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# Geriatric considerations in the treatment of advanced prostate cancer

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## Abstract

Prostate cancer is the most common non-cutaneous cancer in US men and mainly affects elderly patients, with most new diagnoses occurring in those over 65. As the geriatric population in the US continues to grow, the incidence of this disease is likewise expected to rise. Many older patients are diagnosed with advanced disease or are treated only when their disease becomes symptomatic or metastatic. The treatment options for advanced prostate cancer have increased dramatically in the last decade. It is important to understand the nuances of caring for an elderly cancer patient in order to optimally treat prostate cancer, such as the importance of using a geriatric assessment to uncover overlooked or under-reported vulnerabilities. In addition, many of the newly approved agents for the treatment of advanced prostate cancer have a unique mechanism of action and toxicities that warrant consideration when choosing therapies for older patients. This review focuses on the importance of a geriatric assessment as well as the considerations of treating elderly patients with the newer agents approved for prostate cancer.

## Introduction

Prostate cancer is the most common non-skin cancer in men and is largely a disease of the elderly. Sixty-four percent of the new cases diagnosed in the US are in patients over 65 years of age and it is anticipated that the absolute number of cases is likely to increase as the US population continues to age [1,2]. Caring for the majority of prostate cancer patients thus means that providers must incorporate consideration of the unique needs of an older patient population into their approach.

Prostate cancer diagnosis and management is increasingly multifaceted, creating the need for a thoughtful discussion of treatment options for patients at all stages of the disease. With the advent of several newly approved drugs, medical management has become notably more complex and challenging in recent years. In this light, and considering the demographic overlay, there are data to suggest that local treatment options are often restricted by providers caring for older patients [3]. This may be due to the fact that older men present differently from younger men, likely because of over-diagnosis in younger patients and delay of diagnosis until symptom-causing metastasis in older patients. There has been much discussion about whether decreased prostate cancer screening, variable practice styles, or differing biology have contributed to an increase in late-stage diagnosis, as older men in the US are more likely to be diagnosed with poor-prognosis prostate cancer and tend to have lower overall and cancer-specific survival compared to younger men [4-6]. Thus, this patient population is often treated with systemic therapies, and this review will focus on the optimal use of medical therapeutics available to older patients with advanced disease.

In discussing particular therapies, we must emphasize the overall need for a comprehensive health assessment of these patients. In many oncologic specialties, the drug enrollment trials do not include patients over 65 years old, making it difficult to understand how a treatment

may affect one's older patient. Based on the strong demographic bias with this disease, prostate cancer trials generally enroll patients of all ages, although older patients placed on these trials are likely to be of a favorable overall functional status, which still may limit the generalization of the results to a clinic population. Practitioners should evaluate a patient's physiologic age, tumor stage, and life expectancy to guide treatment decision making rather than relying on chronologic age or performance status alone. The International Society of Geriatric Oncology (SIOG) working group on the management of prostate cancer identified three areas (comorbidity, dependency, and nutritional status) of needed assessment in order to cumulatively assign a health status to a patient, which could then be used to estimate physiologic age [7]. The pharmaceutical options in prostate cancer treatment are limited by age alone in very few instances, but one must first understand the global health of a geriatric patient in an effort to then assess the potential tolerance of treatment [7-9]. This assessment may help delineate patients that are *healthy* enough for any treatment, *vulnerable* to the therapy requiring some focus on reversible issues prior to therapy, or *frail* and intolerant of even a modified therapeutic approach. Our standard assessments of the extent of disease and performance status are not often sufficient to predict an elderly patient's tolerance of treatment, but a geriatric-specific assessment could capture a patient's physiologic age, aiding the therapeutic decision-making process [10]. In many cases, healthy elderly men should receive the same treatment as younger patients, and would prefer aggressive treatment for a potential survival benefit [11]. The use of a geriatric assessment is important in identifying the unique needs of our older patients in an effort to treat patients based on their physiologic age rather than chronologic age, which may present a greater array of treatment options and prevent treatment complications.

