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Neoadjuvant Docetaxel and Capecitabine in Patients with High Risk Prostate Cancer

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Abstract

Purpose—Docetaxel is the most active cytotoxic agent in hormone refractory prostate cancer. Pre-clinically docetaxel increases expression of thymidine phosphorylase (TP), an enzyme responsible for activation of capecitabine to 5-fluorouracil resulting in increased anti-tumor activity. We assessed activity and safety of neoadjuvant docetaxel and capecitabine in patients with high risk prostate cancer.

Materials and Methods—Patients with either clinical stage >T2, PSA $\geq$ 15 ng/ml or Gleason sum $\geq$ 8 received 3–6 cycles of docetaxel (36 mg/m² intravenously on days 1, 8, and 15) and capecitabine (1250 mg/m²/day orally divided twice a day, on days 5–18) every 28 days, followed by local therapy. The primary endpoint was rate of $\geq$ 50% PSA decline. Correlative studies included qualitative changes in histology, tissue TP and survivin expression, and CK18Asp396 (serum apoptosis marker).

Results—Fifteen patients were treated. Six of 15 patients (40%) experienced a $\geq$ 50% decline in PSA with infrequent diarrhea or hand-foot syndrome. Eleven patients underwent a radical prostatectomy; there were no pathological complete responses, 4 patients demonstrated mild histological changes, including focal necrosis and vacuolated cytoplasm. While there was no discernable pattern of increased TP expression, 4 specimens showed decreased survivin expression, suggesting a possible mechanism for chemotherapy-induced apoptosis. There was no correlation of PSA response and survivin expression and no increase in serum CK18Asp396.

Conclusions—Neoadjuvant docetaxel and capecitabine is well tolerated but is not associated with significant pathological and PSA responses.

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Keywords

Neoadjuvant Chemotherapy Prostate Cancer

Introduction

High-risk prostate cancer patients (cT3, N1, PSA $\geq$ 20 ng/ml and/or Gleason score $\geq$ 8) have a 5-year biochemical failure rate after surgery or radiation of 50% or greater.¹ Systemic failure accounts for a significant proportion of these clinical relapses. Adjuvant androgen deprivation therapy (ADT) is currently the only systemic treatment that impacts survival in selected patients.^{2,3} Because of heterogeneity of prostate cancer cells and desire to improve on outcome with ADT, chemotherapy in localized, high-risk prostate cancer is being explored. Neoadjuvant treatment has the advantage of rapid assessment of pathologic and molecular treatment effect.

Docetaxel has demonstrated significant anti-tumor effect and impact on survival in hormone refractory prostate cancer.^{4,5} This has led to its evaluation in the neoadjuvant setting either as single agent or in combination with hormones or estramustine.⁶⁻⁸ While these trials report PSA declines of >50% in up to 60% of patients, significant pathological responses are rare. Furthermore, because many of these studies incorporated ADT or estramustine, it is difficult to assess the contribution of chemotherapy on pathological and PSA declines because of the well-described effect of hormones on prostate cancer.

Prostate cancer and other solid tumors express high levels of TP, an enzyme responsible for activation of capecitabine to the active drug, 5-fluorouracil (5-FU).⁹ 5-FU is then catabolized by DPD. In multiple tumor cell lines, including prostate cancer, the activity of capecitabine is related to the ratio of TP/DPD.¹⁰ Docetaxel has been shown to enhance TP levels in tumor models and is synergistic with capecitabine.¹¹ In a phase III trial the combination capecitabine and docetaxel improved overall response rates and survival in patients with advanced breast cancer as compared with docetaxel alone.¹² Because of docetaxel's anti-tumor activity in prostate cancer, its ability to increase TP in preclinical studies, and its enhanced clinical activity with capecitabine in breast cancer, we developed a phase II trial combining neoadjuvant capecitabine and docetaxel in patients with high-risk prostate cancer. A weekly schedule of docetaxel was chosen for its promising rates of PSA declines in neoadjuvant phase II trials,^{7,8} and that weekly docetaxel, rather than every three weeks, could induce further sustained increases in TP, thus enhancing the anti-tumor activity of the combination.¹¹

Simultaneously we initiated a preclinical trial to assess the in vitro anti-tumor effect, as well as changes in gene expression, of the combination of docetaxel and fluorouracil-based therapy to help guide the correlative studies in this trial. Specifically, from our in vitro studies we found that the anti-apoptotic protein, survivin, decreases markedly in prostate cancer cell lines when treated with docetaxel and furtulon (capecitabine is the orally administered pro-drug of furtulon).¹³ Survivin is a member of the inhibitor of apoptosis family of proteins and its over-expression correlates with androgen-independent prostate cancers.¹⁴ Using immunohistochemistry, we evaluated TP expression pre and post chemotherapy to determine the validity of the pre-clinical basis for this combination. Because it is hypothesized that TP would be increased in response to docetaxel, we measured TP alone, and not DPD. We also measured changes in survivin expression by immunohistochemistry.

