Title: Understanding the Current Therapeutic Landscape for Advanced Prostate Cancer

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Take-Home Points:

- Recent advances in treatment have greatly prolonged survival in advanced prostate cancer
- Multiple modalities are now available for the treatment of advanced prostate cancer
- Questions remain regarding optimal combination and sequencing of therapies

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Abstract

Treatment of advanced prostate cancer has improved rapidly in the past two decades with the introduction of many new therapeutics including several entirely new therapeutic classes. Whereas androgen deprivation therapy was previously the first and only line of treatment available, modern therapy also routinely employs second-generation anti-androgens, chemotherapy, immunotherapy, radiopharmaceuticals, bone modifying agents, and poly(ADP-ribose) polymerase (PARP) inhibitors, with a resulting substantial increase in patient survival. This review aims to summarize the current treatment landscape for advanced prostate cancer, with a particular focus on hormone-refractory (also known as 'castration resistant') prostate cancer (HRPC), and we hope will serve as a practical guide for clinicians and trainees.

Introduction

Prostate cancer is one of the most common malignancies in men, accounting for an estimated 249,000 cases in the United States in 2021. Overall, one out of eight men will be diagnosed with prostate cancer in their lifetime. Advances in treatment combined with earlier detection have contributed to a remarkable drop in the death rate: from a peak of 39.3/100,000 in 1993 to 18.4/100,000 in 2019, the most recent year with available data.[1] While these statistics illustrate the enormous impact of prostate cancer in terms of its high prevalence and mortality, and the substantial progress that has been made in the field, they belie vast differences in outcomes – while localized, low- to

intermediate-risk prostate cancer is associated with a 3% 10-year disease-specific mortality,[2] metastatic prostate cancer is invariably progressive and ultimately fatal. Metastatic prostate cancer, when diagnosed *de novo*, is nearly universally susceptible to testosterone depletion, and therefore termed 'hormone sensitive.' Since the discovery of surgical castration with bilateral orchiectomy as an effective therapy in the early 1940s,[3] castration has been the first line of treatment for advanced prostate cancer. Castration, which is defined as a decrease in serum testosterone levels to less than 50 ng/dL, is now typically performed chemically through inhibition of the hypothalamic pituitary-gonadal signaling pathway leading to decreased androgen production. While androgen deprivation therapy (ADT) is effective for a period of time, on average 7.4 months,[4] metastatic prostate cancer ultimately acquires resistance to ADT monotherapy and progresses to the lethal state known as metastatic hormone-refractory prostate cancer (also called metastatic 'castration resistant') prostate cancer (mHRPC).[5] Prior to 2004 and the approval of docetaxel, there were no life-prolonging treatments for mHRPC, and the median survival from the development of castration resistance was approximately 16 months.[5]

In the past 20 years, since the approval of docetaxel as the first effective treatment for mHRPC, and especially in the last 10 years since the approval of abiraterone as the first second-generation anti-androgen, treatment of mHRPC has undergone a revolution resulting in the extension of median time until the development of castration resistance to approximately 33 months,[4] and overall survival (OS) from diagnosis is now a median

of 53 months or more.[4] Modern treatment is likely to incorporate multiple lines of therapy including combined androgen blockade using second-generation anti-androgens, immunotherapy, radiopharmaceuticals, chemotherapy, and others. In addition, new advances on the horizon promise additional options for patients with advanced prostate cancer.

