PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

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Prognostic and Predictive Biomarkers in Metastatic Castration-Resistant Prostate Cancer

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H&O What are biomarkers in the context of metastatic castration-resistant prostate cancer (mCRPC)?

AJA Biomarkers are any manifestation of a biological process, particularly in patients, that can be measured quantitatively. They can reflect either normal (physiologic) or disease (pathophysiologic) processes.

Biomarkers are used in various contexts in prostate cancer. Prognostic biomarkers are related to the natural history of a disease over time, whereas predictive biomarkers are linked to the benefit of specific therapies. Surrogate biomarkers are intermediate outcomes that are associated with gold standard outcomes, such as improved survival. Surrogate biomarkers can relay information on whether a treatment is benefitting a patient.

Other biomarkers commonly applied in oncology are pharmacokinetic biomarkers, which measure the effect of the host (patient) on drug metabolism and disposition, and pharmacodynamic biomarkers, which measure the effect of a treatment on a tumor or patient.

The biomarkers that are most relevant to this discussion are prognostic and predictive biomarkers because they help us identify patients in need of therapy, and they also help us select patients for the specific treatments that are most likely to be beneficial.

H&O How do oncologists determine prognosis in mCRPC?

AJA For many years, oncologists have used clinically available biomarkers to help them determine long-term outcomes in patients. These biomarkers, which have been validated in large-scale studies involving thousands of patients, include such factors as the patient's functional status, what prior therapies have been used, and a cancer's visceral vs bone vs nodal pattern of spread. Patient-reported outcomes also are critically important, such as whether opiates are required for analgesia. Other biomarkers whose levels are routinely measured in the clinic are hemoglobin to detect anemia, lactate dehydrogenase (LDH) as a metabolic indicator of cell turnover and cancer aggression, albumin to determine nutritional status, and alkaline phosphatase to determine the burden of bone metastases. The markers that are most strongly associated with decreased survival in men who have mCRPC are pain necessitating the use of opiates, a high LDH level, and a visceral pattern of spread, particularly liver metastases.

All these factors are incorporated into the nomograms or risk group models that we use to determine median survival at 1, 2, or 5 years. These models are important for stratification based on risk factors in clinical trials.

H&O How effective are biomarkers for determining prognosis in mCRPC?

AJA We can quantify how effective a prognostic model is with a concordance index (C index). Most models in the CRPC setting have a C index of approximately 0.7 out of a possible 1.0, which is good but not excellent—it leaves a lot of room for improvement. Many research groups, including my own, are working to develop new biomarkers in large-scale studies that we can add to the ones we already measure in the clinic.

H&O Does ethnicity affect how well biomarkers work?

AJA African American men are known to have a higher risk for aggressive prostate cancer that can lead to mCRPC. But once a patient has metastatic disease, race is no longer felt to be an independent prognostic variable. However, this may be due to the underrepresentation of African American men in large phase 3 trials and data sets; only trials with a large proportion of African American men could be used to determine whether race is associated with outcome independently of all these other biomarkers. But as of now, race is not part of the prognostic models for prostate cancer in the metastatic setting.

H&O What emerging prognostic biomarkers are being developed?

AJA Some of the emerging biomarkers related to prognosis are based on prostate cancer genomics because specific mutations can be linked to outcome. Mutations such as *TP53* loss and *RB1* loss, or splice variants in the androgen receptor (AR), have all been linked to poor outcome. Much effort is going into the genomic landscape and characterization of mCRPC.

Disease burden can be measured through the number of circulating tumor cells (CTCs) or the level of circulating cell-free, tumor-derived DNA (ctDNA), both of which are prognostic factors. For example, high levels of the AR variant AR-V7 or extra copies of full-length AR, as well as a high number of CTCs or high levels of ctDNA, are clearly associated with a poor prognosis. Ongoing studies are adding these measurements to the ones already in routine use.

Another novel prognostic marker is the histologic subtype of prostate cancer. For example, we now know that the outcomes of patients with neuroendocrine prostate cancer or small cell prostate cancer are worse than those of patients with typical adenocarcinoma.

