

PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

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Prostate Cancer in Military Veterans



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H&O How much of your work is with military veterans?

BM I have worked at the VA Puget Sound Health Care System for the past 25 years, providing clinical care and doing both basic and clinical research to help veterans deal with the challenges of cancer. I spend most of my research time now focused on developing a prostate cancer clinical trials network at the US Department of Veterans Affairs (VA) to efficiently identify molecular targets, and on putting clinical studies in place to improve treatment for men whose cancers contain targetable alterations, such as mismatch repair deficiency and mutations in *BRCA2* and *CDK12*.

H&O Do military veterans have any special risk factors for prostate cancer?

BM Prostate cancer is the most common malignancy in veterans, diagnosed in approximately 11,000 men in the VA system each year.¹ Veterans are unique in that those men exposed to Agent Orange during the Vietnam War are at elevated risk for prostate cancer.² Other risks for development of prostate cancer include age (incidence increases with increased age), ethnicity (African Americans have the highest incidence among all ethnicities), and germline pathogenic variants in genes such as *BRCA2* and *HOXB13*.³⁻⁵ Diet, smoking, and other factors have been suggested to play a role in the risk of developing prostate cancer, but the level of

evidence supporting those factors is significantly less. As a result of Agent Orange exposure, a substantial number of veterans received a diagnosis of prostate cancer that is connected to their military service. Whether prostate

The VA is committed to improving access to germline testing for men with metastatic prostate cancer.

cancers that develop in men exposed to Agent Orange are more aggressive than other prostate cancers remains an area of active investigation.

H&O What special considerations exist regarding prostate cancer treatment and research in military veterans?

BM Prostate cancer is a disease that is most commonly diagnosed in older men, with the average age of diagnosis being 66 years. Because a substantial proportion of veterans are men, and the median age of veterans is 64 years, this group has an elevated risk for prostate cancer.⁶ Prostate cancer is the most common solid tumor diagnosis among veterans.¹

H&O Could you describe the VA's role in prostate cancer research?

BM The VA system is very active in prostate cancer research, which reflects the importance of the disease among veterans. Many investigators are carrying out preclinical work in laboratories to define relevant targetable pathways, and many VA clinical researchers are participating in trials, including investigator-initiated and industry-sponsored studies. At least 32 active prostate cancer studies are being led or supported by VA investigators at this time. The laboratory studies and clinical studies carried out in the VA are supported by multiple mechanisms, including industry, VA Merit Award funding, and support from the National Institutes of Health and the Department of Defense. In addition, the VA is conducting a system-wide effort in precision oncology, with sequencing of tumor tissue available at no charge to sites for patients with advanced cancers of any histology, through the National Precision Oncology Program (NPOP). NPOP recently entered into an agreement with Foundation Medicine as the sole-source sequencing platform for the NPOP effort. This effort is very important in prostate cancer because of work showing that 20% to 30% of metastatic prostate cancers are driven by genes for which potentially effective therapy already exists (eg, mutated *BRCA1/2* and *CDK12*, mismatch repair deficiency).⁷⁻¹¹ Significant investments in VA-specific clinical trials recently have been pursued through a joint agreement between the Prostate Cancer Foundation and the VA. The Prostate Cancer Foundation is supporting tumor and germline sequencing of prostate cancer for veterans with advanced disease and providing resources to set up research infrastructure at 10 centers nationwide. This network of centers in turn has multisite studies that can be supported by any funding source. At present, 2 of these multisite studies are being supported through the VA Merit Award mechanism. The entire VA has access to these studies, and support exists to allow eligible veterans to travel to the network sites.

H&O What are some of the most important trials that are available now in the VA system for men with advanced prostate cancer?

BM The VA system has a very concerted focus on improving clinical outcomes for veterans with prostate cancer through clinical research. As a reflection of that, the VA is participating in a number of precision oncology studies targeting homologous recombination deficiency. The VA was one of the lead accruers of patients to the PROFOUND study (Study of Olaparib Versus Enzalutamide or Abiraterone Acetate in Men With Metastatic

Castration-Resistant Prostate Cancer; NCT02987543). This study recently met its primary endpoint of change in radiographic progression-free survival. VA investigators are participating in additional studies of agents that target DNA repair, specifically using the poly(ADP-ribose) polymerase (PARP) inhibitors rucaparib (Rubraca, Clovis Oncology; NCT02975934, NCT02952534) and niraparib (Zejula, Tesaro; NCT02854436) as well as carboplatin or docetaxel (NCT04038502), all of which carry the potential for exceptional responses.

H&O Do men with prostate cancer routinely undergo molecular testing/sequencing at the VA, and are there any unique findings relevant to veterans?

BM The National Comprehensive Cancer Network guidelines recommend germline testing in men with metastatic prostate cancer. The reason is that 12% of men with metastatic prostate cancer carry a pathogenic germline alteration that could warrant the use of PARP inhibitors or platinum chemotherapy, neither of which is part of standard care.¹² In addition, the family members of veterans who carry these alterations could benefit from undergoing testing and taking advantage of potentially life-saving interventions and surveillance strategies if they are also carriers. The VA is committed to improving access to germline testing for men with metastatic prostate cancer in several ways. First, the VA has a system-wide genetic counseling and testing resource called the Genomic Medicine Service (GMS), and participating VA centers can order testing through the GMS. The GMS is also piloting a project to streamline the testing process by engaging the providers of men with metastatic disease to give pretest counseling, and to facilitate remote testing so that the maximum number of men can have access. Somatic testing is available across the VA through the National Precision Oncology Program. As mentioned, both of these programs can be extremely important to veterans because they provide access to precision oncology studies, along with off-label use of treatments, such as PARP inhibitors, that can be extremely effective.

H&O What makes the VA a good site for clinical trials?

BM The VA is a good site for clinical trials because it is the largest health care system in the United States, it utilizes a common electronic medical record, and a commitment exists on the part of many stakeholders to improve care for veterans, particularly veterans with prostate cancer. Because access to care is uniform, data are relatively straightforward. Challenges to performance

of clinical studies within the VA can be a lack of a dedicated research infrastructure (available research coordinators and regulatory support) and inconsistent paths for negotiation of contracts and budgeting among medical centers. A highly active effort is being made in all levels of the VA to improve precision oncology for all veterans, but particularly those with prostate cancer, by leveraging these resources to maximum effect.

H&O What are you most excited about in working with veterans regarding prostate cancer research and clinical trials?

BM Because of the very rapid dissemination of results from the discovery of targetable alterations in somatic and germline tissues, and the wholehearted enthusiasm for finding men who can be exceptional responders, precision oncology is the most rapidly moving area in prostate cancer. In the VA, this has been embraced as a very specific need to find these therapeutic options for all veterans as quickly as possible. I am most excited by how the enthusiasm for these approaches is supported at all levels, both nationally and locally, because it makes implementing very significant changes to research and treatment possible.

Disclosure

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