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Chemotherapy for prostate cancer: implementing early systemic therapy to improve outcomes

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Abstract Prostate cancer remains a significant health concern for men in the USA as it is a leading cancer diagnosis and a cause of death. With the use of prostate-specific antigen for screening, a stage migration has occurred with an increase in the number of men diagnosed with early-stage disease. The optimal primary management of these men is evolving, but despite adequate local treatment a significant percentage will develop either biochemical or clinical evidence of recurrent disease. Several criteria for risk stratification have been developed, thus, improving the ability to identify a high-risk population. Small studies have been reported demonstrating the feasibility of neoadjuvant or adjuvant chemotherapy in conjunction with either radiation or radical prostatectomy in this high-risk population, and large phase III studies are ongoing. With the advent of life-prolonging chemotherapy in the hormone-refractory setting, attention must now also be given to early-stage disease so as to develop multi-modality approaches with the hope of increasing survival and ultimately providing a cure.

Keywords Prostate cancer · Adjuvant therapy · Neoadjuvant therapy · Multimodality therapy · Chemotherapy

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Introduction

In 2005, an estimated 230,090 men will be diagnosed with prostate cancer and 30,350 will die secondary to their disease [24]. Radical prostatectomy and radiation therapy can be curative for many men with early-stage disease, but a portion will experience relapse following local therapy. Medical or surgical castration remains the initial treatment of choice for men who present with or develop metastatic disease. While the majority of these patients will initially respond to androgen deprivation, the duration of their response is only in the order of 18–24 months [10, 16]. After progressing to androgen independence, median survival is approximately 16–18 months [36, 48, 51] and the majority of these patients die of metastatic prostate cancer.

Historically, chemotherapy has not been viewed as having a crucial role in the management of patients with prostate cancer. The failure of a variety of regimens to show significant responses and survival benefits in the hormone-refractory population led many researchers to believe that chemotherapy should not be considered standard for advanced prostate cancer patients, with the exception of participation in clinical trials for select patients [49]. This opinion began to change with the inclusion of quality-of-life endpoints in clinical trials evaluating the utility of chemotherapy for men with androgen-independent prostate cancer. Two randomized phase III trials have shown improved pain control with mitoxantrone and either prednisone or hydrocortisone over steroids alone in this patient population, but these studies did not demonstrate significant impacts on overall survival [26, 50].

Building on these findings, efforts have focused on utilizing newer agents. Of the cytotoxic therapies, taxanes have been extensively investigated with particular attention given to docetaxel, which targets the cellular microtubules. The drug binds to tubulin, stabilizes microtubule formation and inhibits depolymerization. Phase II trials have demonstrated prostate-specific

antigen (PSA) declines of >50% in 38–46% of hormone-refractory patients treated with 75 mg/m^2 of docetaxel every 3 weeks, and measurable disease responses occurred in 28–60% of patients [17, 38]. Weekly schedules have also been investigated and reports suggest that they have significant levels of activity [2, 4]. Hematologic toxicity was a concern in all of these trials, and grade 3 or 4 neutropenia occurred in 43% of patients who received docetaxel once every 3 weeks. Although the frequency of neutropenia was less with weekly regimens, neutropenic fever and hospitalization were rare events with either dosing schedule.

These encouraging phase II data led to two phase III randomized trials comparing docetaxel versus mitoxantrone regimens in men with androgen-independent prostate cancer. The Southwest Oncology Group (SWOG) demonstrated in SWOG 9916 a significantly improved median survival of 18 months with the combination of docetaxel and estramustine administered every 3 weeks as compared to 15 months with mitoxantrone and prednisone. Time to progression was also superior for docetaxel plus estramustine: 6 months versus 3 months for mitoxantrone and prednisone [36]. The second study, TAX 327, also showed superiority of docetaxel over mitoxantrone. Docetaxel, when given 75 mg/m^2 every 3 weeks with a daily dosage of prednisone, provided median survival of 18.9 months. These results were statistically significant compared with the 16.5-month median survival in patients who received mitoxantrone and prednisone. A third arm utilized 30 mg/m^2 of docetaxel which was given weekly for 5 weeks of 6-week cycles, and the median survival of 17.4 months was not statistically significant compared with the mitoxantrone arm [51]. From a quality-of-life standpoint, the 3-week docetaxel regimen resulted in significantly improved pain control over mitoxantrone. These studies are important in that they are the first to report a survival advantage as well as palliative benefits with chemotherapy in hormone-refractory prostate cancer, thus establishing docetaxel as the standard therapy in this setting, and laying the foundation for investigating chemotherapy in earlier stages of prostate cancer.

