

# CLINICAL UPDATE

Current Developments in the Management of Prostate Cancer

## Assessing the Risk of Cognitive Impairment Among Men With Prostate Cancer



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### **H&O** How prevalent is cognitive impairment in men with prostate cancer?

**CR** Prostate cancer preferentially affects older men, and the older population in general is at higher risk for cognitive impairment. Furthermore, standard systemic treatment for prostate cancer includes androgen deprivation therapy, which lowers the patient's testosterone level for an extended period. Testosterone and other hormones have significant effects on cognition. Reduction in hormones over time is thought to contribute to cognitive impairment.

Studies have focused on 2 facets of cognitive impairment in men with prostate cancer: long-term dementia and short-term mild deficits. Claims-based data analyses have suggested that there may be a slight increase in the risk for Alzheimer's disease and other types of dementia among men treated with androgen deprivation therapy for prostate cancer. The risk appears to manifest after 8 to 12 years of therapy. It is not known whether hormonal therapy for prostate cancer causes cognitive impairment or is merely associated with it. Ongoing studies are evaluating this phenomenon.

Some studies have suggested that a substantial proportion of patients with prostate cancer will experience some degree of acute or short-term impaired cognitive performance after initiation of androgen deprivation therapy. One study showed that after 6 months of androgen deprivation therapy, there was an increase of approximately 15% in patients who experienced some degree of impaired cognitive performance vs age-matched men without prostate cancer. Among healthy men of a similar age who undergo rigorous cognitive

testing, up to 50% will show some deficits. That is not to say that these men have dementia or noticeable cognitive dysfunction, but rather that test scores will show lost points in areas such as memory, attention, executive function, and spatial memory. A substantial proportion of people in this age group are living life with some mild degree of cognitive impairment that may or may not be recognized by them, their loved ones, or their coworkers.

### **H&O** What other treatment-related factors might contribute to cognitive impairment?

**CR** Some studies have suggested that patients receiving chemotherapy for cancer can develop some cognitive impairment. However, this association is not yet fully characterized.

Several novel androgen receptor inhibitors have been shown to be effective in the treatment of prostate cancer. These therapies are potent inhibitors of testosterone signaling. Some of these drugs, such as enzalutamide (Xtandi, Astellas/Pfizer) cross the blood-brain barrier, and therefore may have additive effects on hormonal signaling in the brain. There are anecdotal reports of patients who believe that their cognition has been impaired by treatment. Until now, no well-designed, rigorously conducted studies have examined cognitive impairment during treatment with these new drugs. In partnership with the Alliance for Clinical Trials in Oncology and Alicia K. Morgans, MD, MPH, at Northwestern University, we are about to launch a study evaluating the cognitive effects of a series of therapies for prostate cancer that do or do not penetrate the central nervous system.

### H&O Do reports from clinical trials provide an accurate assessment of cognitive impairment?

**CR** Clinical trials of treatment in prostate cancer have typically not required performance of detailed assessments of cognitive function. Some of the more recent trials of androgen receptor inhibitors have included cognitive impairment in the adverse events analysis. The phase 3 trial of darolutamide (Nubeqa, Bayer) known as ARAMIS (Efficacy and Safety Study of Darolutamide [ODM-201] in Men With High-Risk Nonmetastatic Castration-Resistant Prostate Cancer) provided separate rates for cognitive disorder, memory impairment, and change in mental status. The phase 3 PROSPER trial (Safety and Efficacy Study of Enzalutamide in Patients With Nonmetastatic Castration-Resistant Prostate Cancer) of enzalutamide included a category for cognitive and attention disorders, which included memory impairment, disturbance in attention, cognitive disorders, amnesia, Alzheimer's disease, senile dementia, mental impairment, and vascular dementia. The report for the phase 3 SPARTAN trial (A Study of Apalutamide [ARN-509] in Men With Non-Metastatic Castration-Resistant Prostate Cancer) of apalutamide (Erleada, Janssen) reported rates of memory impairment disorder, which included disturbance in attention, memory impairment, cognitive disorder, and amnesia. Given the lack of standard measurements and agreement on their clinical significance, it may be difficult to interpret cognitive outcomes across these studies. However, the fact that such analyses are being conducted speaks to the growing recognition and concern about the issue.

An important challenge is that toxicity assessments in cancer trials are based on an assessment tool created by the National Cancer Institute called the Common Toxicity Criteria for Adverse Events (CTCAE). The CTCAE was developed to report toxicities associated with chemotherapy, and it can provide a crude assessment of subtle side effects, such as fatigue and mental impairment. In addition, with this approach, assessment of mental impairment is based on the clinician's observation of the patient, rather than rigorous testing. Throughout the history of cancer clinical trials, researchers have lacked the right tools to establish cognitive impairment. Part of our work seeks to bring these tools into oncology.

