



## Platinum Priority – Editorial

Referring to the article published on pp. 184–192 of this issue

# An Imprecise Path to Precision Medicine

Alicia K. Morgans\*

Division of Hematology/Oncology, Department of Medicine, Northwestern University, Chicago, IL, USA

In this month's issue of *European Urology*, Zafeiriou and colleagues [1] report a case series of three exceptional responses to treatment with carboplatin by men with metastatic castration-resistant prostate cancer (mCRPC). Two men had evidence of homologous recombination defects (HRDs) with deleterious germline *BRCA2* and *ATM* mutations, and the third had a mutational signature with a high homologous recombination repair deficiency score. Responses were rapid and durable despite initial indications of aggressive disease that was unresponsive to traditional therapies. These cases provide hope that the field is getting closer to characterizing disease heterogeneity in mCRPC, but simultaneously raise questions about the imprecise nature of our understanding of which patients and treatments will ultimately be the best match.

The history of platinum and prostate cancer without neuroendocrine differentiation has been relatively disappointing, possibly due to a lack of patient selection [2,3]. A phase 2 study of men with mCRPC assessed responses to the addition of carboplatin to retreatment after progression on docetaxel and found that 18% of men achieved a prostate-specific antigen (PSA) decline of  $\geq 50\%$  [2]. A phase 3 trial of satraplatin evaluated an unselected population of men with mCRPC and found a reduced the risk of progression or death versus placebo, but not improved survival [3]. In contrast, studies including molecularly selected patients have been more promising. A case series including three men with prostate cancer with biallelic *BRCA2* loss also reported exceptional responses to treatment with carboplatin [4]. A separate retrospective study [5] evaluated 141 men with mCRPC who received carboplatin and found that among eight men with germline *BRCA2* mutations, 75% experienced  $\geq 50\%$  decline in PSA by 12 wk. This body of evidence suggests that treatment with carboplatin may induce

disease response in select populations that may be identified by the presence of germline HRDs and other signatures that are still being defined. If responsiveness to platinum may serve as a biomarker for a *BRCAness* phenotype in mCRPC, as it is in ovarian cancer, we could consider using a combination of genetic and functional screening for clinical trials to more accurately enrich study cohorts with patients who may be responsive to treatments targeting HRDs [6].

Germline testing for heritable mutations was recently included in clinical practice guideline recommendations. Based on evidence suggesting that the incidence of germline HRDs in men with metastatic prostate cancer exceeds 10% (11.8%), the National Comprehensive Cancer Network guidelines in the USA now recommend consideration of genetic counseling for men with metastatic prostate cancer [7,8]. The recommendation does not apply only to men who are young at the time of diagnosis or have a strong family history, as neither of these factors was associated with the presence of HRDs in the analysis [7]. In the case series presented by Zafeiriou and colleagues [1], it is interesting to note that all the included patients had family histories that were considered higher than average risk, and two of the three patients were under 55 yr of age at the time of diagnosis. Although the men in this case series fit the traditional mold that we have used to implement genetic testing, this should not induce clinicians to limit testing to those patients alone. Efforts to continue characterization of high-risk populations that may benefit most from a referral for genetic counseling and screening remain critical. As evidenced in this report, not all patients will be identified through traditional next-generation sequencing efforts, and techniques to identify these currently unidentified patients

DOI of original article: <https://doi.org/10.1016/j.eururo.2018.09.048>.

\* 676 N. St. Clair St., Suite 850, Chicago, IL 60611, USA. Tel. +615-695-6180.

E-mail address: [alicia.morgans@northwestern.edu](mailto:alicia.morgans@northwestern.edu).

<https://doi.org/10.1016/j.eururo.2018.10.023>

0302-2838/© 2018 European Association of Urology. Published by Elsevier B.V. All rights reserved.



must be standardized. Strategies to systematically incorporate methods to identify and test appropriate patients must also be incorporated into standard clinical workflow processes if we are to successfully deliver these services, particularly given the shortage of individuals trained to counsel these patients on testing and result interpretation [9].

