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INVITED REVIEW

Prostate Cancer

Role of chemotherapy in prostate cancer

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Chemotherapy in prostate cancer (PCa) has undergone dramatic landscape changes. While earlier studies utilized varying chemotherapy regimens which were found to be largely palliative in nature and hardly resulted in durable or meaningful responses, docetaxel resulted in the first chemotherapy agent that showed improvement in overall survival in metastatic castration-resistant prostate cancer (mCRPC). However, combination chemotherapy or any agents added to docetaxel have failed to yield incremental benefits. The improvement in overall survival as well as secondary endpoints of prostate-specific antigen (PSA) and time to recurrence when using docetaxel in the metastatic hormone-sensitive state has changed the standard of care for treatment of newly diagnosed *de novo* metastatic PCa. There are also promising results in locally advanced PCa and high-risk PCa in both the neoadjuvant and adjuvant settings. This review summarizes the historical as well as the more contemporary use of chemotherapeutic agents in PCa in varying states and phases of disease.

Asian Journal of Andrology (2018) 20, 221–229; doi: 10.4103/aja.aja_40_17; published online: 20 October 2017

Keywords: docetaxel; metastatic castration-resistant prostate cancer; prostate cancer

INTRODUCTION

The first case of prostate cancer (PCa) was described as a very rare disease by J Adams at the London Hospital in 1853.^{1,2} Today, PCa has emerged as the most common noncutaneous malignancy in men with 161 360 cases projected to occur in 2017 alone in the United States.³ For localized PCa, apart from active surveillance that is emerging as a viable form of management, radical prostatectomy or radiotherapy represents the two main curative forms of therapy.⁴ Androgen deprivation therapy has been considered the backbone of treatment for advanced and metastatic cancer.⁵ The aim of this review article is to explore the role of chemotherapy in the treatment of varying stages and phases of PCa, from high-risk locally advanced PCa to hormone-sensitive metastatic disease and to metastatic castration-resistant prostate cancer (mCRPC).

HISTORY OF CHEMOTHERAPY USE IN PCA – FROM PALLIATIVE TO SURVIVAL ADVANTAGE

In the 1940s, Dr. Charles Huggins and Dr. Clarence Hodges were the first to demonstrate that bilateral orchiectomy or estrogen therapy resulted in shrinkage of prostate tumors by decreasing testosterone levels and inducing castration.⁶ Since then, androgen ablation therapy has been the mainstay of treatment of PCa. Initially, most patients responded to androgen-ablative therapy or androgen deprivation therapy (ADT), but became resistant with time and developed fatal disease.² At that time, there were no clear methods to measure tumor burden. Most patients would have soft tissue diseases involving the prostate and lymph nodes where they could not be easily measured, along with extensive bone metastases. They mostly suffered from bone pain which when localized usually transiently responded to radiation therapy. Obstructive symptoms were treated with transurethral resection. It was the patients with generalized bone pain in whom

effective palliation was difficult, and so came the need for clinical trials of chemotherapy in these selected patients.⁷

Between the 1950s and 1970s, several small trials took place using alkylating agents but these investigations along with results were poorly documented. A large number of single agents have been studied. However, most of these trials were broad, unfocused Phase II clinical trials without specific criteria for response and with a small number of patients.⁸ PCa was largely considered a chemotherapy unresponsive disease.⁹ This is why for a certain drug, results varied widely among different investigators and showed a lack of reproducibility. For this reason, several trials using two or more drugs in combination were performed. None of the combinations showed any major impact on response or survival. In 1972, the National Prostatic Cancer Project (NPCP) began a series of randomized Phase II and III studies on single agents and combinations in what was then termed “hormonally-resistant” but later coined “castration-resistant” PCa patients. They used response as their main endpoint and compared chemotherapy drugs to the standard treatment which consisted of palliative therapies (radiation, hormonal therapies, or analgesic use). The NPCP criteria were complete response (CR), partial response (PR), and objective stabilization as endpoints of therapeutic efficacy. These trials showed higher rates of objective responses on the chemotherapy arms, but there was no survival advantage, and most of the response was stable disease with CR and PR occurring rarely. Whether the stability of the disease was due to the chemotherapy or to the slow progression of PCa in general could not be determined. The NPCP also tested the efficacy of chemotherapy in combination with hormonal therapy but also showed no difference between the study arms. At that time, all existing data did not show any evidence that the addition of chemotherapy would prolong survival and there was no solid evidence

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Received: 18 May 2017; Accepted: 20 July 2017

to support the use of any chemotherapeutic agent as a standard of care.¹⁰ Reports of NPCP and other trials suggested that patients may have improvement of pain and other symptoms after treatment with any of several drugs, but all drugs added toxicity.⁷ The different chemotherapy regimens that have been studied were vast and some of the earlier trial results during that period are summarized.

