.
Conclusion: This is the first report of combined docetaxel and radiation in the post

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prostatectomy setting. Patients tolerated the combined treatment very well. Toxicities of the full dose docetaxel are consistent with what's reported in the literature and appear tolerable.

Keywords: Prostate cancer; prostatectomy; radiation therapy; chemotherapy; combined modality.

1. INTRODUCTION

Over 200,000 men are diagnosed each year with prostate cancer in the United States [1]. Approximately half of them are treated with radical prostatectomy and unfortunately, 30-50% have a rising PSA by 10 years [2,3]. For most patients, this consists of a rising PSA only, with the site of disease undetectable. The most widely reported salvage modality is radiation therapy to the lower pelvis. Most patients respond with a decline in the PSA, but unfortunately, by 5 years less than 40% are still controlled [4,5] and by 10 years only 26% [5]. More significantly, 24% will die of prostate cancer [5].

That the PSA declines in most patients with radiation indicates the predominant site of residual disease is being targeted. This area includes the prostate fossa, residual periprostatic tissue, nerve bundles, bladder neck, periurethral tissue, perirectal nodes and, depending on the volume covered, other deep pelvic nodes including the presacral nodes. The lack of a durable response indicates either the radiation is not able to totally eradicate the targeted disease, or there has been progression of disease outside the prostate fossa. A potential way to improve outcomes is through combining radiotherapy with chemotherapy to enhance local response and also address systemic disease.

Docetaxel is a known radiation sensitizing drug [6]. In addition, randomized studies in patients with disseminated prostate cancer show a survival advantage in the docetaxel treated men, indicating a significant effect directly on prostate cancer [7]. Therefore, it should be an excellent agent to help improve the results seen with radiation alone.

Limited phase I studies indicate that docetaxel can be safely delivered with pelvic radiation. Initial phase I experience in multiple different tumor types (brain, chest, and pelvic tumors) found a maximally tolerated dose (MTD) of docetaxel at 15 mg/m^2 twice a week in pelvis and chest tumors [8]. The complete response rate in the pelvis was 45% (4 of 9 patients). The most common toxicities were asthenia and in the pelvic patients, diarrhea.

With the twice a week regimen, monocytopenia and lymphocytopenia became a problem during the fourth week of treatment. In patients with prostate cancer, tolerance was better with once a week docetaxel. As a radiation sensitizer in intact prostates with documented cancer, a weekly dose of 20 mg/m^2 was safely administered for the entire 7 weeks of radiation [9].

Docetaxel administered by itself has a much higher tolerable dose. When given on a more standard 3 week schedule, numerous studies support the safety and superiority of a docetaxel dose of 75mg/m^2 [7].

The goal of this study was to prospectively verify the safety of combined treatment specifically in the recurrent prostate cancer model, something that had previously not been

done. With the goal of improving the local effect of radiation, we planned to give docetaxel weekly with standard prostate bed salvage radiation, to be followed by 4 cycles of full every three week dose docetaxel to address the systemic risk.

2. METHODOLOGY

Patient eligibility: Patients were eligible if they had undergone radical prostatectomy for prostate cancer and had a persistent or rising PSA >0.2 ng/ml on two separate tests and were referred for standard salvage radiation therapy. Lymph nodes had to be negative at the time of surgery and on pre-study CT of the abdomen and pelvis. Patients had to be without bone pain, or have had a negative bone scan. This was their first salvage treatment.

This was an institutional review board (IRB) approved study. All patients required a complete history and physical exam before study entry. Pre-study laboratory required the absolute neutrophil count (ANC) to be ≥ 1,500 cells/KL, the platelet count to be ≥ 100,000 /KL, hemoglobin ≥ 9 g/dL, total serum bilirubin less than institutional upper limit of normal (ULN), ALT and AST ≤ 1.5 times institutional ULN and alkaline phosphatase ≤ULN. Pre-treatment androgen ablation and herbal products were not allowed. The performance status of all patients was Karnofsky 100.

Study design/therapy: A lower pelvis field (below the acetabula) with 2 cm margins around the prostate fossa was treated to 45 Gy and then a cone down boost of 24 Gy in 12 fractions was delivered to the prostate fossa with 1 cm margins for a total dose of 69 Gy. The total number of fractions was 37, given once daily 5 days a week (therefore taking 7 weeks and 2 days to deliver). The prostate fossa is defined by the pelvic floor inferiorly, the pubic bone anteriorly, the levator and obturator muscles laterally and the base of the bladder superiorly. Based on the doses used in the phase I studies, docetaxel was given by IV infusion once weekly during the radiation at a dose of 20 mg/m^2 on day 1 (+/- 1 day) starting either on a Monday or Tuesday. Patients were medicated with either oral or IV dexamethasone. If chemotherapy could not be administered due to toxicity, radiation was to continue without delay.