### H&O Does it appear that clinicians may underestimate the risk of cognitive impairment in their patients with prostate cancer?

**CR** It seems likely that the percentage of healthy people ages 70 or 75 years who have some degree of cognitive impairment is underreported. (This number will vary

according to the rigor of the tests and instruments used to test cognition.) In the short-term, there is probably a link between hormonal status and cognition. Given these factors, I suspect that we do in fact underestimate the true prevalence of cognitive impairment.

An important point is that many patients with prostate cancer are treated by urologists or oncologists, who are not necessarily trained in cognitive analysis or the diagnosis of cognitive impairment. Clinicians who treat prostate cancer should recognize that these patients are at risk for cognitive impairment. There is a risk that cognitive impairment is underdiagnosed because clinicians are not looking for it. To address this challenge, we are working to identify and characterize the nature and scope of the problem in order to empower clinicians—whether they be oncologists or urologists—with an understanding of this phenomenon, as well as the initial steps to establish a diagnosis.

### H&O What is the relationship between cognitive impairment and fatigue?

**CR** Patients with cognitive impairment may report fatigue, and clinicians may misinterpret cognitive slowing as fatigue. We have been considering the hypothesis that fatigue encompasses other phenomena. In clinical trials of treatments for cancer, especially prostate cancer, fatigue is usually listed as the most common adverse event. Cancer therapies in general are known to cause fatigue. In some cases, however, fatigue may contribute to cognitive impairment or patients may misreport cognitive impairment as fatigue.

### H&O Are there any other symptoms that might be associated with cognitive impairment?

**CR** Falls may indicate cognitive impairment, and may reflect a drug effect on the brain. Among older patients treated with drugs that penetrate the central nervous system, falls are not uncommon. The various causes of falls can include neuromuscular symptoms impacting the legs, cognitive issues, and brain disorders.

### H&O What is your perspective on the link between dementia and treatment of prostate cancer?

**CR** In 2015, the *Wall Street Journal* published an article about a study from the *Journal of Clinical Oncology* examining Alzheimer's disease in patients treated with hormonal therapy for prostate cancer. The report in the *Wall Street Journal* led to some misconceptions and overreaction. The slight increase in the risk for dementia

seen in prostate cancer patients treated with long-term hormonal therapy may result not from the treatment but from extreme old age. There have been no rigorous prospective studies of dementia in patients with prostate cancer. The link has been based on analyses of data from Medicare records of patients with a claim for use of androgen deprivation therapy for prostate cancer who then have a subsequent claim of dementia. In one of these studies, a diagnosis of all-cause dementia was seen in 12% of patients treated with approximately 7 years of androgen deprivation therapy, vs 5% of age-matched men who had not received androgen deprivation therapy. This increase has the potential to be significant, but the actual cause and effect is not yet known. In Alzheimer's disease specifically, the data appear to suggest rates of 5% or 6% after approximately 10 years of androgen deprivation therapy, compared with rates of 3% or 4% among the general population of men in the same age group. Even with this increased risk, in absolute terms, the number of cases of Alzheimer's disease or dementia among patients with prostate cancer is relatively low. It is also important to know that there may be other confounding variables that are not accounted for, such as other illnesses, exercise, and diet, all of which may be different in patients receiving androgen-deprivation therapy vs those who are not.

### H&O Should all patients with prostate cancer undergo evaluation for cognitive impairment?

**CR** It is not yet known. As I mentioned, studies suggest that cognitive testing of older individuals in the general population will uncover some type of impairment in up to 50%. These data raise the issue of whether all older individuals should undergo screening with cognitive impairment tests. The reason to perform a screening test is to treat an underlying problem. For example, women undergo screening for breast cancer because early-stage disease responds to treatment. With cognitive impairment, however, the situation is different. We lack clear understanding of what should be done if cognitive impairment is identified in a patient with prostate cancer. Therefore, we may not be able to recommend that all patients undergo testing. A common problem in medicine is overdiagnosis of a problem that lacks a solution.

### H&O What patient characteristics should be considered in the assessment of cognitive function or impairment?

**CR** Important characteristics include age, comorbidities, and polypharmacy. In addition, a history of prior trauma may increase a patient's baseline risk for cognitive impairment.

### H&O How do you evaluate your patients for cognitive impairment?

**CR** I typically counsel my patients with prostate cancer about the risk for cognitive impairment before therapy begins. I am attentive to any complaints a patient may have, and I would refer him to a specialist if needed. On occasion, I have referred patients in clinical trials for testing in our neurology/psychology department.

### H&O Does the risk for cognitive impairment impact your treatment decisions?

**CR** It does, to some degree. Clinicians might avoid therapies, such as enzalutamide, that penetrate into the central nervous system among patients with baseline cognitive impairment. However, the benefits to this approach are not yet confirmed. Clinical trials exploring these issues are under way.

#### Disclosure

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#### Suggested Readings

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