Cyclophosphamide is an alkylating agent that affects cell division by cross-linking deoxyribonucleic acid (DNA) strands and thus decreasing DNA synthesis. In early conducted trials, these drugs were collectively felt to deliver suboptimal responses in urologic tumors.¹¹ Carter and Wasserman showed a response in 8 out of 57 patients, although response criteria used were unclear.¹² In the NPCP trials, CR was reported in 0% of patients and PR in 7% of patients, and 26%–46% of patients had stable disease.⁹ Cyclophosphamide was also used orally with modest responses,¹³ though later repurposing with interest in cyclophosphamide's role in angiogenesis inhibition through metronomic cycling,¹⁴ brought a resurgence of interest in the use of this drug for docetaxel failures.¹⁵

Cisplatin is a platinum-containing compound that inhibits DNA synthesis by cross-linking and denaturing DNA strands. Cisplatin was studied using a weekly schedule for 6 weeks then every 3 weeks maintenance,¹⁶ and was found to have a complete and partial remission in 17 patients (31%) out of 54. Another study reported four CRs and PRs in 21 patients (19%).¹⁷ Yagoda *et al.*¹⁸ observed only three CRs and PRs (12%), while an Eastern Cooperative Oncology Group (ECOG) study observed no response in 17 evaluable patients.¹⁹ The NPCP 1100 study showed no CR in patients treated with cisplatin,²⁰ but 4% PR and 32% stable disease, making up 36% objective response rates, and protocol 1200 showed a CR and PR in none of patients, and stable disease in 21%.²¹ In 209 cases reviewed, cisplatin showed a modest antitumor activity with a PR in 12% (95% confidential interval [CI]: 4%–20%) and thus was continued to be investigated as a single agent and in combination.⁹

Carboplatin, a cisplatin derivative that results in intra- and inter-strand cross-linkage DNA damage, had been studied in earlier trials as a single agent with minimal responses.^{22,23} However, when combined with other chemotherapy drugs such as paclitaxel and estramustine, declines in serum prostate-specific antigen (PSA) levels of 50%, 80%, and 90% were seen in 67% (95% CI: 55%–79%), 48% (95% CI: 35%–61%), and 39% (95% CI: 26%–52%), respectively. There were two patients (6%) of 33 patients who had a CR and 13 (39%) had a PR.²⁴

Satraplatin, the first oral 4th generation platinum analog found to be effective against cisplatin- and carboplatin-resistant cell lines,²⁵ held a lot of promise in castration-resistant PCa,²⁶ and while it showed improvement in time to pain progression, it failed to improve overall survival (OS) in the Phase III SPARC registration trial.²⁷

5-fluorouracil (5-FU) is a pyrimidine analog that inhibits DNA synthesis during the synthesis (S) phase by inhibiting thymidylate synthetase. Studies in the aggregate comprising of 124 patients receiving 5-FU in various doses and schedules showed modest antineoplastic activity with a response rate of around 9% (95% CI: 4%–14%).^{28,29} In one of the larger trials that included 147 patients comparing doxorubicin to 5-FU, doxorubicin yielded 25% (15 out of 61 patients) response compared to 8% (3 out of 42 patients) treated with 5-FU alone.³⁰

Capecitabine, an oral fluoropyrimidine carbamate that delivers 5-FU to tumor cells, was studied in castrate-resistant PCa with PSA response rates in the 12%.³¹

Methotrexate, a dihydrofolic acid reductase inhibitor which inhibits purine and thymidyl acid synthesis, serves to interfere with DNA synthesis. It has been investigated in several earlier Phase II trials and

by the NPCP. In the NPCP Phase III randomized trial (protocol 1100) using methotrexate at varying doses,³² only one out of 63 patients had a PR (2%, 95% CI: 0–6%), and stable disease occurred in 20%.

Doxorubicin is an anthracycline that intercalates between DNA base pairs and impairs topoisomerase II function inhibiting replication and transcription. Doxorubicin has also shown only marginal responses against PCa. In the earliest trials, responses varied from a 29% response rate as reported by O'Bryan *et al.*³³ to a 5% response rate as reported by Scher *et al.*³⁴ Each study had a different response criteria which explain the variability in results. The NPCP results showed clinical benefit with a response rate that included stable disease reaching 84%.¹⁰ Subsequent trials utilizing additional ketoconazole with doxorubicin alternating with vinblastine and etoposide chemotherapy showed no additional benefit to hormonal therapy alone.³⁵

Etoposide alters DNA replication, induces G2 phase arrest, and kills cells in G2 and late S phases. Studies showed poor response rates with an overall response rate of 3% (95% CI: 0–7%) in the aggregate.^{36–38} Vinblastine, a vinca alkaloid that inhibits microtubule formation, had been shown in older studies to induce a 21% remission rate in a small number of 39 patients.²⁹

Estramustine, an estradiol and nornitrogen mustard carbamate-linked combination which has an antiandrogen effect and antimicrotubule effect, was extensively studied by the NPCP and had been reported to have a palliative effect in castration resistant PCa patients, but objective response was rare in NPCP trials. Estramustine as a single agent was evaluated in varying NPCP protocols that included 163 patients, where CR plus PR rates varied between 0–4%, but with SD included, rates increased to 18%–34%.⁹ Similarly, when estramustine was studied in combination with prednimustine, vincristine, and cisplatin, no remarkable added benefit was shown.²⁹ Given notable side effects of estramustine such as nausea and diarrhea, its use was not widely adopted,⁷ though it did garner the first the United States Food and Drug Administration (FDA) approval for a cytotoxic therapy in 1981 for its clinical response given lack of other active agents.^{39,40} While later studies combining it with docetaxel showed promising results,^{41,42} efficacy was felt to be more due to docetaxel, omitting use of estramustine altogether due to side effect profile.