After the completion of radiation, the patients were given a 3 week break and then started 4 cycles, every 3-4 weeks of 75 mg/m^2 docetaxel. Patients were started on 5 mg prednisone twice daily which continued through cycle 4, after which it was gradually tapered. Diuretics were allowed to treat fluid retention. The use of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) was not permitted. Toxicity was recorded utilizing the National Cancer Institute Common Toxicity Criteria (version 3.0).

During the combined radiation and chemotherapy treatments, patients were seen weekly with a CBC and determination of performance status. A metabolic panel was obtained every 3 weeks. During the chemotherapy alone portion, patients were seen every three weeks with a CBC and metabolic panel. BSA calculation, performance status and toxicity assessment were completed.

One month after the last chemotherapy patients were evaluated with a performance status and toxicity determination and a CBC, metabolic panel and PSA were obtained. Patients were then followed at the minimum of every 6 months for two years with toxicity determination and a complete blood count (CBC), metabolic panel and PSA were obtained.

No patient has been lost to follow up and have been followed for an average of 3.6 years (range of 1.9 to 4.9 years).

3. RESULTS AND DISCUSSION

From May 2007 to April 2009, 19 patients were accrued to the study and are evaluable for toxicity and response.

Patient characteristics are shown in Table 1. All the patients completed the weekly docetaxel with radiation except one who missed a single dose due to a decline in performance status. Sixteen patients received the subsequent 4 cycles of full dose docetaxel. One patient received only one cycle due to what appeared to be an exacerbation of a pre-existing anxiety disorder by prednisone. Two patients stopped at 3 cycles; one due to an abscess and the second at his request due to a decline in performance status.

Table 1. Patient characteristics

		Mean	**Range**
age@radiation		64.4 years	49-74
Pre RRP PSA		7.34 ng/dl	2.16-20.06
PSA @ start of XRT		1.48 ng/dl	0.26-11.7
Follow up		3.62 years	1.92-4.92
Pathology			
Gleason score	**Number (percent)**		
6	2 (11%)		
7	8 (42%)		
8-9	9 (47%)		
bilateral	19 (100%)		
Margin +	7 (37%)		
SV+	3 (16%)		

Toxicity was collected for the chemotherapy-radiation and the chemotherapy alone portions of the study. For combined chemotherapy-radiation, utilizing the common toxicity criteria, there were three episodes of grade 3 toxicity. These consisted of one patient each with grade 3 hyperglycemia, diarrhea and decline in hemoglobin. They all resolved. There was no Grade 4 toxicity. Grade 2 toxicity was more common (Table 2), the most common of which were in the radiation field. These were diarrhea (7 patients), proctitis (12 patients) and cystitis (8 patients).

Table 2. Grade 2 toxicity during chemotherapy and radiation. Number of patients (n=19) experiencing each toxicity

Diarrhea	7	Incontinence	2	Hemoglobin decline/anemia	1
proctitis	12	cystitis	8	Allergic reaction	2
Heme + stool	2	fatigue	3	Dizziness	2
mucositis	1	Insomnia	2	Flu-like syndrome	2
Urinary frequency	3	Radiation dermatitis	2	Anxiety/irritability	1
Tooth infection	1				

Toxicity was collected separately for the full dose chemotherapy portion of the study. Toxicity was assessed continuously for the duration of the follow up. Only one patient did not receive all seven weekly docetaxel cycles. Due to dizziness (resulting in a fall), he received only 6 cycles, with the last at a 20% dose reduction (although the problem was not thought to be study related). No other patient required a dose reduction. In evaluating the 4 cycles of full dose chemotherapy post radiation, it should be noted that the patients had already completed the seven weeks of radiation and weekly docetaxel, so we would expect some of these effects are cumulative. There was one patient each with grade 3 fatigue, hyperglycemia, diarrhea, febrile neutropenia, port infection and abscess (at an EMG needle site). Due to the abscess, the latter patient received only 3 cycles of post radiation chemotherapy. One patient had grade 3 anxiety related to the steroids for chemotherapy prophylaxis (and only received 1 cycle of the post radiation chemotherapy) Two patients manifested urinary retention with bladder neck contracture. Three patients manifested a grade 3 decline in WBC count and absolute neutrophil (ANC) count. Two of those patients went on to manifest a grade 4 decline in ANC. One additional patient received only 3 cycles of post radiation chemotherapy at his request. Only two patients were treated at a reduced dose; one for the last cycle due to neuropathy and one for the last two cycles due to fatigue and a decline in performance status.

The most predominant grade 2 toxicities were hand-foot syndrome rash (6 patients), fatigue (4 patients), alopecia (3 patients) and sensory neuropathy (3 patients). Those as well as the less common Grade 2 toxicities are demonstrated in Table 3.

Table 3. Grade 2 toxicity during chemotherapy only treatment

Hand-foot rash	6	Urinary retention	1	Dizziness	1
Fatigue	4	Incontinence	1	Mucositis	2
Alopecia	3	Diarrhea	1	Infection (normal ANC)	1
Sensory neuropathy	3	Otitis	1	Infection (decreased ANC)	1
Motor neuropathy/ cramps	1	Hemoglobin decline	1	Scalp and teeth sensitivity	1
Cystitis	2	WBC decline	2	Headache	1
Urinary frequency	1	Nail changes	1	Rash (non hand-foot)	1

During the course of treatment, two (11%) patients developed bladder neck contractures. It is uncertain whether this is increased by the addition of chemotherapy as retrospective review from a previous study showed an occurrence of at least 10% after surgery alone, increasing to 18% after postoperative radiation [10].

