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Case Report

Promising Response with PI3K Inhibitor for a Patient with Heavily Pretreated *PIK3CA* Mutation Head-and-Neck Cancer

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Abstract

The treatment options for patients with head-and-neck squamous cell carcinoma (HNSCC) are limited when the disease progresses after taking platinum, a PD-1 inhibitor, and cetuximab. To develop new agents for managing such pretreated malignancies, therapies targeting carcinogenic pathways could be possible in HNSCC patients. Several pathways have been identified in HNSCC, including the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway. The PI3K/AKT/mTOR pathway is frequently dysregulated in various cancers due to activating mutations or amplification of *PIK3CA*. The inhibition of this pathway has been proven to improve clinical outcomes in some malignancies with *PIK3CA* mutations. We report a heavily pretreated HNSCC patient with a good treatment response to alpelisib, a PI3K inhibitor. Furthermore, we discuss the possible limitations of alpelisib monotherapy and possible solutions to overcome these limitations.

Keywords: Alpelisib, head and neck squamous cell carcinoma, PIK3CA mutation

Introduction

For patients with recurrent or metastatic head-and-neck squamous cell carcinoma (HNSCC), the standard first-line treatment includes pembrolizumab, cetuximab, and platinum-based chemotherapy. The treatment options and the efficacy of these treatments are limited in second or later-line settings. Currently, there is no established targeted therapy according to genetic alterations in HNSCC. New personalized treatment options for patients with HNSCC are urgently needed. *PIK3CA* mutations are common in HNSCC, and the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway is a possible druggable target. Here, we report a *PIK3CA*-mutated HNSCC patient with a rapid clinical response to alpelisib monotherapy.

Case Report

A 51-year-old man without smoking, alcohol consumption, or betel-quid chewing habits suffered from right tonsillar pain and odynophagia in May 2019. Magnetic resonance imaging (MRI)

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showed a right tonsillar tumor, with clinical staging cT3N2bM0. He received a right tumor tonsillectomy as a biopsy in August 2019, and the pathology report showed poorly differentiated squamous cell carcinoma with positive p16 expression. He received two cycles of induction chemotherapy with the TPF regimen (3-week cycle of docetaxel at a dose of 60 mg/m^2 on day 1, cisplatin at a dose of 70 mg/m^2 on day 1, and fluorouracil at a dose of 1000 mg/m^2 on day 1 through 3) followed by definitive concurrent chemoradiotherapy (CCRT) (cisplatin total dose, 240 mg/m^2, radiation dose 70 Gy in 33 fractions).

CCRT was completed in November 2019, and the patient achieved a good partial response clinically. In March 2020, a residual neck lymph node at the right level II area was disclosed in a follow-up MRI, and he underwent elective neck dissection of the right neck lymph node. The pathology report of the resected lymph node revealed metastatic squamous cell carcinoma. He subsequently received adjuvant chemotherapy with three cycles of cisplatin (40 mg/m^2 on day 1, day 8, 21 days a cycle) and tegafur/uracil (tegafur 200 mg BID, day 1 to day 21) from April 2020 to June 2020. However, follow-up computed tomography (CT) in July 2020 showed recurrent right neck lymph nodes and multiple new lung metastases. He was then enrolled in a phase I trial with a combination therapy of pembrolizumab and a chemokine receptor 4 antagonist from August 3, 2020. The study treatment was discontinued in October 2020 due to a larger neck lymph node and lung metastasis. Combination therapy with cetuximab-paclitaxel-cisplatin (cetuximab 400 mg/m^2 loading, followed by 250 mg/m^2 weekly; cisplatin 35 mg/m^2 on day 1 and day 8, 21 days a cycle; paclitaxel 80 mg/m^2 on day 1, day 8, 21 days a cycle), cetuximab-methotrexate (cetuximab 250 mg/m^2 weekly; methotrexate 40 mg/m^2 weekly), afatinib-etoposide (afatinib 40 mg QD; etoposide 70 mg/m^2 on day 1, day 2, day 3, 21 days a cycle), and gemcitabine-vinorelbine (gemcitabine 800 mg/m^2 on day 1, day 8, 21 days a cycle; vinorelbine 20 mg/m^2 on day 1, day 8, 21 days a cycle) were administered sequentially. However, the right neck tumor enlarged and the tumor encased the right carotid artery. He was enrolled in another clinical trial (NCT03719690) in which genetic testing of HNSCC was performed using the OncoKDM platform, an experimental 320-gene target-sequencing strategy. A *PIK3CA* E542K mutation was detected, and he received alpelisib 150 mg twice a day as salvage treatment. One week later, Grade 1 diarrhea and Grade 3 hyperglycemia developed. Metformin and pioglitazone were administered, which controlled hyperglycemia. On the 24th and 55th days of alpelisib therapy, he received CT, which showed that the tumor had become smaller with increasing central necrosis compared to the previous image [Figure 1]. Alpelisib was held on the 68th day due to poor digestion, aspiration pneumonia, and sepsis. Ten days after discontinuing alpelisib, the neck tumor and lung metastases enlarged without new metastatic lesions in a follow-up CT. Due to severe sepsis, acute kidney injury, and liver failure, the patient died on July 14, 2021, the 51st day after discontinuing alpelisib.