Mitoxantrone is an anthracenedione, a Type II topoisomerase inhibitor that serves to interfere with DNA intercalation and damage. Prednisone, on the other hand, was believed to produce a negative feedback on the pituitary gland that would inhibit the secretion of adrenocorticotropic hormone leading to decreased dehydroepiandrosterone (DHEA) and dehydroepiandrosterone-sulfate (DHEAS) which can be metabolized to small amounts of testosterone. In patients no longer responding to primary androgen ablation, up to about 30% may have improvement of symptoms, mainly bone pain, with low-dose prednisone and mitoxantrone.⁴³ In 1996, a randomized controlled trial was published that compared mitoxantrone plus prednisone versus prednisone alone in symptomatic CRPC patients with a total of 161 fairly symptomatic men with pain.⁴⁴ The primary endpoint of the study was palliation with pain relief as its primary indicator. In the patients who received mitoxantrone with prednisone, a 29% palliative response over a duration of 48 weeks was observed versus 12% over 18 weeks in patients who received prednisone alone. Progression-free survival (PFS) was also shown to be better in the mitoxantrone with prednisone arm although OS was similar in both arms. Mitoxantrone was well tolerated except for possible cardiac toxicity in 5 patients.

Another Phase III trial, the Cancer and Leukemia Group B (CALGB) 9182, randomized 244 CRPC patients to mitoxantrone

plus hydrocortisone versus hydrocortisone alone.⁴⁵ It also showed improvement in pain control but no effect on survival (12.3 vs 12.6 months, $P = 0.3298$). Once these studies demonstrated mitoxantrone's palliative benefits, mitoxantrone became the next cytotoxic drug to be approved by the United States FDA for use in mCRPC for quality of life results.⁴⁰ Other trials were done to evaluate mitoxantrone's role in OS, but failed to demonstrate any benefit. Today, mitoxantrone is used with the goal of improving quality of life and pain control as second- or third-line or beyond chemotherapy.

PCA WORKING GROUP CRITERIA FOR RESPONSE

Given the challenges and lack of standardization in defining PSA responses as well as progression, the PSA working group initially convened a consensus conference and published the guidelines in 1999 in order to guide selection of candidate agents for further testing and choosing which agents that can proceed to Phase III trials especially if they are based on different gauge of PSA changes.⁴⁶ They also proposed that response duration and time to PSA progression may be important clinical endpoints. The working group criteria were further revised in 2009 with an emphasis on using different parameters, not just PSA progression alone, and patients with early changes in PSA and/or pain are not encouraged to be acted upon without other evidence of objective disease progression such as radiographic technetium scan or computed tomography scans using the Response Evaluation Criteria in Solid Tumors (RECIST) criterion and pain scales.⁴⁷ In addition, given drugs that were felt to be more cytostatic than cytotoxic, treatment was encouraged to be continued for at least 3 months so that drug exposure was ensured to be adequate. The Prostate Cancer Clinical Trials Working Group 3 (PCWG3) reconvened and published updated guidelines in 2016. The emphasis was to be able to distinguish between first progression and the clinical need to switch treatment, with the provision for using blood-based diagnostics, novel imaging and biologic profiling wherever applicable.⁴⁸

DOCETAXEL: ROLE IN MCRPC

Up until 2004, there was still no standard front-line or second-line chemotherapy for mCRPC that improved OS. Treatment options for mCRPC at the time often included second-line hormonal therapy, radiation therapy, cytotoxic chemotherapy, investigational therapy, or supportive care. Chemotherapy was clearly shown to provide palliative benefit but no survival benefit, and the regimens available at the time, as aforementioned, were mitoxantrone, estramustine, or docetaxel.⁴⁹

Docetaxel is a taxane derivative that works by binding to microtubules and preventing androgen receptor nuclear translocation and causing apoptosis through B-cell lymphoma (Bcl-2) phosphorylation.⁵⁰ Studies using docetaxel as a single agent or in combination with estramustine showed objective response rates in up to 38% of patients, PSA declines of more than 50% in 69% of patients.^{51,52} These findings encouraged subsequent two trials: the TAX 327 trial and the Southwest Oncology Group (SWOG) 99-16 trial.

In 2004, the pivotal TAX 327, a randomized nonblinded Phase III trial, was published.⁵³ It involved 1006 men with PCa refractory to hormonal treatment who were assigned to three arms: 12 mg m⁻² of mitoxantrone every 3 weeks compared to 75 mg m⁻² every 3 weeks, or 30 mg m⁻² of docetaxel weekly for 5 out of every 6 weeks and all these patients were followed for about 20 months. The primary endpoint was OS and secondary endpoints were pain, PSA levels, and quality of life. The results showed that the survival rate in the group of docetaxel every 3 weeks was significantly higher than the mitoxantrone group, 18.9 months versus 16.5 months, respectively ($P = 0.009$).

The group of weekly docetaxel did yield an OS of 17.4 months, not significantly higher than the mitoxantrone group ($P = 0.36$), and the every 3 weeks of docetaxel therefore became the default standard of care thereafter. Pain reduction was more frequently observed among patients receiving docetaxel every 3 weeks than those receiving mitoxantrone (35% vs 22%, $P = 0.01$), while weekly docetaxel did not significantly differ than mitoxantrone alone (31% vs 22%, $P = 0.08$). PSA response, defined as >50% reduction in PSA levels in this study, was also significantly higher in the patients receiving docetaxel every 3 weeks (45%) as compared to mitoxantrone (32%), as well as in the patients receiving docetaxel weekly (48%). This study concluded that cytotoxic chemotherapy, more specifically docetaxel with prednisone, can significantly prolong OS in men with mCRPC and was the basis of the United States FDA approval of docetaxel in 2004.

