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Illuminating and Instructive Clinical Case

Significant Response to Palbociclib Plus Lenvatinib as Second-line Treatment for CDKN2A/2B Deletion Intrahepatic Cholangiocarcinoma: A Case Report

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Abstract

Cyclin-dependent kinase inhibitor 2A/2B (*CDKN2A/2B)* deletions are frequently identified in patients with biliary tract cancer; however, standard treatment options for this genetic alteration are lacking. Here, we present the case of a 64-year-old woman diagnosed with intrahepatic cholangiocarcinoma and hilar lymph node metastasis who underwent radical surgery. Postoperative pathology confirmed moderately differentiated adenocarcinoma. The tumor recurred during the second cycle of adjuvant chemotherapy following surgery, and the metastatic sites included the cranial region, right lung, and right adrenal gland. Genetic analysis revealed a *CDKN2A/2B* deletion, indicating palbociclib sensitivity. Subsequently, the patient received palbociclib plus lenvatinib as systemic therapy, along with stereotactic radiotherapy for the intracranial lesion. Notably, the right pulmonary metastasis significantly regressed after 12 months of treatment, with the complete disappearance of the intracranial tumor. However, the disease progressed at 32.2 months, with significant enlargement of the right adrenal gland metastasis and new metastasis in the right lung. The progression-free survival and overall survival were 32.2 months and 34.4 months, respectively. In conclusion, our case demonstrates that palbociclib plus lenvatinib is a promising chemotherapy-free second-line treatment for intrahepatic cholangiocarcinoma with a *CDKN2A/2B* deletion.

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Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common type of primary malignant liver cancer after hepatocellular carcinoma.[1,2] Owing to its highly aggressive nature and significant heterogeneity, ICC often lacks specific clinical indications in the early stages, and diagnosis is typically made at an advanced stage. Radical surgical resection is the best option for achieving long-term survival. However, only 30–40% of patients with ICC are candidates for curative surgery.[3] Moreover, the postoperative recurrence rates of ICC are very high, ranging from 40% to 80%,[3] with fewer than one-third of patients undergoing curative-intent surgery surviving beyond five years after resection.[4]

Currently, the first-line treatment for ICC is chemotherapy, with or without programmed cell death protein 1 and programmed cell death ligand 1 inhibitors. However, an effective second-line treatment is still lacking for patients who cannot tolerate chemotherapy or who experience disease progression after first-line therapy.[5] Molecular-targeted therapy based on genetic testing has emerged as a potential therapeutic option for ICC. Cyclin-dependent kinase inhibitor 2A/2B (*CDKN2A/2B)* deletion is common in ICC, and the targeted drug palbociclib (a *CDK4/6* inhibitor) is used to treat solid tumors harboring the *CDKN2A/2B* deletion.[6] However, a phase 2 clinical trial demonstrated that palbociclib monotherapy lacked clinical efficacy in advanced biliary tract cancer with *CDKN2A/2B* deletions.[7] Moreover, the clinical benefit of lenvatinib as a second-line treatment for advanced ICC is limited.[8] The combined application of multiple targeted drugs produces a synergistic anti-tumor effect, maximizing anti-tumor efficacy.[9] Here, we report a case of ICC with *CDKN2A/2B* deletion treated with palbociclib plus lenvatinib, which resulted in long-term survival after chemotherapy progression.

Case presentation

A 64-year-old Chinese woman had a history of drinking and smoking but no history of hepatitis B, other infectious diseases, cirrhosis, or a family history of genetic disorders. She was scheduled for a physical examination, during which a space-occupying lesion in the liver was detected on imaging. Malignancy was suspected, and intrahepatic cholangiocarcinoma was diagnosed by fine-needle aspiration. Subsequently, she