Discussion

This case showed a rapid and significant treatment response to alpelisib in an HNSCC patient with a *PIK3CA* mutation. *PIK3CA* alterations are detected in approximately 30.5%–34.5% of HNSCC patients.[1-4] The PI3K pathway is initiated by activating receptor tyrosine kinases or G protein-coupled receptors. After PI3K activation, the p110 catalytic subunit catalyzes the phosphorylation of phosphatidylinositol 4,5-bisphosphate to phosphatidylinositol 3,4,5-trisphosphate, which then activates AKT signaling pathways. Activated AKT further phosphorylates downstream targets, including mTOR, a regulator of cellular proliferation, metabolism, and protein translation.[1] Targeting the PI3K pathway could be a possible strategy to improve survival in HNSCC patients.

Several trials have used PI3K targeting agents in patients with HNSCC. Buparlisib is a pan-PI3K inhibitor. The effect of buparlisib monotherapy is modest, with an objective response rate (ORR) of 3% in unselected HNSCC patients.[5] The BERIL-1 study was a randomized, placebo-controlled, phase II study using paclitaxel with buparlisib or placebo in platinum-refractory HNSCC patients. Compared with paclitaxel (P) alone, buparlisib with paclitaxel (B + P) had a better ORR (B + P vs. P, ORR: 39% vs. 14%), progression-free survival (PFS) (B + P vs. P, median PFS: 4.6 months vs. 3.5 months, hazard ratio [HR]: 0.65, $P = 0.011$), and overall survival (OS) (B + P vs. P, median OS: 10.4 months vs. 6.5 months, HR: 0.72, $P = 0.041$). The BERIL-1 study showed the improved efficacy of using pan-PI3K inhibitor-based combination therapy. However, 22% of the patients in B + P arm had Grade 3 or 4 hyperglycemia, and 37% had Grade 1 or 2 diarrhea.[6] Drugs targeting the PI3K pathway could therefore

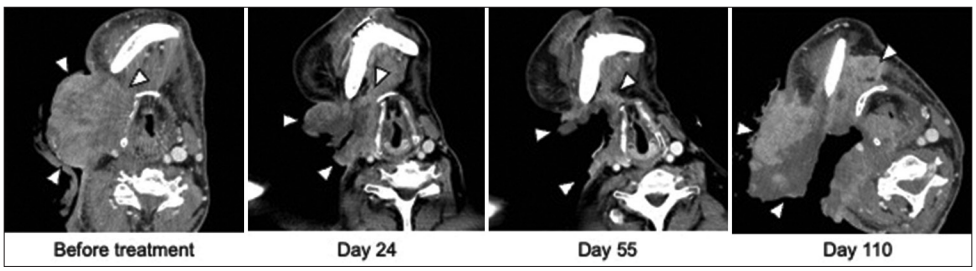

Figure 1: The treatment response of the right neck tumor. Serial contrast-enhanced CT images showed a huge protruding tumor at the right upper neck, with an invasion of the thyroid cartilage. After taking alpelisib, the tumor became smaller in the following image (day 24 and day 55). However, 10 days after discontinuing alpelisib, the neck tumor enlarged in a follow-up CT scan (day 110). CT: Computed tomography

provide clinical benefits in specific groups of patients with proper monitoring and management of side effects.

