Possible Risk Factors Associated with Relapse in Patients Treated with Neoadjuvant Chemohormonal Therapy for High Risk Prostate Cancer

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Abstract: Objectives: To perform a pilot hypothesis generating study of neoadjuvant docetaxel, estramustine, and androgen deprivation therapy for high-risk patients prior to radical prostatectomy.

Patients and Methods: Twenty-eight patients received 4 cycles of docetaxel and estramustine administered on an every three week schedule in combination with androgen deprivation therapy (LHRH analog and bicalutamide) prior to radical prostatectomy. Following the prostatectomy, androgen deprivation therapy was continued for 8 months. End-points were pathological complete response (pCR), time-to-relapse (TTR), feasibility and tolerability, and biochemical or clinical correlates of relapse.

Results: With a median of 80 months (6.6 years) of follow-up, 18/28 patients have relapsed and one patient died from unrelated causes while in remission, with median TTR of 44 months (3.6 years). Tumor downstaging, perhaps as a result of neoadjuvant therapy, was associated with a decreased risk of relapse (P=0.0002). Consistent with this result, positive margin status was associated with an increased risk of relapse, which was not affected by adjuvant radiation therapy. Increased expression of a possible tumor stem cell marker, (Sry-related high mobility group box-9) Sox-9, both at the time of prostatectomy (P=0.005) and in the pre-treatment tumor biopsy cores was associated with an increased risk of relapse (P=0.03).

Conclusions: The neoadjuvant chemohormonal regimen may have benefited some patients, especially those who exhibited pathologic downstaging. Sox-9 expression in prostate cancer specimens warrants prospective validation in both pre-prostatectomy tissue as well as patients undergoing an ongoing randomized trial using a similar neoadjuvant regimen.

Keywords: Neoadjuvant, high-risk prostate cancer, Sox-9.

INTRODUCTION

Multiple studies have defined risk factors for recurrence and death from prostate cancer. The three independent parameters consistently identified are high clinical stage (>cT2), elevated PSA (>10) and high Gleason score (>7) [1]. In patients with one or more of these poor prognostic factors, the likelihood of cure from primary therapy (prostatectomy or radiation therapy) decreases significantly [2] and the management of high risk, localized prostate cancer remain uncertain.

Androgen deprivation therapy (ADT) has proven to be a useful adjuvant therapy for men with high-stage prostate cancer treated with external beam radiotherapy (EBRT) [3, 4]. In contrast, ADT as neoadjuvant therapy in conjunction with radical prostatectomy (RP) has not improved survival [5-7]. Because docetaxel has been shown to result in a survival advantage for castrate resistant metastatic disease [8,9] it has been given alone and with ADT in the neoadjuvant setting for high risk prostate cancer [10-17]. The rationale for combining chemotherapy and hormonal therapy is derived from tumor models that demonstrate that a combined approach is better than sequential therapy with either modality alone [16-18]. However, although neoadjuvant chemohormonal therapy has been shown to be safe [10-17], and sometimes has resulted in better than expected outcomes
[15-17], consistent clinical or pathological markers associated with improved outcome have yet to be identified.

We performed a trial that combined ADT with docetaxel and estramustine for 4 [3] week cycles prior to radical prostatectomy (RP). ADT was continued post-RP for 8 months. Because PSA recurrence can be prolonged even in high risk prostate cancer, this cohort has had long-term follow-up. Goals were to correlate time-to-relapse (TTR) with clinical and biochemical parameters. In addition, we generated a tissue microarray from the RP specimens to assess the effect of expression of a number of conventional biomarkers, as well as a possible prostate cancer stem cell marker, Sox (Sry-related high-mobility group box)-9 [19-21].