## Current treatment of advanced disease

### *Androgen deprivation therapy (ADT)*

Varied treatment options exist for patients with metastatic or recurrent prostate cancer and selection of therapy is influenced by the life expectancy, cancer grade, previous therapy, and comorbidity of a patient. However, ADT remains the first-line choice of systemic therapy and encompasses treatment with luteinizing hormone-releasing hormone (LHRH) agonists or antagonists, or orchiectomy, in order to suppress circulating levels of testosterone and thus decrease tumor growth (at least initially) in nearly all patients. Given the meaningful adverse event profile associated with ADT, we recommend reservation of ADT for older patients with defined metastasis in most cases, rather than prostate specific antigen (PSA) elevation alone. This is based on the long natural history of biochemical relapse in prostate cancer, with one report noting that in men with a rising PSA after a radical prostatectomy, the median time to the metastases was 8 years [12]. ADT is highly effective yet accompanied by significant side effects and, as the backbone of any treatment regimen, these effects are endured for the duration of a patient's anti-cancer therapy, which is generally measured in years. Several side effects may be of particular importance to older patients: osteopenia, sarcopenic obesity, fatigue, metabolic syndrome, reduced strength/endurance, as well as psychological and cognitive effects [13-19]. The older male is already dealing with aging-associated hypogonadal changes that limit his functional status reserve, and this reserve is then further stressed by the medical castration of ADT [20]. In addition, ADT-associated changes in body composition (such as sarcopenic obesity and osteoporosis) may diminish a patient's functional status to the point of limiting their ability to perform independent activities of daily living. The metabolic changes incurred with this therapy may hasten or worsen many of a patient's pre-existing comorbidities as well. While ADT is an effective therapy for controlling symptomatic and life-threatening disease, a baseline assessment of a patient's geriatric health would allow for identification of potential areas of heightened risk in need of proactive support in an attempt to prevent further morbidity.

If the concern over a patient's decline on ADT is too great to recommend this therapy, and yet a patient would benefit from a systemic hormonal approach, one may consider the use of non-steroidal antiandrogen monotherapy. Non-steroidal androgen receptor antagonists are commonly used in conjunction with ADT, but block testosterone's interaction with the androgen receptor as opposed to lowering circulating testosterone levels [21-23]. Gynecomastia, breast pain, sexual dysfunction and abnormal liver function tests are the most commonly encountered complaints. Based on a large meta-analysis, androgen blockade monotherapy is inferior to ADT or combined blockade therapy but represents a reasonable treatment option for patients in whom the consequence of hypogonadism could significantly impact performance status [24]. Additionally, practitioners may choose to offer intermittent ADT in an attempt to preserve quality of life and maintain disease control, in select patients. Recent data suggest that this may be inferior to continuous ADT, yet without statistical significance and, in specific patients, this approach is warranted [25]. Particularly in geriatric patients, it may take many months to achieve recovery to non-castrate testosterone levels after stopping ADT, and thus continuous ADT administration is not always necessary.

As with all treatment options, a careful discussion with your patient is needed to select a therapy in keeping with their goals of care.

