Precision medicine against metastatic prostate cancer: proposed actions to reverse current challenges

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Barcelona, November 26, 2020. Despite recent progress in rendering treatments more precise against advanced prostate cancer—largely driven by genomic sequencing and the deeper subtyping of this disease—therapeutic options to more effectively treat late-stage prostate cancer remain limited. Improving clinical outcomes for these patients consequently represents a critical, unmet need.

Published this month in *Nature Cancer*, an expert Perspective piece* shines important light on today’s treatment landscape of metastatic prostate cancer by reviewing progress to-date, exposing some of the challenges that are impeding the advancement and extension of precision medicine for this particular patient population, and proposing priority points and actions to deliver on their defined short-term and longer-term goals.

First authored by Joaquín Mateo, Principal Investigator of WHO’s Prostate Cancer Translational Group, with corresponding author Himisha Beltran, Dana Farber Cancer Institute (Boston, USA), the investigators begin by updating on the current promise and limitations of personalized treatment strategies and anti-cancer medicines for patients suffering from advanced prostate cancer.

They first discuss how patient outcomes vary tremendously due to both the heterogeneity of disease and disparities in patients’ access to therapies. While the more precise classification of disease is increasingly guiding clinical decision making matched to the specificities of individual patients’ tumors, harnessing the precision and power of genomic sequencing in the current era of personalized medicine against cancer falls short. Additionally, the integration and application of genomic-based platforms and technologies in the clinic pose additional challenges.

Commenting for WHO’s Global Communications Joaquín Mateo noted, “Prostate cancer affects almost 1.3 million men globally each year. There is a critical and unmet need to improve outcomes for patients with metastatic disease in particular.”

He continued, “While we are beginning to see improved outcomes for certain patients that are largely driven through genomic insights, there is much more to be done to accelerate precision medicine and develop more effective treatments matched to the genetic specificities of each individual’s cancer, as well as predict and combat resistance to therapies as disease progresses.”

In their elegant review of the current landscape of genomic classification of metastatic prostate cancer, the authors assess the value of genomic-generated data in unmasking predictive and prognostic biomarkers as well as emerging mechanisms of resistance. These precious insights undoubtedly hold promise in improving patient stratification, guiding the selection of matched therapies, and more precisely developing anti-cancer medicines.

As an example, the authors consider recent results from the phase III PROfound biomarker-based study that provide clear rationale for molecular testing in patients with advanced disease; particularly for men with BRCA2 alterations. Co-authored by Joaquin Mateo, the findings that he presented during a Presidential Session of the European Society for Medical Oncology’s (ESMO) Virtual Congress 2020 (19-21 September), published simultaneously in *The New England Journal of Medicine***. Results showed significantly longer overall survival of metastatic castration-resistant prostate cancer (mCRPC) patients with at least one alteration in BRCA1, BRCA2, or ATM genes, who received treatment with PARP inhibitor (PARPi) rucaparib versus second line of enzalutamide or abiraterone plus prednisone.

This study demonstrates the importance of incorporating genomic sequencing for the optimal stratification of these patients and the relevance of the results was reflected by the fact that the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have now authorized rucaparib for treating mCRPC.

Similarly, the authors of this *Nature Cancer* Perspective piece also highlight findings from the phase II single-arm TRITON2 study of PARPi rucaparib for mCRPC patients with germline or somatic BRCA alterations, published in *Clinical Cancer Research***. Importantly, results from the study led to FDA approval of rucaparib in this setting.

They then go on to discuss other genomic alterations that may also better enable more precise treatment decision making for individual patients. They call for strategies to selectively target tumors with aggressive or atypical histologic, clinical or molecular findings, stressing the importance for genomic landscape studies and clinical trials to embrace diversity in patient populations, and the need for prospective registries that capture success and failures in the evaluation of precision medicine strategies.

Getting ‘personal’: check listing challenges & defining next directions

The authors identify six major obstacles that are currently preventing the effective implementation of precision oncology for these patients and signpost future directions and collaborative strategies to help overcome these challenges. In each case, they expertly propose both short-term and longer-term goals to overcome these obstacles.

Defined challenges include access to tumor tissue for molecular profiling, tackling tumor heterogeneity, detection of complex drivers, clinical and genomic integration, understanding the impact of genomics in diverse patient populations, and access to matched therapies and clinical trials.

If precision medicine is to significantly improve outcomes for patients with prostate cancer, and indeed, extended to a greater number of patients, we first need to reverse the major obstacles that are currently standing in our way in doing so. More than a perspective piece, our review aims to be a white paper in a complex field; a starting point for discussing how can we accelerate progress for our patients and emphasize the value of collaborative science,” added Joaquín Mateo.

He concluded, “As a call to act, we must all now work together to bring about necessary change and further spur progress. Only then will we be able to deliver on the real promise of precision medicine for an increasing number of men suffering from advanced prostate cancer as a priority setting.”

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