Long-Term Outcomes of a Phase I Trial of Weekly Docetaxel, Total Androgen Blockade, and Image Guided Intensity Modulated Radiation Therapy for Localized High-Risk Prostate Adenocarcinoma

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Abstract

Purpose: Our purpose was to describe the long-term outcomes seen with the addition of concurrent weekly docetaxel to high-dose intensity modulated radiation (IMRT) to the prostate and androgen deprivation therapy in patients with high-risk nonmetastatic adenocarcinoma of the prostate.

Methods and Materials: Nineteen patients with high-risk, localized prostate cancer were treated in a phase I trial with concurrent docetaxel at doses of 10 to 30 mg/m², in a dose-escalated scheme, in addition to IMRT (77.4 Gy/43 fx) and neoadjuvant and concurrent combined androgen blockade (gonadotropin-releasing hormone agonist and antiandrogen). A gonadotropin-releasing hormone agonist was continued for an additional 24 months post radiation. Kaplan-Meier analysis was used to estimate the survival probabilities.

Results: At a median follow-up of 10.5 years, 5-year and 10-year overall survival were found to be 89.5% and 68.4%, respectively. The median metastasis-free survival and progression-free survival were determined to be 11.3 years and 9.0 years, respectively.

Conclusions: This regimen produced a 10-year overall survival of 68% with a 10-year metastasis-free survival of 58%. Grade >2 toxicity was minimal. These limited data suggest that the addition of concurrent weekly docetaxel to high-dose IMRT for high-risk prostate cancer warrants further investigation.

Introduction

In high-risk, localized prostate cancer, as defined by a Gleason score ≥ 8, a prostate-specific antigen (PSA) ≥ 20 ng/mL, or a clinical disease stage ≥ T3N0M0, the standard of care in management is dose-escalated radiation therapy with long-term androgen deprivation. However, even with this treatment paradigm, outcomes are less than ideal, particularly in the very high-risk subset. There is, therefore, significant interest in improving outcomes by intensifying treatment in this patient population.

One of the areas of attention is the addition of chemotherapy, particularly docetaxel, to the treatment regimen. In the metastatic setting, several studies have demonstrated an

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overall survival (OS) benefit with the use of docetaxel in both castrate-resistant4,6 and castrate-sensitive disease.7,8 In the locally advanced setting its utility is theorized to be due to its ability to induce apoptosis of cancer cells by phosphorylation of BCL-29, its well-documented function as a potent radiosensitizer,10 and its ability to target hormone-resistant prostate cancer clones.11

Because of these potential benefits of docetaxel, this phase I study was designed to find the maximum tolerable dose (MTD) of weekly docetaxel when combined with high-dose intensity modulated radiation (IMRT) and androgen deprivation therapy (ADT) in patients with high-risk prostate cancer. Our previous publication was able to demonstrate an MTD for docetaxel of 25 mg/m² with acceptable acute toxicities and long-term side effects.12 In this study, we describe the long-term outcomes that can be expected with this novel treatment approach.

Methods and Materials

Our methods and materials have been previously described.12 In short, we enrolled 19 patients with high-risk, localized prostate cancer as defined by the presence of 1 or more of the following: (1) clinical stage T2c or higher (American Joint Committee on Cancer 7th Edition, 1997), (2) pretreatment PSA ≥ 20 ng/mL, and (3) Gleason score ≥ 8. Patients were ineligible if they had evidence of nodal or metastatic disease or had had prior treatment for prostate cancer (radiation, surgery, chemotherapy, immunotherapy, or alternative treatments). An exception was made for ADT of 4 weeks or less. Participants were required to be ≥18 years of age with an Eastern Cooperative Oncology Group performance status of ≤2. Blood counts and chemistries had to be conducive to receiving systemic therapy. All research was done in compliance with institutional review board rules and regulations.

All patients received combined androgen blockade using a gonadotropin-releasing hormone agonist (goserelin or leuprolide) and an antiandrogen (bicalutamide 50 mg/d) for 2 months. Patients then began definitive radiation to a dose of 77.4 Gy/43 fx with concurrent weekly docetaxel and combined androgen blockade. No pelvic/nodal radiation therapy was administered. The gonadotropin-releasing hormone agonist was continued for an additional 24 months post radiation. Weekly docetaxel was administered in a dose-escalated scheme requiring a minimum of 3 patients per cohort, starting at 10 mg/m² and increasing to 30 mg/m² in 5 mg/m² increments.

