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ADVANCES IN MEDICAL MANAGEMENT OF PROSTATE CANCER: A REVIEW

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ABSTRACT
Prostate cancer remains the number 1 male cancer in terms of incidence after skin cancer, and the number 2 cancer mortality; with a seemingly increasing trend in advanced and resistant prostate cancers. This report shows to outline the progression of prostate cancer medical management from its earliest days of discovery to present day experimental treatments. We show its beginnings with surgical castration and its slow gradual move towards medically, Sophisticated treatment protocols. At first orchidectomy was the first-choice procedure but proved to be too crass. Luteinizing hormone releasing hormone (LHRH) agonists complemented by androgen receptor antagonists were presented as the solution and used in conjugation with radiotherapy as a frontline management of metastatic disease but patients often relapsed citing to the treatment's inability to withstand time. Cytotoxic therapy was then introduced and proved to prolong overall survival with patients of newly diagnosed prostatic growth; agents such as docetaxel became one of the most commonly used due to its success with patients. However not all found success so there is a push to further specialize treatments that encompass the rest, particularly the older and late stage population. Recent FDA approvals of vaccine therapies, next generation hormonal treatments, and radiation particle-based therapies have shown varying progress ranging from a reduction in PSA levels to suspending symptoms. Currently there are several drugs undergoing clinical trials which boast remarkable results with individuals after receiving cytotoxic therapy, some of which are vector-based therapeutic cancer vaccine and monoclonal antibodies. Today researchers are working towards increasing the survival rate amongst prostate cancer patients; it is no longer a death sentence as new drugs are consistently outdoing their predecessors becoming more effective in the long term.

KEYWORDS: Prostate cancer; metastatic castration-resistant prostate cancer; advanced prostate cancer.

INTRODUCTION
Among American men, prostate cancer is the most common non-cutaneous cancer and the second leading cause of cancer-related death in men. In 2018, an estimated 164,690 new cases of prostate cancer were diagnosed, and 29,430 deaths resulted.[1] The three undisputed risk factors include older age greater than 65 years, race – with African American men having the highest risk, and positive family history.[2]

In this paper, we review the management of prostate cancer, the outcomes, challenges and advantages of medical management of this ailment.

MATERIALS AND METHODS
We conducted a review of literature and articles on evidence-based management of prostate cancer with particular reference to medical management and management of advanced c prostate cancer. The following search items were used: prostate cancer, advanced prostate cancer, castration-resistant prostate cancer, and clinical trial. Cross-sectional, observational, and randomized control trials' literature on the subject published between 2003 and 2018 served as the main sources of information. These works were obtained from the commonly used medical databases such as PubMed (Medline), New England Journal of Medicine and Google Scholar.

Data Analysis
The search generated many related articles; however, this paper was limited to the 25, which included randomized and quasi-randomized trials on medical management of advanced prostate cancer, which met at least one of the following inclusion criteria: (i) comparison between orchiectomy and chemical castration; (ii) cytotoxic drugs in management of prostate cancer; (iii) comparison between the cytotoxics used in management of prostate cancer; (iv) recently approved drugs; (v) drugs under clinical trials for advanced prostate cancer.

A review of the effectiveness of Prostatectomy
Prostatectomy has long been the mainstay of management of patients with prostate cancer, however,

with development of medical therapies, the use of medications is far outweighing surgeries. Various surgical approaches has been proposed and utilized, however, treatment is individualized on the severity of the cancer and the patient's age.[3] Yoo, et al. studied the long-term outcomes of 111 prostate cancer patients receiving robotic-assisted radical prostatectomy (RARP) with a follow-up at 103.43 months. The studied showed the mean 8-year cancer specific survival and overall survival to be about 97% and 96% respectively.[4] 3 patients reportedly died from malignancy and 2 patients died from non-cancerous cause. Postoperative risk factors have been widely studied; and include complications of lymphocele, thromboembolic events, ureteral injury and nerve injury.[3,4,5]

Orchiectomy versus chemical castration

Following the discovery by the physician, Charles Huggins in 1941 that surgical removal of the testes led to regression of advanced prostate cancer following his observation that testosterone activates the androgen receptor, which determines growth and proliferation of prostatic tissues; this became a standard procedure for decades. However, with advances in medication, "surgical castration" has largely been opted out for "chemical castration", which uses luteinizing hormone releasing hormone (LHRH) agonists, such as leuprolide, or antagonists such as degarelix; frequently complemented by androgen receptor antagonists, such as bicalutamide, nilutamide, and flutamide. This approach are often used as an adjunct to radiotherapy for more aggressive localized prostate cancer and for the frontline management of metastatic disease.[3] A study done by Lin et al. comparing orchiectomy and chemical castration in patients with advanced prostate carcinoma showed that in patients with good prognosis, the results of progression-free survival and overall survival rate were similar in both groups; however, in patients with poor prognosis, those who received orchiectomy survived significantly longer than those in the medical castration group.[6] Though effective, side effects of medical castration include fatigue, hot flashes, insomnia, decreased libido, mood changes, and decreased bone density.[3]