Studies on *PIK3CA*-mutated breast cancer have shown the importance of using drugs that act on the PI3K pathway, such as alpelisib, a PI3Kα inhibitor. The SOLAR-1 trial is the first clinical trial targeting advanced breast cancer patients with *PIK3CA* mutations. In a cohort of patients with *PIK3CA*-mutated cancer, PFS and ORR in the alpelisib-fulvestrant (A + F) group were better than in the placebo-fulvestrant (F) group (A + F vs. F, median PFS: 11.0 months vs. 5.7 months, HR: 0.65, $P < 0.001$, ORR: 35.7% vs. 16.2%).[7] The BYLieve trial was a noncomparative clinical trial of advanced breast cancer patients previously treated with cyclin-dependent kinase 4/6 inhibitors. In the cohort of patients receiving alpelisib and fulvestrant, the median OS was 26.4 months and the median PFS was 7.3 months, with an ORR of 21.0%.[8,9] According to the results of the SOLAR-1 and BYLieve trials, alpelisib changes the standard of care for breast cancer. Using alpelisib-based combination therapy could be promising in other *PIK3CA*-mutated cancers. In a phase I trial of alpelisib in tumors with *PIK3CA* mutations, 2 of 19 HNSCC patients had smaller tumors under alpelisib monotherapy, but the response was not durable.[10] Alpelisib-based combination therapy could be considered. Several early-phase clinical trials of PI3Kα inhibitor monotherapy and combination therapy are ongoing. However, trials targeting *PIK3CA*-mutated HNSCC are lacking. A prospective trial targeting *PIK3CA*-mutated HNSCC would be of interest.

Our case report also highlights some important issues of using PI3K inhibitors in HNSCC patients. First, due to anatomical dysfunction, HNSCC patients often need the assistance of nasogastric or other feeding tubes to take the medication, and the form of pills matters. Our patient was given crushed pills at a dose of 150 mg twice daily, and the adverse events of high blood sugar and dyspepsia were possibly partially related to the administration of crushed pills. Second, the SOLAR-1 trial reported that a lower dose level was probably related to a shorter PFS.[11] Appropriate symptomatic medications for hyperglycemia and diarrhea will lead to better patient compliance and more adequate drug dosage, and consequently, a longer duration of response. Third, the rapid but short-lasting therapeutic effect may be caused by the drug resistance of the tumor. Its resistance mechanism, as well as whether combination therapy can eliminate such drug resistance, need to be confirmed by subsequent clinical trials.

In our case, a next-generation sequencing (NGS) study disclosed a druggable target, a *PIK3CA* mutation. The strong effect of alpelisib monotherapy in our HNSCC patient with a *PIK3CA* mutation is impressive. However, the toxicity of crushed alpelisib highlights the need for further pharmacokinetic studies in HNSCC cancer patients who cannot swallow a whole tablet. Studies using different dosing formulations of PI3K/AKT/mTOR inhibitors or studies using PI3K inhibitor-based combination therapy may further increase the efficacy of PI3K/AKT/mTOR inhibitors for HNSCC patients with *PIK3CA* mutations. Moreover, an NGS study could be considered for each refractory HNSCC patient to provide a new direction of treatment. Further clinical trials are needed to confirm the role of an early NGS study and PI3K inhibitors for HNSCC patients.

Declaration of patient consent and ethical approval

We have submitted the study to the Institutional Review Board (IRB) of National Taiwan University Hospital (approval number: 202206022W), and the patient consent is waived from review by IRB because of its retrospective aspect.

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Conflicts of interest

There are no conflicts of interest.

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