Chronological Liquid Biopsy Reveals the Impact of Platinum-Based Chemotherapy on a Prostate Cancer Patient’s CDK12 Mutation: A Case Report

Sha Zhu1,*, Yige Bao1,*, Linmao Zheng2,*, Jinge Zhao1, Yuntian Chen3, Rui Huang4, Guangxi Sun1, Fengnian Zhao1, Xingming Zhang1, Jiayu Liang1, Junru Chen1, Zhipeng Wang1, Yuchao Ni1, Ni Chen2, Pengfei Shen1, Hao Zeng1

1Department of Urology, West China Hospital, Sichuan University, Chengdu, People’s Republic of China; 2Department of Pathology, West China Hospital, Sichuan University, Chengdu, People’s Republic of China; 3Department of Radiology, West China Hospital, Sichuan University, Chengdu, People’s Republic of China; 4Department of Nuclear Medicine, West China Hospital, Sichuan University, Chengdu, People’s Republic of China

*These authors contributed equally to this work

Correspondence: Pengfei Shen; Hao Zeng, Department of Urology, West China Hospital, Sichuan University, Chengdu, 610041, People’s Republic of China; Tel +86-18980602129, Fax +86-28-8542-2451, Email cdhx510@163.com; zengh@scu.edu.cn; kucaizeng@163.com

Abstract: CDK12 (Cyclin-Dependent Kinase 12)-mutated prostate cancer patients often respond badly to current therapies. Immunotherapy and platinum-based chemotherapy are recommended based on the molecular features of CDK12-mutated tumors, but the reported patient outcomes are still unsatisfying. Here we report a prostate cancer patient with CDK12 somatic mutation who received multiple therapy options, including platinum-based chemotherapy and immunotherapy. His sequential circulating tumor DNA (ctDNA) -based liquid biopsy tests showed that his original CDK12 mutation fell undetectable twice. This phenomenon was observed only when he was responding well to platinum-based chemotherapy. His responses to immunotherapy were not satisfying. This case indicates that platinum-based chemotherapy can be a good option for treating patients with CDK12 mutation. More importantly, dynamic ctDNA-based liquid biopsies to monitor patients’ CDK12 mutation status are critical in evaluating patients’ response and tolerance during platinum-based chemotherapy, therefore may lead to a better overall prognosis. In conclusion, CDK12-mutated prostate cancer patients are likely to benefit from platinum-based chemotherapy, especially with the help of dynamic ctDNA-based liquid biopsies to monitor their CDK12 mutation status.

Keywords: CDK12, liquid biopsy, platinum, prostate cancer, case report

Introduction

Androgen targeted medication (such as abiraterone1 and enzalutamide2) and cytotoxic drugs (such as docetaxel3 and cabazitaxel4) are the mainstream treatments in metastatic castration-resistant prostate cancer (mCRPC). Even though they demonstrate a strong effect, some mCRPC patients still have poor survival, and the lethal ones usually harbor certain genomic dysregulations. Therefore, emerging data focus on PARP inhibitors, immunotherapy, prostate-specific membrane antigen theranostics, etc.5

Prostate cancers with CDK12 (Cyclin-Dependent Kinase 12) mutation are aggressive and respond poorly to traditional therapies. CDK12-mutated prostate cancer delineates a distinct molecular phenotype. Although not directly participating in the homologous recombination (HR) repair machinery, CDK12 tightly regulates the transcription of several HR genes by phosphorylating RNA polymerase II.6,7 Thus, CDK12-mutated tumors harbor a characteristic genomically unstable phenotype. Since CDK12-mutated patients can also be considered HR-deficient, synthetic lethality, i.e., PARP inhibitor and platinum chemotherapy, seems a compelling strategy for treating these patients. Nevertheless, PARP inhibitor did not perform well in CDK12-mutated prostate cancer patients.8-11 At the same time, platinum creates more potent double-strand breaks, while limited evidence supports its use in these patients (only one case report and...
a study in 2020 noted a platinum response but did not discuss it).\textsuperscript{7,12} Besides, due to the high neo-antigen burden, CDK12-mutated tumors are also speculated to benefit from immune checkpoint inhibitors (ICI).\textsuperscript{13,14} While currently, there has not been any clinical evidence for the rationality of this method. Therefore, to date, there are no treatment standards for CDK12-mutated prostate cancers.