Clinically localized prostate cancer

With the development of PSA-based early detection strategies for prostate cancer, a stage migration has occurred with a resultant increase in the number of men with clinically localized prostate cancer [21]. Five-year survival rates in men with prostate cancer have significantly improved over the last few decades, perhaps due to earlier detection and improvements of local control [23]. However, local therapy does not cure all patients with localized disease, as shown in a pooled analysis of men who received radiation where 34% exhibited biochemical recurrence at 5 years [47]. In large reported series of men who underwent radical prostatectomy, 15–31% went on to exhibit biochemical evidence of recurrent disease [25, 40, 41]. Specifically, Pound et al. [40] reported that 34% of men with a rising PSA after radical prostatectomy were found to have metastatic disease at a median of 8 years; moreover, once metastases were detected they had a median time to death of 5 years. Therefore, while a large portion of men are essentially cured of their prostate cancer by local therapy, a segment of patients with clinically localized disease are at high risk for future relapse and possibly death from their disease.

Experience with other solid tumors including breast, lung and colon cancer suggests that even modestly active systemic chemotherapy can have curative potential when administered in the adjuvant setting. In prostate cancer, efforts have begun to evaluate the role of systemic therapy in patients with high-risk localized or locally advanced disease. For obvious reasons, the most studied treatment option has been androgen ablation. Several trials have been performed to evaluate the role of neoadjuvant and adjuvant hormonal therapy in combination with radical prostatectomy or radiation therapy. Neoadjuvant hormonal therapy prior to radical prostatectomy for patients with localized or locally advanced prostate cancer has resulted in decreased positive margin rates but with no survival benefit [8, 46, 52]. Alternatively, men who are found to have lymph node metastases at radical prostatectomy have been shown to have a survival benefit and a decreased risk of recurrence with immediate as opposed to delayed adjuvant hormonal therapy [32].

Trials evaluating radiation therapy in conjunction with androgen deprivation have shown benefits with the addition of hormonal therapy. In a European Organization for Research and Treatment of Cancer (EORTC) study, men with locally advanced prostate cancer had improved overall and disease-free survival with radiation combined with 3 years of androgen deprivation versus radiation alone [6]. In this study, 5-year disease-free survival was 62% in the combination arm, and distant metastases accounted for the majority of recurrences suggesting that androgen deprivation is not sufficient systemic therapy to prevent metastatic disease.

Prostate cancer is thought to be heterogeneous in composition, with both androgen-dependent and androgen-independent clones, and hormonal manipulations may select for insensitive cells that remain viable and capable of uncontrolled growth. This concept is supported by the observed suboptimal outcome with adjuvant hormones and would argue for the need to investigate early chemotherapy. While more progress is needed, data from recent phase III trials demonstrate for the first time that prostate cancer is not a chemoresistant disease, thus opening the door to a new era of investigations in the setting of early-stage disease. Critical to the success of this effort is the ability to identify high-risk patient populations whose benefit from treatment will likely outweigh chemotherapy-related toxicities and complications.

Identifying high-risk disease

Until recently, stage and Gleason score have been the backbone for risk prediction. PSA has also been incorporated into risk assessment, and several models and nomograms have been developed that stratify patients for risk of recurrence. Partin et al. [34] were the first to combine these three characteristics so as to predict preoperatively the final pathologic stage and likelihood of organ-confined prostate cancer. Serum PSA, pretreatment biopsy Gleason score, and clinical stage each independently predicted pathologic stage, but results were improved by combining all three factors. This model has been validated in retrospective analyses of men treated with either radical prostatectomy or radiation therapy [5, 31], and an updated version of the tables has been published [35].

