Editorial

Case reports are a valuable resource in the era of genomic testing

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Introduction

The paper by Zafeiriou *et al.* (1) describes exceptionally prolonged remission ranging from 3 to 15 years observed in three cases with homologous DNA repair mutations in metastatic castrate resistant prostate cancer (CRPC). The exceptional response has always been the most intriguing part of the clinical practice of medicine. Every physician sees at least one unexpected/exceptional responder during their medical practice careers. For decades the standard practice that followed is to try and identify common clinicopathologic features between the index exceptional responder, and future patients presenting with the same diagnosis, and using similar treatment strategies. Every clinical specialist has been attempting to practice "personalized medicine" throughout the history of medicine. Invariably doctors are repeatedly disappointed with the results in subsequent patients. Recently genomic testing that is widely available and easily applicable has considerably broadened the possibilities of identification of predictive biomarkers. The medical community continues to attempt to locate a clear biomarker for every disease, and pair it with an available therapy to prove targeted efficacy and safety.

Noteworthy breakthroughs

Hematologic malignancies have had successes in identifying the genomic marker that will help define therapeutic choice. A sterling example is the Philadelphia chromosome in chronic myelogenous leukemia that enabled this condition to be treatable with imatinib. In solid tumors multiple examples exist such as the Estrogen and progesterone and her-2 receptors in breast cancer, c-kit in gastrointestinal stromal tumors and Alk fusions in lung cancer. There are also tumor agnostic mutations such as microsatellite instability, and homologous repair defects that have drastically impacted our clinical management. The recently approved NTRK inhibitor in the rare cases that have the specific fusion is another example of the impact of delving into therapeutic development for the rarest of subtypes. Clearly taking note of these responses, has spearheaded drug development for the subtypes that can be identified by genomic testing and therapeutically targeted. It is the striking function of literally saving the world of cancer "one patient at a time".

NCI exceptional responder program

In 2014 the National Cancer Institute (NCI) started their "Phenotype to Genotype" exceptional responder initiative (2,3). The inspiration for this program came from a phase II study of everolimus conducted in advanced bladder cancer (4). The study was stopped after the first stage as it did not meet the prespecified response rates but one patient derived an exceptional response (3). This patient had the TSC-1 mutation which was a predictor of response to MTOR inhibition (2). The main objectives of the program consisted of the following:

(I) To identify molecular indicators in malignant tissues from patients who were exceptional responders on clinical trials or other systemic cancer treatments, using whole exome, targeted, and mRNA sequencing, and potentially molecular characterization methods.

(II) To explore associations between the identified molecular indicators and the putative mechanism of

Table 1 Carboplatin based regimens in phase II trials in prostate cancer

Ref	No	Response rate	Median PFS	Median OS
Oh *et al.* (5), E + Doce + Carbo	40	23/34 (68%) PSA decline ≥50%; 11/21 (52%) measurable disease	8.1 months	19 months
Ross *et al.* (6), Carbo + Doce	34	18% PSA decline ≥50%; 14% measurable disease	3 months	12.4 months
Vaishampayan *et al.* (7), Carbo + everolimus	26	4 pts with PSA decline ≥30%; no measurable disease responses	2.5 months	12.5 months
Aparicio *et al.* (8), Carbo + Doce, Then Carbo + VP-16	120	50% response rate	Not reported	16 months
Regan *et al.* (9), meta-analysis, Carbo + Doce + E	310	69% PSA decline ≥50%	Not reported	18 months

action of the treatment received by the patient.

(III) To test the feasibility of identifying "exceptional responders", obtaining the relevant tumor and normal tissue and clinical data, and performing whole exome sequencing on these samples.

This kind of program needs to be made available across multiple academic and non-academic sites within the country and developing this database will open the possibility of capturing more correlations between specific mutations impacting therapeutic efficacy and will create a powerful tool for the future. The exceptional response model should be implemented as a blueprint for future drug development and research. It highlights the growing importance of publishing and disseminating exceptional responder case reports within the genomic testing era.

PARP inhibition and platinum-based chemotherapy

This paper is a wonderful example of generating a hypothesis based on a very detailed study of a small number of cases. These cases clearly demonstrated a remarkable response to therapies. The first case demonstrated near complete response despite the presence of liver and brain metastases, a typical marker of dismal prognosis in metastatic castrate resistant prostate cancer. In addition response was reproducible with multiple rechallenges of carboplatin therapy. The homologous repair defects (HRD) were not detected on routine next generation sequencing but on whole exome sequencing (WES) only after using multiple bioinformatic approaches. The second case was that of a patient with a known BRCA2 frameshift truncating mutation of germline origin and a family history of multiple cancers. Interestingly the patient revealed an unexpectedly suboptimal response to a PARP inhibitor but demonstrated a prolonged response to carboplatin. The third case had a ATM loss that was noted in germline and somatic testing. However clinically the histopathology in this case had shown 90% synaptophysin staining and clinical features suggested neuroendocrine differentiation of prostate cancer (NEPC). This case should receive carboplatin therapy even in the absence of NGS testing result and dramatic responses have been reported in NEPC. So the role of the HRD genetic mutation in predisposing the patient to a remission from carboplatin therapy is not clear in case 3 given the distinct neuroendocrine histology.

