High-Risk Localized Prostate Cancer: Integrating Chemotherapy

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Key Words. Prostate cancer • High risk • Adjuvant • Neoadjuvant • Docetaxel

Learning Objectives
After completing this course, the reader will be able to:

1. Discuss the importance of prostate cancer to public health.
2. Describe the evolving role of systemic treatment in managing high-risk and metastatic disease and discuss the factors that predict for high-risk local disease.
3. Explain the importance of multimodality input in managing high-risk prostate cancer.

Abstract
Docetaxel (Taxotere®; Aventis Pharmaceuticals Inc., Bridgewater, NJ, http://www.aventispharma-us.com) is the first agent to significantly extend survival in hormone-refractory prostate cancer. Because agents active in advanced cancers tend to be beneficial in earlier stage disease, docetaxel is now to be assessed, along with hormonal therapy, in the adjuvant setting among patients whose localized prostate cancer has features that put them at particular risk for recurrence and cancer-specific mortality. Data from a pilot study suggest that neoadjuvant treatment with docetaxel may be appropriate for selected high-risk patients and that such treatment can be undertaken without increasing surgical morbidity. Gene-expression profiling of tissue before and after docetaxel treatment is providing further insight into its effects. A randomized trial, conducted by the Cancer and Leukemia Group B, will evaluate neoadjuvant docetaxel in high-risk patients, whereby patients will be randomized to either immediate radical prostatectomy or surgery preceded by hormonal therapy plus docetaxel. Another large randomized trial will be evaluating the effect of adjuvant hormonal therapy with or without docetaxel in high-risk men after radical prostatectomy. The Oncologist 2005;10(suppl 2):18–22

Introduction
In patients with localized but high-risk disease, prostate cancer-specific survival is significantly compromised [1]. With local therapy alone, there is a high risk for failure in patients with clinical stage T3 or T4 disease, those with a serum prostate-specific antigen (PSA) level of 20 ng/ml or greater, and those with Gleason scores of 8–10 [1–3]. Even when localized, prostate cancer can be a systemic disease and may need to be managed as such.

As D’Amico and colleagues showed, while long-term survival exceeds 90% in patients with intermediate- and low-risk prostate cancer, men in the highest risk group have a 25% chance of dying from their disease before 5 years and up to a 50% risk for death from prostate cancer at 10 years [1]. In a disease in which the median age at diagnosis is in the sixties, these figures are significant and contribute to prostate cancer remaining the second leading cause of cancer death among U.S. men [1, 4].

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Nomograms, such as those developed at Memorial Sloan-Kettering Cancer Center, are aids in stratifying risk and can be consulted at http://www.nomograms.org.

Patients at high risk have many treatment options. These include radical prostatectomy, hormonal therapy plus external-beam radiation, brachytherapy, cryosurgery, and hyperthermia. However, none of these approaches has proven to be a solution to the problem of systemic disease. It is in this context that chemotherapy may play a role.

**Adjuvant Chemotherapy**

In men with hormone-refractory prostate cancer, two recent trials have demonstrated that chemotherapy based on docetaxel (Taxotere®; sanofi-aventis Pharmaceuticals Inc., Bridgewater, NJ, http://www.aventispharma-us.com) is superior to that based on mitoxantrone [5, 6]. In the Southwest Oncology Group (SWOG) 9916 trial, the hazard ratio (HR) for death in docetaxel-treated patients was 0.80 \((p = .02)\) [5]. In study TAX-327, the HR was 0.76 \((p = .009)\) [6]. Patients receiving docetaxel-based chemotherapy also had a longer progression-free survival, better pain control, and better quality of life. The likelihood of a PSA response was also greater. Docetaxel is the first agent to significantly extend survival in hormone-refractory prostate cancer.

These findings have challenged the traditional linear approach to treatment in which local therapy is followed in patients who recur by hormonal treatment and then, on further relapse, by chemotherapy. The success of the randomized controlled trials in advanced disease has also led to the planning of an adjuvant docetaxel trial (described below) because it is clear from other tumors, notably colon and breast cancer, that agents active in the metastatic setting can prove to be even more beneficial when used in patients with earlier stage disease (Fig. 1) [7–10].