D'Amico et al. have utilized clinical characteristics to risk-stratify patients by likelihood of biochemical recurrence at 5 years [12] and 10 years [11] following local therapy. Results suggest that patients can be stratified by pretreatment PSA, biopsy Gleason score and 1992 AJCC T stage in terms of risk of biochemical recurrence at 5 years. Low-risk patients (stage T1c or T2a, and PSA $\leq$ 10 ng/ml, and Gleason score $\leq$ 6) have an estimated 5-year biochemical failure-free rate of $>$80%. Intermediate-risk patients (stage T2b, PSA 11–20 ng/ml, Gleason score 7) have failure-free rates of about 60%, and high-risk patients (stage $>$T2c or PSA $>$20 ng/ml or Gleason score $>$7) have an estimated rate of $<$40%.

Kattan et al., using similar clinical characteristics, have developed a continuous probability nomogram to predict likelihood of biochemical recurrence following primary therapy for localized prostate cancer. While risk-stratification models are easy for clinicians to remember and apply to patients, these probability nomograms place patients on a continuous spectrum of risk recurrence rather than in heterogeneous risk groups, potentially resulting in a more accurate assessment. Pretreatment nomograms for radiation therapy [29] and radical prostatectomy [27] as well as a postprostatectomy nomogram [28] have been developed to predict freedom from recurrence. Both the pre- and postoperative nomograms have been validated [18, 19]; furthermore, the preoperative nomogram was validated using a large international dataset suggesting that the model is accurate even in the setting of a heterogeneous patient population [19].

Prostate-specific antigen kinetics, which have been shown to be predictive of prostate cancer-specific mortality in the hormone refractory setting [13], may also be useful in identifying men with clinically localized disease who are likely to die of their disease. A recent study suggests that men with T1c or T2 disease who have a PSA velocity $>$2.0 ng/ml in the year prior to treatment, are at significantly increased risk of biochemical disease recurrence, death from prostate cancer, and death from any cause [14].

These tools are useful to clinicians when counseling their patients and for risk stratification in clinical trials. However, consideration must be given to the fact that they have not been tested prospectively.

Adjuvant chemotherapy

By comparison with other solid tumors, multimodality approaches to early-stage prostate cancer are still in their infancy. Several trials dating back to the 1970s and 1980s have attempted to address this issue. With an adjuvant approach, patient selection is improved since treatment decisions are based on accurate pathologic surgical staging, and the number of patients who unnecessarily receive cytotoxic chemotherapy is reduced.

Between 1978 and 1985, the National Prostate Cancer Project (NPCP) initiated two protocols which were designed to test the efficacy and toxicity of adjuvant chemotherapy following radical prostatectomy (Protocol 900) or definitive radiation (Protocol 1000) [43–45]. Men at high risk of recurrence were randomized to receive 2 years of either cyclophosphamide or estramustine versus observation alone following primary therapy. Patients who received cyclophosphamide did not have improved progression-free survival relative to the observation arm in either the prostatectomy or radiation protocol. However, node-positive patients treated with radiation and estramustine had a 60% recurrence rate versus 81% in the observation arm ($P < 0.05$). In particular, stage C patients who underwent prostatectomy and patients with grade 3 tumors, regardless of local therapy, benefited from estramustine. While this is the largest study published on the investigation of the use of adjuvant chemotherapy in high-risk disease, the trial was underpowered to reliably answer the question regarding efficacy of systemic therapy in this population.

The remaining published trials of adjuvant chemotherapy in patients with high-risk disease suffer from small sample sizes and methodological limitations (Table 1). One of the most recent trials suggesting benefits of early chemotherapy is a study by Wang et al. [53] who evaluated adjuvant mitoxantrone in men with advanced prostate cancer, a number of whom had locally advanced disease. Patients were randomized to receive either hormonal therapy alone consisting of luteinizing hormone-releasing hormone agonist and flutamide or hormonal therapy with mitoxantrone. No advantage to mitoxantrone was identified in the metastatic population. However, patients with localized disease, who received hormonal therapy and mitoxantrone, had improved median survival over patients on hormonal therapy alone [53].

