PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

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Update on Metastatic Hormone-Sensitive Prostate Cancer

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H&O How often do men present with de novo metastatic prostate cancer?

KC In places where we do a lot of screening, such as the United States, Canada, and certain parts of Europe, the percentage of men whose prostate cancer presents as metastatic disease is approximately 5% to 10%. The rate began to increase in the United States after the U.S. Preventive Services Task Force in 2012 issued a grade D recommendation against prostate-specific antigen (PSA)–based screening, but it remains at less than 10%.

In areas of the world where less screening is performed, the percentage of men with metastatic prostate cancer at presentation is higher; it is up to 50% in some regions of the world.

H&O Is it more common for metastatic hormone-sensitive prostate cancer (mHSPC) to present de novo or as relapsed disease?

KC The overall rate of mortality from prostate cancer is approximately 10%. When we look at the medical records of men who have died of prostate cancer, we see that approximately half of them presented with metastatic disease and half presented with high-risk localized disease that later recurred and metastasized.

H&O How long does it take for resistance to androgen receptor (AR) therapy plus androgen deprivation therapy (ADT) to develop in men with mHSPC?

KC Recent studies have shown that when men used to be treated with ADT or castration alone, the time to castration resistance was approximately 7 to 12 months. Now that we are adding AR pathway inhibitors such as apalutamide (Erleada, Janssen), enzalutamide (Xtandi, Astellas), abiraterone, and darolutamide (Nubeqa, Bayer) to ADT, we are seeing a big change. In fact, the median time to castration resistance—defined as rising PSA or progression—was not reached in most of the studies of ADT plus AR pathway inhibition; approximately 60% of patients continued to respond to treatment after a follow-up of roughly 4 years.

H&O What clinical and genomic factors predict for differential outcomes in this setting?

KC We use several clinical factors to predict a patient's outcome. The CHAARTED study, which defined high-volume disease as that in which patients have either visceral metastases or 4 or more bone metastases, at least one of which is outside the vertebral column or pelvis, found that patients with high-volume disease have a worse prognosis than those with low-volume disease. The LATITUDE study used slightly different criteria to determine whether patients had high-risk or low-risk disease. Disease was considered high-risk if it met 2 of the following 3 criteria: a Gleason score of 8 or higher, the presence of 3 or more bone metastases, and the presence of visceral metastases.

Regarding genomic or genetic factors, some studies have shown that patients with alterations in genes associated with DNA repair (eg, *BRCA2*) or in common tumor suppressor genes (eg, *TP53, RB1,* and *PTEN*) can have worse outcomes. Recognizing patients with prostate cancers in which genes

associated with homologous recombination repair (HRR) are altered is particularly important because poly(ADP-ribose) polymerase (PARP) inhibitors have demonstrated clinical benefit in such patients when they have metastatic castration-resistant prostate cancer (mCRPC). This finding also has implications for the patient's family because of the risk for hereditary cancers.

H&O What treatment options are used and have proved to be effective in men with mHSPC?

KC A real change has occurred over the last decade in how we treat mHSPC. ADT became the standard of care after Dr Charles Huggins in 1942 reported that orchiectomy is an effective treatment in men with prostate cancer. ADT remained the standard of care for more than 70 years on the basis of this finding and can be considered the first example of targeted therapy.

This standard evolved with the 2014 presentation and 2015 publication of the CHAARTED study, in which adding 6 cycles of the chemotherapy agent docetaxel to ADT improved overall survival (OS), with a hazard ratio (HR) of 0.72 (95% CI, 0.59-0.89). As a result of this study, ADT plus docetaxel became the new standard of care, especially in patients with high-volume disease, who accounted for 65% of the participants. These results were subsequently confirmed by results in the docetaxel arm of the STAMPEDE study from the United Kingdom. In this study, adding docetaxel to ADT also improved OS, with an HR of 0.78 (95% CI, 0.66-0.93). In a subsequent analysis, the results of the STAMPEDE trial suggested that this combination improved survival in patients with both high-burden and low-burden disease, although many still chose to restrict the use of docetaxel to patients with high-volume disease.