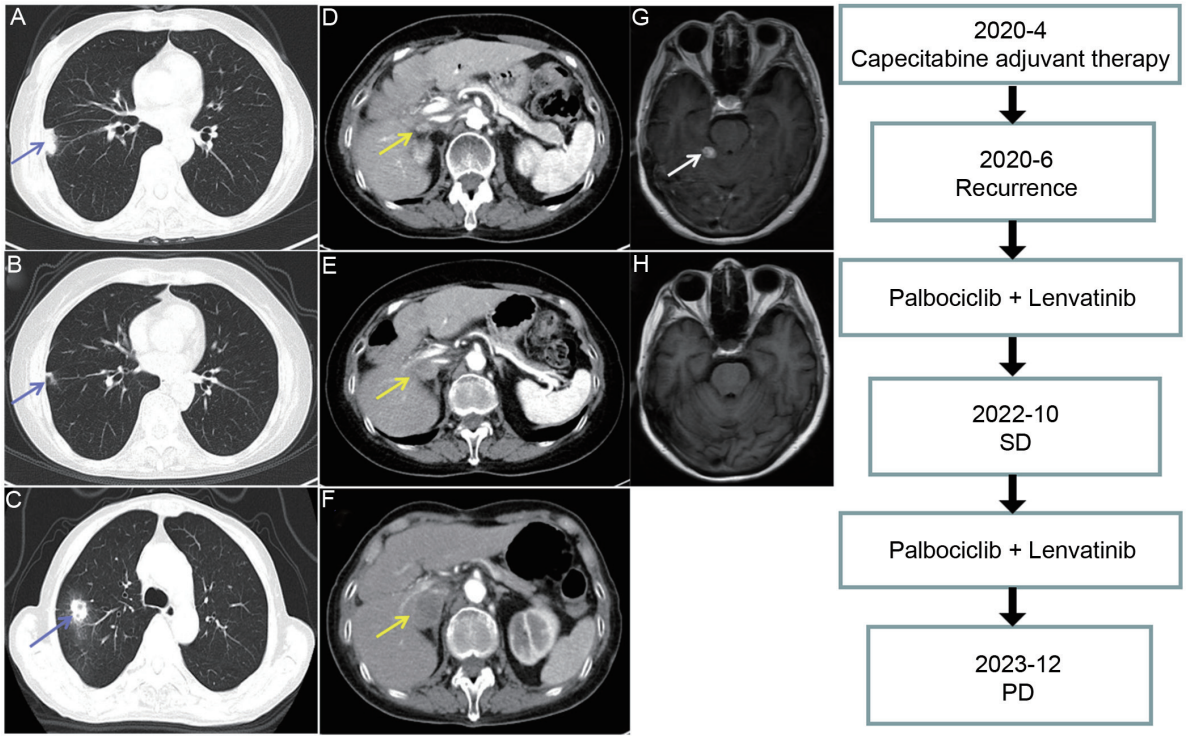

Fig. 1. Images of the patient during treatment. (A) CT showed tumor recurrence in the right lung. (B) CT showed that the lung metastasis had significantly shrunk. (C) CT showed a new metastasis appeared in the right lung. (D) CT showed tumor recurrence in the right adrenal gland. (E) CT showed the right adrenal gland metastasis was slightly larger than before. (F) CT showed the right adrenal gland metastasis was more than 20% larger than before. (G) MRI showed an intracranial metastasis. (H) MRI showed the intracranial metastasis had disappeared. Blue arrows point to lung lesions; Yellow arrows point to adrenal lesions; White arrows point to intracranial lesions. CT, computed tomography; SD, Stable disease; PD, Progressive disease; MRI, magnetic resonance imaging.

underwent radical resection at Peking Union Medical College Hospital. Pathological analysis revealed adenocarcinoma, and genetic testing identified a *CDKN2A/2B* deletion. The *CDKN2A/2B* status of the patient was determined using a large-panel next-generation sequencing assay. Next-generation sequencing results did not indicate mutations in vascular endothelial growth factor receptor and/or fibroblast growth factor receptor (*FGFR*) but predominantly revealed deletions in the *CDKN2A/2B* genes (Supplementary Tables 1 and 2). One month after surgery, the patient received capecitabine as adjuvant therapy. She repeatedly experienced severe nausea, vomiting, and diarrhea with oral capecitabine treatment, which was only slightly relieved by symptomatic treatment. Enhanced computed tomography (CT) performed after two cycles of treatment showed a 1.9-cm metastasis in the right lung and a 1.1-cm metastasis in the right adrenal gland. Additionally, due to headache, cranial magnetic resonance imaging (MRI) was performed, revealing a 1.2-cm intracranial metastasis. Tumor recurrence was diagnosed based on enhanced CT and MRI findings. Glucoprotein antigen 199 levels, liver and kidney functions, and routine blood values were within the normal range. Oxaliplatin in combination with infusional 5-fluorouracil/leucovorin regimen was administered as the standard second-line treatment according to the National Comprehensive Cancer Network guidelines;[2] however, the patient refused chemotherapy due to concerns about toxicity. Genetic testing revealed palbociclib sensitivity. The patient requested targeted anticancer drugs. Nevertheless, a phase II trial demonstrated that palbociclib monotherapy lacked clinical activity.[7] Recognizing the limitations of palbociclib monotherapy, a combination therapy with lenvatinib was proposed to enhance efficacy through synergistic mechanisms. After a comprehensive discussion of the potential benefits and risks of palbociclib plus lenvatinib, the patient opted for the combination therapy: palbociclib[6] (100 mg orally per day for two weeks, followed by one week off) and lenvatinib (8 mg orally daily).[8] Stereotactic radiotherapy was used to treat the intracranial metastasis.