Unfortunately, medical castration often fail after a period of time, and result in a state termed metastatic hormone-refractory prostate cancer (mHRPC), a progression in the disease despite androgen depletion therapy (ADT) and the appearance of new metastases.[7]

The use of cytotoxic drugs

The early 2000s saw the introduction of cytotoxic drugs in the management of advanced prostate cancer. In 2005, docetaxel was approved for advanced prostate cancer, after it was shown to prolong overall survival in mHRPC and improve survival in a phase III studies in patients with newly diagnosed metastatic disease. A multicenter randomized phase II study of two schedules of docetaxel, estramustine and prednisone (DEP) versus mitoxantrone plus prednisone (MP) in patients with metastatic hormone-refractory prostate cancer involving 127 patients showed that the DEP combination was superior to the MP in HRPC patients.[8] Most recently, data from the CHAARTED (Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) trial comparing straightforward chemotherapy plus androgen deprivation therapy (ADT) to ADT alone in men with metastatic prostate cancer was reported and showed men with high-volume disease (defined as visceral metastasis and/or ≥4 bone metastases) had a median overall survival of 49.2 months with docetaxel plus ADT compared with 32.2 months with ADT alone, a difference of 17 months;[9] suggesting that patients with high-volume, androgen-dependent disease may benefit from up-front docetaxel.

In contrast, another study of similar setup proved otherwise. The GETUG-AFU 15 trial reported no difference in overall survival between patients with non-castrate metastatic disease receiving ADT plus docetaxel versus ADT alone, with the median survival rate at 58.9 months in the group given ADT plus docetaxel and 54.2 months in the group receiving ADT alone.[10] However, the researchers believe this may be due to differences in patient populations and post progression treatments. While clinical experience strongly supports that some patients with metastatic disease will benefit from early use of cytotoxic chemotherapy, it is best to be offered on a case-by-case basis.[11]

Delaying cytotoxic therapy until second-line hormonal options have been explored as these therapies focused more on improving quality of life rather than prolonging it.[11] Given the limitations of docetaxel-based chemotherapy and the growing rise of docetaxel refractory HRPC, research has been done using combination agents with docetaxel. However, this has proved to be futile; antiangiogenic drugs such as sunitinib and avastin did not improve overall survival compared with a placebo in docetaxel-refractory mHRPC but did result in improvements in median progression-free survival in phase II trials.[12] Similarly, bone microenvironment targeting agents such as zibotentan, atrasentan, and dasatinib were each tested in phase III trials and all failed to improve on standard docetaxel.[13] These results suggest that a subset of patients did benefit, and that moving forward, clinical trial designs that incorporate predictive biomarkers to detect patients most likely to respond will be necessary to developing novel treatment strategies.[11] A study by Ross, et al. demonstrated clinical responses to platinum-based therapy in combination with the agents. They tested the activity of docetaxel with carboplatin in patients that had progressed during or within 45 days after completion of docetaxel therapy. The results showed PSA declines of ≥50% noted in 18% of patients, and measurable responses occurred in 14% of patients, supporting their claim that carboplatin has the potential to overcome docetaxel resistance mechanisms.[14]

Recent FDA approvals

Though the cytotoxic agents are accommodating for metastatic prostate cancer, novel classes of agents have been developed for mHRPC. They include vaccine therapies, next generation hormonal treatments, and radiation particle-based therapies. An FDA approved autologous dendritic cell vaccine therapy, sipuleucel-T, administered as a subcutaneous injection, has been promising, with few side effects as mild infusion reactions and chills.[3] The vaccine proliferates within the body by isolating the leukocytes of the patient and ensuing stimulation of these cells in the presence of prostate cancer antigens.

In a randomized, double-blind, placebo-controlled trial, the immunologic treatment was given to a total of 127 patients who were carefully selected. An improvement in the endpoint of overall survival was demonstrated, however, there was no improvement in progression of disease.[15] Researchers have identified the lack of surrogate endpoints for survival as a challenge towards designing trials of sipuleucel-T.

Biosynthesis of extragonadal androgen may contribute to the progression of castration-resistant prostate cancer. Two next generation hormonal treatments approved for the treatment of cHRPC are abiraterone and enzalutamide. The former, a CYP17-lyase inhibitor, is a potent androgen synthesis inhibitor that serves to stop intratumoral androgen production; while the former, similar to abiraterone in structure, is a competitive androgen receptor antagonist, and has been demonstrated to inhibit nuclear translocation of the protein complex, thus, targeting androgen-receptor-signaling, a major drive of prostate cancer growth.[3] Abiraterone has been reported to cause potential drop in serum cortisol, requiring replacement with prednisone.