Materials and Methods

Patient eligibility

Eligible patients had newly diagnosed prostate cancer with at least ONE of the following: (1) clinical stage >T2, (2) PSA ≥ 15 ng/ml, (3) biopsy Gleason's sum ≥ 8 . A minimum PSA > 5 ng/ml, no evidence of distant metastasis as determined by CT of the abdomen and pelvis and bone scan within 6 weeks of registration, an ECOG performance status of 0 or 1, and no previous or current anti-androgen therapy, chemotherapy or radiotherapy were required. Patients were also required to have an absolute neutrophil count > 1500/ml, platelet count >100,000/ml, a serum creatinine < 2.0 mg/dL, normal total bilirubin, and liver enzymes < 2.5 x the upper limits of normal. Patients with a baseline peripheral neuropathy > grade 2, were excluded. Pre-therapy biopsy materials must have been submitted for pathologic review. All patients provided signed, written informed consent for the trial approved by the institutional review board.

Study design

Treatment plan and dose reductions—Patients were treated with docetaxel 36 mg/m² intravenously on days 1, 8, and 15 every 28 days. Capecitabine was administered orally at 1250 mg/m²/day divided in 2 equal doses 12 hours apart on days 5 to 18. Patients were pretreated with 8 mg of dexamethasone orally 12 hours and 1 hour prior, and 12 hours after docetaxel chemotherapy. The doses and schedule of capecitabine and docetaxel that were used in this study were based on a phase I study by Nadella et al.¹⁵ The sequencing of docetaxel and capecitabine is based on the observed increase in the enzyme activity 4 days after treatment with docetaxel.¹¹ Two dose reductions of docetaxel (30 mg/m² and 25 mg/m²) were allowed for neutropenia, thrombocytopenia, neuropathy, or liver function abnormalities. A maximum of two dose reductions (1000 mg/m² and 800 mg/m²) were allowed for capecitabine in the event of hand foot syndrome, mucositis, or diarrhea. In the absence of progression or unacceptable toxicities, treatment continued for three cycles. Patients with PSA decline <50% were withdrawn from the study and treated with local therapy. Responding patients were offered three additional cycles to maximize benefit.

Monitoring—Prior to each cycle patients had a complete physical exam including a digital rectal examination, serum chemistries, testosterone and PSA level measurements. After 3 and 6 courses, CT of abdomen and pelvis were performed. Patients who elected definitive radiation therapy were asked to provide a post therapy prostate biopsy (12 cores).

Pathologic evaluation and immunohistochemistry—The morphology and immunostaining profile of all samples were reviewed by a genitourinary pathologist at University of Michigan. Complete eradication of tumor would be considered a complete pathologic response. All pre-chemotherapy needle biopsy samples were evaluated and compared to post chemotherapy samples. Post chemotherapy samples were examined for recognized effects of therapy on normal and malignant tissue.¹⁶ Effects of chemotherapy on the tumor were scored (0= none, 1= mild or very focal, 2= moderate or multifocal and 4 =strongest or diffuse) for: presence of necrosis; pyknosis; cytoplasmic vacuolation; fibrosis; glandular breakdown; and extravasated mucin. Immunohistochemical stains for thymidine phosphorylase (Neomarker clone PGF.44C, pH6 antigen pretreatment, 1:200 for 60 minutes) and Survivin (Novus Cat #NB 500-201, Citrate Buffer pretreatment, 1:150 for 30 minutes) were performed on pre and postchemotherapy specimens.

Apoptosis assay—An assay of apoptosis was evaluated to explore its utility in this setting. Cleavage of cytokeratin 18 (CK 18) by caspases after the aspartic acid residue 396 during apoptosis results in exposure of a neoepitope (CK18Asp396), which is believed to be a surrogate marker for apoptosis. Plasma was collected and stored at -80C. Levels of

CK18Asp396 were measured using a commercially available ELISA, M30-Apoptosense® (PEVIVA AB).¹⁷

Statistical considerations—The primary end point was the response rate of the combination of capecitabine and docetaxel defined as a reduction in the PSA by at least 50%. Using a two-stage Simon's minimax design, if ≤ 7 responses were seen in the first 14 patients, the study was stopped, and the regimen deemed not worthy of continued study. Otherwise, a total of 23 patients were to be accrued. If ≤ 15 responses were observed in the final set of 23 patients at the end of the study, the regimen would be deemed ineffective. If ≥ 16 responses are observed, the regimen would be considered promising. This two-stage design allowed for a 5% type I error, and 80% power.

Secondary endpoints included assessment of feasibility and toxicity of neoadjuvant chemotherapy, evaluation of intra-tumoral changes in 5-FU metabolism, and molecular responses to chemotherapy.

