Significant benefit of everolimus in a patient with urothelial bladder cancer harboring a rare M1043I mutation of PIK3CA

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Summary
Urothelial bladder cancer (UBC) is a common malignancy with considerable mortality worldwide. However, the treatment options of UBC are mainly chemotherapy and immunotherapy, as few targeted agents have demonstrated efficacy against UBC. In recent studies, everolimus has exhibited antitumor activity in patients harboring aberrations in the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway in multiple tumor types. Herein, we report the case of a patient with metastatic UBC harboring a rare M1043I mutation of PIK3CA which was detected using DNA-based next-generation sequencing. The patient received everolimus as first-line therapy after palliative transurethral resection. The treatment resulted in complete response within 1 month, and the patient achieved a progression-free survival (PFS) of >6 months according to reports from the last follow-up visit. To our knowledge, this is the first reported case of PIK3CA-mutant UBC for which everolimus therapy demonstrated a significant benefit suggesting that the rare M1043I mutation variant may be a potential biomarker of sensitivity to everolimus. Further insights into its mechanism and clinical studies are needed to clarify the effectiveness of everolimus therapy in patients with PIK3CA M1043I mutation.

Keywords Bladder cancer · PIK3CA · Everolimus · mTOR · Complete response

Short report
Urothelial bladder cancer (UBC) is a common carcinoma that has considerable mortality. However, the major treatment options for UBC are chemotherapy and immunotherapy, as few targeted agents, such as those used in precision therapy, have been reported to be efficacious against UBC [1]. Everolimus, as an inhibitor of the mammalian target of rapamycin (mTOR), has demonstrated antitumor activity in patients harboring aberrations in the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mTOR pathway in multiple tumor types such as renal cell and breast cancers [2]. Herein, we report the case of a patient with metastatic UBC with a rare M1043I mutation of PIK3CA who responded well to everolimus therapy.

In June 2020, an 81-year-old male patient was admitted to our hospital because of a 1-month history of weakness and low back pain. Pelvic computed tomography (CT) revealed a space-occupying lesion in the left anterior wall of the bladder (Fig. 1a); additionally, multiple lymph node metastases were confirmed. Moreover, osseous metastasis was considered due to ostealgia, although this was not verified by CT. A palliative transurethral resection was performed, and postoperative immunohistochemical staining showed the following findings: CK20 (−), CK7...
(+), Ki-67 (+30%), p53 (+), p63 (+), GATA-3 (+), Syn (−), CgA (−), CD3 (−), and CD20 (−). These results suggested a diagnosis of stage IV UBC (T3bN1M1).

The patient refused chemotherapy because of poor physical condition. As an alternative, precision therapy was considered, and next-generation sequencing analysis was performed on formalin-fixed and paraffin-embedded specimens. The M1043I mutation of PIK3CA was detected (Fig. 2), and the concurrent alterations are listed in Table 1. The patient received everolimus therapy (10 mg orally daily) as first-line treatment since July 15 and attained complete remission of lymph node metastases, without ostealgia within 1 month after treatment initiation. The disease outcome was evaluated as complete response (CR; Fig. 1b). No progression was observed in the last follow-up visit on January 26, 2021; PFS exceeded 6 months.

To our knowledge, this is the first reported case of bladder cancer (BC) in a patient with M1043I mutation of PIK3CA who responded well to everolimus therapy. PIK3CA alteration occurs in approximately 20% of UBCs [1]. In our case, the patient harbored a rare M1042I mutation. This mutation is located in the kinase domain of PIK3CA and could enhance the activation level and lipid-binding capacity of the coded protein p110α, which constitutively activates the Akt/mTOR pathway and contribute to tumorigenesis and cancer progression [3].

Previous studies have indicated that PIK3CA mutation was associated with better response to PI3K/Akt/mTOR inhibitors [2, 4]. Further, studies on breast cancer revealed that patients with the H1047R mutation variant showed better response to everolimus therapy than those with the non-H1047R mutation/wild-type cancer cells (PFS of 8.8 months vs. that of 4.1 months) [5]. As for UBC, everolimus therapy exhibited a growth inhibitory effect on tumor cells with PI3K/Akt/mTOR aberrations in preclinical studies [6], although clinical evidence for the effectiveness of everolimus therapy for PIK3CA-mutant BC is lacking. So far, only an early phase II study on BC found a case of partial response/stable disease with E542K mutation and 2 cases of progressed disease with E545K mutation of PIK3CA [4]. Therefore, the efficacy of everolimus therapy for PIK3CA-mutant BC remains unclear. Our patient attained CR within 1 month of everolimus treatment, which implies that everolimus therapy might be a promising treatment option for UBC in patients with PIK3CA mutation.

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

![Fig. 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 month's treatment of everolimus.](image)

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         |
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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, Mingzhe Xiao, Dongsheng Chen.
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Declarations

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.

Conflict of interest

The authors declare that they have no conflict of interest.

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