Although the patient stories presented in the accompanying article are compelling, change in clinical practice must be driven by the highest-quality data gathered from double-blind randomized trials. Even before the publication of this case series, guidelines and consensus statements acknowledge that men with HRDs may benefit from early treatment with platinum chemotherapy [8,10]. Clinicians are able to use platinum to treat patients off label, and many already are. Despite this, we must complete rational trials that assess these treatments prospectively in comparison with standard of care approaches. Multiple studies are being conducted internationally that will characterize the effect of treatment with platinum-based therapy in select populations, shedding light on which patients should receive this treatment, how it should be delivered, and what we can expect in terms of response. Subsequent steps should include comparative effectiveness studies between platinum agents and PARP inhibitors, as well as with other standard of care therapies, to provide more granular information on where platinum and other targeted agents fit in sequence in the larger treatment landscape. Decisions regarding how to optimally integrate these agents must include estimates of value based on cost and benefit, as well as an understanding of toxicity and tolerability from a patient's perspective. If broadly effective and tolerable, platinum approaches may be attractive for men with HRDs or *BRCAness* profiles in part because of their relative affordability compared with other treatment approaches.

Although the cases presented by Zafeiriou and colleagues [1] are insufficient in themselves to change practice, they add to a growing body of literature that demonstrate that men with HRDs may have additional options for effective treatment of advanced prostate cancer. The time has come to incorporate germline and somatic testing into routine care for men with metastatic prostate cancer by standardizing clinic workflows and ensuring payers are covering the cost of counseling and testing. Further work to characterize the tail of the curve of responders, including identifying mutational signatures that may be associated with HRDs and a *BRCAness* phenotype, is critical. Finally, we

as clinicians must continuously educate ourselves regarding the expanding body of literature that will increasingly contribute to treatment decisions. With each step, reports similar to these and the clinical trials they inspire move us further down the imprecise path to precision medicine, and provide hope that there is progress to be made.

**Conflicts of interest:** The author reports no conflicts of interest related to the manuscript, but she has received honoraria in the last 12 mo from consulting relationships with Janssen, Bayer, Astellas, Sanofi, AstraZeneca, and Genentech.

## References

- [1] Zafeiriou, et al. Genomic analysis of three metastatic prostate cancer patients with exceptional responses to carboplatin indicating different types of DNA repair deficiency. *Eur Urol* 2019;75:184–92.
- [2] Ross RW, Beer TM, Jacobus S, et al. A phase 2 study of carboplatin plus docetaxel in men with metastatic hormone-refractory prostate cancer who are refractory to docetaxel. *Cancer* 2008;112:521–6.
- [3] Sternberg CN, Petrylak DP, Sartor O, et al. Multinational, double-blind, phase III study of prednisone and either satraplatin or placebo in patients with castrate-refractory prostate cancer progressing after prior chemotherapy: the SPARC trial. *J Clin Oncol* 2008;27:5431–8.
- [4] Cheng HH, Pritchard CC, Boyd T, Nelson PS, Montgomery B. Biallelic inactivation of BRCA2 in platinum-sensitive metastatic castration-resistant prostate cancer. *Eur Urol* 2016;69:992–5.
- [5] Pomerantz MM, Spisak S, Jia L, et al. The association between germline BRCA2 variants and sensitivity to platinum-based chemotherapy among men with metastatic prostate cancer. *Cancer* 2017;123:3532–9.
- [6] Konstantinopoulos PA, Spentzos D, Karlan BY, et al. Gene expression profile of *BRCAness* that correlates with responsiveness to chemotherapy and with outcome in patients with epithelial ovarian cancer. *J Clin Oncol* 2010;28:3555–61.
- [7] Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med* 2016;375:443–53.
- [8] National Comprehensive Cancer Network. Prostate cancer. Version 4. 2018. [https://www.nccn.org/professionals/physician\\_gls/pdf/prostate.pdf](https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf).
- [9] Cheng H, Powers J, Schaffer K, Sartor O. Practical methods for integrating genetic testing into clinical practice for advanced prostate cancer. *Am Soc Clin Oncol Educ Book* 2018;38:372–81.
- [10] Gillessen S, Attard G, Beer TM, et al. Management of patients with advanced prostate cancer: the report of the Advanced Prostate Cancer Consensus Conference APCCC 2017. *Eur Urol* 2018;73:178–211.