We also have started to study the use of C-reactive protein and the neutrophil-to-lymphocyte ratio as inflammatory biomarkers; my group recently described the independent prognostic ability of the neutrophil-to-lymphocyte ratio observed in the phase 3 PREVAIL trial (A Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer), along with many other factors, in a poster presentation at the Genitourinary Cancers Symposium in February 2017.

H&O Moving on to predictive biomarkers, why is it important to predict response to treatment in mCRPC?

AJA Prediction is important because we want to make sure that the therapies we offer benefit specific patients. We want to maximize benefits, even if an agent benefits only a small subgroup of patients. We also want to minimize the risks and side effects of ineffective therapies, and their costs to patients and society. A good example is the use of human epidermal growth factor 2 (HER2) overexpression in breast cancer. HER2 overexpression is both a prognostic biomarker indicating poor outcome and a predictive biomarker indicating a positive response to anti-HER2 therapy.

Currently, we do not have any independently validated predictive biomarkers in prostate cancer that are like HER2 in breast cancer. The biomarker that is probably the farthest along is AR-V7 measured in CTCs. AR-V7 is a key AR splice variant, and it can be measured in CTCs with either a protein-based assay from Epic Sciences and Genomic Health or an RNA-based assay from Qiagen and Tokai Pharmaceuticals that was developed by the laboratory of Dr Jun Luo at Johns Hopkins. The presence of AR-V7, which is one of the more common AR variants and is clearly translated into protein, in the blood of men with CRPC is associated with a lack of response to enzalutamide (Xtandi, Astellas/Medivation) or abiraterone acetate (Zytiga, Janssen), but it is not associated with any difference in response to taxane chemotherapy. Knowing a patient's AR-V7 status could make it possible to avoid inappropriate treatment with enzalutamide or abiraterone and proceed directly to another treatment, such as docetaxel or radium-223 (Xofigo, Bayer HealthCare), or to a clinical trial. Unfortunately, the assay typically does not detect AR-V7 until after the patient has taken enzalutamide or abiraterone and resistance to frontline AR-directed therapy has developed, so it does not appear to be useful at this point as a frontline clinical decision-making tool. In addition, AR-V7 is not detected in the CTCs of many men with mCRPC that does not respond to enzalutamide or abiraterone, indicating that there are likely other mechanisms operating to cause resistance to these agents. Thus, AR-V7 has a strong positive predictive value but a modest negative predictive value. Many predictive biomarkers that can be linked to both standard and investigational therapies are under development for use in prostate cancer (Table).

My group is leading a validation study of AR-V7 funded by the Prostate Cancer Foundation and the Movember Foundation as a Global Treatment Sciences Network PCF Challenge Award (NCT02269982). This is a large-scale, multicenter validation study of AR-V7 in which the 2 assays that I mentioned are used, but we are also conducting whole-genome sequencing of CTCs and ctDNA to understand resistance mechanisms beyond AR-V7 that may be important and targetable in these patients over time. We are trying to validate AR-V7 as a predictive biomarker of

