High-Risk Localized Prostate Cancer: A Case for Early Chemotherapy

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Abstract

High-risk tumors exhibit a more aggressive natural history and have higher positive margin and recurrence rates after radical prostatectomy or radiotherapy alone, where unimodality therapy likely represents undertreatment. Hence, the therapeutic ratio (patients who actually realize a survival benefit from a therapeutic intervention) may, therefore, be greater in high-risk disease if its natural history can be altered by multimodality therapy. It is, thus, important to investigate therapies that optimize complete extirpation of all cancer cells and reduce the incidence of positive surgical margins and disease recurrence. Neoadjuvant therapy extends the logic of early adjuvant therapy further by applying systemic therapy earlier in the course of the disease before definitive locoregional therapy. In prostate cancer, outcomes have not been improved significantly when neoadjuvant hormone therapy is used before surgery; although outcomes are improved when androgen ablation is combined with radiotherapy, many patients remain at risk for systemic recurrence. With recent data confirming improved survival data with docetaxel chemotherapy in metastatic disease, future trials are now focusing on earlier combinations of chemohormonal or biologic therapies in high-risk patients.

Introduction

Despite remarkable advances in surgical techniques and delivery of radiotherapy over the last two decades, residual disease at the primary site or the presence of microscopic disease outside the surgical or radiotherapy fields ultimately lead to biochemical and/or disease recurrence in most patients with high-risk disease. The use of early and prolonged androgen ablation therapy with radiotherapy delays disease progression and improves overall survival; however, most patients still relapse, develop androgen-resistant disease, and eventually die as a result of their cancer. More effective therapy is needed in these high-risk patients that target the local and distant disease and the androgen-dependent and -independent (hormone-refractory) subpopulations of malignant cells (Fig 1). Introducing systemic cytotoxic chemotherapy earlier in these high-risk patients has been hampered by the lack of effective chemotherapy in hormone-refractory prostate cancer (HRPC). More recently, docetaxel-based regimens have shown a clinical benefit and survival advantage in patients with HRPC, allowing us to move cytotoxics forward in the treatment of patients with localized HRPC.

Prior Experience with Early Chemotherapy in Patients with High-Risk Localized Prostate Cancer and Radical Prostatectomy

There are no adequately powered randomized studies that have been completed using adjuvant or neoadjuvant chemotherapy in conjunction with surgery or radiotherapy. Numerous small trials with variable inclusion criteria have evaluated the use of early chemotherapy, and used a microtubule-based chemotherapy regimen such as docetaxel or
paclitaxel with or without androgen ablation (Table 1). The primary outcomes for these trials were feasibility and safety. Secondary end points assessed the pathologic response in the primary tumor and post-therapy changes in biochemical markers. Consistent in all trials is that the addition of chemotherapy increased the morbidity of the therapy, but most of the adverse effects were reversible once the treatment was discontinued. Toxicities included mild to moderate anemia, neutropenia, fatigue, nausea and vomiting. However, more serious complications such as deep-vein thrombosis occurred in up to 22% of patients who received an estramustine-based regimen.9-12 These adverse events were manageable and not significantly different from what has been experienced in the more advanced disease setting. Importantly, these trials confirmed the safety and feasibility of administering chemotherapy before radical prostatectomy. The systemic therapy in general did not complicate the surgical procedure; however, some studies reported an increase in periprostatic fibrosis that increased the average difficulty of surgery compared with non–chemotherapy-treated patients.9,13,14 These observations may also reflect that fact that patients with more locally advanced tumors were enrolled in these trials. The mean surgical time, estimated blood loss, or the median hospital stay were not increased compared with non–chemotherapy-treated patients.9,13,14 The reported rates of erectile