The primary objective of the study was to determine the MTD of weekly docetaxel in combination with high-dose radiation and long-term ADT in patients with high-risk locally advanced adenocarcinoma of the prostate.12 The MTD was defined as a dose level immediately below the dose at which 2 out of the first 3 patients in any cohort, or at least 2 out of 6 patients in an expanded cohort, experienced dose-limiting toxicity. This was determined to be a dose of 25 mg/m² throughout the 9 weeks of radiation therapy. After completion of chemoradiation, patients were followed with history, physical, performance assessment, and PSA measurement every 3 months for 2 subsequent years and at least every 6 months for 4 additional years. Biochemical failure prompted a full metastatic workup. After disease progression was noted, patients were followed for survival and second malignancies.

For the purposes of this analysis, biochemical failure was based on the Phoenix definition of a PSA ≥ nadir plus 2.0 ng/mL. The time to PSA failure was measured from radiation start date to the date of biochemical failure. Progression-free survival (PFS) was defined as the absence of biochemical relapse or other radiographic or objective evidence of disease and no reintiation of androgen suppression. This was also measured from the radiation start date. Metastasis-free survival (MFS) and OS were also determined. If an event did not occur, patients were censored at a predetermined date lock (October 7, 2020).

Statistical analysis

Descriptive statistics were used to summarize variables (number and percentage). Kaplan-Meier analysis was used to estimate the survival probabilities. All statistical computations were performed on GraphPad Prism, Version 8.4.2 (GraphPad Software LLC).

Results

A total of 19 patients were enrolled on this phase I trial between February 2006 and September 2010, and their demographic information and clinical characteristics are listed in Table 1. Patients had a mean age at diagnosis of 64.9 years (range, 45-80 years) and a mean PSA at diagnosis of 46.4 mg/dL. Five patients did not complete protocol treatment. Three declined further hormonal therapy due to intolerance, 1 could not receive further chemotherapy due to hyperbilirubinemia, and 1 died of congestive heart failure 14 months after completing radiation therapy while on long-term ADT.

At a median follow-up of 10.5 years (10.8 years for patients still alive), 5- and 10-year OS were found to be 89.5% and 68.4%, respectively. In terms of MFS, the median was found to be 11.3 years with 5- and 10-year MFS of 84.2% and 57.9%. Median PFS was 9.0 years with 5- and 10-years, respectively. The Kaplan-Meier survival curves for these data can be seen in Fig. 1.

Patterns of failure were reviewed. At the time of last follow-up, 5 of the 19 patients had radiographic evidence of
metastatic disease. Two patients had bone metastases as the first site of recurrence, with both having calvarial metastases that were surgically resected and treated with focal radiation therapy. Three patients presented with lymph nodes as first site of recurrence. Two of the three patients with nodal recurrences as the first site of recurrence had adenopathy above the pelvis only. One patient of the 19 treated in the study had a pelvic node recurrence as a site of recurrence.

**Discussion**

There is a need to improve outcomes in high-risk prostate cancer. One approach is to dose escalate radiation in this population. Numerous trials have demonstrated improved prostate cancer outcomes with external beam radiation doses of 78 to 80 Gy. A recent study examining further dose escalation with the use of brachytherapy, specifically in the high-risk population, has been

| Characteristic                  | No. (%)       |
|---------------------------------|---------------|
| **Age**                         |               |
| Median                          | 68.0          |
| Mean                            | 64.9          |
| Age ≤ 60                        | 7 (36.8%)     |
| Age > 60                        | 12 (63.2%)    |
| **Race**                        |               |
| White                           | 9 (47.4%)     |
| Black                           | 10 (52.6%)    |
| **T stage**                     |               |
| T1c                             | 9 (47.4%)     |
| T2a                             | 4 (21.1%)     |
| T2b                             | 0 (0%)        |
| T2c                             | 0 (0%)        |
| T3a                             | 1 (5.3%)      |
| T3b                             | 4 (21.1%)     |
| T4                              | 1 (5.3%)      |
| **Gleason grade group**         |               |
| 2                               | 3 (15.8%)     |
| 3                               | 2 (10.5%)     |
| 4                               | 7 (36.8%)     |
| 5                               | 7 (36.8%)     |
| **Initial PSA (ng/mL)**         |               |
| ≤10                             | 6 (31.6%)     |
| 10.01–20.0                      | 3 (15.8%)     |
| >20                             | 10 (52.6%)    |
| **Completed all treatment**     |               |
| Yes                             | 14 (73.7%)    |
| No                              | 5 (26.3%)     |

*Abbreviation: PSA = prostate-specific antigen.*

![Figure 1](image.png)

**Figure 1** The Kaplan-Meier survival curves for the entire cohort (n = 19) including (a) overall survival, (b) metastasis free survival, and (c) progression-free survival.
shown to produce excellent disease control. Another tactic is to add chemotherapy to the treatment regimen, the premise being that chemotherapy may be able to target androgen-independent cancer cells that are not affected by ADT. Specifically, there has been significant attention paid to the use of docetaxel, as it has been shown to produce improvements in OS in the metastatic setting. With this in mind, the potential benefit to using chemotherapy earlier in the disease course has been investigated.