## Next generation androgen targeted agents

### *Abiraterone acetate*

As our understanding of the biology of prostate cancer has improved, we have learned that more robust pharmacologic blockade of the testosterone signaling pathway resulted in a survival benefit for patients with metastatic disease. The previous term "hormone refractory" disease has fallen out of favor, as many patients with castrate levels of testosterone (<50 ng/dL testosterone) have continued dependence on testosterone as a disease driver. Based on this knowledge, abiraterone acetate (Zytiga) has shown a survival benefit for patients with metastatic castrate resistant prostate cancer (CRPC). The agent is an irreversible oral inhibitor of CYP17 that targets adrenal-mediated androgen biosynthesis, in addition to intracrine production, and as such its toxicity profile is largely a result of mineralocorticoid excess including lower extremity edema, hypokalemia, and hypertension [26,27]. These symptoms are minimized with the concomitant dosing of 5 mg of prednisone twice daily. The Cougar 301 (COU-AA-301) trial evaluated the use of abiraterone in patients with chemotherapy-refractory metastatic CRPC and showed a median overall survival in the treatment arm of 14.8 months *vs.* 10.9 months in the placebo with prednisone arm with a hazard ratio (HR) of 0.646 ($P<0.0001$) [28]. Average patient age was 69, but ranged up to 95. The survival benefit was preserved across the spectrum of age, with the HR for death being 0.52 in the over 75 group and approximately 0.66 in the younger age groups, suggesting that older patients enjoy the same if not more benefit from this treatment. The Cougar 302 (COU-AA-302) trial also reported a survival advantage in chemotherapy-naïve patients with asymptomatic or mildly symptomatic metastatic disease (Table 1) [29]. The age range in this study was quite similar to the post-chemotherapy trial. These pivotal results present new options for older patients with castrate-resistant disease who are not candidates for chemotherapy. This therapy is clearly better tolerated than cytotoxic therapy and well suited for an elderly population. One concern with the use of abiraterone acetate earlier in the disease process is that prolonged use of low-dose corticosteroids may have a substantial negative impact in an aging population (Table 2). Given the potential hepato-toxicity of abiraterone acetate, it is recommended that patient liver function tests be monitored every 2 weeks for the first 3 months; these frequent assessments may add an additional burden for older patients reliant on others for transportation. At this time, it is also unclear what effect lowering testosterone to near zero will have long term, but there is no clear increased risk with such a drastic reduction in testosterone, and abiraterone acetate is an effective agent that most elderly patients should tolerate without difficulty.

### *Enzalutamide*

Enzalutamide (Xtandi) is a new generation, small-molecule androgen receptor antagonist that inhibits receptor binding as well as androgen receptor nuclear translocation and DNA binding [30]. Much like abiraterone acetate, this agent has shown a survival benefit in patients with metastatic CRPC given before or after docetaxel chemotherapy [31,32]. The median age of the post-chemotherapy trial patients was 69 and ranged up to 92. Overall the drug is well tolerated but, importantly, there is an increased risk of seizure reported at 0.6%. This agent has the potential to be used earlier in

**Table 1. New agents approved for use in the pre-chemotherapy setting**

| Agent | Mechanism | Survival benefit | Palliative benefit | Year approved |
|---|---|---|---|---|
| Abiraterone acetate | Reduction of non-testicular androgens | Median NR *vs.* 27.2 mos placebo<br>HR 0.75 [29] | Improvement in time to initiation of cytotoxic chemotherapy, opiate use for cancer-related pain, prostate-specific antigen progression, and decline in performance status | 2012 |
| Radium-223 dichloride | Alpha emitting radiopharmaceutical for bone metastasis | Median 14 mos *vs.* 11.2 mos standard care<br>HR 0.70 [45] | Improvement in time to the first symptomatic skeletal event, time to an increase in the PSA level, FACT-P total score | 2013 |
| Sipuleucel-T | Autologous cellular therapy | Median 25.8 mos *vs.* 21.7 mos placebo<br>HR 0.78 [42] | No significant difference in PSA response or time to radiographic progression | 2010 |
| Denosumab | RANK ligand, osteoclast inhibitor | Zero *vs.* zolendronic acid<br>HR 1.03 [49] | Improvement in time to first on-study skeletal-related event | 2010 |

Abbreviations: NR, not reached; *vs.*, *versus*; mos, months; HR, hazard ratio; RANK, receptor activator of nuclear factor kappa-B; PSA, prostate specific antigen; FACT-P, functional assessment of cancer therapy – prostate.