Androgen Synthesis Inhibitor

Abiraterone acetate is the first approved second-generation anti-androgen and the only androgen biosynthesis inhibitor in clinical use. Abiraterone, the active metabolite of abiraterone acetate, is a selective inhibitor of cytochrome P450 c17, an enzyme involved in testosterone synthesis in the testes, adrenal glands, and prostate tissue, in addition to its role in mineralocorticoid synthesis.[6] When added to androgen deprivation therapy (addition of any second-generation anti-androgen is termed ‘intensification’ of ADT), abiraterone further suppresses intratumoral testosterone levels. Although initially approved at a dose of 1000 mg daily on an empty stomach, subsequent work tested a dose of 250 mg daily with a low-fat meal and demonstrated non-inferiority with respect to PSA response rates and time until PSA progression.[7] Abiraterone is always administered with physiologic doses of prednisone to replace lost mineralocorticoid. This combination is typically well-tolerated, but side effects include hypokalemia, fluid retention, hypertension, hepatotoxicity, and arrhythmia - particularly atrial fibrillation. Use of long-term prednisone, even at low doses, is associated with decreased bone mineral density and metabolic syndrome.

Abiraterone was initially approved in the post-chemotherapy mHRPC setting, where it significantly increases median OS versus placebo.[8] Since approval, multiple trials have demonstrated efficacy earlier in the disease course, including in the pre-chemotherapy mHRPC setting.[9,10] Subsequently, the pivotal LATTITUDE and STAMPEDE trials demonstrated improved survival versus placebo in previously untreated patients with metastatic hormone-sensitive prostate cancer (mHSPC),[4,11] although with life expectancy depending strongly on disease burden and disease-specific risk factors such as PSA and Gleason score at diagnosis. Longer-term follow-up of a cohort of STAMPEDE trial participants with high-risk non-metastatic disease found a survival benefit with the addition of abiraterone to ADT for a 24-month course of treatment.[12] Overall, abiraterone has now demonstrated efficacy in all stages of advanced prostate cancer, and is widely considered first-line standard of care in these settings.

Non-steroidal Anti-Androgens

Non-steroidal anti-androgens inhibit androgen signaling by preventing androgen binding to Androgen Receptor (AR), thereby blocking AR activation. Although drugs in this class have been in clinical use for over 20 years, in the past decade a second generation of non-steroidal anti-androgens has been introduced with markedly increased potency and selectivity and increased efficacy when combined with ADT in advanced prostate cancer. There are three currently approved second-generation non-steroidal anti-androgens: enzalutamide,[13] apalutamide,[14] and darolutamide.[15] All three have

overlapping side effect profiles, which are notable for fatigue, liver injury, neutropenia, hypertension, and increased risk of seizures and falls. Apalutamide is unique in its association with hypothyroidism, hyperglycemia, hypertriglyceridemia, fractures, rash, abdominal pain, and diarrhea. Darolutamide is uniquely associated with pulmonary embolism, cardiac arrest, and heart failure, although all are very rare. Interestingly, darolutamide seems to have a reduced association with seizures/falls compared with enzalutamide and apalutamide, which may be due to its reduced CNS penetration.[16]

For patients with non-metastatic HRPC and PSA doubling time <10 months, separate phase III, randomized controlled trials have shown improved OS when treated with either enzalutamide[17], darolutamide[16,18], or apalutamide[19,20] in conjunction with ADT, and therefore any of the three is an appropriate standard of care in these patients. For those with mHSPC, both enzalutamide[21] and apalutamide[22] in conjunction with ADT extend OS and are acceptable treatment options. Darolutamide would be expected to have a similar effect, but this has not been tested. For patients with mHRPC, enzalutamide has shown improved OS both pre- [23] and post-chemotherapy,[24] while neither darolutamide nor apalutamide has been evaluated in this setting.

In general, the second-generation non-steroidal anti-androgens are acceptable alternatives to abiraterone. There is no data to suggest the superiority of one agent

over another, therefore it is reasonable to select an agent based on the side effect profile. In the absence of a clear preference based on side effects, we typically favor abiraterone based on cost savings (abiraterone is available in generic form) and results suggesting improved response rates to enzalutamide administered in the second line after abiraterone compared with the reverse order.[25] An outstanding question is whether or not abiraterone should be combined with a second-generation non-steroidal anti-androgen at any stage of disease. Two large trials, including an arm of the STAMPEDE trial, are currently ongoing to answer this question. For now, in the absence of evidence, we do not offer combination therapy.

