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Case Report

Sotorasib Interaction with Oxycodone: A Case Report

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Abstract

Lung cancer is the leading cause of cancer-related death and the second most common malignancy in the world. Non-Small Cell Lung Cancer (NSCLC) accounts for approximately 85 percent of newly diagnosed lung cancer cases. The discovery of particular driver mutations and the development of targeted therapy are major breakthroughs in the treatment of advanced NSCLC. Cancer-related pain is a common and devastating symptom, and it is important to achieve adequate analgesia in all cancer patients. As new cancer treatments are being developed, clinicians must be aware of unknown and potentially disastrous drug-drug interactions when choosing an analgesic treatment. Here, we introduce a case of a 62-year-old female patient with advanced NSCLC who had a slow progression of the disease on previous anticancer therapy. The tumor had a Kirsten Rat Sarcoma Virus (KRAS) G12C mutation and the patient was therefore able to start sotorasib. The patient complained of left hip pain, which increased markedly after starting sotorasib. She required increased doses of oxycodone and received radiation therapy. Suspecting a radiation flare, the patient was hospitalized with unbearable pain. An opioid rotation to fentanyl had no effect on the pain. With suspected interaction between sotorasib and fentanyl, an opioid rotation to morphine was performed, after which the patient received almost immediate pain relief. Strong opioids, including oxycodone, are the cornerstone of pharmacological treatment of cancer-related pain. This case highlights the need for ongoing education about potential interactions between the cancer treatment and the analgesic treatment.

Keywords: Non-Small Cell Lung Cancer; KRAS G12C Mutation; Sotorasib; Oxycodone; Opioids; Cancer Pain.

Introduction

Lung cancer is the leading cause of cancer-related death and the second most common malignancy in the world [1]. Non-Small Cell Lung Cancer (NSCLC) accounts for approximately 85 percent of newly diagnosed lung cancer cases [2]. Survival after diagnosis has improved, due to screening and treatment advances. In patients with advanced NSCLC, the tumor should be screened for the presence of driver mutations. The identification of oncogenic drivers, particularly the Epidermal Growth Factor Receptor (EGFR), the Anaplastic Lymphoma Kinase (ALK) gene, the c-ROS oncogene 1 (ROS1) and the B-Raf Proto-Oncogene (BRAF), has led to the development of specific targeted therapies for patients [3]. Other driver mutations have also been identified and specific targeted treatments are being developed. Matching a specific targeted drug to the identified mutation profile has resulted in improved therapeutic efficacy, often in combination with reduced toxicity.

Kirsten Rat Sarcoma Virus (KRAS) mutations are observed in up to 30 percent of lung adenocarcinomas [3]. For patients with advanced NSCLC with a KRAS G12C mutation who have progressed on a previous line of therapy, sotorasib is indicated. Sotorasib is an irreversible inhibitor of KRAS G12C, and has shown promising anticancer activity in a phase 1 study in patients with KRAS G12C-mutated advanced solid tumors [4]. Furthermore, in a randomized, open-label, phase 3 trial among 345 patients with advanced NSCLC with KRAS G12C mutation who experienced progression on previous anticancer therapy, sotorasib, compared with docetaxel, showed significantly greater progression-free survival and significantly fewer serious treatment-related adverse

events [5]. However, sotorasib has some important drug-drug interactions and should not be co-administered with proton pump inhibitors and H2-receptor antagonists [6]. Sotorasib is also a strong Cytochrome P450 3A4 (CYP3A4) inducer and co-administration with a CYP3A4 substrate decreases the plasma concentrations of the substrate, which may reduce their efficacy. Therefore, co-administration of sotorasib with a CYP3A4 substrate should be avoided.