**Case Presentation**

A 55-year-old man with a prostate-specific antigen (PSA) of 16.56 ng/mL was diagnosed with localized prostate cancer (NCCN high-risk group) at West China Hospital (Chengdu, China) in May 2018. He underwent laparoscopic radical prostatectomy soon after his diagnosis. His post-surgical pathological reports showed T-stage 3b (Figure 1), and his specimen was sent for whole-exome sequencing (2018/5/30), which showed a CDK12 mutation. Plus, his PSA decrease was not satisfying, so he received a total of 66 Gy’s adjuvant radiotherapy concomitant with ADT. Then his PSA remained undetectable for over a year until a drastic increase to 2.19 ng/mL. He was diagnosed with mCRPC in Nov. 2020, with metastases in lung, thoracic vertebra 6, neck, and mediastinum showing on PET/CT. First-line docetaxel barely led to a PSA decrease, which was maintained at around 6.00 ng/mL for a month. Thus, he was recommended to do a liquid biopsy-based genetic test (2021/2/5). The results showed a CDK12 mutation, which was also validated using the metastatic tissue in the lung. Due to the limited therapeutic efficacy of PARP inhibitors in patients with CDK12 mutation,\textsuperscript{8,9} we suggested adding cis-platinum to his chemotherapy regimen.\textsuperscript{7,12} He immediately displayed a PSA response to platinum-based chemotherapy, which dropped to 0.26 ng/mL within four cycles. At the same time, another liquid biopsy-based genetic test (2021/5/10) of him showed no CDK12 mutation anymore. However, the patients suffered from hematopoietic side effects (WBC decrease). We had to interrupt this treatment plan and change to abiraterone instead. The patient immediately started showing a constant PSA increase, even after adding apalutamide. And his liquid biopsy-based genetic test (2021/8/11) at this moment showed CDK12 mutation again. When he recovered from the chemotherapy-related side effects, his PSA increased to 4.19 ng/mL. We did a fully MDT panel discussion and decided to give him a platinum-based chemotherapy rechallenge under strict medical observation. However, although his PSA

Figure 1 MRI, SPECT, and pathology (including HE, KI-67, P53, PTEN, RB1 immunohistochemistry) of the patient at first diagnosis. The arrows point to the primary tumor lesions.

**Abbreviations:** MRI, magnetic resonance imaging; SPECT, single-photon emission computed tomography; PTEN, phosphatase and tensin homolog; RB1, retinoblastoma.
was dropping rapidly, the side effects were much more serious WBC decrease combined with severe edema; thus, we had to disrupt his platinum-based chemotherapy. Noticeably, right after the platinum treatment, his CDK12 mutation disappeared again (2021/10/4). Later, we changed to PD-1 inhibitor as recommended by literature. Unfortunately, the PD-1 inhibitor did not stop his PSA increase. During the PD-1 inhibitor treatment, the patient’s liquid biopsy genetic test (2021/11/29) showed CDK12 mutation again, and its mutation abundance significantly increased. The patients died at the end of 2021 due to cerebral infarction. His PSA results with important treatment annotations were displayed in Figure 2. All liquid biopsy test protocols in this study were described in our previous publication.

Discussion

Here we report a CDK12-mutated mCRPC patient who responded to second-line platinum-based treatment. His status of CDK12 mutation periodically changed along with the chemo-therapeutic periods. We performed immunohistochemistry for common biomarkers such as Ki-67, P53, PTEN, and RB1 on his primary tumor to understand more about its aggressiveness. The results showed that except for P53 loss, a common feature in human cancers, it displayed low cell proliferation, no loss of PTEN, and indeterminate RB1 level. Our patient’s treatment experience does not support the use of PD-1 inhibitors. Instead, this case demonstrates the efficacy of platinum in a CDK12-mutated patient. The patient achieved progression-free survival (PFS) of 8.3 months for platinum-based chemotherapy (even as a second-line therapy), which is much longer than the previously reported 3 months’ median PFS in patients with all HR mutations or CDK12 mutation specifically.

