Dr. Kim N. Chi, Professor of Medicine at the University of British Columbia, Director of Research and Chair of the Genitourinary Tumor Group at the BC Cancer Agency, and Co-Director of Clinical Research at the Vancouver Prostate Centre, discussed challenges in the selection and sequencing of therapies for castration-resistant prostate cancer, with a focus on the limitations of therapy and emerging predictive factors to aid in selection.

**SUMMARY:** Dr. Chi described the “spiderweb of possibilities” in deciding what treatment to use at a given time. “You could either start with docetaxel, abiraterone, enzalutamide or radium-223, and go on from there. It becomes even more confusing when we add docetaxel into earlier disease, because we now have 2 trials showing benefit of adding docetaxel to ADT (androgen deprivation therapy) early on.” What to do after that remains uncertain. Newer agents were developed in parallel and frequently tested against placebo, leaving open questions about the efficacy of prior and subsequent therapies. “It is not a foregone conclusion that benefits are additive and treatments are not cross-resistant,” he cautioned.

Previously, men with castration-resistant prostate cancer (CRPC) would be treated with second-line hormone therapies and bone-targeted therapies, then chemotherapy and radiopharmaceuticals like strontium-89. Dr. Chi sees similar patterns emerging with newer classes of these categories of agents, starting with hormones (abiraterone, enzalutamide) and bone-targeted agents (denosumab), then at progression switching to chemotherapy for those who are candidates, with radium-223 after or instead of chemotherapy.

**ARE THERE PATIENTS WHO MIGHT BENEFIT FROM CHEMOTHERAPY FIRST?**
Dr. Chi observed that there are patients who do not respond to abiraterone or enzalutamide, with a primary resistance rate of about 10%; about 20% of patients discontinue these treatments in the first 3 months due to early progression or toxicity. The challenge then is to pick out patients who will not do well on these agents. Unfortunately, there are no validated means to do this.

Dr. Chi and others have developed a prognostic index from the COU-AAA 301 study with abiraterone post docetaxel. It includes 6 simple clinical factors that help predict poor prognosis on the drug: left ventricular hypertrophy (LVH), Eastern Cooperative Oncology Group (ECOG) performance status, liver metastases, low albumin/high phosphatase, and time from ADT to the actual start of abiraterone. Although patients can be predicted to do poorly with abiraterone, this does not mean that they would do any better with alternative therapy. Prospective randomized trials would be required to determine whether these patients would do better with chemotherapy upfront or as second-line treatment.

**SHOULD ABIRATERONE AND ENZALUTAMIDE BE SEQUENCED? WHAT IS THE ACTIVITY OF CHEMOTHERAPY AFTER THESE DRUGS?**
While they work on different targets, abiraterone and enzalutamide have common mechanisms of resistance, including androgen receptor (AR) mutations that can activate the AR. Docetaxel may also exert some of its effects through inhibition of AR translocation from the cytoplasm to the nucleus.

Dr. Chi described findings of cross-resistance between the newer agents. Clinical data show a very low — under 10% — prostate-specific antigen (PSA) response rate with abiraterone given after enzalutamide. Response to enzalutamide after abiraterone is between 10% and 20%, and a little higher still in patients who are chemotherapy-naive (20% to 30%), but the time to progression is relatively short, between 2 and 6 months. On the other hand, docetaxel given after abiraterone
LANDMARKS

is still active with the same response rate (47%) as in the original docetaxel trials. Cabazitaxel given after docetaxel, abiraterone or enzalutamide has a response rate around 30% to 40%, which is again similar to the TROPIC study of cabazitaxel after docetaxel. Dr. Chi concluded that chemotherapy does not seem to be affected by prior exposure to abiraterone or enzalutamide.