This docetaxel trial will take place against a background of relatively little previous activity in the assessment of adjuvant therapy in prostate cancer. In fact, the issue has been addressed in only one modern, controlled trial, which randomized patients to receive either leuprolide (Lupron®; TAP Pharmaceutical products inc., http://www.tap.com) alone or leuprolide plus mitoxantrone for four cycles [11]. That study had limitations: of the 93 patients enrolled, only 38 had T3 or T4 disease, and no radiotherapy was administered. Nevertheless, survival was superior in patients treated with mitoxantrone \((p = .044)\), despite the small size of the study, the short duration of follow-up, and the relatively modest activity of the cytotoxic agent used.

The SWOG 9921 study set out to compare hormone therapy with hormone therapy plus chemotherapy in high-risk patients who had undergone radical prostatectomy (Fig. 2). In that trial, hormone therapy is administered for 2 years. Patients randomized to additional chemotherapy receive six cycles of mitoxantrone plus prednisone. The primary end point is overall survival, and accrual has been slow to its target of 1,360 patients. This slow accrual may be a result, in part, of the culture change required on the part of urologists, but a perceived lack of activity of mitoxantrone is probably also a factor. Accrual is ongoing.

**Adjuvant Docetaxel**

Docetaxel, in contrast, has demonstrated a survival benefit in advanced disease. In a pilot phase II study of adjuvant docetaxel in high-risk prostate cancer patients following radical prostatectomy, six cycles of docetaxel, 35 mg/m² given on days 1, 8, and 15 of a 28-day cycle, were well tolerated by the 77 patients enrolled [12]. Outcome will be compared with that of historical controls matched for clinical and pathological features.

Based on data from this preliminary study, an industry-sponsored phase III study is planned to determine the effect of relatively little previous activity in the assessment of adjuvant therapy in prostate cancer. In fact, the issue has been addressed in only one modern, controlled trial, which randomized patients to receive either leuprolide (Lupron®; TAP Pharmaceutical products inc., http://www.tap.com) alone or leuprolide plus mitoxantrone for four cycles [11]. That study had limitations: of the 93 patients enrolled, only 38 had T3 or T4 disease, and no radiotherapy was administered. Nevertheless, survival was superior in patients treated with mitoxantrone \((p = .044)\), despite the small size of the study, the short duration of follow-up, and the relatively modest activity of the cytotoxic agent used.

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of adjuvant docetaxel following radical prostatectomy in patients at high risk, defined in this instance as a 60% or less chance of being free from progression at 5 years (based on the Kattan nomogram).

In the TAX-3501 study (Fig. 3), which should begin in late 2005, patients will be randomized to one of three arms: observation, androgen deprivation therapy (ADT) for 18 months; or ADT plus docetaxel, 75 mg/m² every 3 weeks for six cycles. Patients in the observation arm who progress will be randomized at that stage to ADT alone or ADT plus docetaxel and followed to second progression. That study, with a projected enrollment of more than 2,000 patients, should provide valuable information on the roles of both hormonal therapy and chemotherapy in the adjuvant setting.

Another study, the Radiation Therapy Oncology Group (RTOG) 9902 trial (which started 5 years ago and failed to meet its accrual target), set out to compare hormonal therapy plus radiotherapy with hormone therapy plus radiation plus chemotherapy (paclitaxel [Taxol®; Bristol-Myers Squibb, Princeton, NJ, http://www.bms.com], estramustine [Emcyt®; Pfizer Pharmaceuticals, New York, http://www.pfizer.com], and etoposide [Etopophos®, VePesid®; Bristol-Myers Squibb]) in high-risk patients. Study accrual was held when an excess of thromboembolism was noted. This is probably attributable to estramustine, which may not be a necessary part of the regimen. However, slow study accrual also raised wider issues about the interaction among radiation oncology, urology, and medical oncology.

Neoadjuvant Chemotherapy

Neoadjuvant therapy prior to local treatment may be appropriate in well characterized high-risk groups (Fig. 1). In addition to ensuring early treatment of micrometastases, the neoadjuvant setting offers us the ability to assess chemosensitivity in vivo and possible molecular determinants of response in pathological specimens. Compared with the adjuvant setting, neoadjuvant trials should allow the more rapid evaluation of promising new agents.

Soloway et al. showed that neoadjuvant leuprolide does not improve 5-year disease-free survival (DFS) in patients undergoing radical prostatectomy [13]. At 5 years, the DFS rates were 64.8% in the group given neoadjuvant hormonal therapy and 67.6% in controls (p = .663). It therefore seems that short-term hormonal therapy does not have a meaningful impact on clinical outcome when used prior to R.P.