Our interest in Sox-9 stems from previous work from our group that demonstrated that Sox-9 expression is significantly increased in recurrent castrate resistant prostate cancer compared to primary cancers [19]. Sox-9 is a transcription factor important in the development of male testes and is expressed in areas of the developing prostate associated with stem cell properties [19]. Furthermore, Sox-9 expression is correlated with higher Gleason grade disease [20]. While silencing endogenous Sox-9 expression in PCa xenografts causes reduced tumor growth, Sox-9 over-expression enhances PCa xenograft growth, angiogenesis and invasion [21]. These results suggest a potential role for Sox-9 in PCa aggressive behavior and possibly in the setting of treatment resistance.

METHODS

Patients

Between September 28, 1999 and May 17, 2005, 28 patients with high-risk localized prostate cancer were enrolled on this IRB approved phase II protocol. Eligible patients were required to demonstrate one or more of the following criteria: clinical stage (T3), elevated PSA (≥ 20ng/ml) or high Gleason score (>7). In addition patients with 5 of 6 positive core biopsies or the equivalent with Gleason 4+3 disease were also eligible. Patients had to have normal renal, liver, cardiac and hematopoetic function, and no other active cancers, infection, or significant neuropathy. Endorectal MRI evaluation was not required.

Staging Evaluation

Patients were assigned a clinical stage according to the tumor-node-metastasis (TNM) staging system based on digital rectal examination (DRE). Clinical stage T3 or extraprostatic extension was assigned on the basis of a DRE performed by one Urologist (WCD) and confirmed by the study PI (GIB). Chest x-ray, CT of the abdomen and pelvis, and bone scans were required of all patients before study entry to exclude the presence of metastatic disease.

Treatment

Patients were treated with a combination regimen of 4 cycles (administered every 3 weeks) of docetaxel (70 mg/m2) and estramustine (280 mg orally tid on days 1-5). An LHRH agonist and bicalutamide (50mg/day) were initiated one week prior to chemotherapy and continued for one year. Patients were treated with dexamethasone prior to docetaxel infusion and 1 mg of warfarin was administered as prophylaxis for DVT through cycle 4 of chemotherapy. Complete blood counts, liver function tests and serum PSAs were obtained on day 1 of each cycle. RP was performed 16-19 weeks after beginning therapy.

Pathology

One of two pathologists (SR, EG) assessed pathological staging on post-prostatectomy specimens. Staging including a description of all tumor foci within the gland, presence or absence of perineural invasion and/or lymphovascular invasion, presence of extraprostatic extension of tumor (including seminal vesicle invasion), and margin status.

Immunohistochemistry

Immunohistochemistry (IHC) was performed as previously described for Sox-9, AR, and Ki-67 antibodies (18-20) or following manufacturer’s recommendations using the following antibodies: rabbit anti-androgen receptor antibody (PG-21, and Cell Signaling #3202;1:30); rabbit anti-phospho-Histone H3 (Ser10, 06-570:1:250, Upstate Biotechnologies); rabbit anti-Sox-9 (1:1500) (Dr. M. Wegner, Institut fur Biochemie, Emil-Fischer-Zentrum, Universitat Erlangen Erlangen, Germany); mouse anti-Ki67 (1:300) (a gift from Dr. S. Signoretti, DFCI, Boston, MA); Bcl2 (1:500, Cell Signaling 2870); p53 (1:500 Cell Signaling 2527); HIF1α (Novus: 1:200). IHC staining was performed on pre-treatment prostate cores biopsies and a TMA having 2 to 3 samples involved with cancer from different regions of the gland.

Tissue Microarray Construction and Core Biopsy Analysis

The paraffin blocks containing tumor were obtained from 23 of 28 patients in this study, and tissue blocks were designated as to their location within the prostate. In 18 cases, tumor for the TMA was obtained from the left and right lobe of the prostate. In 3 other cases, tumor was obtained from the apex and base. In two cases, tumor was derived from only one remaining focus of tumor. In 16 cases, three separate cores with tumor were obtained, in 4 patient samples two cores with tumor were obtained and three patients had only one core with tumor. Normal non-malignant tissue was available from three areas of the prostate in all 23 patients sampled.