Tumor assessments were conducted every six to nine weeks using enhanced CT or MRI, with clinical responses evaluated based on RECIST v1.1 criteria.[10] At nine months, MRI showed resolution of the intracranial metastasis, and CT revealed significant shrinkage of the pulmonary metastases, with a 22% reduction in gross tumor volume. The disease remained stable until progression at 32 months when CT showed a new 1.7-cm right lung metastasis and growth of the right adrenal gland metastasis to 2.0 cm (Fig. 1). The patient succumbed to progressive disease at 33 months. The overall survival (OS) was 33.4 months, with progression-free survival (PFS) of 32.2 months. No serious adverse events occurred, besides mild stomach discomfort during treatment.

Discussion

This case represents the first report of significant survival improvement in advanced ICC with *CDKN2A/2B* deletion using palbociclib plus lenvatinib as a new second-line treatment. The combination of palbociclib and lenvatinib demonstrated substantial clinical benefits and a favorable safety profile, highlighting its potential as a promising second-line treatment option for this patient population.

Second-line options for ICC are limited, with the oxaliplatin

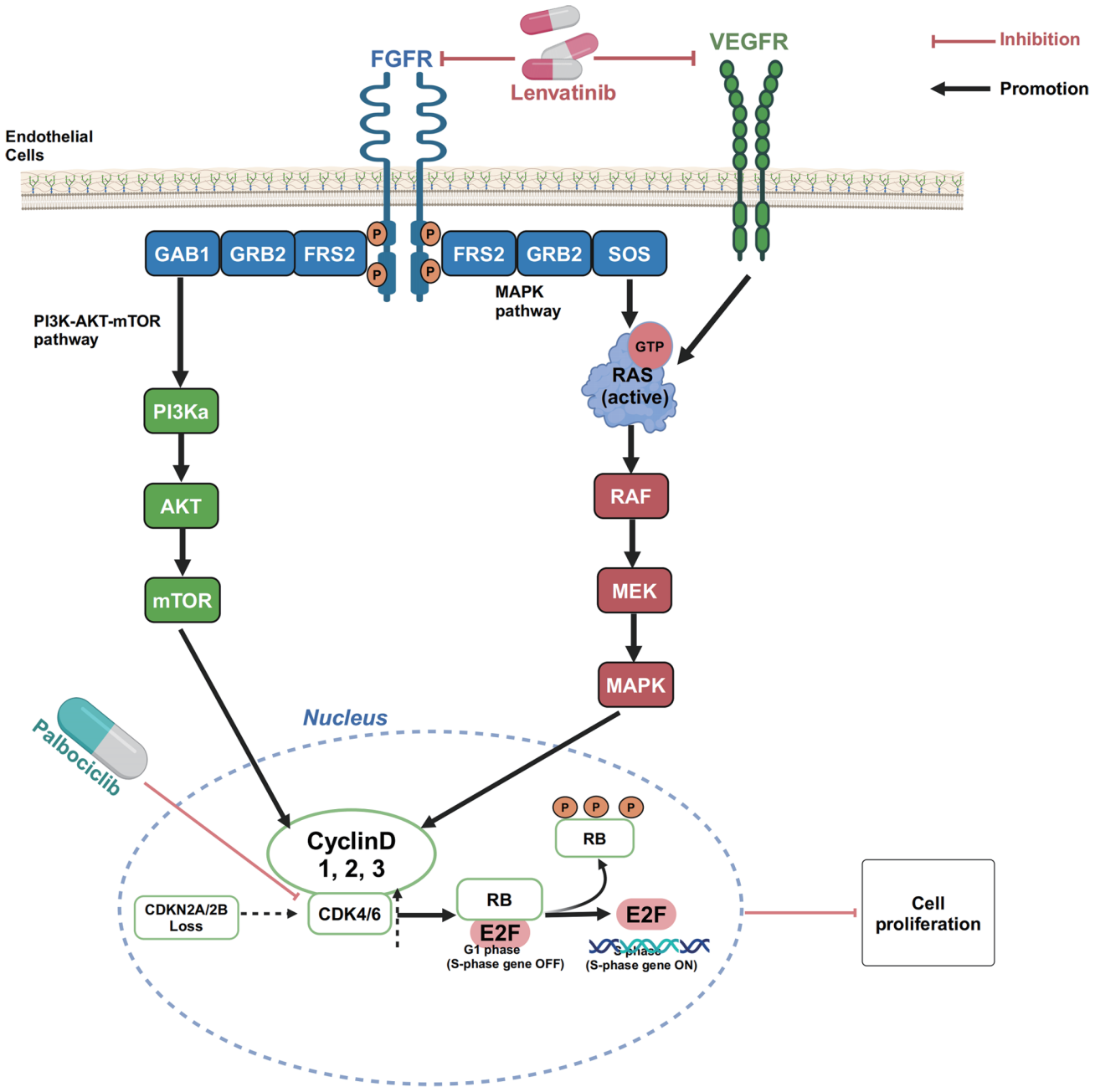

Fig. 2. Schematic representation of the synergistic mechanism between lenvatinib and palbociclib. FGFR, fibroblast growth factor receptor; VEGFR, vascular endothelial growth factor receptor; AKT, the serine/threonine kinase Akt, also known as protein kinase B(PKB); mTOR, mammalian target of raparmycin; RAF, rapidly accelerated fibrosarcoma; MEK, mitogen-activated protein kinase kinase; MAPK, mitogen-Activated Protein Kinase; RB, retinoblastoma; E2F, a transcription factor, is a significant regulator of proliferation, differentiation, and apoptosis; RAS, rat sarcoma; GTP, guanosine triphosphate.

in combination with infusional 5-fluorouracil/leucovorin regimen recommended for patients with good performance status and chemotherapy tolerance.[11] However, many patients are either unable or unwilling to undergo chemotherapy or are ineligible for immunotherapy, necessitating alternative treatment approaches.

A phase II clinical trial showed some clinical activity for palbociclib monotherapy as a first-line treatment for biliary tract cancer with *CDKN2A/2B* deletions; however, the mOS was only 11.1 weeks,[7] suggesting that palbociclib monotherapy may not be a suitable second-line treatment. Recently, multi-target drugs have been explored for second-line therapy in ICC. Another phase II clinical trial showed an mOS of 7.35 months for lenvatinib monotherapy as a second-line treatment.[8] Combining palbociclib with other anticancer drugs may offer a superior effect by enhancing therapeutic efficacy and overcoming drug resistance.[12] Hence, we adopted a combination regimen (palbociclib plus lenvatinib) in this case. Our patient showed long PFS and OS without serious adverse events. This result may be attributed to the potential

synergistic mechanisms between the two drugs.

