Oncology

Next Generation Sequencing in metastatic castrate-resistant prostate cancer

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Introduction

Although the outcomes have improved in metastatic castrate-resistant prostate cancer (mCRPC), there is a limited arsenal of treatment options at the oncologist’s disposal. The options range from enzalutamide and abiraterone (hormone-based therapies), docetaxel and cabazitaxel (chemotherapy), and radium-223 (radioactive isotope), but beyond these medications there are no other options and additionally none of these options are curative.1 Next Generation Sequencing (NGS), including Guardant360, allows clinicians to sequence tumor tissues or blood samples in a short timeframe. The use of NGS for patients is a new outlet to identify therapies that would otherwise not be selected when potentially appropriate.

The NGS platform Guardant360 constructs a genomic profile by analyzing 72 somatic cancer-associated genes from circulating tumor DNA (ctDNA) derived from serum. The implications of the data from NGS can be used to guide treatment with the potential for finding a sui generis target within a tumor sample giving patients personalized therapeutic options. Herein, we discuss a case of mCRPC treated with a targeted therapy based on the patient's ctDNA results and provide insight into the future considerations for NGS.

Case presentation

The patient was diagnosed with mCRPC at 63-years-old with no concomitant health issues. The metastases are located in the bilateral sacrum, various ribs, and vertebrae on bone scan. The patient was first treated with leuprolide injections and oral bicalutamide. After progression of disease on CT and bone scans, the patient was given docetaxel. After a subsequent progression, he was started on enzalutamide followed by cabazitaxel after another progression on scans.

The patient did not respond to cabazitaxel with a dramatic rise in PSA and was started on cabozantinib, a drug FDA-approved for medullary thyroid and renal cell carcinoma, based on his ctDNA results revealing an alteration in the \textit{MET} gene (Fig. 1).2 In the phase III COMET-1 study, cabozantinib was shown to be safe and efficacious for prostate cancer despite not meeting endpoints.2 The patient has been receiving cabozantinib 40mg daily for 4 months with bone scans showing a remarkable dissolution of disease. The contrast of bone scans from the inaugural day of receiving cabozantinib to day 75 is marked (Fig. 2).

Discussion

The clear benefit that we have described in this patient could be extrapolated and become a reasonable approach for every patient. The goal of personalized medicine is to analyze a patient's genome or tumor genome and choose a therapy targeting a specific aberration causing minimal side effects. In our patient with mCRPC, he is able to elude the inevitable side effects of abiraterone and enzalutamide including fatigue, hot flashes, and erectile dysfunction along with evading the side effects of continuing chemotherapy. More importantly, this gene-directed therapy provides a visible attenuation of his disease.

A meta-analysis has been performed on the impact of personalized medicine on solid tumors. Jardim et al. assessed the significance of a biomarker-guided therapy strategy for FDA-approved cancer treatments selected based on patients' biomarker data. This study of 38,104 patients found that personalized treatments were associated with higher median response rates (48% vs 23%; P < 0.001), longer median progression free survival (8.3 vs. 5.5 months; P = 0.002), and higher median overall survival (19.3 vs. 13.5 months; P = 0.04).3 The conclusion of this study was that biomarker-guided strategies were associated with better patient outcomes. This large study helps to prove benefit from both NGS and gene-targeted treatments as described in our...
Another promising note is the fact that the Centers of Medicare & Medicaid Services (CMS) have recently decided to extend coverage to NGS for recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancers. This decision by CMS is an indisputable impetus for private insurers to cover NGS for the same indication and most likely sets the groundwork for the approval of NGS for all tumor samples regardless of stage.

Fig. 1. Succession of treatments from diagnosis to current.

Fig. 2. a. Day 0 of cabozantinib 40mg daily. b. Day 75 of cabozantinib 40mg daily.
Conclusion

NGS for every patient’s tumor is a noble goal and will likely become standard of care. Changing the landscape of how oncologists treat cancers is a large hurdle, but as sequencing techniques improve in speed and accuracy, the use and development of targeted agents will become more prevalent. Improving patient outcomes while reducing overall costs and side effects to the patient is the overall goal for personalized medicine. As current technology and laboratory techniques only become more adept through innovation, the fastidiousness of how medicine is practice will only become more precise. The era of sequencing every tumor and being able to identify driver mutations is not a distant one from now.

Consent

Verbal consent was obtained from the patient to use his case for this manuscript.

Conflict of interest statement

The authors have no conflicts of interest to report.

Disclosures

The authors have no disclosures to report.

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