Research by Kumar et al examining the MTD of weekly docetaxel delivered concurrently with 3-dimensional conformal radiation therapy (3D-CRT) in patients with high-risk prostate cancer found an MTD of 20 mg/m² with a dose-limiting toxicity of grade 3 diarrhea. In this study, radiation consisted of 46 Gy to the pelvis using a 4-field approach with a boost to the prostate to 70.2 Gy. Docetaxel was escalated from a weekly initial dose of 5 mg/m². A subsequent phase II trial used this dose of docetaxel concurrently with luteinizing hormone-releasing hormone agonist and 70 Gy to the prostate and seminal vesicles (46 Gy to the pelvis via 3D-CRT 4-field approach with a boost to the prostate via 3D-CRT or IMRT). Docetaxel was given weekly starting with radiation therapy for 3 weeks followed by a 1-week break, then reintroduced for 3 additional weeks (6 cycles total). This was followed by 3 cycles of adjuvant docetaxel at 60 mg/m². At a median follow-up of 54 months, they found a 5-year disease-free survival (DFS) of 66.7% and 5-year OS of 92.2%. Ninety-two percent of patients completed the full treatment regimen, with 10.9% experiencing a grade 3 acute toxicity (dysuria [1], diarrhea [2], proctitis [1], and neutropenia [1]). Another phase I/II study combined Kumar’s established MTD of docetaxel with an IMRT-based approach to radiation. In this analysis, patients received a total dose of 72 Gy to the prostate. No additional information is available regarding the irradiated volumes for this trial. Three patients experienced treatment interruptions (dehydration [2] and gastrointestinal bleed [1]), and at a median follow-up of 11.7 months, 85% of patients were free of recurrence, and all patients were alive.

The drawbacks of these studies are that 2 of them included the use of older radiation techniques that result in increased dose to normal tissue that could lower the MTD of docetaxel, and they all used lower doses of radiation that have been shown to produce inferior disease control. In addition, at least 2 of the 3 studies included the pelvic lymph nodes in the initial 46 Gy, increasing the dose to the bowel and bone marrow and decreasing the tolerance to docetaxel. We therefore designed our study to determine the MTD of weekly docetaxel in the setting of standard of care high-dose IMRT-based radiation to the prostate with concurrent long-term ADT. This was determined to be a dose of 25 mg/m², predictably higher than that established by Kumar et al, who treated the pelvic nodes. In addition, our long-term results showed a 10-year OS of 68.4%, a 10-year MFS of 57.9%, and a 10-year PFS of 42.1%. Our previous publication highlighted very low rates of grade ≥ 3 acute toxicity at this dose, and at a median follow-up of 41 months no patient had a late toxicity of any grade ≥ 2. Diarrhea was not a dose-limiting toxicity. The premise of treating the known disease in the prostate with IMRT to 77.4 Gy combined with ADT and concurrent weekly docetaxel at 25 mg/m² to radiosensitize the disease in the prostate, while simultaneously treating potential microscopic disease in the pelvic nodes and distant sites with ADT and docetaxel seems theoretically advantageous. Our preliminary results suggest this regimen to be both safe and efficacious. Although limited by the low number of patients in this trial, our results are compelling enough to warrant further investigation in larger studies.

The addition of docetaxel to ADT and radiation has been looked at in 5 major randomized trials, with conflicting results. There were a wide range of definitions of high-risk across studies, which could be responsible for the difference in results. Two of the trials were designed to examine whether 6 cycles of adjuvant docetaxel improved outcomes after radiation therapy and ADT in patients with intermediate and/or high-risk prostate cancer. The Radiation Therapy Oncology Group (RTOG) 0521 study (RTOG 0521) observed an absolute 4-year OS benefit of 4% with the addition of chemotherapy (89% vs 93%; hazard ratio [HR], 0.69; P = .034) in addition to improvements in 6-year DFS (55% vs 65%; HR, 0.76; P = .043) and the rates of distant metastasis (14.0% vs 9.1%; HR, 0.60; P = .044). The treatment regimen was also very well-tolerated, with a predictable increase in grade ≥ 3 hematologic toxicity in the docetaxel arm (1.8% vs 22%; P < .001). With longer follow-up the benefit of docetaxel remained (restricted mean survival time at 10 years was 0.42 years; 2-sided P = .048), but the OS curves appeared to be converging. In contrast, the Scandinavian Prostate Cancer Study Group-13 study (SPCG-13) found no benefit to 5-year biochemical DFS with the addition of docetaxel in their population (HR, 1.14; P = .5), though there were far fewer relapses than expected, lowering the planned statistical power of the study.