**Table 2. Notable side effects of newly approved therapies**

| Agent | Effect | Concomitant medication |
|---|---|---|
| Abiraterone acetate | Mineralocorticoid excess (hypokalemia, edema, hypertension) | Prednisone |
| Enzalutamide | Seizure, falls | None |
| Docetaxel | Cytopenia, neuropathy, fatigue | Prednisone |
| Cabazitaxel | Febrile neutropenia, neuropathy, fatigue, diarrhea | Prednisone GCSF (recommended) |
| Sipuleucel T | Acute infusion reaction | None |
| Radium 223 dichloride | Chance of cytopenia, GI symptoms | None |

Abbreviations: GI, gastrointestinal; GCSF, granulocyte colony stimulating factor.

the treatment continuum, perhaps even as a single-agent prior to ADT, such that some of the hypogonadal effects of treatment may be avoided or at least partially abrogated [33]. Such an approach is certainly of interest in an aging population that has an increased risk of functional decline from many of the adverse effects associated with standard ADT. The efficacy of these two agents in the pre-chemotherapy setting has truly changed the management of CRPC in older patients. There is less fear over treatment side effects in vulnerable or frail patients, and many will derive a meaningful benefit in survival and palliation. Given that both treatments are clearly effective, the choice between abiraterone acetate plus prednisone or enzalutamide must incorporate assessment of risk of the most common side effects and a decision tailored to the individual patient.

## Chemotherapy

As we improve upon the targeting and disruption of androgen signaling, the biology of the prostate cancer emerging after such an approach may rely on other driver pathways. In end-stage prostate cancer, we oftentimes will see a transformation to a phenotype similar to a small cell/neuroendocrine cancer, with a differing pattern of metastasis to visceral sites accompanied by a disproportionally low PSA value based on the extent of disease. In these cases, further androgen-focused therapy may not be as effective as cytotoxic therapy. Additionally, recent data suggest that offering initial chemotherapy along with androgen deprivation therapy may be more effective for patients with high-risk metastatic disease [34]. Yet many older men are denied chemotherapy due to age or other limitations, despite a potential for improved survival and palliation of symptoms for many with extensive disease [35].

The current cytotoxic approach to metastatic CRPC is *via* the targeting of microtubules with taxane agents. Both docetaxel and cabazitaxel have been approved based on an improvement in survival in metastatic CRPC. The two randomized phase III trials evaluating the efficacy of docetaxel each demonstrated an overall survival benefit of almost 2 months in comparison to mitoxantrone [36,37]. The Southwestern Oncology Group (SWOG) 9916 trial had an average patient age of 70. The TAX 327 study [36] evaluated docetaxel plus prednisone in two different dosing schedules in relation to mitoxantrone plus prednisone. Docetaxel given every 3 weeks showed a 24% relative risk reduction in the HR for death ($P$=0.009) and patients experienced a statistically significant improvement in quality of life measures. This study included a patient population with an average age of 68, and a significant proportion >75 years old (20%) with a Karnofsky performance status of at least 60%. Grade 3/4 neutropenia occurred in 32% of patients treated with docetaxel every 3 weeks. Low-grade adverse events were most commonly fatigue, nausea, vomiting, neuropathy, nail changes, stomatitis and edema. A 2011 exploratory analysis looked at over 3000 men aged >75 treated with docetaxel and found that these elderly patients had more dose reductions than other age groups, but there was a trend for improved quality of life, response and survival [38].