Bone metastases are a common manifestation of distant relapse from many types of solid tumors, especially those arising in the lung, breast, prostate, and kidney, and they represent a prominent source of morbidity [7]. Metastatic bone disease causes pain by several mechanisms, namely structural disruption, inflammatory mediator release, and changes in sensory innervation. Pharmacological treatment guidelines for cancer-related pain are in line with the World Health Organization (WHO) "three-step ladder" algorithm, in which opioids have been the cornerstone of pharmacologic treatment of cancer pain for the last decades. It is important to note that many opioids are metabolized primarily by the CYP3A4 enzyme. Thus, co-administration of sotorasib and opioids could potentially have disastrous consequences.

Case Presentation

A 62-year-old female patient with a history of hypertension, transient ischemic attack, chronic hip pain and advanced NSCLC was referred to our university hospital for a possible inclusion in a clinical trial studying novel treatment options for NSCLC. She had previously received immunotherapy (durvalumab), chemotherapy (carboplatin and gemcitabine) and radiation therapy. Despite the previous treatment, she had a persistent slow progression of the disease.

Her score on the Eastern Cooperative Oncology Group Scale of Performance Status was 1 at referral. Her physical examination was normal. Blood tests revealed hemoglobin of 6.3 mmol/L, creatinine 80 μmol/L, urea 4.6 mmol/L and normal liver function tests. Computed Tomography (CT) scan showed a lung lesion in the right upper lobe (23.1 mm), a lung lesion in the right lower lobe (19.6 mm), and mediastinal pathological glands. It also showed a slow onset dilatation of the pancreatic duct, and at the level of the pancreatic head a vaguely demarcated hypodense deviation (10.2 mm). The tumor had a KRAS G12C mutation. The patient was included in a clinical trial and received a novel treatment for her tumor. Unfortunately, a follow-up CT scan showed growth of the known lesions and no new lesions. Therefore, the patient discontinued the clinical trial and started sotorasib once daily 960 mg.

In addition, the patient complained of left hip pain that had existed for years without a noticeable radiological substrate on multiple imaging occasions performed at her previous hospital, including a Magnetic Resonance Imaging (MRI) scan of the hip, a CT scan of the pelvis and an X-ray of the pelvis. Hip pain increased markedly after starting sotorasib, and the patient had required increased doses of oxycodone since. She requested for a second opinion, where the orthopedist performed a bone scan. Unexpectedly, the bone scan showed metastases of the hip, the sacroiliac joint and the lower lumbar region, with still normal imaging of the pelvis on a CT scan. Accordingly, the patient was referred to palliative radiotherapy for pain relief. She received radiation therapy fifteen times three gray on the fifth lumbar vertebra, on the first and second sacral vertebrae, and on the left acetabular bone.

Two days after radiation therapy the patient was admitted to the hospital with unbearable pain in her left hip radiating to her left leg. After ruling out other possible causes, it was thought that the cause of the worsening of the pain was a radiation flare. She was using acetaminophen tablet four times a day 1000 mg, pregabaline tablet twice daily 150 mg, oxycodone tablet slow release twice daily 60 mg and oxycodone capsule immediate release six times a day 20 mg with minimal effect. On admission, the pain specialist was consulted. Given the high dose of analgesics at home, a basal intravenous infusion of fentanyl-based Patient-Controlled Analgesia (PCA) with a dose of 75 μg/h, a demand dose of 35 μg, and a lockout interval of 20 minutes was immediately started. Ketamine perfusion 5 mg/h and etoricoxib tablet once daily 90 mg were also added to the therapy. This procedure follows regular protocol and has been used safely under adequate monitoring in situations of pain crisis in our hospital for more than 20 years. Radiation flare was treated with dexamethasone 8 mg once daily.

Despite the extensive analgesia treatment plan, the patient had inadequate pain relief. With a suspicion of interaction between sotorasib and fentanyl, an opioid rotation was performed. Intravenous PCA morphine without continuous morphine, a bolus dose of 1 mg, and a lockout time of 6 minutes was started. After the opioid rotation, the patient received immediate pain relief. The ketamine perfusion could be stopped, and after dose finding, oral morphine tablet slow release twice daily 30 mg and morphine tablet immediate release six times a day 10 mg as needed, could be started. The patient could be discharged from the hospital with adequate analgesia a few days after the opioid rotation. She received an outpatient appointment for follow-up by a pain specialist.