Results

Patients characteristics

From June 2003 until June 2005, 15 patients were enrolled in the study. Patient characteristics are outlined in Table 1. Most patients (73%) had 2 or more high-risk features. The high-risk features that most commonly qualified patients for the study were a Gleason score of ≥ 8 in 14/15 (93%) and/or PSA ≥ 15 ng/mL in 12/15 (80%).

Efficacy

Of the 15 patients, 9 completed three cycles, 2 completed 2 cycles, and 4 completed greater than 3 cycles of chemotherapy. Weekly docetaxel and capecitabine had a significant effect on the median serum PSA (Figure 1), falling from a median of 23.2 ng/mL pre therapy to a median of 12.2 ng/mL post therapy ($p < 0.001$). All but one patient had a fall in the PSA on therapy. The median testosterone did not change pre and post chemotherapy (3.58 ng/ml versus 3.63 ng/ml). Only 6/15 (40%) experienced a $\geq 50\%$ decline in serum PSA, the primary end point of the study. Because the protocol called for at least 8 patients with a $\geq 50\%$ decline, accrual to the second stage was not pursued.

Toxicity

Grade 1 or 2 fatigue was experienced by 66% of patients, gastrointestinal side effects such as nausea in 46%, changes in taste 40%, nail changes 40%, and tearing 40%. Six patients (40%) experienced a Grade 1 or 2 hand foot syndrome. Three and two patients experienced Grade 3 diarrhea and mucositis, respectively. Only 1 patient experienced a grade 4 neutropenia. However, 11 of the 15 patients experienced a Grade 1 or 2 fall in hemoglobin. There were no episodes of neutropenic fevers, however, one patient experienced a peri-rectal abscess and facial cellulitis in the absence of neutropenia.

Local therapy and follow-up

Thus far median follow up is 17.5 months (range 9–34 months). Eleven patients underwent radical prostatectomy, 6/11 had positive margins, and 2/11 had involved lymph nodes. Of the 8 patients who were treated with radical prostatectomy alone (no adjuvant radiotherapy or anti-androgen therapy), 5 developed a biochemical recurrence in a median 11 months. Of the 6 patients who achieved at least a 50% decline in PSA, 5 had either involved surgical margins and/or lymph nodes with prostate cancer. Gleason sum and pathological stage post chemotherapy is shown in Table 2. Three patients elected definitive radiotherapy (two with

concurrent androgen blockade). One patient never underwent definitive therapy as he was diagnosed with a locally advanced gallbladder carcinoma while on trial.

Chemotherapy-effect, immunohistochemistry and apoptosis assay

Pre and post-chemotherapy biopsies specimens were available for 7 of the 11 patients who underwent radical prostatectomy. For the remaining 4 patients, samples from outside institutions were not available for review. Of the 3 patients who underwent definitive radiation therapy, one underwent a post chemotherapy transrectal biopsy, but was of insufficient quality for interpretation. The other two patients were not offered biopsy due to poor response and need for definitive radiation with androgen blockade. Four of the 7 post-chemotherapy, prostatectomy specimens showed overall chemotherapy response; all of these were mild. The most common features were focal cytoplasmic clearing or vacuolization (n=6 with score=1–2) and glandular breakdown (n=5 with score 1–3). Four specimens showed focal apoptosis/pyknosis (score=1–2) and a few (n=1–2) showed focal (score=1) necrosis of the tumor cells. Only one of the three PSA responders (>50% decrease in PSA) showed mild chemotherapy response. There was no discernable pattern of increased TP expression in prostatectomy specimens compared to pre-chemotherapy biopsies (3 increased, 3 decreased, 1 with unchanged TP expression). Four prostatectomy specimens showed decreased survivin expression in the tumor cells. TP and survivin expression did not correlate with PSA response. Figure 2 shows an image of a representative case of decreased survivin expression post-chemotherapy, as well as the observed chemotherapy effects.

Plasma samples for apoptosis assays were available for eleven patients at baseline and after cycle 1 of neoadjuvant chemotherapy. No significant differences in levels of apoptosis-associated neo-epitope, CK18Asp396, were found pre-chemotherapy (mean value of 109.6 U/L) versus post-chemotherapy (mean value of 112.3 U/L), or in PSA responders versus non-responders.

Discussion

Neoadjuvant docetaxel and capecitabine in men with high-risk localized prostate cancer resulted in a significant decline in serum PSA, but did not reach the threshold set prospectively by the study for continuation of the study, nor was it associated with significant pathologic responses. Overall, the regimen was well tolerated, with infrequent grade 3 or 4 adverse events. The clinical outcome for these men appears to be consistent with what is expected for the extent of their local disease.