Table. Predictive Biomarkers in Development for Metastatic CRPC

Predictive Biomarker	Context of Use	Mechanism	Therapies Linked to Predictive Biomarker	Novel Strategic Approaches
AR variants (ie, AR-V7) in CTCs (assays from Epic Sciences and Qiagen)	Second-line mCRPC following enzalutamide or abiraterone failure	Lack of AR LBP and drug target of abiraterone or enzalutamide (ligand-independent signaling)	Lack of benefit with enzalutamide or abiraterone (requires validation) Not predictive of taxane benefit clinically	N-terminal AR inhibitors, BRD4 inhibitors
AR copy gain (amplification) in CTCs or ctDNA, biopsy specimens	mCRPC	High levels of receptor may lead to altered splicing decisions, activity despite low testosterone levels	Possible lack of benefit with abiraterone or enzalutamide (unclear, requires validation)	Novel AR pathway inhibitors
AR mutations (ie, F876L, T878A, H875Y, L702H) in ctDNA, biopsy specimens, CTCs	mCRPC	Agonistic mutations for antiandrogens, glucocorticoids	May be associated with resistance to bicalutamide, enzalutamide, abiraterone/prednisone	Novel AR pathway inhibitors
HSD3B1 mutation (N367T)	mHSPC/CRPC	Gain-of-function mutation promoting DHT synthesis from DHEA	Resistance to ADT, early CRPC development	Early use of AR pathway inhibition in mHSPC
Homologous DNA repair defects (ie, *BRCA1, BRCA2, FANCA, PALB2, ATM*) in tissue, ctDNA	mCRPC	Sensitivity to synthetic lethality of PARP inhibition	May be associated with greater benefit of PARP inhibitors, platinum-based chemotherapy	PARP inhibitors or platinum-based chemotherapy
DNA mismatch repair defects (ie, Lynch syndrome genes) in tissue, ctDNA	mCRPC	High mutational load, neoantigen generation, immune responsiveness and infiltration, PD-L1 upregulation	PD-1 or PD-L1 inhibition possibly based on small trials in patients with MMR deficiency	Requires prospective validation of PD-1/PD-L1 inhibition
PTEN loss, PI3K/AKT pathway activation in tissue	mCRPC	Activation of PI3K/AKT/mTOR pathway	Possible benefit to PI3K or AKT inhibition, ideally in combination with AR inhibition given reciprocal feedback of pathways	PI3K/AKT inhibition with abiraterone or enzalutamide
MAPK activation (*RAF1* mutations, MEK activation) in tissue	mCRPC	MAPK signaling, survival, metastasis	MEK or BRAF inhibitors potentially	Trametinib (Mekinist, Novartis), regorafenib (Stivarga, Bayer HealthCare), others
Visceral pattern of spread (particularly liver metastases)	mCRPC	Poor prognosis, resistance to immunotherapy, radium 223	Taxane chemotherapy, cell cycle inhibitors, platinum chemotherapy	Combination strategies of chemotherapy or immunotherapy
Intact RB, gain in CDK4/6 or cyclin D1	mCRPC	Intact cell cycle pathway checkpoints	Susceptibility to CDK4/6 inhibitors	CDK4/6 inhibitors +/- AR-directed therapies

(Table continued on next page)

Table. *(Continued)* Predictive Biomarkers in Development for Metastatic CRPC

Predictive Biomarker	Context of Use	Mechanism	Therapies Linked to Predictive Biomarker	Novel Strategic Approaches
WNT pathway alterations	mCRPC	β-Catenin activation and WNT canonical or noncanonical pathway activation	WNT pathway inhibition under study	Porcupine inhibition, immunotherapy

ADT, androgen deprivation therapy; AR, androgen receptor; AR-V7, androgen receptor splice variant-7; CDK4/6, cyclin-dependent kinases 4 and 6; CRPC, castration-resistant prostate cancer; CTCs, circulating tumor cells; ctDNA, circulating cell-free, tumor-derived DNA; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; LBP, ligand-binding pocket; MAPK, mitogen-activated protein kinase; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; MMR, mismatch repair; mTOR, mammalian target of rapamycin; PARP, poly(adenosine diphosphate-ribose) polymerase; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; PTEN, phosphate and tensin homolog; RB, retinoblastoma tumor suppressor protein.

response to enzalutamide or abiraterone. We recently completed enrollment of 120 patients in this study, and we are now following patients with serial CTC- and ctDNA-based biomarker studies to learn how mCRPC evolves over time within and among patients.

Predictive biomarkers from tissue, ctDNA, CTCs, exosomes, and circulating RNA also can be used in clinical trials to determine which patients are eligible for treatment with a range of novel therapeutics, including poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors, newer AR-directed therapies, immunotherapies, and other agents.

H&O Are there other ways in which oncologists can determine which agents to use in these patients?

AJA The guidelines on prostate cancer from the National Comprehensive Cancer Network reflect that some therapies are already being guided by biomarkers. For example, sipuleucel-T (Provenge, Dendreon) is indicated only for men who do not have significant pain and do not have metastasis to the liver; pain and pattern of spread are the prognostic biomarkers. Another treatment, radium-233, is only for men with metastasis to bone because the agent acts primarily on bone. We recently published recommendations from the Prostate Cancer Working Group 3, which is seeking to redefine clinical trial conduct, eligibility, and design in men with CRPC (Scher and colleagues in the *Journal of Clinical Oncology*). The goal is to establish a predictive biomarker–based molecular classification of this disease that is linked to specific therapies.