Collectively, however, these studies are too small to draw firm conclusions regarding the effects of adjuvant chemotherapy on survival in men with high-risk prostate cancer, but they suggest that multimodal therapy is feasible in this population. Only through carefully designed

Table 1 Adjuvant trials for high-risk prostate cancer

Author	Number of patients	Inclusion criteria	Adjuvant regimen	Primary therapy	Results
NPCP 900 [43, 45]	184	Stage B2, C, or D1; lymph node dissection or lymphangiogram and aspiration; no distant metastases; no prior HT, orchiectomy, RT, CT	Estramustine 600 mg p.o. t.i.d. + cyclophosphamide 1 g/m^2 every 21 days vs. observation	RP	Lymph node involvement 29%; Increased PFS with estramustine in stage C/grade 3
NPCP 1000 [43, 45]	235	Stage B2, C, or D1; lymph node dissection or lymphangiogram and aspiration; no distant metastases; no prior HT, orchiectomy, RT, CT	Estramustine 600 mg p.o. t.i.d. + cyclophosphamide 1 g/m^2 every 21 days or observation	RT	Lymph node involvement 63%; Increased PFS with estramustine in extensive nodal involvement/grade 3
Pilepich [39]	9	T2 or T3 (AJC staging system; 1983) with no spread beyond pelvis	Cyclophosphamide 400 mg/m^2, doxorubicin 40 mg/m^2, cisplatin 75 mg/m^2 every 28 days until disease progression or 6 cycles	RT	Dose reduction required in 67%; Four pts delayed therapy by 1–14 weeks due to myelosuppression; Regimen not suitable for further evaluation as adjuvant to RT
Carter [7]	16	Stage D1 at RP	RT alone, adjuvant cyclophosphamide alone, or both	RT	Actuarial 5- and 10-year survival 86%. No local recurrences and 12% distant recurrences at 5 years
Bagley [1]	25	Positive lymph nodes; seminal vesicle involvement; stage II disease not amenable to surgery; positive surgical margins with high GS	Vinblastine 3 mg/m^2 on days 1, 3; doxorubicin 40 mg/m^2 on day 1 of 21-day cycles × 6; mitomycin 10 mg/m^2 on day 1 of cycles 1, 3, 5; AD	RP/RT	bRFS 79% at 5 years and 73% at 10 years. Ten-year RFS in patients with positive nodes 82%; 10-year cancer-specific survival 81%
Wang [53]	96	cT3 or cT4 or M1 disease	AD ± mitoxantrone 12 mg/m^2 every 21 days × 4	AD	Mitoxantrone significantly better than AD in localized PC: objective response rate 95% vs. 53%; median survival: 80 vs. 36 months

NPCP National Prostate Cancer Project, *RP* radical prostatectomy, *HT* hormonal therapy, *RT* radiation therapy, *CT* chemotherapy, *PFS* progression-free survival, *GS* Gleason score, *bRFS* biochemical relapse-free survival, *AD* androgen deprivation, *PC* prostate cancer

and conducted prospective, randomized, controlled trials will questions regarding the utility of adjuvant chemotherapy be adequately answered.

Neoadjuvant chemotherapy

Neoadjuvant chemotherapy has also been actively investigated (Table 2), and this approach has several benefits. Micrometastatic disease, which is present at the time of diagnosis and is a source of potential failure for local treatment, is treated without delay. Locally advanced tumors, if responsive to chemotherapy, are reduced in size such that they are more amenable to local therapy. Postoperative pathologic specimens may be collected and analyzed to confirm efficacy of treatment. Such an approach may also provide a model for efficient drug development, with opportunities to evaluate targeted therapies as well as improve understanding of mechanisms of response and resistance to treatment utilizing human specimens. Several groups have published results of trials evaluating neoadjuvant chemotherapy with or without androgen ablation for clinically localized prostate cancer. However, these studies are difficult to compare due to the small numbers of patients included, the differences in eligibility criteria, and the variety of chemotherapeutic agents and regimens utilized.

Many of the high-risk prostate cancer neoadjuvant trials have included estramustine combined with other chemotherapeutic agents [9, 30, 37]. Thromboembolic events related to estramustine were reported in each of these studies. Positive surgical margin rates have been favorable, and clinical downstaging of patients after neoadjuvant treatment prior to prostatectomy has been reported [9, 30]. However, residual disease was identified in post-prostatectomy specimens of all patients included in these trials.

