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Case Report

CHEK2 gene in metastatic prostate cancer: A cordial check on DNA damage repair pathway

Sheereen Fatima[1], Imran Nisar Shaikh[1], Amrit Kaur Kaler[2]

[1]Centre for Cancer, Kokilaben Dhirubhai Ambani Hospital and Research Centre, [2]Department of Molecular Pathology and Genomics, Kokilaben Dhirubhai Ambani Hospital and Research Centre, Mumbai, Maharashtra, India.

***Corresponding author:**
Imran Nisar Shaikh,
Centre for Cancer, Kokilaben Dhirubhai Ambani Hospital and Research Centre, Mumbai, Maharashtra, India.

imran.shaikh@kokilabenhospitals.com

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ABSTRACT

Mutation in homologous recombination repair (HRR) pathway is well established in ovarian cancers. Multiple trials have shown variable efficacy in prostate cancers. Mutations other than BRCA1/BRCA2 have been recently reported in prostate cancers. We describe a unique case of an elderly male with metastatic castration-resistant prostate cancer. He responded to hormonal therapy for 6 months but later progressed. Chemotherapy with docetaxel produced severe side effects in the patient and, thus, was discontinued. Next-generation sequencing was performed on tissue sample which selected a pathogenic mutation (TIER 1) in CHEK2 gene, which is a missense mutation, leading to loss of function of protein. CHEK2 is a cell cycle regulator and a tumor suppressor gene mediating homologous recombinant DNA repair pathway and genetic alterations in it makes tumor susceptible to newer targeted therapies.

Keywords: Metastatic prostate cancer, Olaparib, Chek2, Non-BRCA

INTRODUCTION

Prostate cancer is the most commonly diagnosed non-cutaneous malignancy in men and remains the second-leading cause of cancer-related death in men.[1,2] Despite advances in screening for and early detection of prostate cancer, a large portion of men continue to present with advanced or metastatic disease-approximately 20% of men in recent reports.[3]

Metastatic castration-resistant prostate cancer (mCRPC) is an aggressive and fatal disease with an estimated 34,130 deaths in the US in 2021 and a median survival of 36 months[4,5] There are multiple treatment options available for use in mCRPC, including taxanes, sipuleucel-T, abiraterone acetate, enzalutamide, and radium-223, but outcomes continue to remain poor due to progressive resistance to therapies.

In the past decade, genetic sequencing has identified new molecular targets in prostate cancer in the pathways that promote tumorigenesis and can be targeted therapeutically. We present a unique case of mCRPC in an elderly male responsive to targeted therapy due to presence of a rare mutation.

CASE REPORT

A 76 year old diabetic male, came to us in February 2022 with complains of lower urinary tract symptoms, constipation, and pain while passing stools starting December 2020. He also

complained of pain in the back for the past 1 year, which increased in intensity since 2–3 months, inability to walk due to pain, and bedridden associated with extreme weakness for the past 1 week. On examination, he had bilateral lower limb swelling extending till knee joint. He had catheter inserted for acute retention of urine a month back.

He was initially investigated and treated in Nairobi. His PSA level in January 2021 was 300 ng/mL. TRUS biopsy was done which revealed adenocarcinoma prostate, Gleason score: 4 + 5 = 9, Grade 5/5. PET-CT whole body highlighted metastatic disease spread to lymph nodes and bones. He was, thus, started on tablet Abiraterone, injection Zoladex and tablet Bicalutamide, which he took for 6 months.

Initially, PSA levels came down but later increased and the disease showed progression in July, 2021. Hence, he was started on taxanes (Docetaxel) for three cycles which were later stopped due to drug toxicity (myelosuppression and diarrhea). He developed pulmonary embolism in December 2021 and was started on low molecular weight heparin.

When he reported to us in February 2022, with the above complaints, we did our own set of investigations. His complete blood count, liver, and renal function test are as follows: Hemoglobin (10.7 mg/dL), white blood cells (2400 cells/mm^3), platelet counts (150,000), serum bilirubin (2.22 mg/dL), SGOT (75.6 U/L), SGPT (154.9 U/L), alkaline phosphate (509.1 U/L), gamma glutamyl transferase (1715 U/L), albumin (2.68 gm/dL), serum calcium (6.5 mg/dL), and serum creatinine (0.65 mg/dL).

His PSA level was 366 ng/mL. MRI spine showed lumbosacral spinal metastases. PSMA PET-CT scan [Figure 1] expressed PSMA avid uptake seen in prostate, regional and retroperitoneal lymph nodes, extensive liver metastases, and multiple axial skeletal metastases. Urine routine and microscopy showed urinary tract infection.

The patient was hospitalized and started on intravenous antibiotics, analgesics, and anti-diabetic medications. He was referred for palliative radiation therapy and received five Gray in five fractions to lumbosacral spinal metastases. He still had coccydynia, hence underwent USG guided ganglion impar block, and experienced moderate relief. He was, then, referred to Nuclear Medicine Physician but found unsuitable for Lutetium 177 therapy due to liver metastases, low WBC, and platelets.

A trucut biopsy from liver lesion was done at our hospital which confirmed the diagnosis of metastatic adenocarcinoma of prostate origin (NKX3.1 and AMACR positive). Considering the poor responses to all currently available therapies, we performed HRR gene analysis on patient's biopsy block. The assays were done using a commercial test. The tumor percent on slide was 40%. Multiple ribbons of tissue were taken using microtome. DNA was extracted using Quagen DNA extraction kit and the library was prepared using amplicon based technology. The final sequenced data on MiSeq (next-generation sequencing) was aligned with human genome 19, analyzed at ×500, and minimum average depth using illumine Dragon pipeline. As results would take 2–3 weeks, he was put on Enzalutamide 160 mg/day and discharged from the hospital. His PSA level after 20 days was 266 ng/mL.