Another Phase III trial, which was published at the same time with the TAX 327 trial, was the SWOG 99-16 which enrolled 770 men with a similar eligibility criteria with mCRPC patients randomized to two treatment arms each given in 21-day cycles: 280 mg of estramustine three times daily on days 1 to 5, 60 mg m⁻² of docetaxel on day 2 and 60 mg of dexamethasone before docetaxel, versus 12 mg m⁻² of mitoxantrone on day 1 plus 5 mg of prednisone twice daily.⁴¹ The primary endpoint of OS was shown to be significantly longer in the docetaxel plus estramustine arm compared to mitoxantrone arm (17.5 vs 15.6 months, $P = 0.02$). The secondary endpoints such as the median time to progression were significantly better in the docetaxel and estramustine arm (6.3 vs 3.2 months, $P < 0.001$), although pain improvement was not shown to be different in either group. Adverse events and Grade 3/4 toxicities, such as gastrointestinal, cardiovascular, thromboembolic events, infections, and neuropathy, were all shown to be higher in the arm that contained docetaxel and estramustine (54% of patients) compared to the mitoxantrone arm (34% patients). However, this difference was not associated with an increased rate of treatment-related deaths or discontinuation of treatment. This study concluded that treatment with estramustine and docetaxel moderately not only increases the survival but also increases the rate of adverse events. Despite demonstrated survival advantage, the combination of docetaxel plus estramustine is rarely used now due to significant toxicity of the regimen.

These two studies, primarily the TAX 327 and secondarily the SWOG 9916, have set the standard of care for men with mCRPC. Numerous subsequent combination trials have been performed in an attempt to improve upon the efficacy of docetaxel, but most of these have been largely negative trials.

CABAZITAXEL: ROLE AS SECOND-LINE SALVAGE CHEMOTHERAPY

After failure of docetaxel as first-line chemotherapy, second-line treatment options included mitoxantrone, retreatment with docetaxel, or clinical trials.⁸ It was not until 2010 that another chemotherapeutic drug, cabazitaxel, was FDA approved for the treatment of PCa.

Cabazitaxel is a third-generation, semisynthetic tubulin-binding taxane drug that was developed after resistance was seen with the other taxanes.⁵⁴ It was found to be as potent as docetaxel in cell lines and has antitumor activity in models resistant to paclitaxel and docetaxel. A randomized Phase III open-label clinical trial termed the TROPIC trial (XRP6258 Plus Prednisone Compared to Mitoxantrone Plus Prednisone in Hormone Refractory Metastatic Prostate Cancer), was reported in 2010, in which the aim was to assess the role of cabazitaxel plus prednisone in patients with mCRPC who progressed after docetaxel.⁵⁵ Seven hundred and fifty-five patients were randomized to

receive either cabazitaxel (25 mg m⁻²) or mitoxantrone (12 mg m⁻²) on day 1 of each 21-day cycle, and all patients received prednisone 10 mg daily. The primary endpoint of the trial was median OS and was superior in the cabazitaxel arm at 5.1 (95% CI: 14.1–16.3) months compared to mitoxantrone group at 12.7 (95% CI: 11.6–13.7) months translating to a 30% reduction in relative risk of death (HR: 0.70, 95% CI: 0.59–0.83, $P < 0.0001$). On the other hand, cabazitaxel showed higher adverse events, the most frequent was hematological mostly neutropenia, leukopenia, and anemia, thereby adding on to the label of cabazitaxel upon FDA approval in 2010 with use of growth factors for prophylaxis for patients older than 65 years of age or those with significant comorbidities.

The PROSELICA trial (Cabazitaxel at 20 mg m⁻² compared to 25 mg m⁻² with Prednisone for the Treatment of Metastatic Castration Resistant Prostate Cancer) was a Phase III study that sought to compare two different dosing of cabazitaxel at 20 mg m⁻² versus cabazitaxel at the standard dose of 25 mg m⁻² in 1200 patients with mCRPC who progressed after docetaxel. The study results showed the noninferiority of the 20 mg m⁻² as compared to 25 mg m⁻² dose of cabazitaxel every 3 weeks in combination with prednisone (median OS: 13.4 vs 14.5 months, respectively) and it showed that the 20 mg m⁻² dose had less adverse events (39.7% vs 54.5%). Particularly, the rate of Grade 4 neutropenia was 21.3% in the lower dose and 48.6% in the higher dose groups.⁵⁶ The FIRSTANA trial (Cabazitaxel vs Docetaxel Both With Prednisone in Patients With Metastatic Castration Resistant Prostate Cancer) was a Phase III study that compared cabazitaxel to docetaxel in chemotherapy-naïve patients with mCRPC and recent results did not reveal superiority in OS (median: 24.5 months, 25.2 months, and 24.3 months in the cabazitaxel 20 mg m⁻² group, cabazitaxel 25 mg m⁻² group, and docetaxel 75 mg m⁻² group, respectively; HR: 0.97, 95% CI: 0.819–1.16, $P = 0.7574$),⁵⁷ therefore showing that docetaxel remains the most appropriate first-line chemotherapy regimen for patients with mCRPC.

Cabazitaxel therefore remains an option for patients with mCRPC who have failed docetaxel and there are no data to support greater efficacy of cabazitaxel over docetaxel in the chemotherapy-naïve patients.