To fully evaluate effects of neoadjuvant chemotherapy independent of clinical variables (PSA) it was essential to evaluate pathological samples pre and post-chemotherapy. By not using ADT, we were able to evaluate the effect of chemotherapy alone. Only focal and mild effects were observed in 4 of the 7 patient samples. Even with relatively more significant pathologic changes seen with the use of neoadjuvant hormone-based therapy, pathologic complete responses are rare.¹⁸ In contrast, in neoadjuvant studies with breast cancer, complete pathological response rates up to 30% are reported with impressive increase in disease free survival.¹⁹ The lack of significant pathologic complete responses with neoadjuvant therapy in prostate cancer does not necessarily mean lack of “benefit.” However, until better clinical or molecular response surrogates are identified, it is reasonable to use pathologic complete response rates as a metric for screening agents in this setting in the context of uncontrolled clinical trials. Alternatively randomized phase II designs can be implemented evaluating several indicators of potential clinical activity including progression free survival (clinical/biochemical) and tissue-based indicators.

The choice to combine capecitabine with docetaxel was based on the preclinical knowledge that docetaxel increased TP levels in tumor samples, and that higher TP levels would translate into greater conversion of capecitabine to active drug. We found that TP expression increased only mildly in 3 of the 7 samples, and did not correlate to PSA response. It is not clear why we did not detect an increase in TP expression in our study. It is possible that increased TP expression in response to docetaxel may only be transient, and thus not detected at the time of radical prostatectomy. Alternatively, docetaxel given every three weeks may have had a more profound effect on TP expression in vivo despite the in vitro data in support of weekly docetaxel. In fact, schedule may be very important given the knowledge that, docetaxel's greatest impact on survival in HRPC occurs when given every three weeks, rather than weekly.

Our neoadjuvant study was unique in that we investigated the regimen in cell-line experiments and used the data to prospectively evaluate expressed genes that potentially could be altered by the chemotherapy used in our patients in this trial. In our pre-clinical studies, we observed a marked decrease in survivin expression after treatment of a prostate cancer cell line with docetaxel and furtulon.¹³ In this study we found that 4 of the 7 samples showed declines in survivin expression by immunohistochemistry, suggesting that in vivo, docetaxel may decrease survivin expression. Evaluation of survivin expression post chemotherapy in a larger sample size may help to further characterize the effects of docetaxel in vivo. Combining drugs with docetaxel, that further lower the apoptotic threshold by decreasing the activity or expression of anti-apoptotic proteins such as survivin would be an important new hypothesis to explore in future neoadjuvant trials.

Conclusions

With only modest PSA declines and subtle pathologic changes, this treatment failed to meet the per protocol efficacy parameters.

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Abbreviations and Acronyms

CT	computerized tomography
ECOG	Eastern Cooperative Oncology Group
PSA	prostate specific antigen
TP	thymidine phosphorylase
ELISA	enzyme linked immunosorbent assay
HRPC	Hormone refractory prostate cancer

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Figure 1.
Box plots of serum PSA and testosterone pre and post treatment.

Figure 2. Morphologic features of chemotherapy effects included apoptosis/pyknosis (A) and cytoplasmic vacuolization (B). Compared to prechemotherapy specimens (C), survivin expression was decreased in postchemotherapy specimens (D) in four patients.

Table 1

Baseline Characteristics

Number of patients	15
Age, median (y)	58 range, 40–71
Race	
White	11
Black	4
Clinical Stage	
T1c	1
T2a	2
T2b	3
T2c	4
T3	2
T4	1
+Nodes	1
Gleason, median	8, range 7–10
PSA, median	23.2, range 8.1–282.2
Median number of qualifying criteria	2, range 1–3

Table 2

Pathologic and PSA responses

Pre-chemotherapy				Post-chemotherapy			
Patient	Stage	Gleason	PSA	Stage	PSA (% change)	Gleason	Margin
1	T2c	8	12.1	NA	12.6 (+4)	NA	NA
2	T1c	7	33.8	T2a	22.1 (-34)	7	-
3	T2c	8	8.1	T3a	4.7 (-42)	7	-
4	T2a	9	19.5	T3a	9.4 (-52)	9	+
5	T2c	8	15.1	T3b	9.7 (-36)	7	+
6	T2b	8	282.1	T3b	64.3 (-77)	7	+
7	T2b	9	30.1	T3b	19.9 (-34)	9	+
8	T2b	8	10.2	T3a	6.6 (-35)	7	-
9	T2c	8	198	T2b	27.3 (-86)	8	-
10	T2c	8	21.2	T2b	19.4 (-8.4)	8	-
11	T2a	9	23.2	NA	12.2 (-47)	NA	NA
12	T4	8	15.2	T4	3.3 (-78)	8	+
13	T2a	6	26.8	T3	7.2 (-73)	7	+
14	T3	10	78.7	NA	60.2 (-24)	NA	NA
15	T2N1	9	24.7	NA	12.2 (-51)	NA	NA