Disease monitoring during the mCRPC phase has always been troublesome due to limited indicators. PSA, as an efficient and straightforward biomarker in localized prostate cancer, however, is insufficient to direct modern systemic therapeutic options. On one hand, a proportion of mCRPC tumors display low PSA while being highly aggressive (neuroendocrine prostate cancer, etc.). On the other hand, PSA change does not necessarily reflect the clinical benefit of treatment targeting pathways other than AR. Therefore, combining clinical symptoms and radiographic evidence with PSA change is usually required. Even so, both clinical manifestations and radiographic progression have inherent hysteretic nature. The recent decade has seen the development of various prostate cancer therapies targeting the DNA
damage repair (DDR) pathway and tumor immune microenvironment. Thus, there is a great need for new methods to monitor these mCRPC patients’ responses and to provide comprehensive, sequential management. Blood-based liquid biopsies are an attractive tool to stratify prostate cancer patients and inform treatment guidance due to their minimally invasive nature, especially in the advanced metastatic setting when obtaining tissue biopsies samples is restricted by practical situations. Currently, ctDNA-based liquid biopsy is becoming the mainstream in precision oncology for selecting therapy, anticipating responses, developing novel biomarkers, monitoring tumor evolution, etc.\(^\text{21}\) As in our case, the reappearing \(CDK12\) mutation was prior to his PSA increase. This suggests that our dynamic ctDNA-based monitoring approach is more timely than traditional PSA, which offers us a longer window of opportunity to alter treatment plans for aggressive patients with explicit pathogenic mutations.

HR-related genes usually remain stable during prostate cancer progression.\(^\text{22}\) Nevertheless, in this case, sequential ctDNA-based liquid biopsy results clearly show that besides the good response, his periodical \(CDK12\) mutation status directly reflects his reactions to this therapy. The \(CDK12\) mutation in his ctDNA was undetectable each time he reached PSA nadir during platinum-based chemotherapy treatment. No similar phenomenon has been reported before, and we suppose that strong selection pressure caused by platinum can diminish the corresponding \(CDK12\)-mutated tumor clones. This implies platinum could indeed be a strong candidate for treating tumors with \(CDK12\) mutation as the driver event. Also, dynamic liquid biopsy for the \(CDK12\) mutation status is a valuable tool to monitor treatment response and stratify patients by selecting out those more likely to show a satisfying response to platinum. We hypothesize that for patients with \(CDK12\) mutation, their ctDNA \(CDK12\) mutation status at the PSA nadir timepoint when receiving platinum-based chemotherapy is probably crucial for adjusting the treatment regime accordingly. In addition, the long-term use of many therapies is currently restricted by side effects and the emergence of resistance. With the help of dynamic liquid biopsy tests, clinicians may be more confident in providing intermittent therapy plans according to concrete molecular evidence of the patient rather than his/her own clinical experience. Furthermore, this case also gives us insight into the use of dynamic liquid biopsy monitoring in other targeted drugs or synthetic lethal agents.

**Conclusions**

Our report shows the potential of platinum-based chemotherapy in \(CDK12\)-mutated advanced prostate cancer patients and underscores the significance of dynamic ctDNA-based liquid biopsies for \(CDK12\) mutation status in monitoring these patients’ responses. Further prospective studies of platinum-based regimens in \(CDK12\)-mutant prostate cancer patients, with at least another liquid biopsy test at PSA nadir timepoint during therapy, are warranted.

**Abbreviations**

ctDNA, circulating tumor DNA; PSA, prostate-specific antigen; mCRPC, metastatic castration-resistant prostate cancer; HR, homologous recombination; ICI, immune checkpoint inhibitors; PFS, progression-free survival; DDR, DNA damage repair.

**Availability of Supporting Data**

Data in this study is available upon reasonable request to the contact author.

**Ethical Approval and Consent to Participate**

Protocols in this study obtained West China Hospital institutional review board approval. The patient provided written consent to participate in this study and to publish his data.

**Consent for Publication**

All authors give their consent for publication.

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Author Contributions
All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure
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