DOCETAXEL – ROLE IN EARLY HORMONE-SENSITIVE PCA

For metastatic hormone-sensitive PCA, the cornerstone of treatment has been aimed toward addressing the androgen pathway, but most of these patients will progress to castration resistant PCA in 1–2 years. The mechanism of action of docetaxel raised the question of its possible benefit in hormone-sensitive PCA, which led to further investigations.⁵⁸

A randomized study from the Genito-Urinary Group and the French Association of Urology (GETUG-AFU) 15 was a Phase III trial that evaluated the role of docetaxel in 385 men with metastatic hormone-sensitive PCA. Patients were randomized to receive either androgen deprivation therapy alone or with docetaxel (75 mg m⁻² every 3 weeks) and were followed up for 50 months. Results for the primary endpoint, OS, were not statistically significant (58.9 months in ADT plus docetaxel vs 54.2 months in the group given ADT alone, HR: 1.01, 95% CI: 0.75–1.36), but the ADT plus docetaxel reported more adverse events (72 more serious adverse events). The authors concluded that the results of the trial did not support the use of docetaxel as part of first-line treatment for patients with noncastrate metastatic PCA.⁵⁹ In 2015, long-term follow-up results were published that also showed no statistically significant benefit (62.1 vs 48.6 months; HR: 0.88, 95% CI: 0.68–1.14, $P = 0.3$) but did show an absolute difference in median OS of 14 months.⁶⁰

Another larger study, the ECOG-run ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) study, enrolled 790 metastatic hormone-sensitive PCA patients and randomized them to receive either ADT alone or ADT with docetaxel (75 mg m⁻² every 3 weeks).⁶¹ OS was 16.6 months longer, 57.6 months with the addition of early docetaxel to ADT versus 44 months with ADT alone (HR: 0.61, 95% CI: 0.47–0.80, $P < 0.001$). This study showed that combining docetaxel with ADT early only for patients diagnosed with *de novo* castration-sensitive PCA resulted in longer OS, longer time to develop castration resistance, and better cancer control especially for the high volume disease group.

The Systemic Therapy in Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial was the largest of the trials that aimed at investigating the efficacy of using various treatments including docetaxel and zoledronic acid as front-line with hormonal therapy in men with newly diagnosed locally advanced or metastatic PCA and men who have relapsed after local therapy.⁶² It enrolled 2862 eligible patients with PCA who were newly diagnosed as metastatic, node positive, or high-risk locally advanced (with at least two of disease features pT3/4, Gleason score of 8–10, and PSA ≥ 40 ng ml⁻¹) or previously treated with radical surgery, radiotherapy, or both and relapsing with high-risk features. They were randomized in a 2:1:1:1 ratio to standard of care only, standard of care plus zoledronic acid, standard of care plus docetaxel, and standard of care plus zoledronic acid and docetaxel. Patients who received docetaxel along with standard of therapy have improved OS with a 10-month difference (77 vs 67 months; HR: 0.76, 95% CI: 0.63–0.91, $P = 0.003$), in addition to improvements in failure-free survival. However, subgroup analyses showed that patients with nonmetastatic (M0) disease did not benefit (HR: 1.01, 95% CI: 0.65–1.56). They concluded that standard of care for patients with metastatic castration-sensitive disease should include docetaxel chemotherapy.

A subsequent meta-analysis published in 2015 reviewed all relevant trials on docetaxel with standard of care in castration-sensitive PCA to study the effects of this therapy.⁶³ It showed that the addition of docetaxel improves survival in men with M1 disease, but not M0 disease. Results of the 3 trials (CHAARTED, GETUG-15, and STAMPEDE) all showed that docetaxel as an addition to standard care would improve 4-year survival by 9% (HR: 0.77, 95% CI: 0.68–0.87, $P < 0.0001$), and reduces 4-year failure rates by 16% (HR: 0.64, 95% CI: 0.58–0.70, $P < 0.0001$). However, based on the results of STAMPEDE as well as two other trials (GETUG-12, RTOG 0521) in men with locally advanced but M0 disease, unanimous benefit was not shown from the addition of docetaxel (HR: 0.87, 95% CI: 0.69–1.09, $P = 0.218$). While strong evidence was found to support the addition of docetaxel to standard care with ADT for men with metastatic castration-sensitive PCA, more evidence is still needed to use early chemotherapy for men with M0 disease.

Table 1 lists ongoing trials that utilize chemotherapy in castration-sensitive or hormone-sensitive metastatic PCA. The promising results of early docetaxel chemotherapy have paved the way for dramatic changes in the current standard of care to include docetaxel chemotherapy as part of the cornerstone of treatment in men with newly diagnosed metastatic hormone-sensitive PCA.

NEOADJUVANT CHEMOTHERAPY PRIOR TO RADICAL PROSTATECTOMY

The majority of patients with localized PCA who undergo radical prostatectomy are cured but as many as one-third experience

Table 1: Selected ongoing clinical trials in metastatic hormone-sensitive prostate cancer

| Clinical trial | Phase | Arms | Population studied | Primary endpoint |
|----------------------|-----------|---|-------------------------------------|---|
| NCT02799602; ARASENS | Phase III | ADT + docetaxel + darolutamide ADT + docetaxel + placebo | Metastatic hormone-sensitive PCa | OS |
| NCT02649855 | Phase II | Standard ADT followed by docetaxel + prostatic Standard ADT followed by simultaneous prostatic and docetaxel | Metastatic hormone-sensitive PCa | Immune response, response score |
| NCT02677896 | Phase III | Enzalutamide + ADT ADT alone | Metastatic hormone-sensitive PCa | Radiographic progression-free survival |
| NCT02058706 | Phase II | Enzalutamide and LHRH analog therapy Bicalutamide and LHRH analog therapy | Metastatic hormone-sensitive PCa | PSA remission |
| NCT02489318 | Phase III | Apalutamide plus ADT ADT | Metastatic hormone-sensitive PCa | Radiographic progression-free survival and OS |

ADT: androgen deprivation therapy; LHRH: luteinizing hormone releasing hormone; OS: overall survival; PCa: prostate cancer; PSA: prostate-specific antigen

recurrence.⁶⁴ Recently, there has been a growing interest in neoadjuvant treatment in an attempt to eradicate micrometastases and improve surgical outcomes in patients with varying cancers. Given the lack of mature Phase III trials evaluating the role of neoadjuvant chemotherapy in PCa and the availability of a multitude though limited number of patients in Phase II trials that utilizes different chemotherapy agents⁶⁵⁻⁸¹ (Table 2), there remains to be a limited role of neoadjuvant chemotherapy with or without ADT in the management of localized PCa prior to radical prostatectomy.