Subsequent studies looked at the addition of next-generation AR-targeted therapies to ADT. The LATITUDE study found a benefit in OS with the addition of abiraterone to ADT in patients with high-risk disease (HR, 0.62; 95% CI, 0.51-0.76). In addition, the STAMPEDE study showed that the addition of abiraterone to ADT improved OS in an all-comers patient population with both high-burden (HR, 0.54; 95% CI, 0.41-0.70) and low-burden (HR, 0.66; 95% CI, 0.44-0.98) disease.

Improvements in progression-free survival (PFS) with the addition of the direct AR inhibitors apalutamide and enzalutamide were demonstrated in 3 subsequent studies published in 2019. The TITAN study, which evaluated the benefit of adding apalutamide to ADT, had dual primary endpoints of radiographic PFS and OS. The benefit from adding enzalutamide to ADT was addressed in the ENZAMET and ARCHES studies, which had primary endpoints of OS and radiographic PFS, respectively. All 3 trials were positive, demonstrating substantial benefits in survival and leading to the regulatory approval of apalutamide and enzalutamide internationally. Updated results from TITAN and ARCHES in 2021 confirmed the long-term benefits of apalutamide and enzalutamide.

Most recently, the results of the ARASENS trial were presented at the 2022 American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium and published in the *New England Journal of Medicine* by Smith and colleagues. This study demonstrated improvement in OS with the addition of darolutamide to ADT and docetaxel. Darolutamide had previously been approved for nonmetastatic CRPC. Darolutamide is not currently approved for mHSPC, but I think we can expect this approval soon on the basis of the results of ARASENS. When that happens, we will have another AR-targeted pathway inhibitor in our treatment armamentarium.

ARASENS also raised the question of triplet therapy, given that the trial demonstrated an OS benefit when darolutamide was combined with the ADT/docetaxel doublet. From a subgroup analysis of the PEACE-1 trial, which was presented by Dr Karim Fizazi at the 2021 European Society for Medical Oncology (ESMO) Congress and recently published, we learned that the addition of abiraterone to ADT/docetaxel improves OS in patients with high-volume disease. We need to be cautious about these results because they are subgroup data, but they are consistent with what we would expect to see according to ARASENS. Together, the data support that if a patient is receiving ADT/docetaxel, then an AR-targeted pathway inhibitor should be added.

However, on the other hand, we are seeing some conflicting results with the ENZAMET trial. Approximately half of the patients in the ENZAMET study received docetaxel in addition to ADT or in addition to ADT plus enzalutamide. In the subgroup analysis, no benefit of enzalutamide on OS was observed in patients receiving ADT/docetaxel plus enzalutamide.

In addition, the design of the current trials does not address the specific contribution of docetaxel. That is, we do not have any trials looking at the doublet of ADT plus a next-generation AR pathway inhibitor with or without docetaxel. It may be that docetaxel does not add to the benefit of an ADT/AR pathway inhibitor doublet. As a result, the value of triplet therapy remains an unanswered question. Should we be using it at all, and if so, in which patients? Should it be used in the highest-risk patients, who have high-volume disease, especially if they had M1 disease at diagnosis or have liver metastases? Or are there specific genomic biomarkers, such as mutations in *TP53* and other tumor suppressor genes, that can identify patients who would benefit from more-intensified therapy? These are important questions to address.

H&O What is the role of radiation treatment in these patients?

KC STAMPEDE randomly assigned more than 2000 men with newly diagnosed metastatic prostate cancer to standard care plus radiation to the primary tumor or to standard care alone. Although the addition of radiation therapy failed to improve OS in the group overall, a preplanned subgroup analysis found an OS advantage among those who had low-burden disease, defined as 3 or fewer bone metastases.

One caveat regarding this study is that most of the enrolled patients received systemic treatment with ADT alone rather than ADT plus an AR pathway inhibitor or ADT plus docetaxel. If the patients had received a more intensified systemic regimen with proven survival benefits, would radiation to the tumor still have improved OS? Or conversely, is ADT intensification necessary if a patient has undergone local therapy to the prostate? Although these questions remain unanswered, radiation to the primary tumor has become widely adopted as a component of therapy, given its tolerability and presumed survival benefit.

In addition, small, randomized phase 2 trials (STOMP and ORIOLE) suggest that stereotactic body radiation therapy (SBRT) to metastases in men with oligometastatic HSPC can improve intermediate outcomes. Larger, phase 3 trials of SBRT are underway.

During the worst waves of COVID, we wanted to keep patients away from hospitals, clinics, and laboratories.