Locally advanced breast cancer offers those concerned with prostate cancer an important paradigm [14]. In the period 1989–2002, more than 6,000 patients were accrued to 14 phase II and six phase III trials. Overall response rates of 60%–90% were achieved, with 15%–30% of patients enjoying clinical complete responses (CRs). With doxorubicin (Adriamycin®; Bedford Laboratories, Bedford, OH, http://www.bedfordlabs.com)-based regimens, pathologic CRs were documented in 5%–15% of cases, and pathologic CRs were documented in 25%–30% of cases in which chemotherapy was docetaxel-based. Kuerer et al. showed that attaining a pathological CR (pCR) confers considerable survival benefit when compared with breast cancer patients not achieving such a response [15]. Breast cancer is a chemosensitive disease. However, if these data hold true in prostate cancer, even low rates of pCR could improve overall outcome in the disease.

There have been several pilot studies of neoadjuvant chemotherapy with estramustine-based and other regimens [16]. With the former, deep vein thrombosis and pulmonary embolism were notable risks, but the overall approach appears feasible, and data suggest that nonhormonal neoadjuvant regimens are capable of reliably producing reductions in PSA levels.

Neoadjuvant Docetaxel

A phase II trial of neoadjuvant docetaxel prior to radical prostatectomy in high-risk localized prostate cancer was undertaken at our institution in 19 patients [17]. Docetaxel was administered weekly for up to 6 months. PSA measurements and digital rectal exams (DREs) are performed monthly, with an endorectal coil magnetic resonance imaging (erMRI) exam performed at baseline and at 2 and 6 months. The primary end point of the study was a pCR rate of 10%. In a correlative science element, gene-expression analysis was undertaken on tissue obtained before and after docetaxel therapy and compared with tissue from untreated patients matched for Gleason grade and percent tumor.

Figure 3. Study design of the TAX-3501 trial. Accrual target: 2,172 patients. Abbreviations: ADT, androgen deprivation therapy; RP, radical prostatectomy.
Though pCRs were not seen, weekly neoadjuvant docetaxel was clearly feasible and well tolerated. The most common side effect was grade 1/2 fatigue. There have been no appreciable problems with neutropenia, thrombocytopenia, neuropathy, diarrhea, or infection. Two thirds of patients completed 6 months of therapy. Sixteen proceeded to prostatectomy, and experienced no significant surgical complications.

PSA declines of 50% or greater were seen in 58% of patients. PSA decline occurred steadily following an initial rise during the first cycle and was independent of effects of testosterone (Fig. 4).

Two thirds of patients showed at least a 25% radiographic reduction in tumor by erMRI. Median prostate volumes were 28.9 cc at baseline, 24.8 cc at 2 months, and 25.3 cc at 6 months. Maximum tumor volume showed a trend toward a decrease from 3.1 cc at baseline to 2.3 cc at 2 months and 1.6 cc at 6 months.

We studied gene-expression profiles in eight specimens of treated tumor and 18 matched non-chemotherapy-treated samples. Gene set enrichment analysis covering the top 15 signaling pathways suggests that the major effect of treatment is upregulation of genes involved in androgen and estrogen metabolism. Conclusions are preliminary. However, if prostate cancers that survive cytotoxic chemotherapy upregulate genes that decrease androgen bioavailability, this would have the effect of slowing the rate of cell division. This may lower the tumor’s sensitivity to the microtubule-stabilizing effects of docetaxel. In principle, this could represent a shift toward a more quiescent, primitive form of prostate cancer cell [17].

The CALGB 90203 trial will investigate neoadjuvant docetaxel in high-risk patients, defined as those having a 40% chance of DFS at 5 years (the study’s primary end point) (Fig. 5). Patients will be randomized to receive either immediate radical prostatectomy or surgery preceded by up to 8 cycles of docetaxel plus ADT.

**CONCLUSION**

As with other common solid tumors, multimodality therapy is the key to improving outcome in patients with localized prostate cancer who are at high risk for recurrence and death from their disease. There may be a role for both adjuvant and neoadjuvant chemotherapy. However, there is a pressing need for more effective systemic agents, both cytotoxic and hormonal, and for investigations into their optimum combination.

**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

Dr. Oh has received research support from sanofi-aventis and has served on a speakers bureau for sanofi-aventis, Bristol-Myers Squibb, and Amgen.

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