Tissue was removed using a minute tissue cylinder (0.6mm) by an experienced technician into areas of tumor and normal prostate and subsequently transferred into a pre-made hole at defined array coordinates into the recipient tissue block. The location for the tumor “punch” was guided by an H & E stained section overlaid on the surface of the donor block.

Additionally, 13 of 28 patients had pre-therapy core biopsies available for IHC analysis, 12 for which prostatectomy specimens were also available. These were not analyzed by TMA due to limitations of tissue depth. However, fresh cut slides from the blocks were cut and used for IHC analyses.

Follow-Up

Patients were evaluated 1 month after surgery, then at 3 month intervals by history, physical examination, and routine laboratory tests including PSA.
Patients with positive surgical margins or seminal vesicle involvement were treated with adjuvant radiation therapy at the discretion of the treating physician. Following PSA relapse, patients were treated with salvage radiation therapy if they had not already undergone adjuvant radiation therapy.

Statistical Considerations

The primary objective of the study was to determine the pCR rate and TTR for the cohort. Secondary objectives of this study were to assess overall survival, feasibility and toxicity. Correlative aims were to identify possible clinical or IHC markers that predicted for relapse.

Descriptive statistics summarized clinical characteristics either as number and percent or as median and interquartile range of values. Relapse was defined as a confirmed post-RP PSA rising to a level > 0.2 ng/ml or the need for an additional therapy (other than adjuvant treatment), whichever came first. One patient who died from an unrelated cause before relapse occurred was censored at the last PSA date prior to death. TTR was summarized using Kaplan-Meier method and comparisons were made using a log rank test.

To assess the relevance of a change between clinical and pathological staging, patients were categorized as upstaged, downstaged or not changed using the T-stage. Each protein assessed by IHC was categorized into high and low staining, where high was 75% of cells staining at an intensity of 3+.

RESULTS

Patient Characteristics

The clinical characteristics of the study population are summarized in Table 1. The Gleason score was >7 in 18 of 28 patients and one patient was not assigned a Gleason score based on a poorly differentiated ductal histology. Eight (29%) patients had PSA values between 10 and 20 ng/ml and 9 had PSA values of > 20 ng/ml (32%). Two (7%) patients were clinical stage T1c (Gleason 8 and Gleason 9 scores). Three patients were clinical stage T2 (1 with a PSA of 32 ng/ml and 1 with Gleason 8) and 23 (82%) patients were clinical stage T3. One T2 patient was enrolled who did not meet the PSA criteria of >20ng/ml, T3 clinical stage or Gleason score >7, this patient had 6 of 6 positive cores with Gleason 4 + 3 disease. Many of the clinical stage T3 disease patients also exhibited high PSA values and Gleason scores >7 (Table 1).

Feasibility/Toxicity

All 28 patients completed 4 cycles of neoadjuvant chemotherapy and underwent RP. There were no unanticipated adverse events from chemo-hormonal therapy, although 4 patients experienced fever and neutropenia and 1 developed a grade 3 elevation of transaminases that normalized after discontinuation of bicalutamide therapy. Following RP, two (7%) patients suffered protracted ileus that prolonged their hospitalization, one patient developed pancreatitis, and one developed a pulmonary embolus. One-half (14/28) of the patients required RBC transfusions post RP.

Clinical Characteristics and Outcome

Table 2 shows the PSA level prior to surgery, the pathological staging after RP, and the type of radiation therapy administered after RP. All patients had undetectable PSA levels post-operatively. Approximately half the patients had an undetectable PSA prior to RP.

Pathological assessment of RP specimens demonstrated that 10 (36%) patients had carcinoma confined to the prostate, 15 (54%) had evidence of extraprostatic extension or seminal vesicle invasion and 3 (11%) had evidence of bladder invasion. Three (11%) patients had microscopically positive lymph nodes.