A Phase II study enrolled 19 patients with high-risk PCa defined as biopsy Gleason scores of 8–10, serum PSA levels >20 ng ml⁻¹, and/or clinical stage T3 disease.⁸² The recruited patients received weekly docetaxel (36 mg m⁻²) for 6 months, followed by radical prostatectomy. PSA declines of >50% were seen in 11 of 19 patients and endorectal magnetic resonance imaging (MRI) showed maximum tumor volume reduction of at least 25% in 13 of 19 patients and at least 50% in 4 patients. Sixteen patients completed chemotherapy and had radical prostatectomy and none of them achieved pathologic complete response.

Another Phase II trial also evaluated the role of weekly docetaxel for 6 weeks followed by radical prostatectomy.⁸³ The study showed a statistically significant reduction in PSA ($P < 0.03$) with 79% of patients experiencing any reduction and 24% of patients experiencing >50% reduction in PSA. There was no complete pathologic response and the positive surgical margin rate was 3.5%.

Neoadjuvant chemotherapy in combination with ADT has also been evaluated.⁸⁴ In a Phase II study that included 22 patients with high-risk PCa, neoadjuvant docetaxel and estramustine was given and followed for a PSA nadir with a gonadotropin-releasing hormone (GnRH) agonist. One patient achieved a pathologic CR and six patients achieved low residual tumor confined to ≤10% of prostate volume. The mean 5-year disease-free survival at 53 months was 80% for patients with ≤10% residual cancer and 20% for those with >10%.

The Canadian Urologic Oncology Group (CUOG) conducted another larger Phase II trial of combined neoadjuvant chemotherapy with ADT.⁸⁵ A total of 72 men with high-risk PCa were treated with docetaxel (weekly for 6 of 8 weeks for 3 cycles) and ADT (buserelin acetate every 8 weeks for 3 doses and an antiandrogen for 4 weeks) followed by radical prostatectomy. Median PSA before surgery was 0.14 μg l⁻¹ representing a median decrease of 98.4%. Of the 64 patients completing the protocol, two (3%) had a pathologic CR and 16 patients (25%) had ≤5% tumor in the RP specimen. There were 34 patients (53%) with pathologic T2 disease, 17 patients (27%) with positive margins, and 4 patients (6%) with regional lymph node involvement. After

a median follow-up of 42.7 months, a total of 19 patients (30%) had PSA recurrence.

The CALGB 90203 trial (Preoperative Use of Neoadjuvant ChemoHormonal Therapy [PUNCH trial]) is a Phase III neoadjuvant trial that randomized patients with clinically localized high-risk PCa and having opted for radical prostatectomy to receive neoadjuvant ADT and docetaxel prior to surgery versus surgery alone. The trial has finished accrual and results are eagerly awaited. The use of neoadjuvant chemotherapy prior to radical prostatectomy remains investigational and is currently not part of the standard of care of patients with PCa.

THE ROLE OF ADJUVANT CHEMOTHERAPY

The role of adjuvant chemotherapy after radiation therapy in PCa was recently evaluated in a large Phase III trial, the RTOG 0521 that randomized a total of 563 high-risk PCa patients to either ADT and radiotherapy or ADT and radiotherapy followed by sequential docetaxel and prednisone.⁸⁶ Androgen suppression was given for 24 months; external-beam radiation therapy was given for 8 weeks; and docetaxel was given at 75 mg m⁻² on day 1 for 6 cycles, starting 4 weeks after the completion of radiotherapy along with prednisone 10 mg. The enrolled patients had Gleason scores between 8 and 10, PSA ≥20 ng ml⁻¹ (but <150 ng ml⁻¹), or ≥T2 stage. At a median follow-up of 5.5 years, 4-year OS was 89% in ADT/radiation arm and 93% with the addition of docetaxel, for an absolute benefit of 4% (one-sided $P = 0.04$) resulting in a 30% reduction in risk of death favoring adjuvant docetaxel. In addition, there was an absolute 10% reduction in the rate of disease-free survival at 6 years (65% vs 55%, $P = 0.04$) and the risk of biochemical failure was reduced by 20% in the docetaxel-containing arm. As expected, there was more Grade 3 or 4 hematologic toxicity in the chemotherapy arm. This was one of the promising trials that evaluated adjuvant chemotherapy after radiation which was included in a provisional statement in the National Comprehensive Cancer Network (NCCN) Guidelines for PCa treatment in men with high-risk disease as a consideration for selected patients who are fit to receive chemotherapy.⁸⁷

On the other hand, adjuvant chemotherapy postprostatectomy has not uniformly shown to be equally as promising (see Table 3). One large trial conducted and reported from the Genito-Urinary Group and the French Association of Urology (GETUG) 12, randomized 207 patients with high-risk disease to ADT in addition to docetaxel and estramustine while 206 patients to ADT alone.⁸⁸ High-risk features were considered one of the followings: stage T3–T4 disease, Gleason score of ≥8, PSA levels of >20 ng ml⁻¹, or pathological node-positive disease as evidenced by patients undergoing lymph node dissection. Results showed that while the 8-year relapse-free survival was superior in the combination arm with ADT plus docetaxel and estramustine