H&O What data do we have so far on how effective these types of biomarkers might be at predicting response?

AJA The Hopkins data, which were published by Antonarakis and colleagues in the *New England Journal of Medicine* in 2014, found a very low chance, less than 10%, of a response to treatment with abiraterone or enzalutamide in patients with AR-V7–positive CTCs. These patients also had very poor outcomes, with short progression-free survival (PFS) and overall survival (OS). This was confirmed in a study that used the AR-V7 protein–based CTC assay made by Epic Sciences and Genomic Health.

These same investigators have shown that the presence of AR-V7 does not affect outcome in patients treated with taxane-based chemotherapy; the findings are specific to enzalutamide and abiraterone. This makes sense because enzalutamide and abiraterone do not bind to AR variants, whereas taxanes appear to have an antiproliferative effect in CRPC regardless of whether the AR has spliced or not.

These biomarkers are not yet approved for use by the US Food and Drug Administration, but as I mentioned, we are doing the multicenter validation study now and expect to have results within the year. Other groups are embedding these biomarkers in the context of novel immune or AR-directed therapies to enrich for response. Some of the trials have not succeeded, however. For example, Tokai's ARMOR3-SV trial (Androgen Receptor Modulation Optimized for Response: Splice Variant) was unable to demonstrate greater efficacy of galeterone than enzalutamide in an AR-V7–selected mCRPC patient population.

H&O What other studies are looking at predictive biomarkers in mCRPC?

AJA One of the most exciting areas is the finding of DNA repair defects in mCRPC, which makes it possible for

patients to be treated with a class of drugs that otherwise would not work. Approximately 20% of men with metastatic prostate cancer harbor DNA repair defects in their germline or their tumor. A test to detect such defects could allow a patient who has a *BRCA1*, *BRCA2*, or *ATM* mutation to receive a PARP inhibitor or platinum-based chemotherapy, both of which are associated with clinical responses in patients with these mutations. Phase 3 trials of these agents in biomarker-defined populations of men with mCRPC and DNA repair defects are being planned or ongoing. The trials are testing the idea that only patients who harbor these DNA repair defects would be eligible for treatment because of the link to the predictive biomarker.

Other ongoing or planned trials of biomarkers that are linked to specific novel therapies include those looking at RAS pathway activation and phosphoinositide 3-kinase (PI3K) pathway activation (Table).

H&O How are surrogate biomarkers used in mCRPC?

AJA Surrogate biomarkers can be used as an early signal that a drug is working, on both a patient level and a trial level. For example, a surrogate biomarker can help a pharmaceutical company predict earlier whether it will be possible to proceed with a phase 3 trial of a specific drug; this has the potential to accelerate research and drug approval. Potential surrogates that have been examined in prostate cancer include declines in prostate-specific antigen (PSA) level, changes in CTCs detected with the CellSearch Circulating Tumor Cell Kit, and radiographic PFS.

Our guidelines from the Prostate Cancer Working Group 3 discuss the best way to develop these surrogates. Regulatory authorities have not accepted any surrogates for use in drug approval, so improved OS remains the gold standard and requirement for drug approval in men with mCRPC. There are good reasons for this; some drugs, including antiangiogenic agents, produce a high response rate or improvements in PFS without improving OS. Other therapies, such as immunotherapies, may affect survival without a noticeable effect on response or PFS.

Developing surrogate endpoints is difficult because some therapies in men with mCRPC, such as immunologic therapies, improve survival without clearly affecting any known intermediate endpoints. Sipuleucel-T and the investigational vaccine rilimogene galvacirepvec/rilimogene glafolivec (Prostvac, being developed by Bavarian Nordic) are examples of treatments that have been shown to improve survival (Prostvac so far only in phase 2 trials) without affecting response rate or PFS. The use of surrogate biomarkers, such as metastasis-free survival, radiographic PFS, radiographic response rate, and PSA or CTC declines, remains controversial and context-dependent at this time and clearly is not acceptable to regulatory authorities for the approval of new agents in men with CRPC.

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Suggested Readings

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