Chemotherapy

The taxane chemotherapeutic agents docetaxel or cabazitaxel are both frequently used in metastatic prostate cancer. Taxanes are small molecule microtubule stabilizers, which prevent the dynamic remodeling of microtubules required for mitosis and cell division.[26] They may also specifically antagonize androgen signaling.[27] Prednisone is usually co-administered with docetaxel, largely for historical reasons but this combination may have increased efficacy.[28] Taxane side effects can be severe and include cytopenias, nausea/vomiting, hair loss, hypersensitivity reaction, fluid retention, peripheral neuropathy (less for cabazitaxel), and fatigue.

Three large randomized phase 3 trials have evaluated the use of docetaxel + ADT in mHSPC: STAMPEDE,[29] CHAARTED,[30] and GETUG-AFU-15.[31] STAMPEDE and

CHAARTED found a significant improvement in survival with the addition of docetaxel, while GETUG-AFU-15 found a trend towards improved survival that did not reach statistical significance. A meta-analysis of these trial results found an OS benefit.[32] Importantly, the CHAARTED trial evaluated subgroups of participants with either high volume (defined as visceral metastases or at least four bone metastases with at least one outside the vertebral bodies and pelvis) or low-volume disease, and found a survival advantage only in those with high-volume disease. Docetaxel is commonly administered for 6 cycles of 3 weeks each, per the CHAARTED trial protocol, for patients with mHSPC.[30]

For patients with mHRPC, docetaxel improves survival compared with mitoxantrone,[5] a previously used chemotherapeutic shown to improve quality of life but not to extend survival. Cabazitaxel seems to be equally efficacious as a first-line chemotherapeutic,[33] although docetaxel is still generally preferred because cabazitaxel is effective in the second-line setting as well, while docetaxel has not been tested after cabazitaxel.[34] Notably, cabazitaxel has not been approved by the FDA for use prior to docetaxel. Both docetaxel and cabazitaxel were limited to a maximum of 10 cycles of 3 weeks each in the randomized, phase III TAX 327[5] and TROPIC[34] trials respectively, and are therefore typically continued for up to 10 cycles if tolerated and demonstrating clinical benefit.

Despite extensive investigation and attempts, no other chemotherapeutic agents, either alone or in combination with the taxanes, have demonstrated efficacy in prostate

cancer. Docetaxel has also been investigated in the setting of non-metastatic prostate cancer, without clear evidence of benefit.[32]

Overall, taxane chemotherapy has demonstrated efficacy in mHRPC and high-volume mHSPC. Although second-generation anti-androgens (abiraterone, enzalutamide, darolutamide, apalutamide) are generally preferred first-line options when feasible given their favorable toxicity profiles, chemotherapy is an acceptable alternative with likely similar efficacy. Notably, chemotherapy is often sequenced after progression on second-generation anti-androgens and seems to be effective in this setting based on retrospective analysis,[35] although this has not been formally tested in prospective trials.

An outstanding question is whether docetaxel should be used sequentially or in combination with second-generation anti-androgens. Recently published data from the phase III ARASENS trial demonstrates increased OS with the addition of darolutamide to docetaxel and ADT for patients with mHSPC.[36] Similarly, the PEACE-1 study, a large multifactorial phase 3 trial, shows a significant increase in OS with the addition of abiraterone and prednisone to docetaxel and ADT in patients with mHSPC.[37] However, because both trials had no ADT + 2nd generation anti-androgen comparison group, which is our currently preferred regimen for first-line treatment of mHSPC, it is unclear whether or not combination therapy is truly superior to the current standard of care.

