Perspective

Genomic analysis of circulating tumor DNA to predict endocrine resistance and clonal evolution in patients with prostate cancer: Clinical perspectives and research opportunities

Dario Trapani, Giuseppe Curigliano

Division of Experimental Cancer Medicine, European Institute of Oncology, Milano, Italy

Correspondence to: Giuseppe Curigliano. Division of Experimental Cancer Medicine, Istituto Europeo di Oncologia, Via Ripamonti 435, 20141 Milano, Italy. Email: giuseppe.curigliano@ieo.it.

Comment on: Lallous N, Volik SV, Awrey S, *et al*. Functional analysis of androgen receptor mutations that confer anti-androgen resistance identified in circulating cell-free DNA from prostate cancer patients. Genome Biol 2016;17:10.

Abstract: Metastatic castration-resistant prostate cancer (mCRPC) is a multi-faceted disease and clinicians treating and managing the disease face several challenges. Progressive disease on androgen deprivation therapy (ADT) commonly occurs. With the approval of several survival-prolonging endocrine agents, the question of sequential treatment administration becomes increasingly important and new biomarkers beyond PSA should be identified to predict resistance and prognosis of mCRPC. A step forward has been made with the identification of splicing variants of androgen receptor (AR) associated with a resistance to ADT. The direct identification of AR mutants from patients' serum, and the functional characterization of these mutants may provide personalized recommendations regarding the best future therapy. Genotyping circulating tumor DNA in blood samples can be used to identify the molecular profile of prostate cancer and to closely follow its evolution during therapy. This approach can also be used to detect minimal residual disease after surgery and to identify actionable therapeutic targets, and uncovering mechanisms of endocrine resistance *ex-vivo*. Importantly, by identifying mechanism of drug response by functional characterization of AR, novel compounds may be introduced in the treatment of mCRPC.

Keywords: Androgen receptor mutation; cell-free DNA (cf-DNA); castration-resistant prostate cancer (CRPC); liquid biopsy; NGS

Submitted Sept 07, 2016. Accepted for publication Sept 19, 2016.
doi: 10.21037/tcr.2016.10.24
View this article at: http://dx.doi.org/10.21037/tcr.2016.10.24

Prostate cancer is a global health problem. Approximately 1.1 million cases are diagnosed per year, making this malignancy the second most common cancer in men worldwide and the most common cancer in men in more developed regions (1). Actually, treatment choice for castration-naïve as for metastatic castration-resistant prostate cancer (mCRPC) patients is based on clinical features of disease (2-4). The standard treatment for metastatic castration naïve prostate cancer is androgen deprivation therapy (ADT). ADT can be achieved by orchiectomy, gonadotrophin releasing hormone (GnRH) agonists, or GnRH antagonists. Through constant stimulation of the receptor, GnRH agonists lead to a down-regulation (2-4). In patients with castration-naïve metastatic prostate cancer, the upfront addition of docetaxel to ADT should be discussed with patients who are fit for chemotherapy (2-4). Progression on ADT generally occurs and optimal sequencing of endocrine agents, abiraterone acetate and enzalutamide, should be defined. A milestone for primary and acquired androgen resistance was described in 2014 by Antonarakis *et al*. (5). The splicing androgen receptor (AR) variant 7 (AR-V7) in circulating tumor cells were shown to be predictive factor for resistance to next-generation AR axis-targeting agents. In the current issue,