CDKN2A/2B deletions activate pathways such as p16INK4α-*CDK4/6*-pRb and p14ARF-*MDM2*-p53, promoting cell proliferation and tumor progression.[13] Palbociclib, a *CDK4/6* inhibitor, induces apoptosis and cell cycle arrest but has shown limited efficacy as monotherapy.[7,13] Lenvatinib, a multi-target tyrosine kinase inhibitor, targets vascular endothelial growth factor receptors 1–3 and *FGFR*1-4.[8] Additionally, it suppresses tumor angiogenesis and proliferation by targeting the vascular endothelial growth factor/vascular endothelial growth factor receptor and fibroblast growth factor/FGFR signaling pathways. This dual inhibition confers greater anti-tumor activity to lenvatinib than other drugs, such as sorafenib. Furthermore, lenvatinib modulates the immune microenvironment, reducing programmed cell death ligand 1 expression and inhibiting Treg differentiation. Taken together, lenvatinib demonstrates anti-tumor activity in ICC through the inhibition of the *FGFR* signaling pathway and immune-modulatory effects.[8,14]

The combination of palbociclib and lenvatinib may offer a synergistic effect through multiple mechanisms. Firstly, FGFR1 amplification or upregulation can cause resistance to *CDK4/6* inhibitors. When lenvatinib blocks FGFR1,[15] it may improve the sensitivity of palbociclib in ICC. Secondly, lenvatinib can induce cell cycle arrest in *CDKN2A/2B*-deleted ICC cells, effectively inhibiting tumor cell proliferation and significantly reducing the migration and invasion abilities of tumor cells.[16] Thirdly, lenvatinib's inhibition of autophagy and modulation of immune responses further enhance its anti-tumor activity.[16] Finally, *CDK6* is an important protein kinase that contributes to lenvatinib resistance. *CDK4/6* inhibitors can inhibit *CDK6*, reducing tumor resistance to lenvatinib (Fig. 2).[12]

Preclinical studies suggest that combined treatment remodels the immune microenvironment, increasing memory effector T cells and reducing immunosuppressive $CD8^+$ T cells, thereby improving immune-mediated tumor suppression.[12]

Conclusions

Palbociclib plus lenvatinib demonstrated significant and synergistic efficacy as a second-line treatment for advanced ICC with *CDKN2A/2B* deletions, achieving prolonged PFS and OS without severe adverse events. This chemo-free regimen warrants further investigation in clinical trials for this subset of ICC patients.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conception and design (HZ, LZ), data analysis and interpretation, and manuscript writing (KL). All authors contributed to data collection. All authors approved the final version and publication of the manuscript.

Ethical statement

This study was approved by the Ethics Committee of Peking Union Medical College Hospital (NCT02715089). Informed consent to participate in this study was obtained from the patient's direct relatives.

Data sharing statement

The data and materials used and/or analyzed during the current study are included in this case. The data are available from the corresponding author upon reasonable request.

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