Cabazitaxel (Jevtana) is another taxane approved for patients who have progressed on docetaxel. The phase III TROPIC trial [39] randomized patients to treatment with cabazitaxel or mitoxantrone and the median overall survival was 15.1 months *vs.* 12.7 with an HR for death of 0.70 ($P$<0.0001). Median age was 67 years old with almost 20% of patients over the age of 70, and 93% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. A dose reduction or delay occurred twice as often in cabazitaxel-treated patients (10% *vs.* 5%) and 82% of the cabazitaxel patients experienced grade 3/4 neutropenia with an 8% febrile neutropenia rate, leading to 7 toxicity-related deaths. For this reason, there is a recommendation for the use of growth factor support in patients at a high risk of neutropenic fever with this drug, which generally includes patients over the age of 65. Other common adverse events included diarrhea, fatigue, nausea, vomiting, and asthenia. If one uses the fit/vulnerable/frail labels of geriatric assessment, chemotherapy is likely appropriate for our fit and vulnerable patients. There are some data to suggest that weekly dosing of docetaxel may lessen hematologic toxicity, yet still offer meaningful efficacy [40]. Another consideration in the era of newer, highly effective hormonal agents used prior to chemotherapy is that patients' response to chemotherapy may be muted and the disease that emerges from such androgen receptor targeting may have a more

aggressive character. It has also been reported that weekly carboplatin administration is effective in those not treated with docetaxel, and may have increased activity in patients with small cell histology. This is another well-tolerated consideration in an older population, as its weekly administration may lessen hematologic toxicity [41]. Offering chemotherapy is appropriate for many fit older patients and the available trial data included patients with an age range reflective of the routine clinic population.

## Immunotherapy

### *Sipuleucel-T*

Sipuleucel-T (Provenge) is an approved autologous cellular immunotherapy for minimally symptomatic patients with metastatic CRPC, designed to stimulate an immune response. The therapy involves isolation of a patient's peripheral blood mononuclear cells (PBMCs) *via* leukophoresis, activation with a recombinant fusion protein composed of prostatic acid phosphatase (PAP) linked to a granulocyte-macrophage colony stimulating factor (GM-CSF), and reinfusion of the activated cells every 2 weeks for a total of 3 sessions. The combined analysis of multiple phase III trials revealed an overall survival benefit of approximately 3 months for patients with minimally symptomatic metastatic disease [42-44]. Patients aged 40 to 92 were studied, with a median age of 72 years. Most adverse events were grade 1/2 and temporally related to the infusion, including chills, fever, headache, flu-like illness, myalgias, and hypertension. These reactions may be more important in a patient with underlying cardiopulmonary disease and thus understanding the control of your patient's comorbidities is important to avoid severe toxicities. In general, this is an effective, well-tolerated agent, yet there is a considerable amount of time commitment and organization required in the leukophoresis for cell collection and subsequent therapy administration. Additionally, in our current limited understanding, it appears that response to immunotherapy requires time, and this therapy is likely best suited for patients with a reasonable life expectancy. This is an important issue as we move forward in the care of older patients with sipuleucel-T and other immunotherapies.

## Radiopharmaceuticals

### *Radium 223*

The recent approval of radium 223 (Xofigo) is important, in that this agent offers another mechanism of action to treat metastatic CRPC to the bones. This alpha-emitting radionucleotide offers palliation for many of the bone related symptoms (time to first Skeletal Related Events (SRE) 13.6 *vs.* 8.4 months) seen in metastatic prostate cancer [45]. However, treatment with radium 223 in both patients previously treated with docetaxel or chemo naïve also improves overall survival from 11.2 months in the placebo arm to 14 months [46]. The alpha emitting particles minimize general marrow toxicity compared to older (beta emitting) radiopharmaceuticals with grade 3/4 hematologic toxicities observed at <5%. In older patients that are likely to have less marrow reserve, or delayed marrow recovery after chemotherapy, this agent offers a safer option for palliation of bone symptoms. Most toxicities were mild and included nausea, bone pain, fatigue, diarrhea, and vomiting and patients on the trial were also treated with standard of care therapies that included secondary androgen deprivation agents, corticosteroids and others. This drug is approved for patients that have not yet received docetaxel because it is not available or appropriate, which will certainly be of use in older patients that are too frail for chemotherapy yet still would benefit from additional palliative therapy. This agent will likely be used more frequently as practitioners and centers become more comfortable with its administration and appropriate licensure for using an alpha-emitting agent is obtained.

