Significant Benefit of Everolimus In a Patient With Urothelial Bladder Cancer Harboring A Rare M1043I Mutation of PIK3CA

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Research Article

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Abstract

Urothelial bladder cancer (UBC) is a common malignancy with significant mortality worldwide. However, treatment options of UBC were mainly chemotherapy and immunotherapy since few targeted agents had shown efficacy in UBC. In recent studies, everolimus has showed antitumor activity in patients harboring aberrations in PI3K/Akt/mTOR pathway in multiple tumor types. Here we report a patient with metastatic UBC harboring a rare M1043I mutation of PIK3CA detected by DNA based next-generation sequencing. The patient received everolimus as first-line therapy after palliative transurethral resection. Within one months, the residual lymph node metastases achieved complete response and no more ostealgia was reported. To our knowledge, this is the first case reporting a significant benefit from everolimus in PIK3CA mutant UBC, suggesting the rare M1043I mutation variant may be a potential biomarker of sensitivity to everolimus. Further mechanism insights and clinical studies are needed to clarify the effectiveness of everolimus in patients with *PIK3CA* M1043I mutation.

Short Report

Urothelial bladder cancer (UBC) is a common malignancy with significant mortality. However, treatment options of UBC were mainly chemotherapy and immunotherapy since few targeted agents had shown efficacy in UBC [1]. Everolimus, as an inhibitor of mammalian target of rapamycin (mTOR), showed antitumor activity in patients harboring aberrations in phosphatidylinositol 3-kinase (PI3K)/ protein kinase B (Akt)/mTOR pathway in multiple tumor types such as renal cell and breast cancer (Janku et al. 2013). In this case, we report a patient with metastatic UBC harboring a rare M1043I mutation of *PIK3CA*, who responded well to everolimus.

In June 2020, an 81-year-old male was admitted to the hospital for 1-month-history of weakness and low back pain. Pelvic computed tomography (CT) revealed a space-occupying lesion in the left anterior wall of bladder (Fig. 1a); meanwhile, multiple lymph node metastases were confirmed. Besides, osseous metastasis was considered due to ostealgia although nothing was verified by CT. Palliative transurethral resection was performed and post-operational immunohistochemical (IHC) staining showed: CK20 (-), CK7 (+), Ki-67 (+30%), p53 (+), p63 (+), GATA-3 (+), Syn (-), CgA (-), CD3 (-), CD20 (-). These results suggested a diagnosis of stage IV UBC (T3bN1M1).

The patient refused chemotherapy because of poor physical condition. To seek for precision therapy, formalin-fixed and paraffin-embedded specimens were subjected to next-generation sequencing (NGS) analysis. The M1043I mutation of *PIK3CA* was detected (Fig. 2), the concurrent alterations were listed in Table 1. The patient received everolimus (10 mg orally daily) as first-line treatment and obtained complete remission of lymph node metastases and felt no ostealgia within 1 month. The disease was evaluated as complete response (CR) (Fig. 1b) and no progression was observed before submission.

To our knowledge, this case is the first report of a BC patient with M1043I mutation of *PIK3CA* who responded well to everolimus. Alteration of *PIK3CA* occurred in approximately 20% of UBC [1]. In our case,

the patient harbored a rare M1042I mutation. This mutation located in the kinase domain of *PIK3CA* and could enhance the activation level and lipid binding capacity of the coded protein p110α, which will constitutively activate Akt/mTOR pathway and contribute to tumorigenesis and cancer progression [2].

Previous studies indicated that *PIK3CA* mutation was associated with better response to PI3K/Akt/mTOR inhibitors [3, 4]. Analysis in breast cancer also presented better response of H1047R mutation variant to everolimus than non-H1047R mutation/wild-type (progression-free survival of 8.8 months versus 4.1 months) [5]. As for UBC, Everolimus showed growth inhibitory effect of on the tumor cells with of PI3K/Akt/mTOR aberrations in preclinical studies [6], while the clinical evidence of everolimus in *PIK3CA* mutant BC is lacking. So far, only an early phase II study in BC observed 1 partial response/stable disease with E542K mutation and 2 progressed disease with E545K mutation of *PIK3CA* [3]. Therefore, the efficacy of everolimus in *PIK3CA* mutant BC remained unclear. Our patient reached CR within 1 month of everolimus treatment, this implies that everolimus might be a promising treatment option for UBC patients with *PIK3CA* mutation.

Meanwhile, as the first report of significant benefit from everolimus, we infer that the rare M1043I mutation variant may be a potential biomarker of sensitivity to everolimus. Although a concurrent *PIK3CA* amplification (Table 1) was discovered, it may not be the sensitive alteration responded to everolimus since a recent trial of everolimus in *PIK3CA* amplification/mutation patients with advanced solid tumors failed to observe any response [7]. Further study is needed to investigate the molecular and responding mechanism of *PIK3CA* M1043I mutation in UBC.