Immunotherapy

The ‘cancer vaccine’ Sipuleucel-T (Provenge) was one of the earliest successes in the then-new field of cancer immunotherapy. Treatment requires the collection of a patient’s circulating mononuclear cells by leukapheresis, activation of these cells through exposure to a recombinant immunogen, and then re-infusion of the activated mononuclear cells into the patient.[38] This treatment is very well-tolerated with the exception of generally mild infusion reactions. Efficacy in mHRPC was demonstrated in the IMPACT trial, which enrolled men with minimally symptomatic disease, and found improved survival with Sipuleucel-T versus placebo.[39] Interestingly, despite the clear survival advantage there was no difference in time to disease progression, leading to the hypothesis that Sipuleucel-T slows the trajectory of cancer progression without causing tumor cell death. A later subgroup analysis found a correlation between lower baseline PSA and improved survival benefit from Sipuleucel-T, supporting the idea that treatment earlier in the disease course allows for longer duration of treatment effect and therefore improved efficacy.[40]

Despite high expectations after the approval of Sipuleucel-T, more recent efforts to harness the immune system to treat prostate cancer, including immune checkpoint inhibition, have been largely disappointing. Two phase 3 trials of the anti-CTLA-4 antibody ipilimumab in mHRPC either pre- [41] or post-chemotherapy[42] found no difference in OS. A phase 2 trial of the anti-PD-1 antibody pembrolizumab in mHRPC post-chemotherapy found a disease control (complete response, partial response, or stable disease) rate of only 10%, regardless of PD-1 expression levels, although the

responses were durable with a median time to progression of 16.8 months.[43] Unpublished data from the IMbassador250 trial of enzalutamide +/- the anti-PD-L1 antibody atezolizumab in advanced HRPC shows no difference in survival.[44] A small, non-randomized trial of combined PD-1 and PD-L1 blockade in mHRPC found an impressive 46.9% disease control rate in a pre-chemotherapy cohort along with a less impressive 13.3% disease control rate in a post-chemotherapy cohort, at the expense of significant toxicity.[45] Notably, response rates in this trial were strongly correlated with higher tumor mutational burden (TMB).

Based largely on data from tumor-agnostic studies with poor representation of prostate cancer, immunotherapy is now approved for all solid tumors with mismatch repair deficiency (dMMR), microsatellite instability (MSI-H), and/or high TMB (≥10 mut/Mb).[46,47,48] In contrast to results in cohorts of unselected patients, the largest retrospective study to date of checkpoint inhibitor monotherapy in prostate cancer patients with dMMR and MSI-H shows greater promise, with a response rate of 43%.[49,50] However, larger trials are needed to confirm these findings.

Overall, Sipuleucel-T is an effective treatment option in patients with mHRPC, especially those with a low disease burden and slow disease progression, while checkpoint inhibitor therapy is a useful option for those with mHRPC and dMMR/MSI-H/TMB-high. The use of checkpoint inhibitor therapy in other settings including combination immunotherapy is experimental at this time, although there may eventually be a larger role for immunotherapy in advanced prostate cancer alone or in combination with other

agents, with many trials ongoing.

Radiopharmaceuticals

There are currently two radiopharmaceuticals for use in prostate cancer: Radium-223, which has been approved since 2013, and Lutetium-177 (^{177}Lu)-PSMA-617 (Lu-PSMA), which has recently been approved.

One of the newest therapeutic agents for advanced prostate cancer is Lutetium-177 (^{177}Lu)-PSMA-617, the first of a novel class of molecularly targeted radiopharmaceuticals, which received FDA approval on March 23, 2022. This agent binds prostate-specific membrane antigen (PSMA), a cell-surface protein frequently expressed by prostate cancer cells, thereby recruiting ^{177}Lu to cancer cells throughout the body. Once in close proximity, beta-particles emitted by ^{177}Lu cause irreversible DNA damage leading to cell death.[51] Because approximately 12% of prostate cancer cases lack PSMA or have significant heterogeneity in PSMA expression,[52] PSMA PET imaging is required prior to treatment to confirm high levels of PSMA at all sites of disease. A recent randomized, open-label phase 3 trial in patients with post-chemotherapy mHRPC found a significant improvement in OS with ^{177}Lu-PSMA-617.[52] Notable side effects include fatigue, cytopenias, and nausea, although toxicity should be interpreted cautiously without data from a blinded trial.