Two groups have reported results of neoadjuvant estramustine-based chemotherapy prior to radiotherapy. Zelefsky et al. [54] treated men with unfavorable risk profiles with two cycles of neoadjuvant estramustine/vinblastine followed by a third cycle given concurrently with radiation, while Ben-Josef et al. [3] reported results of two cycles of neoadjuvant estramustine and etoposide followed by concurrent estramustine and three-dimensional conformal radiotherapy. Chemotherapy and radiation-related toxicity profiles were reasonable; however, thromboembolic complications attributable to estramustine were reported by both investigators.

Two groups have reported results of single-agent docetaxel given either for 6 months [33] or 6 weeks [15] prior to prostatectomy. In the study by Dreicer et al. [15], residual disease was identified in all prostatectomy specimens and 89% of the specimens had extracapsular extension. Hussain et al. [22] treated patients with high-risk disease with neoadjuvant docetaxel and estramustine prior to either radiation or radical prostatectomy. Among patients who underwent radical prostatectomy, 70% had negative surgical margins but none achieved pathologic complete remission. Preradiotherapy prostate biopsies were negative in 2 of 11 patients.

These studies are all too small to draw conclusions regarding the efficacy of neoadjuvant chemotherapy. However, like the adjuvant studies they do demonstrate feasibility and acceptability among patients who were administered chemotherapy in the early-disease setting. Aside from some serious thromboembolic complications likely due to estramustine, chemotherapy was overall well tolerated. Surgery following chemotherapy largely did not result in an increased rate of significant surgical complications. Clark et al. [9] noted a desmoplatic reaction around the prostate, potentially making surgery more difficult. They were nonetheless successfully able to perform radical prostatectomies on all patients included in their study. One should note that PSA response does not appear to be as significant in the early stages of disease as believed in hormone-refractory populations. Although several of the neoadjuvant studies noted significant PSA responses prior to primary treatment, residual tumor was identified in all postsurgical specimens. It is unclear why no pathological complete responses were observed. Similarly it is not clear how to assess response/efficacy in phase II trials of neoadjuvant chemotherapy and what the most appropriate endpoints are. In other neoplasms such as bladder cancer, a complete pathologic response is possible following neoadjuvant chemotherapy and has been shown to be a useful prognostic factor [20].

Phase III trials of adjuvant and neoadjuvant chemotherapy

Cooperative groups have led the way by initiating phase III trials to address the role of systemic therapy in early-stage high-risk prostate cancer. Several ongoing and planned protocols are listed in Table 3. These are large trials that are adequately powered to detect meaningful differences in survival with the addition of systemic chemotherapy.

The first is an important trial led by the Southwest Oncology Group (S9921). Eligible men must have Gleason scores 8–10, pathologic stage ≥pT3b, or nodal involvement or Gleason score 7 and positive margins. Following radical prostatectomy, patients are randomized to combined androgen blockade for 2 years or mitoxantrone and prednisone for six cycles and combined androgen blockade for 2 years. Patients with positive surgical margins are permitted to receive adjuvant radiation. A total of 1,360 enrolled subjects are needed to achieve 92% power to detect a 30% increase of median survival in the chemotherapy arm by a one-sided t test and a significance level of 0.05.

A phase III randomized trial investigating the role of neoadjuvant chemotherapy is planned by Cancer and Leukemia Group B (CALGB 90203). Eligible patients must have $<60\%$ chance of being disease-free 5 years