## Bone therapy

It has been estimated that 90% of men who die from prostate cancer have bone metastases, and bone disease contributes to a large percentage of the morbidity of prostate cancer through spinal cord compression, pathologic fractures, and pain [47]. By improving bone health, older patients with prostate cancer may have less need for opiate medications, orthopedic procedures, and less risk of fractures, with the occurrence of any of these potentially causing a dramatic shift in a patient's ability to live independently and contribute to their risk of morbidity and mortality. Beyond its beneficial anti-cancer effects, ADT worsens bone health as it contributes to osteoporosis, compounding the morbidity of this disease in terms of bone health [48]. Providers should monitor vitamin D levels and encourage calcium and vitamin D supplementation as indicated to maintain good bone health in patients on ADT or with bone metastasis. There are also specific agents approved for treatment of bone disease.

Denosumab, an antibody against receptor activator of nuclear factor-kappaB ligand (RANKL), was approved both for patients with bone metastasis as well as patients without bone involvement who are being treated with ADT and are at high risk for fracture [49,50]. This agent reduces skeletal related events in comparison to zolendronic acid and is generally well tolerated [49] with fever, constipation, and joint pain as common mild toxicities. One must note the risk of osteonecrosis of the jaw in a

small number of treated patients. This may be more common in older patients with poor dentition or in need of dental procedures. With a reduction in renal function as patients age, it is important to note that denosumab does not require monitoring of renal function as is needed with bisphosphonates. Reducing the morbidity associated with skeletal related events through use of a bone protective agent is extremely important in older patients with aging-associated body composition changes and with vulnerabilities to fall that could irreversibly affect their ability to live independently or even to tolerate further therapies.

## Conclusion

The treatment options for advanced prostate cancer have certainly expanded in the last few years to include effective agents with toxicity profiles that are favorable for use in an older population. This is important given the demographic distribution of prostate cancer patients. However, providers should still begin the treatment planning for older prostate cancer patients with an assessment of the domains of general geriatric health. When caring for older patients, physicians should employ a geriatric assessment as this can reveal previously unidentified and reversible geriatric conditions, it can predict tolerance of therapy, it can help in the estimation of life expectancy so that prognosis can be calculated, and it can appraise functional status, which influences their tolerance. By estimating life expectancy, one can better weigh the lethal threat of an individual patient's prostate cancer in comparison to other comorbidities. There are data to suggest that performing a geriatric assessment can change planned cancer treatment in up to 20% of patients [51]. A geriatric assessment allows for treatment planning based on a patient's physiologic age and allows for identification of areas of vulnerability that may be rectified or supported.

The data presented with many of these newer agents are based on trials inclusive of patients in all decades of life. Large oncology trials often stratify patients according to previous therapies or ECOG performance status, but it has been suggested that reporting results according to comorbidity or functional status should be included if a significant percentage of the enrolled population is elderly. Similarly, understanding the applicability of the data also includes discerning the importance of overall survival or change in PSA to older patients. Elderly patients may have different goals of care than younger oncology patients and, as such, may value symptom control, quality of life, and ease of administration over survival benefit. While the newer, targeted agents are tolerable, one must consider the length of treatment when considering toxicity profiles.

The recent boom of new agents for prostate cancer treatment has certainly improved our options to support and treat prostate cancer patients of all ages. As more therapeutics are available, providers must remember the unique needs of their individual patient in order to select the agent with likely efficacy and a toxicity profile that will not offset the often tenuous balance in an older patient's life.

## Abbreviations

ADT, androgen deprivation therapy; CRPC, castrate resistant prostate cancer; HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group; LHRH, luteinizing hormone-releasing hormone; PSA, prostate specific antigen.

## Competing interests

The authors declare that they have no competing interests.

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