Availability of ^{177}Lu-PSMA-617 is currently limited but is expected to expand rapidly.

Although clearly beneficial in the post-chemotherapy mHRPC setting, additional studies will be necessary to determine the optimal sequencing of therapies including ^{177}Lu-PSMA 617 as well as the utility of combination therapies including ^{177}Lu-PSMA-617.

Radium-223 is an alpha-particle emitting radioisotope that is incorporated in place of calcium in bone stroma, particularly at sites of bone turnover including sites of osteoblastic or sclerotic metastases, thereby delivering focal doses of radiation to sites of skeletal metastatic disease.[53] Radium-223 is generally very well tolerated with the exception of a slightly increased risk of thrombocytopenia and neutropenia, which are occasionally severe, and therefore patients must have adequate bone marrow function prior to treatment.

In patients with mHRPC and 2 or more bone metastases without visceral metastases or lymph node involvement >3 cm, and who are experiencing symptoms from their bone metastases, Radium-223 prolongs survival versus placebo as well as improving quality of life measures and reducing the risk of pathologic fracture.[54] The role of Radium-223 in modern treatment for prostate cancer is somewhat unclear since it was developed prior to the introduction of the second-generation anti-androgens and has never been tested in sequence with current first-line therapies, with the exception of use after docetaxel in mHRPC where it retains efficacy. Overall, Radium-223 is a reasonable option for patients with mHRPC confined to bone, either before or after chemotherapy.

Radiotherapy

In addition to radiopharmaceuticals, there is increasingly a role for traditional radiotherapy (RT) in select cases of metastatic prostate cancer. There are currently three paradigms for the use of RT in advanced prostate cancer: palliation of painful sites of metastasis to bone (this use is well-established)[55], prostate-directed RT, and oligometastatic RT.

The STAMPEDE trial, arm H, found a survival benefit with the addition of prostate-directed RT to the standard of care therapy for newly diagnosed patients with low metastatic disease burden (per the CHAARTED criterion[30]), but not for those with high metastatic disease burden.[56] Toxicity from RT was modest. One important caveat of this study is that it was completed before the modern era of prostate cancer treatment, prior to the introduction of second-generation anti-androgen therapies, and therefore it is uncertain whether or not prostate-directed RT would afford the same outcomes today. The ongoing PEACE-1 trial addresses this question. For the time being, we continue to recommend prostate-directed RT for patients with a low metastatic burden by extrapolation from the STAMPEDE results, especially given the minimal toxicity associated with treatment.

‘Oligometastatic’ prostate cancer is an important clinical entity without a universally accepted definition, but is typically considered to include disease with no more than 5 metastatic lesions and frequently excluding any component of visceral involvement.[57] Multiple small trials have tested the hypothesis that RT to all sites of oligometastatic prostate cancer can delay progression and increase survival, including most notably ORIOLE[58] and STOMP,[59] which found improved progression-free survival and a trend towards improved progression-free survival, respectively, with the use of metastasis directed RT. Side effects were minor. Importantly, neither trial included any form of systemic or hormonal therapy. In the ORIOLE trial, patients underwent a more sensitive PSMA PET/CT scan prior to enrollment in addition to conventional imaging, although only conventional imaging was used to determine trial eligibility and targeting of RT. In a retrospective analysis, patients with lesions seen on PSMA PET/CT that were not present on conventional imaging (and therefore not treated with RT) had worse progression-free survival than those patients without untreated sites of disease.[58] The SABR-COMET[58] study is larger but of a similar design, with a mixed cohort of cancer types including a significant subset with prostate cancer. Results show an improvement in overall survival with metastasis-directed RT in the entire cohort. Subgroup analysis by cancer type was not reported due to insufficient numbers enrolled.