The median TTR is 44 months (3.6 years), and 18 of 28 patients relapsed with a median follow up of 80 months (6.6 years) (Fig. 1A). Nine patients remain free of PSA relapse, and one patient died from unrelated causes while still relapse-free. Of the 18 relapsed patients, 9 were treated with salvage radiation therapy (Table 2) and 4 of these patients currently demonstrate undetectable PSA values for a median of 29 months from the completion of salvage radiation therapy. Thus with 6.6 years of follow-up, 13/28 patients have undetectable PSA values.

Table 1. Patient and Disease Characteristics at Baseline

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N and % or Median and IQR</th>
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<tbody>
<tr>
<td>Number of Patients</td>
<td>28 100%</td>
</tr>
<tr>
<td>Age at Enrollment (years), median and IQR</td>
<td>57 53-64.5</td>
</tr>
<tr>
<td>PSA at Enrollment (ng/ml), median and IQR</td>
<td>14 6.5-33</td>
</tr>
<tr>
<td>PSA ≤4ng/ml</td>
<td>2 7%</td>
</tr>
<tr>
<td>4ng/ml &lt; PSA ≤10ng/ml</td>
<td>9 32%</td>
</tr>
<tr>
<td>10ng/ml &lt; PSA ≤20ng/ml</td>
<td>8 29%</td>
</tr>
<tr>
<td>PSA &gt;20ng/ml</td>
<td>9 32%</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>2 7%</td>
</tr>
<tr>
<td>T2</td>
<td>3 11%</td>
</tr>
<tr>
<td>T3</td>
<td>23 82%</td>
</tr>
<tr>
<td>Biopsy Gleason Score</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2 7%</td>
</tr>
<tr>
<td>7 (3+4)</td>
<td>2 7%</td>
</tr>
<tr>
<td>7 (4+3)</td>
<td>5 19%</td>
</tr>
<tr>
<td>8</td>
<td>8 30%</td>
</tr>
<tr>
<td>9</td>
<td>10 37%</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>27 96%</td>
</tr>
<tr>
<td>Black</td>
<td>1 4%</td>
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Table 2. PSA Prior to Surgery, Pathological Staging and Adjuvant Radiation Therapy after Surgery

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
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<tbody>
<tr>
<td>PSA Prior to Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA &lt; 0.3 ng/ml</td>
<td>15</td>
<td>54</td>
</tr>
<tr>
<td>PSA ≥ 0.3 ng/ml</td>
<td>13</td>
<td>46</td>
</tr>
<tr>
<td>Pathological Staging</td>
<td></td>
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<tr>
<td>T-stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>10</td>
<td>36</td>
</tr>
<tr>
<td>T3</td>
<td>15</td>
<td>54</td>
</tr>
<tr>
<td>T4</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>N1</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Positive Margins</td>
<td>11</td>
<td>39</td>
</tr>
<tr>
<td>Adjuvant XRT</td>
<td>8</td>
<td>29</td>
</tr>
<tr>
<td>Salvage XRT</td>
<td>9</td>
<td>32</td>
</tr>
</tbody>
</table>

Of the 14 relapsed patients, 2 patients have not required any therapy, 8 are responding to ADT and 4 have developed castrate resistant disease. Of these, 2 have died from prostate cancer, 2 are being treated with docetaxel and another with salvage hormonal therapy. For the 5 deceased patients, 4 had PSA relapse, 2 died of prostate cancer, 1 of lung cancer and 1 of cardiac disease. One patient died while in remission from pancreatic cancer 6.2 years after RP.

The association of PSA values on TTR was evaluated both for PSA levels at enrollment and PSA values prior to RP. Entry PSA levels >10ng/ml were a risk factor for relapse (Fig. 1B) (P=0.032). Patients that had undetectable PSA levels prior to surgery (15/28) had a slight improvement in TTR, but this was not significant (P=0.055). Interestingly, patients older than the median had a significantly better TTR (Fig. 1C, P=0.016).