Table 2: Neoadjuvant chemotherapy trials

| Study | CT | Primary endpoint | Number of patients (n) | Results |
|--|--|--|------------------------|---|
| Clark <i>et al.</i> ⁶⁵ | Neoadjuvant estramustine + etoposide | Feasibility, drug and surgery-related toxicities | 18 | 95% local response and 50% undetectable PSA levels; 28% Grade 3 toxicity; 6% Grade 4 toxicity; No pCR |
| Hussain <i>et al.</i> ⁶⁶ | Neoadjuvant docetaxel + estramustine | Efficacy and safety | 21 | 2 patients with Grade 3 DVT; 1 patient with Grade 4 neutropenia; negative surgical margins in 7 out of 10 patients |
| Dreicer <i>et al.</i> ⁸³ | Neoadjuvant docetaxel | Feasibility and drug-related and surgical-related toxicities | 29 | No unexpected toxicities; 20 patients disease free; significant reduction in PSA with 79% of patients |
| Konety <i>et al.</i> ⁶⁷ | Neoadjuvant paclitaxel + carboplatin + estramustine + hormonal therapy | Perioperative morbidity, mortality and delayed complications | 36 | 45% biochemical recurrence-free survival; 22% deep vein thrombosis |
| Febbo <i>et al.</i> ⁸² | Neoadjuvant docetaxel | Pathologic response | 19 | No pCR; 58% of patients with >50% decrease of PSA |
| Prayer-Galetti <i>et al.</i> ⁸⁴ | Neoadjuvant docetaxel + estramustine | Safety, clinical and pathological response | 21 | 1 patient (5%) pCR; 3 (15%) CR; 16 (80%) PR |
| Magi-Galluzzi <i>et al.</i> ⁶⁸ | Neoadjuvant docetaxel | Pathological response | 28 | No pCR; 43% remained biochemically disease free |
| Sella <i>et al.</i> ⁶⁹ | Neoadjuvant docetaxel plus estramustine plus ADT (goserelin + bicalutamide) | Pathologic response | 22 | No pCR; 54.5% disease-free survival |
| Chi <i>et al.</i> ⁸⁵ | Neoadjuvant docetaxel + ADT (buserelin acetate and antiandrogen) | Pathological response | 64 | 2 (3%) pCR; 16 patients (25%) had ≤5% tumor in the RP specimen; 70% recurrence-free survival |
| Friedman <i>et al.</i> ⁷⁰ | Neoadjuvant docetaxel and capecitabine | Rate of 50% or greater PSA decrease | 15 | 6 (40%) had 50% or greater decrease in PSA; no pCR |
| Mellado <i>et al.</i> ⁷¹ | Neoadjuvant docetaxel + ADT (flutamide + goserelin) | Pathological response | 57 | 6% pCR; 6% near pCR (microscopic residual tumor) |
| Shepard <i>et al.</i> ⁷³ | Neoadjuvant nab-paclitaxel | Pathological and PSA response | 19 | No pCR; 18 (95%) had post-CT PSA decrease by a median of 35% |
| Garzotto <i>et al.</i> ⁷² | Neoadjuvant docetaxel + mitoxantrone | 5-year recurrence-free survival | 57 | 49.8% 5-year recurrence-free survival; 67% negative surgical margins |
| Kim <i>et al.</i> ⁷⁴ | Neoadjuvant docetaxel + estramustine | 2-year progression-free survival | 34 | No pCR; 45% 2-year progression-free survival |
| Womble <i>et al.</i> ⁸¹ | Neoadjuvant docetaxel + ketoconazole | bPFS | 22 | 36% (8/18) biochemical free at 18-month follow-up |
| Narita <i>et al.</i> ⁷⁵ | Neoadjuvant docetaxel + estramustine + CAB (leuprolide + bicalutamide) | Pathological response | 18 | 11% pCR; 100% negative surgical margins; 77.8% disease-free survival |
| Ross <i>et al.</i> ⁷⁶ | Neoadjuvant docetaxel + bevacizumab | PR by endorectal MRI | 41 | 12 (29%) had >50% reduction in tumor volume; 9 (22%) had >50% posttreatment decline in PSA; No pCR |
| Thalgott <i>et al.</i> ⁷⁷ | Neoadjuvant docetaxel + ADT (trimestral buserelin + bicalutamide) | Biochemical (PSA) and local downstaging | 30 | 97.3% PSA reduction; 46.4% median tumor volume reduction; 48.3% pathological downstaging; No pCR |
| Silberstein <i>et al.</i> ⁷⁸ | Neoadjuvant paclitaxel, carboplatin and estramustine + ADT (goserelin acetate depot) | Long-term outcomes (10 years) | 34 | Probability of disease-specific survival at 10 years was 84%; OS was 78% |
| Nosov <i>et al.</i> ⁷⁹ | Neoadjuvant docetaxel versus RP alone | Long-term bRFS, CSS and OS | 44 | 52.4% reduction of PSA >50% post-CT; 90% CSS in neoadjuvant CT group versus 60.9% in the RP group ($P=0.042$); 68.5% bRFS in neoadjuvant CT group versus 37.7% in the RP groups; 75.5% OS in neoadjuvant CT group versus 54.6% OS in RP |
| Bergstrom <i>et al.</i> ⁸⁰ | Neoadjuvant docetaxel + mitoxantrone | 10-year recurrence-free survival | 57 | 34/54 (63%) PSA recurrence; median time to recurrence 51 months; 63% 2 years-RFS at 2 years, 64% at 5 years, and 29% at 10 years |

ADT: androgen deprivation therapy; bPFS: biochemical progression-free survival; bRFS: biochemical recurrence-free survival; CAB: combined androgen blockade; CR: complete response; CSS: cancer-specific survival; CT: chemotherapy; DVT: deep venous thrombosis; MRI: magnetic resonance imaging; OS: overall survival; pCR: pathologic complete response; PSA: prostate-specific antigen; RP: radical prostatectomy; PR: partial response; RFS: relapse-free survival

at 62% (95% CI: 55–69) versus 50% (95% CI: 44–57) in the ADT only group (adjusted HR: 0.71, 95% CI: 0.54–0.94, $P = 0.017$), results on OS and metastasis-free survival were not yet mature.