| Table 1. Neoadjuvant and Adjuvant Chemotherapy Trials in Patients With Locally Advanced Prostate Cancer |
|------------------------------------------|----------------------|-----------------|---------------------------------|------------------|
| Author                        | No. of Patients | Inclusion Criteria                               | Local Therapy | Hormonal Therapy | Chemotherapy Regimen | Clinical Outcome |
| Neoadjuvant trials            |                 |                                                 |                |                  |                    |                  |
| Pettaway et al11              | 33              | cT1-2, GL ≥ 8; cT2b-c, GL ≥ 7; PSA > 10 ng/mL   | RP             | Yes              | KAVE × 12 weeks    | No P0 50% achieved PSA NMA after chemotherapy |
| Clark et al12                 | 18              | cT2b-c or T3 with PSA ≥ 15 ng/mL or GL ≥ 8      | RP             | Yes              | EMP/V-16 × 12 weeks | No P0 50% achieved PSA NMA after chemotherapy |
| Koney et al9                  | 36              | cT1-2 with PSA ≥ 20 ng/mL; cT3-4; GL ≥ 8        | RP             | Yes              | TEC × 12-16 weeks  | No P0 Median PSA nadir 0.17 ng/mL |
| Ko et al26                    | 12              | cT3; PSA ≥ 20 ng/mL; GL 8-10;                   | RP             | Yes              | EMP + docetaxel    | No P0 75% achieved PSA NMA after chemotherapy |
| Hussain et al12              | 21              | ≥ cT2b; PSA ≥ 15 ng/mL; GL > 8                  | RP             | Yes              | EMP + docetaxel    | No P0 100% achieved PSA > 50% decline after chemotherapy |
| Gleave et al18                | 72              | GL ≥ 8 or PSA ≥ 20 plus ≥ 2 positive cores; or T3a or GL ≥ 7 plus PSA ≥ 10 plus ≥ 3 positive cores | RP             | Yes              | Docetaxel weekly + LHRH analog | 2 complete responders (p0), 14 microfoci pT2 |
| Oh et al15                   | 15              | cT2c; PSA > 20 ng/mL; GL ≥ 8                    | RP             | No               | Docetaxel weekly   | 67% achieved PSA > 50% decline after chemotherapy Median PSA decline of 41% |
| Beer et al13                 | 22              | cT2c; cT3a; PSA ≥ 15 ng/mL; GL < 4 + 3          | RP             | No               | Docetaxel weekly + mitoxantrone | 24% achieved PSA > 50% decline after chemotherapy 5yr BFS; T2, 49%; T3, 38%; T4, 17% |
| Drecier et al27              | 29              | T2b-T3; PSA > 15 ng/mL; GL ≥ 8                  | RP             | No               | Docetaxel weekly   | 24% achieved PSA > 50% decline after chemotherapy 5yr BFS; T2, 49%; T3, 38%; T4, 17% |
| Khil et al23                 | 65              | T2-4; GL 4-10; locally advanced prostate cancer | Radiotherapy (65-70 Gy) | Yes | EMP + vinblastine × 7 weeks prior to radiotherapy | Increase grade 2 late G1/G2 toxicity 5-year BFS, 25% 48% No additional therapy |
| Zelefsky et al, Ryan et al24,25 | 23             | GL ≥ 8 plus PSA > 10 mg/mL GL7 plus PSA ≥ 20 mg/mL T3 plus PSA ≥ 20 mg/mL T4N0M0 TxN1M0 | Radiotherapy 75.6 Gy | Yes | EMP + vinblastine × 16 weeks prior and concomitant | Increase grade 2 late G1/G2 toxicity 5-year BFS, 25% 48% No additional therapy |
| Adjuvant trials              |                 |                                                 |                |                  |                    |                  |
| Schmidt et al21              | 184             | Locally advanced prostate cancer                | RP             | —                | Cyclophosphamide × 2 years × EMP × 2 years × observation | 10-year FU: EMP has improved RFS, no difference in OS |
| Wang et al28                 | 96              | > cT3 localized or metastatic disease           | RP             | Yes              | Mitoxantrone + LHRR agonist/antiandrogen | Median OS and DSS 80 and 84 months v 36 and 41 months |

