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Hot Topic

Early use of chemotherapy in metastatic prostate cancer

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ABSTRACT

Since 2010, five new antineoplastic therapies have been FDA approved for the treatment of metastatic prostate cancer. With additional treatment options, questions arose about the optimal sequence of these agents. Until recently, chemotherapy has been deferred until later in the disease course in favor of next-generation androgen deprivation therapy. Prior to the development of abiraterone acetate and enzalutamide, clinical trials were opened investigating the combination of chemotherapy with androgen deprivation therapy in patients with metastatic hormone-sensitive disease. With the development of new oral therapies used to treat castration-resistant disease, these trials were largely forgotten or felt to be obsolete. Recently, two trials have been reported showing an overall survival benefit of the early use of chemotherapy in patients with hormone-naive prostate cancer, changing the treatment paradigm for metastatic disease. Here we review the history of chemotherapy in treating prostate cancer and the emerging evidence favoring its use as first-line therapy against metastatic hormone-sensitive disease.

Introduction

Prostate cancer is the most common non-skin cancer in men with over 180,000 new cases expected to be diagnosed in 2016.[1] Local therapies for early-stage disease are effective leading to favorable clinical outcomes. When metastatic disease develops, patients are initially treated with androgen deprivation therapy (ADT). Although response rates to ADT are near 80%, inevitably, the cancer learns to grow in a low testosterone environment, leading to a clinical state of castration resistance. Docetaxel chemotherapy was among the first treatments to be Food and Drug Administration (FDA) approved for metastatic castration-resistant prostate cancer (mCRPC) based on a survival benefit. When docetaxel became the standard-of-care (SOC) treatment for mCRPC in 2004, several trials were subsequently launched to assess the effect of docetaxel in metastatic hormone-naive disease, but it would be a decade before the data matured. During the years when the trials were ongoing, preclinical research focused on mCRPC and reaffirmed that androgen receptor (AR) signaling continued to drive tumor growth upon developing castration resistance. The next generation of ADT (i.e. abiraterone acetate, enzalutamide) was then developed and shown to prolong survival in mCRPC patients. AR-targeted therapies gained favor over chemotherapy based on perceived safety profile and novelty, a trend many clinicians felt would continue. Docetaxel, and subsequently cabazitaxel, were then deferred until late-stage disease and trials involving chemotherapy in hormone-sensitive disease were all but forgotten.

Recently, these chemotherapy trials in patients with metastatic hormone-naive prostate cancer have been published. The long-awaited evidence favored the use of chemotherapy with ADT, which has changed the treatment paradigm for metastatic prostate cancer. Here we review the history of chemotherapy in prostate cancer and discuss the evidence for its use as frontline therapy in combination with ADT for metastatic disease.

History of chemotherapy in patients with mCRPC

After the pioneering work of Charles Huggins showed an inhibitory effect of testosterone suppression on prostate cancer growth, the history of treatment for metastatic prostate cancer began with surgical castration (i.e. orchiectomy).[2] In the 1960s, drug therapy evolved after the Veterans Administration Cooperative Urologic Research Group (VACURG) demonstrated that oral estrogen, in the form of diethylstilbestrol, was as effective as orchiectomy in treating prostate cancer.[3] Although orchiectomy remained the gold standard of treatment through the 1980s, the VACURG findings fostered the notion of medical castration as an alternative to orchiectomy. Flutamide, an oral, non-steroidal antiandrogen was then developed, which could inhibit AR signaling through receptor blockade. During the 1970s, flutamide showed clinical efficacy against prostate cancer.[4] Subsequently, the structure of luteinizing

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hormone-releasing hormone (LHRH) was identified. In 1980, intranasal buserelin was administered to the first patient with prostate cancer, which resulted in a significant decrease in serum testosterone.[5] However, a transient rise in serum androgens was noted which caused concern for possible disease flare. The combination of an antiandrogen (flutamide) with an LHRH agonist (LHRH ethylamide [HOE-766]) prevented this flare phenomenon, resulting in a decrease in prostatic acid phosphatase levels and symptomatic improvement in 9 of 10 patients.[6] In the decades that followed, several generations of antiandrogens (nilutamide, bicalutamide) and LHRH agonists (leuprolide, goserelin, triptorelin) have been used to treat prostate cancer. Androgen suppression via LHRH agonists has since remained the backbone of therapy for metastatic hormone-sensitive disease. Once progression occurs on AR targeted therapies, treatment options prior to 2004 were limited. This led several investigators to test different therapeutic approaches, including chemotherapy, in patients with mCRPC.

Clinical trials involving the use of cytotoxic chemotherapy in advanced prostate cancer began in the 1950s with alkylating agents. The response rates to chemotherapy were typically low and results were difficult to interpret due to the small number of patients and lack of meaningful endpoints.[7] This prompted many thought leaders in the field to suggest that prostate cancer was a chemotherapy-resistant disease.[7–9] Due to the perceived lack of survival benefit, chemotherapy trials were then designed to assess palliation endpoints. In 1996, mitoxantrone in combination with prednisone was the first FDA-approved chemotherapy for mCRPC based on symptomatic improvement.[10] Mitoxantrone is a topoisomerase II inhibitor given intravenously (12 mg/m^2) on a 3-week schedule. Side effects range from mild (nausea, alopecia) to more severe (dose-dependent cardiomyopathy). Prostate-specific antigen (PSA) responses were low and no survival benefit was shown.[10–12] Although mitoxantrone achieved palliation benefits, there was no chemotherapeutic agent that improved overall survival in prostate cancer until 2004.