Discussion

Cancer-related pain is a complex symptom that affects many aspects of a person's life, including physical functioning, psychological and emotional status, and social interactions. Pain prevalence is estimated to be about 39 percent after curative treatment; 55 percent during anticancer treatment; and 66 percent

in advanced, metastatic, or terminal disease [8]. About 38 percent of all patients report moderate to severe pain. Although treatment of cancer pain has improved over the past decade, analgesic treatment is often inadequate to the intensity of pain. Given the enormous impact of pain, it is essential to achieve adequate analgesia, especially in patients with moderate to severe pain. As novel cancer treatments are being developed, physicians should be aware of unknown and potentially disastrous drug-drug interactions when choosing an analgesic treatment.

To our knowledge, the interaction between sotorasib and oxycodone has not been described before. Opioids are the cornerstone of pharmacologic treatment of cancer-related pain. As mentioned before, sotorasib is a CYP3A4 inducer and co-administration with a CYP3A4 substrate decreases their plasma concentrations. Many opioids, including fentanyl, are metabolized by the CYP3A4 enzyme [9]. Oxycodone is metabolized primarily by the CYP3A4 enzyme, with a small portion being metabolized by the CYP2D6 enzyme. In our case, the patient did not achieve adequate analgesia with oxycodone after starting sotorasib, and needed increased doses of oxycodone, probably due to the drug-drug interaction between sotorasib and oxycodone. Similarly, the patient did not experience pain relief after the opioid rotation to fentanyl. Interestingly, with morphine the patient became pain free almost immediately. The metabolic pathway of morphine, as well as hydromorphone and oxymorphone, involves only phase two metabolism. Therefore, there is no expected interaction between sotorasib and morphine (Table 1). Other analgesics, such as acetaminophen, non-steroid anti-inflammatory drugs and ketamine, which are not metabolized by the CYP3A4 enzyme, should also be considered as part of a multimodal analgesia approach in such cases.

Metabolic pathway		
Opioid	**Phase 1 Metabolism**	**Phase 2 Metabolism**
Morphine	None	Glucuronidation via UGT2B7
Codeine	CYP2D6	None
Hydrocodone	CYP3A4	None
Oxycodone	CYP3A4, CYP2D6	None
Methadone	CYP3A4, CYP2D6, CYP2B6, CYP2C8, CYP2C19, CYP2C9	None
Tramadol	CYP3A4, CYP2D6	None
Fentanyl	CYP3A4	None
Hydromorphone	None	Glucuronidation via UGT2B7
Oxymorphone	None	Glucuronidation via UGT2B7

Table 1: Metabolic pathways of opioids [9].

One of the common causes of cancer pain are bone metastases, which usually affect the axial skeleton. Treatment goals for patients with bone metastases include, among others, maximizing pain or symptom relief, as well as preserving and restoring function, stabilizing the skeleton, and improving local tumor control. Two days prior to admission, the patient had received palliative radiation therapy. External Beam Radiation Therapy (EBRT) is a standard approach for symptomatic skeletal metastases, with 70 to 80 percent of the patients experiencing reduced pain [7]. Although EBRT has proven to be effective, it has a number of side effects, including a transient worsening of pain that occurs in about one third of the patients, often referred to as radiation flare. In our case, the patient received inadequate analgesia prior to radiation therapy. In retrospect, the necessity of radiation therapy for this patient is questionable.

Pain flare following palliative radiation therapy usually occurs in the first few days after radiation therapy, and generally does not last long. The administration of dexamethasone can reduce the flare [7]. As EBRT has proven to be effective in partially or completely relieving pain in a majority of patients with bone metastases, an additional effect of radiation therapy on pain relief in our case is possible. However, the almost immediate effect of morphine suggests that the pain relief is mainly due to an opioid rotation to an opioid with no drug-drug interactions with Sotorasib.

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Consent: Written informed consent was obtained from the patient to publish this report in accordance.

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