Although data is limited, clinicians frequently extrapolate from the ORIOLE trial to treat oligometastatic disease seen on PSMA PET/CT with RT. We also treat with 24 months

of concomitant intensified ADT (using any second-generation anti-androgen) by extrapolation from data showing improved survival with the addition of 24 months of ADT to RT for definitive treatment of locally advanced prostate cancer,[60] as well as from the data discussed above showing improved survival with the addition of a second-generation anti-androgen for both metastatic and high-risk locally advanced disease.

PARP Inhibitor

Defects in DNA repair pathways, specifically in homologous recombination, confer susceptibility to poly(ADP-ribose) polymerase (PARP) inhibition. Important genes in this pathway include *ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D,* and *RAD54L.* Such defects are common: 11.8% of patients with metastatic prostate cancer have a germline DNA damage repair gene mutation,[61] while 23% of patients with prostate cancer have somatic mutations in one or more of these same genes.[62] Two PARP inhibitors have demonstrated efficacy in prostate cancer: olaparib and rucaparib. Toxicity associated with PARP inhibitor therapy includes anemia/neutropenia/thrombocytopenia, nausea/vomiting and diarrhea, fatigue, and rare incidence of treatment-related MDS/AML. Olaparib is uniquely associated with a rare incidence of pneumonitis, which can be severe, while rucaparib is uniquely associated with liver injury and rash.

The phase 3 PROfound trial of olaparib versus placebo in patients with mHRPC that

had progressed on enzalutamide, abiraterone, or both, found improved median survival with olaparib in a cohort of patients with a somatic mutation in *BRCA1, BRCA2, or ATM*. Although the study was not powered to test response for each mutation individually, it is notable that the hazard ratio for PFS benefit was 1.04 in the setting of ATM mutation, suggesting a lack of benefit. A second, smaller cohort included patients with somatic mutations in 12 other genes and did not demonstrate improved survival with olaparib.[63,64] Rucaparib was tested in a single-arm trial in patients with post-chemotherapy mHRPC and germline or somatic mutations in *BRCA1*, *BRCA2, CDK12, CHEK2, and ATM.* The radiographic response rate was approximately 44% in *BRCA1* and *BRCA2*, approximately 10% in *CHEK2* and *ATM*, and 0% in *CDK12*, although all cohorts with the exception of *BRCA1, BRCA2,* and *ATM* had very small numbers.[65]

Overall, PARP inhibition is a good option for patients with mHRPC and *BRCA1* or *BRCA2* mutations and no longer responding to treatment with a second-generation anti-androgen. Although olaparib (but not rucaparib) is approved for use in the setting of other DNA repair pathway mutations, there is minimal supporting evidence. Importantly, olaparib is approved for use after progression on abiraterone or enzalutamide, while rucaparib is approved for use after abiraterone or enzalutamide in addition to chemotherapy. In addition, rucaparib has received accelerated approval and further trials to evaluate efficacy are pending.

Denosumab

Denosumab is an anti-RANK ligand antibody that inhibits the maturation of osteoclasts and thereby antagonizes the breakdown of bone, preventing skeletal-related adverse events from mHRPC and in some cases extending survival.[66] Denosumab is administered as a monthly injection. Toxicities include most notably osteonecrosis of the jaw, especially in those with poor dentition or requiring dental procedures while on treatment, mandating pre-treatment dental evaluation. Other toxicities include nausea, anemia, hypocalcemia, and hypophosphatemia.

Denosumab was tested against zoledronic acid, the previous first-line bone modifying agent used in mHRPC, in a phase 3 randomized trial which found that denosumab was superior in preventing skeletal adverse events (median time to first skeletal-related event 20.7 versus 17.1 months).[67] In patients with nmHRPC, denosumab increased the time to development of bone metastases compared with placebo (29.5 versus 25.2 months, respectively), but had no impact on survival[68] In mHSPC, zoledronic acid was found in a phase 3 trial to have no effect on the timing of skeletal adverse events.[69] Based on these data, denosumab is often preferred to zoledronic acid and is used routinely in the mHRPC setting for the prevention of skeletal adverse events when feasible. In practice, however, zoledronic acid is still frequently used due to cost considerations and lack of impact on survival. In the nmHRPC setting, denosumab is not routinely used as it is felt that the side effects outweigh the modest prolongation of time until the development of metastases.