H&O What are some of the major side effects that differentiate these treatments from each other?

KC We are well aware of the side effects of docetaxel, which are typical of those seen in chemotherapy and include myelosuppression with risk for febrile neutropenia, fatigue, nausea and vomiting, diarrhea, loss of appetite, and temporary hair loss. The CHAARTED and STAMPEDE studies have established that quality of life decreases with the addition of docetaxel, and that recovery from these side effects may take as long as a year.

All the AR pathway inhibitors seem to be very well tolerated by patients. For example, the LATITUDE study showed that quality of life improved when patients received abiraterone in addition to ADT rather than ADT alone. Abiraterone does have the potential to cause side effects related to increased mineralocorticoid production, including hypertension and hypokalemia. In addition, abiraterone requires the concomitant use of prednisone, which carries the risk for corticosteroid side effects. Abiraterone also causes liver toxicity in approximately 5% of patients, so regular monitoring is required. In a randomized phase 2 trial of patients with mCRPC by Khalaf and colleagues, patient-reported quality-of-life outcomes favored abiraterone, particularly in patients older than 75 years of age.

Enzalutamide and apalutamide are very similar chemically, but they have never been directly compared. Apalutamide causes a rash in about 20% of patients, but the rashes are typically mild and rarely result in treatment discontinuation—fewer than 3% of patients discontinued treatment in the TITAN study. Enzalutamide does have a range of side effects that we are familiar with, including fatigue and cognitive effects.

Darolutamide seems to be very well tolerated, with studies showing very few differences between side effects in the experimental arms and those in the control arms, a finding that seems to represent an advantage for darolutamide. However, ODENZA, a phase 2 patient preference study presented at the 2021 ASCO Annual Meeting, compared enzalutamide with darolutamide and failed to find a significant patient preference for either agent.

All the currently approved AR pathway inhibitors are well tolerated, and differences among them with respect to side effect profiles and quality of life are relatively minor. Importantly, the benefit rates for AR pathway inhibitors are consistently high across all the agents, with studies showing improvements of 40% to 50% in OS. Therefore, the use of ADT alone to treat patients with mCSPC should really be the exception.

H&O What ongoing trials are looking at mHSPC?

KC The future is precision therapy with targeted treatments. Several studies are looking at the addition of PARP inhibitors to an ADT/AR pathway inhibitor doublet in patients who have alterations in genes associated with HRR. For example, the AMPLITUDE study is examining whether the addition of niraparib (Zejula, GlaxoSmithKline) to treatment with ADT and abiraterone plus prednisone can improve PFS in men with HRR gene-mutated mHSPC (NCT04497844). Similarly, TALAPRO-3 is comparing the PARP inhibitor

talazoparib (Talzenna, Pfizer) with enzalutamide vs placebo with enzalutamide in HRR gene-mutated mHSPC (NCT04821622).

The CAPItello-281 study is investigating whether the addition of the AKT inhibitor capivasertib to treatment with abiraterone plus prednisone or prednisolone plus ADT can improve outcomes in participants with mHSPC whose tumors are characterized by PTEN deficiency (NCT04493853). PTEN deficiency occurs in approximately one-third of patients with mHSPC.

Another ongoing study in mCSPC is the PSMAddition trial, which is examining whether the addition of lutetium Lu 177 PSMA 617 (Pluvicto, Novartis) to standard treatment with ADT and AR-targeted therapy in men with mHSPC improves radiographic PFS (NCT04720157).

H&O How should physicians go about choosing the best approach for a particular patient?

KC We look at patient factors, such as age and comorbidities, as well as tumor factors, such as volume of disease and potential tumor mutations. We also need to look at cost and availability because the cost of an oral drug (thousands of dollars per month) that may need to be taken for years can be prohibitive. Although docetaxel is relatively inexpensive and the duration of treatment is limited to 6 cycles, not all patients are candidates for chemotherapy.

COVID-19 also became a major consideration in 2020 and continues to be more or less a consideration. During the worst waves of COVID, we wanted to keep patients away from hospitals, clinics, and laboratories—any place where they might become infected. We also wanted to avoid immunosuppression. For these reasons, we stopped using docetaxel and abiraterone in Vancouver and moved entirely to apalutamide and enzalutamide, which have fewer monitoring requirements.

Disclosure

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Suggested Readings

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