Table 2 Neoadjuvant trials for high-risk prostate cancer

Author	Number of patients	Inclusion criteria	Neoadjuvant regimen	Primary therapy	Results
Oh [33]	15	cT3 or PSA >20 ng/ml or GS 8–10; cT2 with seminal vesicle involvement on endorectal MRI or GS 4+3=7 with 5–6 positive biopsy specimens	Weekly docetaxel 36 mg/m^2 for ≤ 6 months	RP	PSA response prior to RP in 67%; no pathologic data reported
Dreicer [15]	29	cT2b or PSA ≥15 ng/ml or GS 8–10	Docetaxel 40 mg/m^2 weekly for 6 weeks	RP	PSA response prior to RP in 24%; 4% with positive margins; no CR
Pettaway [37]	33	cT1–cT2 with GS 8–10 or cT2, GS 7, and PSA >10 ng/mL or cT3	12 weeks of KAVE and AD	RP	50% with undetectable PSA prior to RP; 17% with positive margins; no CR
Clark [9]	16	cT2b/c or T3, PSA >15 ng/ml, or GS 8–10; no metastatic disease	Three 28-day cycles of estramustine 10 mg/kg/day on days 1–28 + oral etoposide 50 mg/m^2/day on days 1–21	RP	50% with undetectable PSA prior to RP; 13% with positive margins; no CR
Konety [30]	36	cT1–cT2, any GS, PSA >20 ng/ml; cT3–cT4, any PSA, any GS; any c, GS 8–10, any PSA	4–6 cycles of paclitaxel + carboplatin + estramustine vs. AD	RP	Median PSA prior to RP 0.17 (range 0–3.5) ng/mL; 22% with positive margins; no CR
Zelefsky [54] Ryan [42]	23	GS 8–10, PSA >10 ng/ml; GS 7, PSA >20 ng/mL; T3N0M0 with PSA >20 ng/ml; T4N0M0; TXN1M0	Three 8-week cycles of estramustine 10 mg/kg/day + vinblastine 4 mg/m^2 weekly on weeks 1–6	RT	Median nadir PSA unmeasurable; median 26% reduction of prostatic volume
Ben-Josef [3]	18	T3 or T4; T1c, T2b, or T2c with GS 7–10 and PSA >15 ng/mL	Two 21-day cycles of estramustine 10 mg/kg/day + oral etoposide 50 mg/m^2/day; estramustine 10 mg/kg/day + RT	RT	Local control rate 71%
Hussain [22]	21	≥cT2b, PSA ≥15 ng/ml, and/or GS 8–10	3–6 × 21-day cycles of docetaxel 70 mg/m^2 on day 1 + estramustine 280 mg t.i.d. on days 1–3	RP/RT	30% with positive surgical margins; 18% with negative biopsy prior to RT

PSA prostate-specific antigen, *RP* radical prostatectomy, *GS* Gleason score, *CR* complete response, *KAVE* ketoconazole, doxorubicin, vinblastine, estramustine, *AD* androgen deprivation, *RT* radiation therapy

Table 3 Phase III neoadjuvant and adjuvant trials in high-risk localized prostate cancer

Trial	Treatment approach	Eligibility criteria	Local therapy	Randomization	Number of patients	Primary endpoint
CALGB 90203	Neoadjuvant	≤ 60% PFS at 5 years estimated by preoperative nomogram	RP	Docetaxel + prednisone + AD vs. surgery	750	PFS
SWOG 9921	Adjuvant	GS 8–10, ≥pT3, or positive nodes; GS 7 and positive margin	RP	AD × 2 years vs. mitoxantrone + prednisone followed by AD for 2 years	1,360	OS
Sanofi-Aventis	Adjuvant	pT3, node positive, or GS 8–10	RP	Early vs. delayed treatment consisting of AD alone or AD and docetaxel	2,172	PFS

CALGB Cancer and Leukemia Group B, *SWOG* Southwest Oncology Group, *PFS* progression-free survival, *RP* radical prostatectomy, *AD* androgen deprivation, *GS* Gleason score, *OS* overall survival

following prostatectomy based on the Kattan nomogram and a life expectancy of ≥10 years. Patients will be randomized to radical prostatectomy alone or neoadjuvant estramustine and docetaxel followed by radical prostatectomy. Planned accrual is 750 men with a 90% power to detect a 36% decrease in 5-year recurrence rates, which is the primary endpoint of the study.

An industry-sponsored trial is also being planned to evaluate the role of early versus delayed treatment, consisting of androgen deprivation alone or with docetaxel, in a high-risk population following radical prostatectomy.

Conclusions

Improvements of systemic therapy for prostate cancer over the past decade have opened the door for active investigation of novel and effective treatments in all stages of the disease. One of the major results of this progress is the initiation of several large randomized clinical trials in early-stage disease. This approach has been enriched by improvements in risk prediction and the recognition that outcome improvement, much like in other cancers, is dependent on multimodal therapy. Such approaches are gaining increasing acceptability among patients and physicians. Defeating prostate cancer will require solid commitment to continued clinical/translational research in this area and to offer access to clinical trials to all appropriate patients.

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