Pathological Characteristics and Overall Outcome

We assessed the association of pathological characteristics and TTR. There was a strong association with relapse comparing 18 pT3 and pT4 patients to 10 pT2 patients (Fig. 2A, P=0.002). In contrast, clinical stage was not associated with RFS, however, this was not surprising as >80% of patients were categorized as clinical stage T3.

Positive surgical margins (11/28 patients) were associated with increased risk of relapse (Fig. 2B, P=0.0002). Although 7 of 8 patients with positive margins and negative nodes were treated with adjuvant radiation therapy, relapse was not prevented for any of these patients.

Although neoadjuvant chemohormonal therapy did not result in pathologic complete responses, there were 7 cases in which the patient had a lower pathologic stage than the clinical stage and of those, 6 are currently relapse free (Fig. 2C, P= 0.017). In contrast, of the 18 patients who relapsed, only one patient was downstaged at surgery, and 11 patients were upstaged at the time of surgery (from T1c to T2c-T4) and 9 have relapsed.

Fig. (1). Kaplan Meier estimate of time to relapse (TTR) for the entire cohort (A), by PSA at enrollment (B) and by age (C) at enrollment. 1A. Entire Cohort: Eighteen patients have relapsed with a median follow up of 80 months (6.6 years). Median time to relapse is 44 months. 1B. By PSA at enrollment: PSA levels greater than 10 ng/ml at diagnosis were associated with an increased risk for relapse (P=0.032). 1C. By age: Age ≤57 years at enrollment was associated with an increased risk of relapse (P=0.016).

Immunohistochemical Analysis and Outcome

IHC analysis on RP specimens was available for 23 of 28 patients. The remaining 5 patients had residual volume too
small to use for tumor microarray analysis. Of these, 4 have not relapsed.

A.

![Kaplan Meier estimate of time to relapse by pathologic T stage](image1)

**Pathological Stage**
- T2
- T3
- T4

**Months from Enrollment to Relapse**
0 12 24 36 48 60 72 84

B.

![Kaplan Meier estimate of time to relapse by surgical margin](image2)

**Surgical Margin**
- Negative Margin
- Positive Margin

**Months from Enrollment to Relapse**
0 12 24 36 48 60 72 84

C.

![Kaplan Meier estimate of time to relapse by staging](image3)

**Staging**
- Downstage
- No change
- Upstage

**Months from Enrollment to Relapse**
0 12 24 36 48 60 72 84

**DISCUSSION**

An important asset of the current study is that it has one of the longest median follow-up periods reported (80 months or 6.6 years) to date, and additional relapses beyond the 18/28 (64%) that have relapsed, are unexpected. Among the relapsed patients, 4 are in remission following salvage radiation therapy, making 13/28 in complete remission. These data compare favorably to other neoadjuvant chemo-hormonal trials. Similar treatment regimens demonstrated a 58% relapse rate (53 month follow-up) (15) and a 55% relapse rate (29 month follow up) [11]. Nonetheless the efficacy of this treatment in a single arm study is not certain and comparisons between these and other neoadjuvant studies [5-7, 22-26] are problematic due to differences in regimens, duration of therapy and patient selection.

In this study, patients who exhibited pathological downstaging had a statistically significant improvement in outcome. Among the 7 patients downstaged, only one relapsed. Alternatively, in the group of 18 patients who relapsed, only one patient was downstaged at RP. Although this could reflect inaccuracies of clinical staging, this is unlikely, since the same urologist performed all clinical staging. Therefore one hypothesis from these data is that unlike neoadjuvant ADT alone, downstaging as reflected by pathological stage may reflect the sensitivity of microscopic cancer to chemo-hormonal therapy. Interestingly, neoadjuvant chemo-hormonal studies have been associated with greater than expected downstaging. In one neoadjuvant chemo-hormonal study, half the patients had organ-confined disease at RP, although only 8% would have been expected to, based on pre-operative Kattan nomogram assessment [15]. Furthermore, patients with pathologic complete remissions (pT0) disease have been detected in other docetaxel-based neoadjuvant studies [14, 15].

