The author is inventor of a patent to use PARP inhibitors in homologous recombination defective cancers and receives royalty from PARP inhibitor sales.

References


Liquid biopsies and plasma DNA: paving the way for personalized medicine in metastatic castration-resistant prostate cancer

Treatment of metastatic castration-resistant prostate cancer (mCRPC) has evolved rapidly over the past years with the development of novel life prolonging therapies. Unlike in other malignancies, such as breast cancer and colorectal cancer, biomarkers to predict response to therapy in metastatic prostate cancer are not available for clinical use. In this issue of Annals of Oncology, Conteduca et al. report on a digital droplet PCR assay using plasma DNA from men with mCRPC treated with abiraterone and enzalutamide [1]. In this study, associations between androgen receptor (AR) copy number, AR mutations and clinical outcome were evaluated retrospectively in two cohorts of 171 (73 chemotherapy naïve and 98 post-docetaxel) and 94 men (all chemotherapy-naïve), respectively. In the primary cohort, AR gain in plasma DNA was detected in 10 (14%) chemotherapy-naïve and 33 (34%) men post-docetaxel. The authors found that men with AR gain had significantly shorter progression-free survival (PFS), overall survival (OS) and lower PSA response rates when compared with patients without AR gain. These findings were then validated in a second cohort confirming the results. AR mutations (L702H and T878A) were much less likely to occur and were only observed in eight men treated with abiraterone post-docetaxel. Although AR mutations were rare, a significant association with OS was found (HR = 3.26; 95% CI 1.47–NR, P = 0.004). For PFS and PSA response, only a trend toward a worse outcome was observed.

The authors should be complimented on this translational effort using non-invasive liquid biopsies to characterize the disease. For years, prostate cancer research has been dominated by one-size-fits-all trials including large numbers of patients without molecular stratification. From these trials, clinical prognostic features were derived, reflecting the disease burden rather than the disease biology [2, 3]. Recent developments have successfully aimed to overcome the unmet need for biomarkers to personalize mCRPC therapy, with the determination of AR-V7 status in CTCs as a promising example [4–6]. Other studies have shown that besides CTCs, cell-free DNA and microRNA provide valuable alternatives to CTCs, especially since CTCs are not always detectable [7]. As a lighting example of a biomarker-driven study, Mateo et al. demonstrated that men with mCRPC harboring defects in DNA repair genes, detected with next-generation sequencing on tumor biopsies, showed high response rates when treated with the PARP inhibitor olaparib [8]. These results show that therapeutic targeting of specific genomic aberrations is feasible to personalize therapy for mCRPC.

Associations of AR gain and AR mutations with clinical outcome in men treated with abiraterone and enzalutamide have been previously identified in plasma DNA by next generation sequencing [8–11]. In the current paper, the authors aimed to implement these findings in a potentially widely available assay using digital droplet PCR. The paper provides a thorough stage one validation of a promising non-invasive biomarker.

There are issues though that remain to be solved in future studies. First, are AR gain and AR mutations predictive of response, or are they just characteristics of more advanced disease.
and a worse prognosis? To answer this question, studies should be conducted comparing AR-targeted drugs with taxane chemotherapy, hypothesizing that response to taxanes might not be affected by AR status. This way we will be able to investigate if AR status in plasma DNA can have true predictive properties, or that it is just another marker of worse prognosis. If differential response between AR-targeted therapy could be confirmed, this marker might ultimately be used for future treatment selection in mCRPC. Secondly, there has been a rapid expansion of the biomarker landscape lately, including several promising biomarkers such as AR-V7, AR-FL, TMPRSS2-ERG, AR copy number gain and AR mutations either in CTCs or cell-free DNA [4, 7, 12, 13]. By reporting these biomarkers separately, it becomes a challenge to determine their independent clinical and biological value. As an example, the AR-V7 status, which plays a key role in resistance to abiraterone and enzalutamide, was not reported for the patients in the current paper. To truly determine the biologically and clinically relevant predictive value of each individual biomarker, studies should be carried out including other relevant markers to determine their individual value together with clinical prognostic factors in multivariable analysis.

Taken together, Conteduca et al. provide a promising first step toward a novel clinical biomarker in mCRPC on a widely available platform. Molecular stratification in biomarker-driven trials will finally take the treatment of metastatic prostate cancer forward. Several hurdles remain to be overcome, but personalized medicine in mCRPC might be closer than ever before.

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Toward common response evaluation criteria for solid tumors and lymphomas: RECIL and RECIST?

Simple and reproducible response criteria are crucial for the clinical evaluation of antinecancer drugs. This is based on diagnostic imaging procedures that have the ability to be standardized and adapted to a second independent set of criteria or lecture. Their reproducibility, their simple use by groups conducting clinical trials and their adoption by pharmaceutical companies and regulatory agencies are necessary.

Tumor response criteria have been modified during the last decades. The ongoing modifications and improvements were necessary because of the learning curve of the investigators who use these criteria in daily practice, as they have the knowledge of what remains to be improved and the solutions that might be implemented. In parallel, the development of new imaging techniques, such as PET, and their potential efficiency with respect to tumor response assessment led to better criteria especially for lymphoma.

However, until now, some differences remained between tumor entities especially between lymphomas and solid tumors.

In regard to lymphomas, the first response criteria were published in 1999 by the International Working Group [1]. These guidelines defined complete remission (CR), partial remission (PR), CR unconfirmed, stable disease (SD), relapsed disease, and...