De Bono, et al. studied the effects of abiraterone on overall survival among patients with mCRPC who have received chemotherapy. The double-blind study involved 1195 patients, in which they were randomly assigned into two groups, with one group receiving abiraterone acetate-prednisone and the other group placebo-prednisone. After a median follow-up of 12.8 months, overall survival was longer in the abiraterone acetate-prednisone group than in the placebo-prednisone group. Other endpoints including time to PSA progression, progression-free survival, and PSA response rate showed statistically significant improvements in the treatment group.[16] However, fluid retention, hypertension, and hypokalemia were more frequently reported in the study group.

In determining if enzalutamide prolongs survival in men with castration-resistant prostate cancer after chemotherapy, a double-blind, placebo-controlled trial of 1199 men with mCRPC was conducted by Howard, et al. It was found that enzalutamide significantly prolonged the survival of men with metastatic castration-resistant prostate cancer after chemotherapy, with a reduction in the PSA level, increased quality of life, increased time to PSA progression and time to the first skeletal-related event, as compared to the placebo group.[17] However, the study was stopped after a planned interim analysis at the time of 520 deaths. Rates of fatigue, diarrhea, and hot flashes were higher in the enzalutamide group and seizures was reported in five patients.[17]

The most recent drug approved for mCRPC is radium-223, an alpha-emitting radio particle.[3] Radio particles have a longstanding history with advanced prostate cancer with beta-emitting radioisotopes such as strontium or samarium administered to patients who needed soothing. These radio particles localize to the bone and deliver radiation to the adjacent tumor tissue.[3] Radium-223 dichloride targets bone metastases with alpha particles.

A randomized double-blind, placebo-controlled study involving 921 patients who had either received, or were not eligible to receive, or declined docetaxel, was utilized to assess the efficacy of radium-223.[18] A prespecified interim analysis was conducted when 314 deaths occurred and an updated analysis when 528 deaths had occurred before crossover from placebo to radium-223. At the interim analysis, which involved 809 patients, radium-223 significantly improved overall survival with a median of 14.0 months vs. 11.2 months with the placebo group.[18] The updated analysis involving 921 patients confirmed the radium-223 survival benefit with the median of 14.9 months vs. 11.3 months with placebos, as well as associated low myelosuppression rates and fewer adverse events.[18] However, though it has shown major improvement in stabilization of health for men with prostate cancer, radium-223 does not have convincing statistics for improved survival for patients with mCRPC.[3]

Drugs that are currently undergoing clinical trial

Currently, only a few drugs are under clinical trial for advanced prostate cancer. Notably among them are discussed below.

JN-56021927, a second-generation oral androgen receptor antagonist, acts by binding to the receptor and blocking nuclear translocation. In a phase II study, PSA response was observed in 91% of nonmetastatic treatment cases, 88% of metastatic treatment cases, and 24% of metastatic post-abiraterone cases.[4] The phase III studies SPARTAN and ATLAS are evaluating JN-56021927 in patients with nonmetastatic CRPC and high-risk prostate cancer respectively, and future trials in combination with abiraterone are planned.[4]

Carboplatin, a platinum-based drug, is reported to induce PSA reduction of ≥50% in patients with prostate cancer that progressed after docetaxel chemotherapy.[14] Everolimus, an mTOR inhibitor, when added to carboplatin has demonstrated increased antitumor effects

and overcame resistance to chemotherapy alone.[19] A phase II study conducted to evaluate the efficacy of combination therapy using carboplatin and everolimus in metastatic progressed patients showed no pharmacokinetic interaction, and an increased median overall survival in mCRPC patients who progressed under docetaxel-based chemotherapy.[20]

Ipilimumab, a monoclonal antibody that blocks the activity of a cytotoxic T-lymphocyte-associated protein, CTLA-4, was approved by the FDA for the treatment of melanoma in 2011. Clinical studies suggest radiotherapy may activate the immune system in patients with prostate cancer so a phase III trial of ipilimumab with radiotherapy for mCRPC patients was initiated.[21,22] However, this did not show any improvement in overall survival (11.2 months vs. 10.0 months) in comparison with radiotherapy followed by placebo.[23]

Prostvac is a vector-based therapeutic cancer vaccine. A phase II study reported prostvac was well tolerated and it improved overall survival compared with control vectors (25.1 months vs. 16.6 months) in patients with minimally symptomatic CRPC.[24] Another phase II study evaluating the effect of combination of docetaxel and prostvac failed to show improvements in overall survival.[25] Currently, combination trials with abiraterone, ADT, sipuleucel-T, and prostvac are underway.[4]

CONCLUSION

Researchers continue to explore new strategies to treat advanced prostate cancer, and with more funds going into research, we see a bright future with prostate cancer in hindsight. A consortium led by Monash University has developed a new way to grow tumors in the lab, derived from donor patients, for testing the efficacy of a variety of drug combinations more quickly and efficiently than ever before. However, we believe that improved detection and early management can effectively curb this problem. It is possible that we are living in the generation where prostate cancer will no longer be a threat to men.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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