An important goal of this study was to analyze the molecular characteristics of residual cancer in RP specimens. Among a large number of IHC tumor makers analyzed in RP specimens, only Sox-9 expression was associated with significant risk of relapse. Given this finding, it was important to determine if Sox-9 expressing tumor cells present prior to therapy affected the outcome or if sox-9 expression might be a marker of chemo-hormonal resistance. Towards that end, we were able to obtain a number of core pre-treatment core biopsy samples from the patients in this study. Analysis of these samples showed that high Sox-9 expression was statistically associated with relapse, suggesting that Sox-9 expression is a marker of intrinsic chemo-hormonal resistance, and less likely that cells expressing this protein are selected for
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The biological significance of Sox-9 in prostate cancer is currently under investigation. Sox-9 levels are higher in castrate resistant prostate cancer and Sox-9 has also been shown to play a role in the propagation of prostate cancer tumor stem cells, as well as invasion and angiogenesis [21].

Other clinical and pathological markers were somewhat informative. Not surprisingly, higher pretreatment PSA values were associated with an increased risk of relapse.

on the basis of resistance to therapy. These data suggest that Sox-9 expression may be a useful marker for future studies.

The biological significance of Sox-9 in prostate cancer is currently under investigation. Sox-9 levels are higher in castrate resistant prostate cancer and Sox-9 has also been shown to play a role in the propagation of prostate cancer tumor stem cells, as well as invasion and angiogenesis [21].

Other clinical and pathological markers were somewhat informative. Not surprisingly, higher pretreatment PSA values were associated with an increased risk of relapse.
likely reflecting tumor burden. An interesting finding was that patients older than the median age had a better outcome. Finally, 7 of 8 patients with positive margins relapsed despite the use of adjuvant radiation therapy and uninvolved lymph nodes, despite recent data that this therapy is useful for patients with positive margins [27]. Salvage XRT was, however, successful in 4 of 9 patients.

There are multiple unknowns associated with the optimal regimen of neoadjuvant chem-hormonal therapy for prostate cancer. We used a docetaxel/estramustine regimen and schedule associated with a survival advantage in metastatic castrate resistant patients [8], but the value of estramustine is uncertain [9]. Identifying effective neoadjuvant strategies for high-risk prostate cancer is important, although this has been problematic and slow-going compared to strategies that have evolved for other solid tumors. Problems such as physician bias, the competing strategy of neoadjuvant hormonal therapy with EBRT, the development of newer androgen ablative therapies [28], and the length of follow up required to study survival, have made completing these trials a difficult task. Important also in future and ongoing trials will be the identification of factors associated with response. An important asset of this study is the identification of Sox-9 expression and degree of down-staging are potentially important parameters to be analyzed. These might be critically important for analysis in the ongoing randomized trial, CALGB 90203 [22] of neoadjuvant ADT and docetaxel prior to RP for high risk prostate cancer patients, similar to the patients included in this trial.

CONCLUSIONS

The current hypothesis generating trial of neoadjuvant chemohormonal regimen detected pathologic downstaging and Sox-9 expression as factors that may warrant prospective validation for patients undergoing these types of experimental therapies. Long term randomized neoadjuvant trials of this combination are necessary to establish this as a useful strategy, but these efforts should be combined with the identification of predictive clinical and biomarkers.

NCT Trial Registration Number: #NCT01230717

ABBREVIATIONS

ADT = Androgen Deprivation Therapy
EBRT = External Beam Radiation Therapy
IHC = Immunohistochemistry
LHRH = Leutinizing Hormone Releasing Hormone
pCR = Pathologic Complete Response
PSA = Prostate Specific Antigen
RP = Radical Prostatectomy
Sox-9 = Sry-related high-mobility group box-9
TMA = Tissue MicroArray
TTR = Time to Relapse

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GRANT INFORMATION

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REFERENCES