Declarations

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Conflicts of interest

The authors declare that they have no conflict of interest.

Availability of data and material

Not applicable.

Code availability

Not applicable.

Authors' contributions

Conception/Design: Junlong Li, Shouhua Pan

Provision of study material or patients: Shouhua Pan, Si Li

Collection of data: Shouhua Pan

Data analysis and interpretation: Si Li

Manuscript writing: Shouhua Pan, Si Li, Dongsheng Chen

Final approval of manuscript: Junlong Li, Mingzhe Xiao

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate & publication

Informed consent was obtained from the patient for participating and publication of this case.

References

1. The Cancer Genome Atlas Research Network (2014) Comprehensive molecular characterization of urothelial bladder carcinoma. Nature 507:315–322. https://doi.org/10.1038/nature12965
2. Gymnopoulos M, Elsliger M-A, Vogt PK (2007) Rare cancer-specific mutations in PIK3CA show gain of function. Proceedings of the National Academy of Sciences 104:5569–5574. https://doi.org/10.1073/pnas.0701005104
3. Seront E, Rottey S, Sautois B, et al (2012) Phase II study of everolimus in patients with locally advanced or metastatic transitional cell carcinoma of the urothelial tract: clinical activity, molecular response, and biomarkers. Annals of Oncology 23:2663–2670. https://doi.org/10.1093/annonc/mds057
4. Janku F, Wheler JJ, Naing A, et al (2013) *PIK3CA* Mutation H1047R Is Associated with Response to PI3K/AKT/mTOR Signaling Pathway Inhibitors in Early-Phase Clinical Trials. Cancer Res 73:276–284. https://doi.org/10.1158/0008-5472.CAN-12-1726
5. Yi Z (2019) Everolimus in hormone receptor-positive metastatic breast cancer: PIK3CA mutation H1047R was a potential efficacy biomarker in a retrospective study. 9
6. Chiong E, Lee I-L, Dadbin A, et al (2011) Effects of mTOR Inhibitor Everolimus (RAD001) on Bladder Cancer Cells. Clinical Cancer Research 17:2863–2873. https://doi.org/10.1158/1078-0432.CCR-09-3202

7. Kim ST, Lee J, Park SH, et al (2017) Prospective phase II trial of everolimus in PIK3CA amplification/mutation and/or PTEN loss patients with advanced solid tumors refractory to standard therapy. BMC Cancer 17:211. https://doi.org/10.1186/s12885-017-3196-6

Table

Table 1. Concurrent gene alterations detected by NGS.

Gene Name	Copy Number Variation	Copy Number
CCND1	Gain	7
CDKN2A	Loss	0
CDKN2B	Loss	0
PIK3CA	Gain	>20