Lallous *et al*. utilized circulating cell-free DNA (cfDNA) sequencing technology to examine the AR gene for the presence of mutations in CRPC patients. By modifying their sequencing and data analysis approaches, they identified four additional single AR mutations and five mutation combinations associated with CRPC. Importantly, they conducted experimental functionalization of all the AR mutations identified by the current and previous cfDNA sequencing to reveal novel gain-of-function scenarios. Finally, they evaluated the effect of a novel class of AR inhibitors targeting the binding function 3 (BF3) site on the activity of CRPC-associated AR mutants (6). We endorse the conclusions of their work demonstrating the feasibility of a prognostic and/or diagnostic platform combining the direct identification of AR mutants from patients' serum, and the functional characterization of these mutants in order to provide personalized recommendations regarding the best future therapy. The detection of cf-DNA provides new opportunities for management of prostate cancer patients adding a new useful tool for diagnosis, staging and prognosis. It offers a new type of very specific biomarker that allow to identify the mutations accumulated from each tumor and to monitor the tumor burden and the response to treatment using a minimally invasive blood analyses. cfDNA analysis may allow a more comprehensive assessment of the molecular heterogeneity of the patient's prostate cancer, which also can lead to a more personalized and combinatorial treatment with targeted therapies. Mechanisms of endocrine resistance are driven by upregulation of specific pathways that can be targeted by new agents. A most unique advantage of circulating tumor DNA analysis is that it enables to follow tumor molecular evolution in time. cfDNA can be investigated repeatedly and non-invasively at different time-points through therapy. As an example, real-time monitoring of AR mutants in cfDNA could be used to design dynamic therapeutic schedules of new generation anti androgen receptor agents. A correlation of treatment response and presence of specific somatic genomic changes associated with target drugs has been observed in a longitudinal monitoring of patients participating in a phase 1 clinical trial of several tumors including PC (7). Providing clinicians with comprehensive catalogs of the key genomic changes in prostate cancer and disease segmentation of prostate cancer subtypes progressive to endocrine therapy will support advances in developing more effective ways to diagnose, treat and prevent cancer. The failure to deliver personalized medicine is often associated with the lack of highly bioactive and specific drugs. Experimental functionalization of AR mutants may help to dissect the intra-tumor heterogeneity and to design new agents that will overcome endocrine resistance. Liquid biopsy may overcome limitations of tumor biopsies (logistical and operational challenges, quality of tissue samples and sequencing technologies). Liquid biopsy may increase accrual in precision medicine trials. As stated in the recent "Consensus on precision medicine for metastatic cancers" (8) in individuals, the level of evidence that a genomic alteration is involved in cancer progression can vary from 'biological interpretation without supporting data' (level IV) to 'evidence from clinical trials' (level I). A most concerning term in this era is "targetable" genomic aberration, because this refers to a hypothesis, not a fact. Nonetheless, unchecked adherence to a belief in the concept of "targetability" or "druggability" of genomic aberrations with available targeted therapy, and even a "signal" of benefit from early clinical development, may reinforce a biological premise to pre-select patients based on the assay result. If a new drug has strong biological rationale and demonstrates a "signal" of activity in phase I or II studies, we still expect that results from a randomized clinical trial must demonstrate efficacy (clinical validity) before accepting that treatment as a potential standard. Functional characterization of AR mutants in order to provide personalized recommendations regarding the best future therapy is an example on how to provide druggability to a genomic tool. Another major challenge in optimizing precision medicine trials design is the appropriate use of relevant biomarkers to the molecularly targeted agents and, in case of combination of targeted agents, the setup of an appropriate treatment algorithms. There are, however, several questions to be answered. One crucial factor in evaluating cf-DNA is the standardization of assays and the definition of the optimal sampling specimen (serum or plasma) to obtain data more consistent and comparative between different laboratories. Despite these technical limitations, "liquid biopsy" may provide a unique opportunity in the field of clinical cancer research and have been already embedded in the design of several clinical trials. Another opportunity to explore the role of cf-DNA is to study the "tumor dormancy" phenomenon, very important in prostate cancer patients in order to stratify risk of relapse. A better stratification of the risk may allow an escalation of treatment. More importantly, the process of identifying specific DNA mutations for each patient's cancer is a laborious process that is currently too time-intensive and costly for more widespread use. Future

development will have to provide a cost effective analysis mainly identifying the genes known to be recurrently mutated in each tumor. Therefore, developing standardized methodologies for cf-DNA analyses and validation in large prospective clinical studies is mandatory to implement the 'liquid biopsy' approach in the clinical management of prostate cancer patients.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Peng Zhang (Department of Urology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2016.10.24). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Cite this article as: Trapani D, Curigliano G. Genomic analysis of circulating tumor DNA to predict endocrine resistance and clonal evolution in patients with prostate cancer: Clinical perspectives and research opportunities. Transl Cancer Res 2016;5(Suppl 4):S800-S802. doi: 10.21037/tcr.2016.10.24

References

1. Lallous N, Volik SV, Awrey S, et al. Functional analysis of androgen receptor mutations that confer anti-androgen resistance identified in circulating cell-free DNA from prostate cancer patients. Genome Biol 2016;17:10.
2. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016;387:1163-77.
3. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N Engl J Med 2015;373:737-46.
4. Mohler JL, Armstrong AJ, Bahnson RR, et al. NCCN Prostate cancer guidelines, version 3.2016.
5. Antonarakis ES, Lu C, Wang H, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med 2014;371:1028-38.
6. Lallous N, Volik SV, Awrey S, et al. Functional analysis of androgen receptor mutations that confer anti-androgen resistance identified in circulating cell-free DNA from prostate cancer patients. Genome Biol 2016;17:10.
7. Frenel JS, Carreira S, Goodall J, et al. Serial Next-Generation Sequencing of Circulating Cell-Free DNA Evaluating Tumor Clone Response To Molecularly Targeted Drug Administration. Clin Cancer Res 2015;21:4586-96.
8. Swanton C, Soria JC, Bardelli A, et al. Consensus on precision medicine for metastatic cancers: a report from the MAP conference. Ann Oncol 2016;27:1443-8.