The PSA repeated on March 10, 2022, was 1.863 ng/mL. The patient complained backache, and thus, his PSA levels were repeated on March 25, 2022, which was 40.71 ng/mL. Considering poor response to therapy, Enzalutamide was stopped. The HRR gene analysis showed pathogenic CHEK2 mutation (alteration in pr389H with MAF 42.8% at ×3699).

Hence, he was started on olaparib 300 mg twice a day from March 2022. Injection Zoledronic Acid was added for bony metastasis and Injection Zoladex was given as patient did not undergo orchidectomy. Counseling for screening of family members was also done.

The patient responded very well to olaparib. He was able to walk on his own and do all his activities of daily living

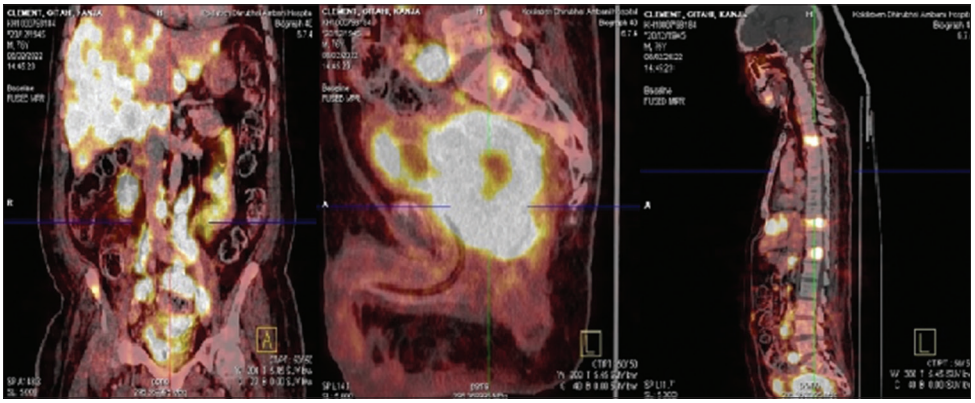

Figure 1: The PMSA PET CT scan showing increased FDG uptake at the region of prostate, liver, multiple axial skeletal bones, and retroperitoneal group of lymph nodes.

within 15 days of starting the therapy. There was significant improvement in complete blood counts, liver, and renal function test.

His PSA level on May 2022 was 4.183 ng/mL. Repeat PSA level in June 2022 was 4.685 ng/mL.

The PSA value after 8 months of therapy with olaparib came down to 0.868 ng/dL. The patient has a well-controlled disease at the end of 8 months and, still, continues to derive the benefit with no known toxicity.

DISCUSSION

In recent years, several genomic studies have shown that mutations in prostate cancer are commonly found in DNA-damage repair (DDR) pathways, and when they occur in the homologous recombination repair (HRR) pathway specifically, the tumor relies on poly (ADP) ribose polymerase (PARP) to correct DNA damage and prevent cell lysis.[6] This results in synthetic lethality with use of PARP inhibitors, opening up new avenues of therapy.

PROfound trial showed that approximately 30% patients with mCRPC show actionable mutation in HRR pathway, out of which, BRCA2 (9.7%) is the most common germline HRR mutation, followed by CDK12 (7.1%), ATM (6.3%), CHEK2 (1.6%), PP2R2A (1.5%), and BRCA1 (1.3%). CHEK2 mutation as found in our case, thus, becomes a rare mutation.

Out of all, the patient considered for the above study, only 11 of them had CHEK2 mutation. Median imaging based progression-free survival in the patient with given mutation was 5.59 months.[7] Our patient showed remarkable fall in his PSA level and improvement in clinical symptoms within 2 weeks of starting the therapy and is progression free at 8 months.

Based on the prolonged survival in men with HRR gene mutations and acceptable toxicity profile, the FDA approved olaparib in May 2020 as treatment for patients with mCRPC with HRR gene alterations who have progressed following prior treatment with androgen-receptor directed therapy.[8] TOPARP B phase II trial reported a CHEK2 alteration participant (1/7) achieving a PSA decrease of 50%.[9]

TRITON2 phase II trial enrolled 78 patients with a non-BRCA DDR gene alteration, in which patient with CHEK2 was only 12. Among patients evaluable for each endpoint, radiographic and PSA responses were observed in a limited number of patients *CHEK2 (*1/9 [11.1%] and 2/12 [16.7%]), respectively, with rucaparib. A confirmed PSA response was observed in 2 (16.7%) of 12 overall patients with a *CHEK2* alteration, one of whom was the patient with a radiographic response. The 6-month clinical benefit rate for patients with a CHEK2 alteration was 37.5% (3 of 8 patients); no patients with a *CHEK2* alteration were still receiving treatment at 12 months.[10] Our patient is still on the therapy with olaparib and has good disease control even after 8 months and no known side effects.

Our study underlines the benefit of the use of single agent Olaparib in a mCRPC patient with a CHEK2 mutation (Non-BRCA) for a prolonged period of time, 8 months compared to 5–6 months highlighted in the previous studies.

CONCLUSION

Contrary to the observation made in PROfound trail that non-BRCA DDR mutations do not derive same clinical benefit from Olaparib as BRCA2 mutations, our patients responded exceptionally well, both clinically and in values of PSA level similar to BRCA mutated patients and until date derives the benefit.

Based on our experience, we recommend thorough screening of non-BRCA genetic alterations, along with BRCA mutations in a newly diagnosed case of mCRPC as they are likely to derive equal benefit from PARP inhibitors.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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