Abbreviations: GL, Gleason score; RP, radical prostatectomy; KAVE, ketoconazole, doxorubicin, vinblastine, and estramustine phosphate; PSA, prostate-specific antigen; NMA, no measurable amount; EMP, estramustine phosphate; VP-16, etoposide; TEC, paclitaxel, estramustine phosphate, carboplatin; LHRR, leukotriene releasing hormone; BFS, biochemical-free survival; GI, gastrointestinal; GU, genitourinary; FU, follow-up, RFS, relapse-free survival; OS, overall survival; DSS, disease-specific survival.
dysfunction and incontinence were similar to patients undergoing wide bilateral or unilateral resection of neurovascular bundles who did not receive chemotherapy.19-21

Identifying benefit in clinical outcomes is difficult due to the absence of a control arm in all of these trials. As expected, post-therapy declines in prostate-specific antigen (PSA) were observed universally in studies that combined androgen ablation with chemotherapy. Of interest are the studies with docetaxel-based therapies alone that demonstrated post-therapy declines in PSA ranging from 24% to 60% after the administration of the chemotherapy, indicating an independent antitumor effect on hormonenaive prostate cancer.13-15 In patients who have recurrent or metastatic androgen-sensitive prostate cancer, Hussain et al16 reported that 49% and 20% of patients had a ≥ 50% or ≥ 75% decline in PSA after docetaxel treatment, respectively. Serum testosterone levels were not altered significantly by chemotherapy, further providing evidence of the activity of chemotherapy in early prostate cancer.

Theoretical concerns regarding a potential risk of detriment rather than benefit from the concurrent administration of hormonal and cytotoxic therapies has raised questions regarding the sequence of administration of chemo-/hormonal therapies. Recently, preclinical data evaluating the optimal timing and combination of androgen withdrawal with cytotoxic chemotherapy in LNCaP and Shionogi prostate cancer xenografts reported that mice receiving simultaneous chemo-hormonal therapy had a significant improvement in median time to progression versus best sequential therapy.17 Interestingly, a marked lack of response to castration was observed after initial paclitaxel therapy, and transcriptional profiling identified increased expression of several survival genes known to play a role in androgen independence after paclitaxel exposure. These findings support simultaneous chemo-hormonal therapy in future neoadjuvant and adjuvant trials.

In neoadjuvant studies, pathologic specimens were noted in some cases to have marked tumor regression, but complete eradication of the tumor was rare. Gleave et al18 reported that two of 64 patients treated with docetaxel plus androgen ablation for 24 weeks had a complete pathologic response (no tumor in final pathologic specimen). Histologic changes observed in specimens included disintegration of the acinar/glandular arrangement of the neoplastic epithelium, cytoplasmic clearing, and vacuolation.12 Squamous metaplasia was also observed with the estramustine-based therapies, likely the result of estrogenic and castration-inducing effects of this compound.

The use of neoadjuvant hormonal and chemotherapy has been shown to be feasible and safe, but more importantly it has provided a platform for understanding prostate cancer biology and drug discovery. The radical

 prostatectomy tissues from these trials are a valuable resource for changes in expression levels of critical regulators of cell cycle and apoptosis after castration and chemotherapy. Tissue microarray and transcriptional profiling can define treatment-induced changes in gene expression (eg, stress-activated cytoprotective chaperones like clusterin and Hsp27; Fig 2), which are, in turn, being targeted to enhance chemo- and hormonal responsiveness.19,20 Future studies such as the randomized Intergroup Cancer and Leukemia Group B study will randomize patients with high-risk localized prostate cancer to androgen ablation with docetaxel-based therapy before radical prostatectomy or immediate radical prostatectomy and provide the opportunity to further study the molecular changes associated with chemotherapy.