Platinum based therapy was never formally established as a therapeutic option in advanced prostate cancer. However multiple phase II studies have shown reasonable efficacy and in neuroendocrine prostate cancer this remains the treatment of choice. In metastatic prostate adenocarcinoma the response rates have ranged from 18% to 68% depending on whether single agent carboplatin or combination chemotherapy was used (5-9) (*Table 1*). The overall toxicity profile remains tolerable. The role of polyadenosine ribose polymerase (PARP) inhibition is gradually being established in prostate cancer. Mateo *et al.* reported the phase II clinical trial results that showed that 16 (33%) of 49 evaluable patients responded to olaparib therapy. However when the subset of mCRPC patients with HRD were assessed the response was noted to be 88% (14 responders of 16 patients) (10). The group at Dana Farber conducted a retrospective analysis of patients with mCRPC and pathogenic germline variants of BRCA2 mutations. Six of eight (75%) BRCA2 carriers experienced prostate-specific antigen decline >50% within 12 weeks, compared to 23 of 133 (17%) non-carriers (absolute difference 58%; 95% CI, 27–88%; P<0.001).

The BRCA2 mutation patients had a significantly better outcome with platinum based chemotherapy (11). The role of platinum in patients with HRD in advanced prostate cancer has not yet been prospectively studied. Most studies evaluating PARP inhibitors have excluded prior treatment with platinum. It appears likely that platinum-based therapy maybe an asset in therapeutic management of mCRPC with HRD. Extrapolating from other cancers such as ovarian cancer with BRCA1 and 2 mutations, recently reported trial results have revealed a large magnitude of benefit when PARP inhibitors were administered as consolidation therapy post platinum-based therapy (12). The review of case 2 indicates potential clues that some patients with ATM defects may show a predisposition to response to platinum over PARP inhibitors. Satraplatin, an oral well tolerated platinum that was evaluated in prostate cancer and may have potentially resulted in a positive trial if risk stratification on the basis of molecular markers was feasible at the time of the study (13,14).

Further validation of carboplatin-based therapy is needed in metastatic CRPC but the study design presents multiple challenges. Studies maybe required in a cohort of neuroendocrine prostate cancer patients with or without HRD, and in a distinct cohort of metastatic adenocarcinoma of prostate with associated presence or absence of HRD. The extensive pathology review to confirm NEPC and the NGS and WES required as shown in the spectrum of the above cases would be very tough to conduct in a real time prospective clinical trial setting. An adequate difference in response rates between the HRD positive and negative patients would be needed for adoption into clinical therapeutic decision making. However these type of studies represent the core future of cancer medicine where biomarker enrichment will enable trials with smaller sample sizes, and hopefully accelerate drug development for a targeted population.

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Footnote

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References

1. Zafeiriou Z, Bianchini D, Chandler R, 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. Mullard, A. Learning from exceptional drug responders. Nat Rev Drug Discov 2014;13:401-2.
3. Takebe N, McShane L, Conley B. Exceptional responders—discovering predictive biomarkers. Nat Rev Clin Oncol 2015;12:132-4.
4. Iyer G, Hanrahan AJ, Milowsky M, et al. Genome sequencing identifies a basis for everolimus sensitivity. Science 2012;338:221.
5. Oh WK, Halabi S, Kelly WK et al. A phase II study of estramustine, docetaxel, and carboplatin with granulocyte-colony-stimulating factor support in patients with hormone-refractory prostate carcinoma: Cancer and Leukemia Group B 99813. Cancer 2003;98:2592-8.
6. 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.
7. Vaishampayan U, Shevrin D, Stein M, et al. Phase II Trial of Carboplatin, Everolimus, and Prednisone in Metastatic Castration-resistant Prostate Cancer Pretreated With Docetaxel Chemotherapy: A Prostate Cancer Clinical Trial

Consortium Study. Urology 2015;86:1206-11.
8. Aparicio AM, Harzstark AL, Corn PG, et al. Platinum-Based Chemotherapy for Variant Castrate-Resistant Prostate Cancer. Clin Cancer Res 2013;19:3621-30.
9. Regan MM, O'Donnell EK, Kelly WK, et al. Efficacy of carboplatin-taxane combinations in the management of castration-resistant prostate cancer: a pooled analysis of seven prospective clinical trials. Ann Oncol 2010;21:312-8.
10. Mateo J, Carreira S, Sandhu S, et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. N Engl J Med 2015;373:1697-708.
11. 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.
12. Moore K, Colombo N, Scambia G, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med 2018. [Epub ahead of print].
13. 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 2009;27:5431-8.
14. Bhargava A, Vaishampayan UN. Satraplatin: leading the new generation of oral platinum agents. Expert Opin Investig Drugs 2009;18:1787-97.

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