Neuroendocrine Prostate Cancer

Prostate adenocarcinoma is by far the most common type of prostate cancer at diagnosis, representing >95% of cases, with neuroendocrine prostate cancer (NEPC) making up the remainder.[70] NEPC more commonly emerges during treatment of prostate adenocarcinoma, in a process known as transdifferentiation, which is estimated to occur in 10-20% of patients.[71] Higher Gleason score is associated with increased risk of transdifferentiation.[72]

NEPC is characterized by small or large cell histology, expression of neuroendocrine markers such as chromogranin A and synaptophysin, as well as low/variable expression of typical prostate markers including PSA, and a lack of dependence on the androgen signaling pathway for growth and survival. As a result, NEPC tends to respond poorly to therapy targeting androgen signaling, including ADT, abiraterone, and non-steroidal anti-androgens. Importantly, neuroendocrine prostate cancer is a heterogeneous spectrum of disease, ranging from small foci of transdifferentiated cells in a background of adenocarcinoma to pure small cell carcinoma.

Although there is no consensus on optimal treatment for NEPC and few trials have been performed, platinum-based chemotherapy is generally recommended based on the limited data available as well as extrapolation from trials in small cell lung cancer, which closely resembles small cell prostate cancer. These regimens include

cisplatin/etoposide[73] and carboplatin/etoposide +/- atezolizumab.[74]

Carboplatin/cabazitaxel has also demonstrated efficacy. [75] While well-validated in small cell lung cancer, only small trials have evaluated chemotherapy in NEPC specifically, overall showing relatively high response rates but short survival of <1 year.[76]

It has been noted that although effective against neuroendocrine prostate cancer, small cell regimens such as cisplatin/etoposide and carboplatin/etoposide frequently result in relapse with adenocarcinoma histology, presumably due to selective killing of the small cell component of mixed lineage prostate cancer allowing for the outgrowth of the adenocarcinoma component.[77]

Overall, we maintain a high index of suspicion for neuroendocrine transdifferentiation during the course of treatment for prostate adenocarcinoma, with a low threshold for repeat biopsy, especially if suspicious clinical behavior develops such as rapid disease progression, atypical sites of metastasis such as the viscera, discordance between PSA levels/trend and disease course, etc. We typically treat patients with pure small cell carcinoma who are candidates for chemotherapy with a small cell lung cancer regimen of carboplatin or cisplatin plus etoposide. If there is mixed adenocarcinoma/NEPC, or neuroendocrine prostate cancer lacking obvious small cell histology, we favor carboplatin/cabazitaxel for its activity against the prostate adenocarcinoma as well as NEPC.

Conclusion

Prostate cancer remains a highly lethal disease, especially in the metastatic hormone-refractory state. Encouragingly, however, advances in the past decade have expanded the therapeutic arsenal to include many new, highly effective treatments resulting in significant improvements in survival, with additional therapies and novel applications of existing therapies on the horizon.

Here we have summarized the current treatment landscape for advanced prostate cancer with an emphasis on practical aspects of disease management, including a discussion of our decision-making approach when multiple reasonable treatment options exist. We have attempted to highlight some of the most impactful work in the field, as well as critical areas of uncertainty and ongoing research. Although a static representation of a rapidly evolving treatment landscape such as that of advanced prostate cancer has inherent limitations, most notably that ongoing research will add to and change the current treatment paradigm, nonetheless we hope that this review will be a useful guide and starting point to clinicians and trainees who encounter and treat patients with advanced prostate cancer.

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