**ADJUVANT CHEMOTHERAPY AND HORMONE THERAPY AFTER RADICAL PROSTATECTOMY**

In the mid-1980s, Schmidt et al21 from the National Prostate Cancer Group randomly assigned 184 patients with localized advanced prostate cancer to one of the three arms: 2 years of oral cyclophosphamide, estramustine phosphate for 2 years, or observation. After 10 years of follow-up, the estramustine-phosphate group had an improvement in relapse-free survival but there was no difference in overall survival, likely reflecting insufficient power of small sample size. It is important to point out that some of the clinical outcomes observed are likely due to the castrating effect of estramustine. A more contemporary trial by Wang et al22 randomly assigned 96 patients with clinical T3 or T4 disease or metastatic disease to mitoxantrone plus combined androgen blockade versus combined androgen blockade alone. In the 38 patients without metastatic disease, a higher initial objective response (95% v 53%; P = .008) and median survival (80 v 36 months; P = .04) was observed in patients treated with mitoxantrone plus combined androgen ablation. In contrast, no survival advantage was seen with combination chemo- plus hormonal therapy for the patients with documented metastatic disease. Although these results are interesting, the sample size is too small to confirm any clinical benefit from the mitoxantrone therapy. An ongoing Southwest Oncology Group trial randomly assigning patients with high-risk features after radical prostatectomy to 2 years of combined androgen ablation with or without mitoxantrone therapy is adequately powered to address the role of mitoxantrone in this setting.

**NEOADJUVANT CHEMOTHERAPY AND HORMONAL THERAPY WITH RADIOTHERAPY**

Androgen ablation, as well as chemotherapy, are potent radiosensitizers that can enhance local tumor control in many other malignancies. Numerous preclinical and clinical trials document improved outcomes in patients treated with
neoadjuvant hormone therapy plus radiotherapy compared with radiation monotherapy. Many investigators are now studying whether the addition of chemotherapy will further enhance the outcomes in high-risk patients treated with radiation therapy. Khil et al\textsuperscript{23} reported the results of 65 men with a clinical stage T2 to T4, Gleason score of 4 to 10, with locally advanced prostate cancer that were treated with 16 weeks of estramustine phosphate and vinblastine concomitantly with external beam radiotherapy (65 to 70 Gy). Therapy was well tolerated, undetectable PSA at 6 weeks was observed in 86% of the patients, and 5-year biochemical-free survival for T2 were 49%, for T3 were 38%, and T4 were 17%. Zelefsky et al\textsuperscript{24} evaluated 23 patients with locally advanced prostate cancer defined as Gleason scores of 7 to 10 with a PSA of 10 to 20; clinical T3 disease with a PSA > 20; or T4 N0 or TXN1M0 disease. Estramustine phosphate and vinblastine were administered before and concurrently with high-dose conformal radiotherapy (75.6 Gy). There was an increase incidence of late grade two gastrointestinal and genitourinary toxicities observed with this combination. The 5-year biochemical-free survival was 25% and 48% of the patients had asymptomatic rise in the PSA without evidence of metastatic disease at 5 years that required no additional therapy.\textsuperscript{25}

![Fig 2. The expression levels of stress-activated cytoprotective chaperones, Hsp27 (A and C) and clusterin (B and D) increase substantially in residual prostate cancer cells after 6 months of neoadjuvant chemo-hormonal therapy (C and D) compared with untreated prostate cancers (A and B).](image-url)
Studies to date confirm that neoadjuvant and adjuvant chemotherapy therapy are feasible, safe and do not significantly complicate surgery or radiotherapy. Whether we actually improve overall survival still needs to be explored in appropriately powered randomized studies (Table 2). The relative benefit of the chemotherapy administered neoadjuvantly or adjuvantly needs further exploration and should not be used outside of a study setting. The potential for chronic adverse effects from chemotherapy and their negative impact on quality of life need to be better quantified. Adjuvant therapy has the advantage of limiting the morbidity of additional therapy to only the highest-risk patients, who typically can be defined more precisely after examining the final pathologic specimen. This approach will not interfere with the primary therapy of surgery or radiotherapy, but may delay the administration of systemic therapy. The use of neoadjuvant therapy may make the interpretation of the pathologic specimen more difficult to interpret; however, it can enhance the effects of radiotherapy and provide researchers an opportunity to investigate the molecular changes associated with therapy. Regardless of the approach in administering early chemotherapy, the relative benefits on residual disease are similar.

Over the years there have been accumulating clinical and most recently preclinical data that would suggest that the use of early chemotherapy will improve the outcomes in patients with high-risk localized prostate cancer. However, the use of early chemotherapy remains investigational until the risks and benefits are better defined in the randomized studies.
Chemotherapy for Localized High-Risk Prostate Cancer

Authors’ Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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REFERENCES