Another adjuvant chemotherapy after radical prostatectomy trial was reported in the Scandinavian Prostate Cancer Group (SPCG) 12 trial, a Phase III study that randomized 459 patients who underwent radical prostatectomy to receive either docetaxel 75 mg m⁻² every 3 weeks for 6 cycles (without corticosteroids or ADT) or to undergo

surveillance.⁸⁹ The primary endpoint of the study was biochemical recurrence of a rising PSA >0.5 ng ml⁻¹. The patients were enrolled if they had high-risk disease postprostatectomy defined as having either a pT2 tumor with Gleason score 4 + 3 or 8–10 and positive margins or any pT3a tumor with Gleason score of at least 4 + 3 or any Gleason Grade 4 tumor with pT3b, or any node-positive tumor if Gleason Grade 4 or higher. During a median follow-up of 56.8 months, the rate of biochemical progression was higher in the docetaxel arm (103 men,

Table 3: Adjuvant chemotherapy studies

| Study | Adjuvant CT | Primary endpoint | Number of patients (n) | Result |
|----------------------------|---|---|------------------------|--|
| RTOG 0521 ⁸⁶ | Randomized: ADT + radiotherapy + docetaxel + prednisone versus ADT and radiotherapy | OS | 563 | Adjuvant CT improved the OS from 89% to 93% at 4 years; 4% absolute benefit of 4%; 30% reduction in risk of death favoring adjuvant docetaxel |
| GETUG-12 ⁸⁸ | Randomized: ADT + docetaxel + estramustine versus ADT alone | RFS in the intention-to-treat population | 413 | 62% 8-year RFS in ADT plus docetaxel and estramustine versus 50% in the ADT only group (HR: 0.71, 95% CI: 0.54–0.94, $P=0.017$) |
| SPCG12 trial ⁸⁹ | Randomized: docetaxel without corticosteroids or ADT versus surveillance | Biochemical recurrence of a rising PSA >0.5 ng ml ⁻¹ | 459 | 103 men (44.8%) in the docetaxel arm had biochemical progression after median follow-up of 56.8 months versus 89 men (38.9%) in the surveillance arm |
| SWOG 9921 ⁹⁰ | Randomized: mitoxantrone + prednisone + ADT versus ADT | OS | 983 | 72% 10-year disease-free survival rate in both arms; 87% 10-year OS in ADT alone versus 86% for ADT plus CT |

ADT: androgen deprivation therapy; CI: confidential interval; CT: chemotherapy; GETUG: Genito-Urinary Group and the French Association of Urology; HR: hazard ratio; OS: overall survival; PSA: prostate-specific antigen; RTOG: Radiation Therapy Oncology Group; RFS: relapse-free survival; SPCG: Scandinavian Prostate Cancer Group; SWOG: Southwest Oncology Group

44.8%) than the surveillance arm (89 men, 38.9%) in the intention to treat analysis ($P = 0.78$ for comparison of Kaplan–Meier curves). The authors concluded that there was no benefit and potential harm from the addition of docetaxel in high-risk PCa patients after prostatectomy.

Another adjuvant trial postprostatectomy was recently reported; results of SWOG 9921 trial were recently presented.⁹⁰ This trial was designed in 1999 to evaluate the role of the addition of chemotherapy (6 cycles of mitoxantrone/prednisone) to 2 years of adjuvant ADT in high-risk PCa after radical prostatectomy. A total of 983 patients were randomized in a 1:1 ratio to either ADT alone or ADT and 6 cycles of mitoxantrone/prednisone. At a median follow-up of 11.2 years, there was no evidence that mitoxantrone improved PCa-specific survival when added to 2 years of ADT and increased the risk of leukemia. The 10-year disease-free survival rate was 72% in both arms, and 10-year OS was 87% for ADT alone compared with 86% for ADT plus chemotherapy. Given the noncontemporary use of an older drug (mitoxantrone), it is unlikely that the findings would result in any meaningful change in the standard practice of adjuvant therapy postprostatectomy.

CONCLUSIONS

Chemotherapy in PCa has evolved from that of palliation to improvement in OS. Docetaxel has been the mainstay of chemotherapy that has been used for PCa with cabazitaxel as second-line therapy. Varying combinations with docetaxel have been attempted but not found to be successful. Changes in the treatment landscape with institution of docetaxel earlier in the disease course have made it the default standard of care for metastatic hormone-sensitive or castration-sensitive PCa along with ADT. Further evaluation as neoadjuvant and adjuvant therapy especially for men with locally advanced high-risk disease is currently underway. Mechanisms of resistance to chemotherapy is discussed extensively elsewhere⁹¹ but certainly an area of active investigation as well. The promising results of decades of investigation have finally changed the treatment paradigm in PCa.

AUTHOR CONTRIBUTIONS

RN, JEA, and JBAC designed the study, wrote the manuscript, had access to all data, and reviewed the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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