Figures

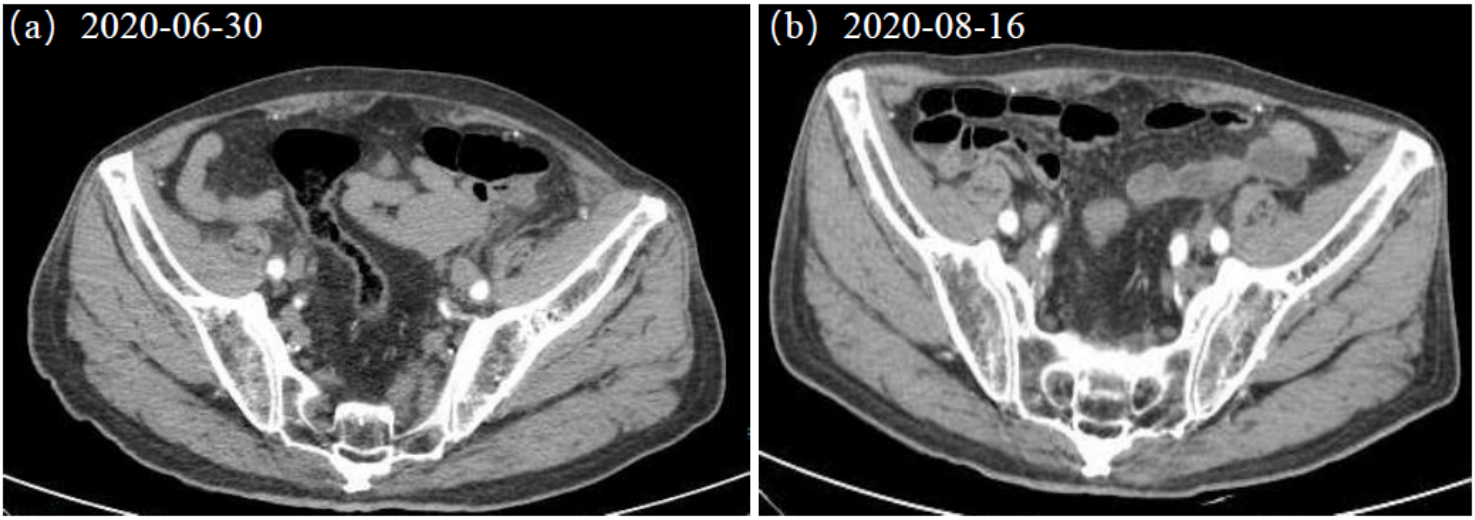

Figure 1

Tumor response of the patient' s right lung lesion during everolimus treatment. (a) Initial diagnosis revealed a space-occupying lesion in the left anterior wall of bladder by pelvic CT; (b) Pelvic CT scans showed complete response after one months' treatment of everolimus.

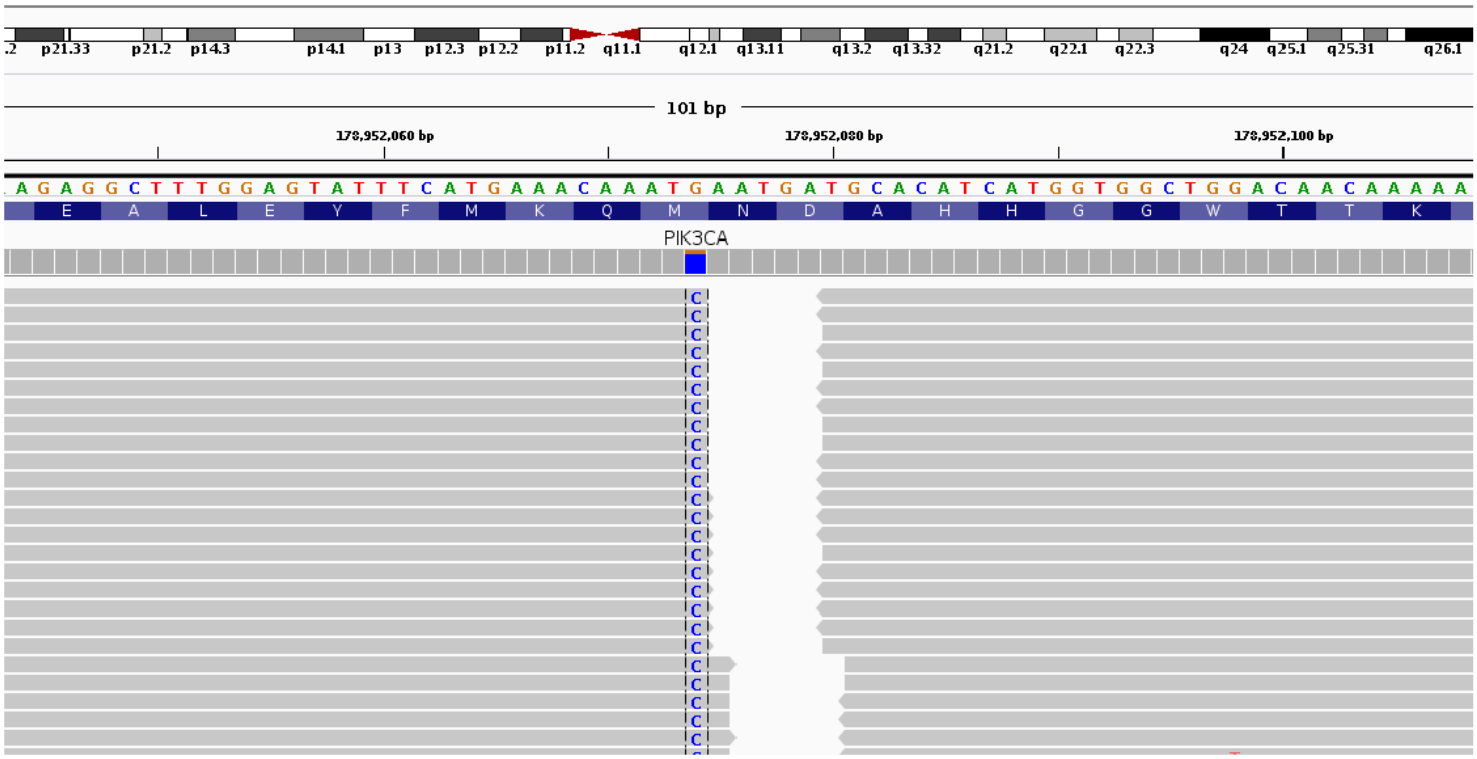

Figure 2

Next-generation sequencing findings of PIK3CA M1043I mutation.