The other 3 phase III trials examined the addition of neoadjuvant and concurrent docetaxel to radiation and ADT. In the French Groupe d’Etude des Tumeurs Uro-Génitales-12 study, patients received concurrent docetaxel and estramustine and they found an 8-year relapse-free survival (RFS) of 62% in the ADT plus chemotherapy group versus 50% in the ADT-only group (HR, 0.71; P = .017). At 12 years, this relationship persisted, with a 12-year RFS rate of 49.4% versus 36.3% (HR, 0.71; P = .01), indicating that 4 cycles of docetaxel-based chemotherapy may reduce the risk of clinical relapse in these men. Similarly, in the predefined nonmetastatic subset of
the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy trial,⁸ docetaxel improved failure-free survival (HR, 0.6; \(P = .283 \times 10^{-3}\)). Comparisons of OS were immature due to fewer than 100 events at the time of analysis. Conversely, D’Amico et al²¹ found no improvement in any of their predefined endpoints at 10 years with the addition of docetaxel. The OS survival curves initially diverged favoring the docetaxel arm, then merged with longer follow-up (10-year OS 9.11 vs 8.82 years; \(P = .22\)). There was also no significant difference in prostate cancer-specific mortality (HR, 1.15; \(P = .65\)), MFS (HR, 1.07; \(P = .69\)), or PSA RFS (HR, 1.05; \(P = .72\)).

The benefit of docetaxel in men with nonmetastatic high-risk prostate cancer is therefore uncertain. There is some indication, however, that specific subgroups may benefit from treatment intensification. D’Amico et al²¹ found that the effect on OS differed significantly in men with a PSA < 4 ng/mL versus 4 to 20 ng/mL (HR, 0.27 and 1.51, respectively), and therefore upfront docetaxel may prolong OS in this subgroup by reducing prostate cancer-specific mortality. This strengthens the hypothesis that chemotherapy may have a role in high-grade, dedifferentiated tumors that are likely to be insensitive to ADT. Data from SPCG-13²³ support this. In that study, the interaction between treatment group and Gleason score trended toward significance (\(P = .059\)), and patients with Gleason 9 to 10 had a nonstatistically significant trend toward achieving a benefit (HR, 0.67; 95% confidence interval, 0.34–1.30; \(P = .2\)) from adjuvant docetaxel. The next steps, therefore, will be to better identify which subgroups may benefit from chemotherapy. Advances in risk stratification with the use of genomics may allow us to select for patients who are at an increased risk of prostate cancer specific mortality and therefore may derive the most benefit from docetaxel.

Other systemic agents are also being explored. There has recently been research into the use of cabazitaxel, a second-generation taxane, in this setting.²⁶ They found the MTD of cabazitaxel to be 6 mg/m² with a 5-year biochemical DFS of 73%. In addition, results from the STAMPEDE trial²⁷ evaluating the upfront use of abiraterone in men who are initiating long-term ADT, found an improvement in OS, prostate cancer specific survival, and MFS in the experimental group. The effect was larger than reported with the addition of docetaxel, and questions remain as to whether these benefits can be combined. Antiandrogens such as enzalutamide (ENZARAD trial, [https://clinicaltrials.gov/ct2/show/NCT02446444] and darolutamide (DASL-HiCaP trial, [https://clinicaltrials.gov/ct2/show/NCT04136353]) are also actively being explored in ongoing randomized clinical trials. Along with concurrent and adjuvant docetaxel, these are all promising therapeutic interventions that warrant further investigation.

Conclusions

In the setting of high-dose IMRT-based radiation to the prostate with long-term ADT, the maximally tolerated dose of concurrent weekly docetaxel is 25 mg/m². In our study, this regimen produced a 10-year OS of 68% with a 10-year MFS of 58%. Grade > 2 toxicity appears to be minimal. These limited data suggest that the addition of concurrent weekly docetaxel to high-dose IMRT for high-risk prostate cancer warrants further investigation.

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