PREDICTIVE FACTORS

Dr. Chi presented forest plots for abiraterone, enzalutamide, cabazitaxel and radium-223 showing that clinical factors did not appear to influence benefit from these therapies. Molecular predictive factors have presented a challenge, as CRPC tumour samples are difficult to obtain. In a recent paper by Robinson et al.1 150 patients with metastatic CRPC were biopsied and had whole transcriptome and exome sequencing to identify mutations and aberrations that are actionable, including DNA repair genes: 20% of patients had tumours that were deficient in DNA repair, or had genomic aberrations in DNA repair genes. Coming out of that study, patients with DNA repair gene aberrations subsequently treated with olaparib, a polyADP-ribose polymerase (PARP) inhibitor that impedes DNA repair, were most likely to respond: their median progression-free survival (PFS) on olaparib was 10 months, vs only 2 or 3 months for patients without the mutation.

Progress is being made in figuring out ways of analyzing circulating tumour cell RNA and DNA, and other liquid biopsy techniques, as predictors of response to abiraterone and enzalutamide. Researchers at the Vancouver Prostate Centre are working on a simple way using whole blood real-time polymerase chain reaction (RT-PCR) to identify patients who express AR splice variants which encode for truncated forms of the AR that are constitutively active and not affected by abiraterone or enzalutamide. “We tested patients who were treatment-naive and found 11% to be...

FIGURE 3. Treatment algorithm for mCRPC progressing on ADT

Enrolment in a clinical trial, if eligible, is an option for all patient situations.
1. Radium 223 is appropriate for patients with symptomatic bone metastases and no significant soft tissue disease at all levels, including those who are chemotherapy-eligible.
2. Closely monitor duration of response to ARAT therapy and make a timely switch to chemotherapy, if warranted.

1. Consider in patients with good performance status and able to tolerate chemotherapy, with one or more of the following clinical characteristics:
   • prior ADT response of < 1 year
   • symptomatic disease
   • visceral disease

2. Consider in patients with one or more of the following clinical characteristics:
   • good response to prior ARAT therapy
   • prior ADT response of > 1 year
   • asymptomatic or minimally symptomatic
   • no visceral disease

ADT: androgen-deprivation therapy; ARAT: AR-axis-targeted; mCRPC: metastatic castration-resistance prostate cancer

androgen receptor splice variant 7 (AR-V7) positive,” said Dr. Chi, “which is about the exact rate you would expect. Those patients showed no PSA response to abiraterone or enzalutamide.”

Dr. Chi also described recent work with cell-free DNA, which is naked DNA present in the bloodstream that can be sampled and sequenced. In cancer, there can be a lot of cell-free DNA from the cancer floating around. In some patients, 90% of the cell-free DNA in the blood is from the cancer, enabling detection of genomic changes from a blood sample. Dr. Chi and colleagues have used this to identify markers predictive of response to abiraterone and enzalutamide, and also to identify actionable aberrations.

Right now, this targeted gene sequencing can be used to select treatment for poor-prognosis patients. Next steps involve a study, likely beginning in 2016, to sequence a much greater number of men with mCRPC who have progressed after abiraterone or enzalutamide, and select further treatment based on their genomic aberrations. “Predictive factors are really promising,” concluded Dr. Chi, “and I think within the next year or two we will see prostate cancer turn the corner and have markers to guide treatment choice.”

References:
3. ARMOR-3 ClinicalTrials.gov: NCT02254785.

NEXT STEPS

• Dr. Chi is working with Dr. De Bono to bring an olaparib study forward in Canada in 2016. “All patients have to get biopsied, and then the tumours will be sequenced, and if you have this DNA repair gene, you will get olaparib,” said Dr. Chi.
• A phase II trial of galeterone, which works as an androgen receptor (AR) antagonist and also degrades the AR, showed activity in patients with the AR-V7 mutation, and a phase 3 trial is now underway.
• A phase 1 trial is also starting with another drug, called EPI-506, derived from sponges in the ocean, which targets the opposite end of the AR (the N-terminal domain) and works well in animal models.
• Researchers at the Vancouver Prostate Centre have also discovered antagonists that fit into a DNA-binding domain, which prevents the AR from binding to DNA. An announcement is forthcoming about a joint effort in this drug’s development.