Docetaxel and paclitaxel were developed in the early 1990s.[13] In prostate cancer, preclinical data suggested a potential synergistic effect of estramustine and docetaxel.[14] Several early-phase trials found the combination to be safe and clinically active against castration-resistant prostate cancer.[15–17] SWOG9916 was a randomized Phase III trial in mCRPC patients, which compared docetaxel + estramustine to mitoxantrone with both arms containing a steroid backbone. The 21-day cycle of docetaxel (60 mg/m^2 given on Day 2) with estramustine (280 mg three times daily on Days 1–5) significantly increased the median overall survival by 1.9 months and included improved PSA and objective responses.[18] Due to concerns about increased thromboembolic events caused by estramustine, docetaxel was studied as a single agent and shown to have activity in advanced prostate cancer.[19,20]

Tannock et al., in the pivotal Phase III TAX327 trial involving mCRPC patients, showed a 2.4-month increase in overall survival in the docetaxel (given every 3 weeks) + prednisone arm compared with mitoxantrone + prednisone.[21] Docetaxel (75 mg/m^2) given every 3 weeks also had a significant survival advantage over weekly docetaxel (30 mg/m^2). Use of docetaxel either weekly or every 3 weeks had increased adverse events (peripheral edema, neuropathy, gastrointestinal toxicities) compared with mitoxantrone, but significant reductions in pain and improved quality of life measures were noted. Although use of single-agent docetaxel was FDA approved in 2004 and most clinicians stopped using estramustine, it was not until 2008 that docetaxel was compared head-to-head with docetaxel + estramustine. One hundred and fifty men with mCRPC were randomly assigned to docetaxel (35 mg/m^2 on Days 2 and 9 every 21 days) and prednisone (10 mg daily) with or without estramustine (280 mg on Days 1–5 and 8–12 every 21 days), which resulted in no difference in PSA response or overall survival.[22] The combination also resulted in increased toxicities confirming the clinical practice to use docetaxel as a single agent. Both SWOG9916 and TAX327 are credited with establishing docetaxel given on a 3-week schedule as first-line chemotherapy in metastatic prostate cancer after developing disease progression on conventional hormonal therapy.

The exact mechanism of action of docetaxel in prostate cancer is unclear. Docetaxel is generally known to stabilize microtubules preventing cellular division and resulting in cell-cycle arrest. However, more recent evidence suggests that docetaxel can inhibit the nuclear translocation of AR in prostate cancer.[23] Resistance to docetaxel may develop through several mechanisms including drug efflux, alterations in microtubule structure, activation of survival pathways, and changes in the tumor vasculature.[24–27] In an effort to overcome resistance, investigators looked at combining targeted therapies with docetaxel. Multi-tyrosine kinase inhibitors and VEGF-targeted therapies did not show significant efficacy in several trials against prostate cancer.[28–32] Although pilot studies suggested thalidomide may have added benefit when given with docetaxel, a randomized Phase III trial with lenalidomide did not increase survival.[33–35] Natural products (i.e. calcitriol, vitamin D analogues), small molecule inhibitors, and vaccination have not improved upon the survival advantage of docetaxel alone.[36–43] With no clear combination strategy evident, attempts were made to identify a second-line chemotherapy for castration-resistant prostate cancer. Several Phase II studies explored combinations of platinum agents with and without antimetabolites, but without a larger Phase III study, these treatments have not been clinically utilized.[44–46] It would not be until 2010 that a chemotherapy would become FDA approved for mCRPC following progression on docetaxel.

Cabazitaxel, a semi-synthetic member of the taxane family, was developed as a derivative of docetaxel. Two potential advantages of cabazitaxel over docetaxel are: (1) the diminished affinity for P-glycoprotein, an important drug efflux pump and (2) the ability to cross the blood–brain-barrier.[47] In the Phase III trial, TROPIC, men with mCRPC and prior exposure to a docetaxel-containing regimen were randomized to receive cabazitaxel (25 mg/m^2 every 3 weeks) or mitoxantrone (12 mg/m^2 every 3 weeks), with both groups receiving prednisone. Cabazitaxel significantly improved overall survival by 2.4 months, which was the primary endpoint of the study.[48] With additional follow-up, 2-year survival was also improved in the cabazitaxel group with similar palliation benefits observed when compared with mitoxantrone.[49] Based on the results from TROPIC, cabazitaxel became the FDA approved, second-line chemotherapy after progression on docetaxel. Mitoxantrone was relegated to third-line chemotherapy.

Despite advances in chemotherapy for castration-resistant disease, researchers continued to focus their efforts on targeting the AR pathway based on the observation that prostate cancer, following progression on conventional ADT, still continued to have an intact AR signaling axis.[50] Subsequently, therapeutic agents that attenuated AR signaling via alternative mechanisms were explored. Inhibitors of extratesticular androgen synthesis, including ketoconazole and abiraterone acetate, suppressed androgen production from the adrenal glands. Ketoconazole can inhibit adrenal androgen synthesis via its effect on multiple cytochrome p450 enzymes and was shown to decrease PSA levels in patients with prostate cancer.[51] However, the ability of ketoconazole to inhibit cytochrome P450 (CYP) – 3A may result in significant drug interactions, particularly with psychotropic medications.[52] Abiraterone acetate is an irreversible inhibitor of the CYP-17, a key enzyme in androgen biosynthesis. After initially being FDA approved for use in mCRPC patients following chemotherapy, abiraterone acetate (1000 mg by mouth daily with prednisone 5 mg twice daily) demonstrated a survival benefit versus placebo (prednisone alone)

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