We were able to measure PSA response rate. Pretreatment, there were 5 patients with a PSA above 1.0 ng/ml and 8 with a PSA above 0.5 ng/ml. All patients but two had a decline in PSA after treatment. Two of the 5 with a pretreatment PSA >1.0 ng/ml became undetectable after treatment. There were 4 patients with a PSA above 0.5 ng/ml after the completion of treatment. Overall, 14/19 (74%) had a > 50% decline in PSA. Eleven patients initially had an undetectable PSA after surgery with subsequent rise and 8 patients did not nadir below 0.2 ng/ml post operatively. For the former group, post treatment 9 (81%) had a PSA <0.2 ng/ml. For the patients with a persistent PSA post surgery, 5 (63%) experienced a nadir < 0.2 ng/ml after chemoradiation.

At the most recent follow up, 11 patients had a PSA equal to or greater than 0.2 ng/ml (the definition of biochemical failure after radical prostatectomy). Six (32%) have been started on

tertiary treatment with androgen ablation. Further follow up will determine the ultimate durability of response.

Ours is the first study to report the effects of combined docetaxel chemotherapy and radiation in the post prostatectomy setting. As a phase II study, the primary endpoint was toxicity. Patients tolerated treatment relatively well. The combination of docetaxel and radiation was well tolerated with all the patients completing radiation uninterrupted. This is consistent with the studies reported in the use of docetaxel and radiation as primary therapy. In the phase I study [9], the dose limiting toxicity was Grade 3 diarrhea, which prompted selection of the next lower dose (20 mg/m^2) as the maximally tolerated dose. At that dose, there was no dose limiting toxicity and grade 2 diarrheas and dysuria was 26% and 23%, respectively. Seven (32%) of the patients had no reported diarrhea and 15 (68%) had no reported dysuria. There was no grade 2 or higher hematologic toxicity (anemia, neutropenia, or thrombocytopenia). One patient had an elevated bilirubin, which required discontinuation of chemotherapy. It should be noted that they treated the whole pelvis for the first 45 Gy, with a total of 70.2 Gy to the prostate. We had one patient with grade III diarrhea, with 37% and 53% incidence of grade II diarrhea and cystitis, respectively. Subsequently, two other studies in intact high risk prostate cancer have been reported. Perottie [11] reported on 20 patients treated with 72 Gy to the prostate combined with 20 mg/m^2 of docetaxel given weekly, although some patients were also receiving androgen ablation.

Three patients experienced treatment interruptions: dehydration requiring inpatient hydration (n =2); NSAID induced GI bleed (n = 1). An additional patient required outpatient hydration (<24 hours) with no treatment interruption. The most common grade 2 toxicities were diarrhea (40%), fatigue (40%) and urinary frequency (35%). Two patients had a treatment interruption from dehydration and one from gastrointestinal bleeding (thought to be secondary to NSAID use). In the second study [12] fifty men on androgen ablation received 70 Gy to the prostate and seminal vesicles with weekly docetaxel (20mg/m^2). They then received 3 cycles of docetaxel at 60 mg/m^2 every 3 weeks. This was given three weeks after the completion of 3D-CRT. The intent to treat analysis shows that four patients out of 15 stopped the chemotherapy prematurely due to grade 3-4 acute toxicity. In the per protocol analysis, 46 patients completed a full dose chemoradiation regimen representing 413 cycles: five patients experienced grade 3 toxicity, and 15 patients experienced grade 2 toxicity. Overall, between these studies and ours, it appears that the most common toxicities during combined treatment are in the radiation field (proctitis and cystitis). The toxicities of the chemotherapy alone are diverse, but most often are hematologic.

Although the primary endpoint of this Phase II study is toxicity, we are able to note some response data. Almost all of our patients responded to treatment with 89% experiencing a drop in PSA. Some patients (47%) have subsequently shown signs of progression (rising PSA). It is difficult to gauge how these patients would have done with radiation alone. We hope that with further follow up and with comparison to larger groups of patients, we can better ascertain the efficacy of the treatment. For now, we were able to demonstrate that combined docetaxel during radiation and subsequent full dose docetaxel post radical retropubic prostatectomy is well tolerated.

4. CONCLUSION

Ours is the first report of combined docetaxel and radiation in the post prostatectomy setting. Overall the toxicity of the combined treatment was similar to that seen with radiation alone and the toxicities of the full dose docetaxel are consistent with what's reported in the

literature and appear tolerable. From our data, it appears that the regimen is tolerable and is open to further investigation as to whether it can improve outcomes.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

The authors have no financial or personal relationships referenced to this study.

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