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A Rare Event of Liver Dysfunction on Sotorasib and Management Strategy

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Author's disclosure of conflict of interest is found at the end of this article.

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Abstract

KRAS mutations are the most common alteration in human cancers, accounting for approximately 30% of mutations in multiple cancer types, including colorectal, pancreatic, non–small lung cancer, and ovarian. Of these, the *KRAS* p.G12C mutation occurs in 13% of non–small lung cancers and 1% to 3% of colorectal and other cancers (Hong et al., 2020). With the approval of the direct *KRAS* p.G12C inhibitor sotorasib in early 2021, this first-in-class small-molecule agent has increased progression-free survival by 6.3 months in patients with p.G12C non–small cell lung cancer. Side effects associated with sotorasib have been mild, with the most frequent being diarrhea and nausea, but grade 3 to 4 toxicity has also been observed, which is clinically significant. Grade 3 toxicity related to aspartate aminotransferase and alanine aminotransferase is defined as an increase of more than 5 to 20 times the upper limit of normal (ULN), while grade 4 is more than 20 times the ULN. This is significant and requires withholding treatment as it can be life-threatening in some cases. The following case study outlines a patient who developed abnormal liver enzyme elevation while on the phase I clinical trial of sotorasib, and the management of this event.

CASE STUDY

A 76-year-old man from Florida was diagnosed in 2018 with moderately differentiated adenocarcinoma consistent with a lung primary after his hairdresser noted a lesion on the left parieto-occipital skull. This prompted him to seek medical attention, initially undergoing CT of the brain followed by MRI of the head. Imaging revealed a mass measuring 2.6 cm in the left parietal skull and scalp. The mass appeared to arise from the calvarium with superficial extension into the scalp. Further CT imaging of the chest, abdomen, and pelvis revealed a right upper lobe (RUL) spiculated mass measuring 3.4 cm and sclerotic bone lesions in the left fourth posterior rib, L2 vertebrae, and iliac crest. MRI of the cervical, thoracic, and lumbar spine revealed osseous metastases arising from the C3 vertebral body and a large mass at the L2 vertebral body without cord compression. The patient underwent craniectomy with resection of the left parietal skull lesion, and pathology was consistent with moderately differ-

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entiated adenocarcinoma from a lung primary. The patient was staged as IVA (cM1b). Medical history was significant for transitional cell bladder cancer in 2005 with clear cystoscopy findings yearly to present date. Social history was significant for cigarette use of 33 pack-years with cessation in 1985. He had a moderate alcohol intake of approximately 12 glasses of wine per week. There was no drug use nor history of hazardous exposures.

Immunohistochemistry for programmed cell death ligand 1 (PD-L1) showed membranous staining in 1% of tumor cells. In addition, he underwent next-generation sequencing of circulating cell-free DNA obtained via plasma. This platform screens for single nucleotide variants, insertions or deletions, copy number amplifications, and gene fusions. Somatic mutations in *BRCA2* and *KRAS* (specifically G12C) were identified.

The patient began first-line treatment with carboplatin, pemetrexed, and pembrolizumab (Keytruda) in April 2018 for approximately 4 months, followed by maintenance with pembrolizumab until March 2019. PET-CT in April 2019 revealed disease progression with an increase in size of the RUL mass, increase in several small pulmonary nodules, and increased bone metastases with a new lesion at the L5 vertebral body. The patient underwent new biopsy of the RUL mass, and next-generation sequencing at MD Anderson Cancer Center confirmed the presence of a *KRAS* G12C mutation in the new tissue sample in addition to an *STK11* mutation.

The patient was referred to the phase I clinic (Investigational Cancer Therapeutics) at MD Anderson in April 2019. He was deemed eligible in May 2019 for the phase I clinical trial of sotorasib, a small molecule that selectively and irreversibly targets *KRAS* G12C (Hong et al., 2020). Sotorasib was US Food and Drug Administration-approved in May 2021 for non–small cell lung cancer with the *KRAS* G12C mutation.

The patient began treatment on May 28, 2019, with 960 mg of oral sotorasib once a day (Figure 1). A cycle was defined as 21 days of continuous therapy. Baseline laboratory studies revealed normal levels of aspartate aminotransferase (AST), alanine aminotransferase

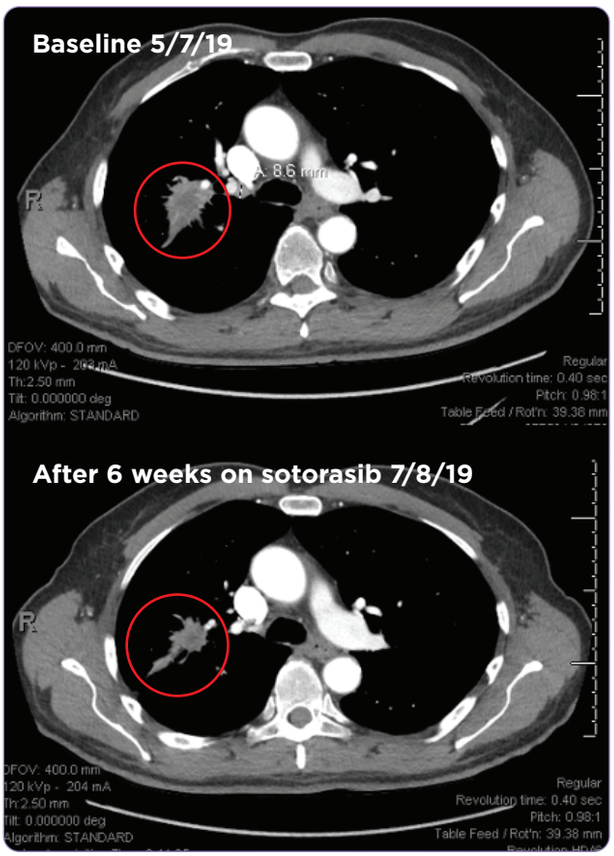

Figure 1. CT scans showing definitive response to sotorasib.

(ALT), total bilirubin, and prothrombin time/international normalized ratio. The patient did well without any adverse events until he presented for cycle 4 clearance when he was noted to have a grade 3 elevation in AST (to 388) and ALT (to 541), per Common Terminology Criteria for Adverse Events v5. Sotorasib was placed on hold, and the patient returned 2 weeks later for a laboratory review and visit by an advanced practitioner and physician. His ALT continued to be elevated (but slightly improved) at grade 2 while his AST had returned to a grade 1. His treatment was held further per protocol guidelines, and he ultimately resumed full dosage on August 19, 2019, after his AST and ALT returned to grade 1 or normal (Figure 2).

Three weeks later, upon clearance for cycle 5, he again was found to have grade 3 AST elevation (615) and grade 4 ALT elevation (937). Sotorasib was again held and upon return in October 2019, the dose was reduced to 720

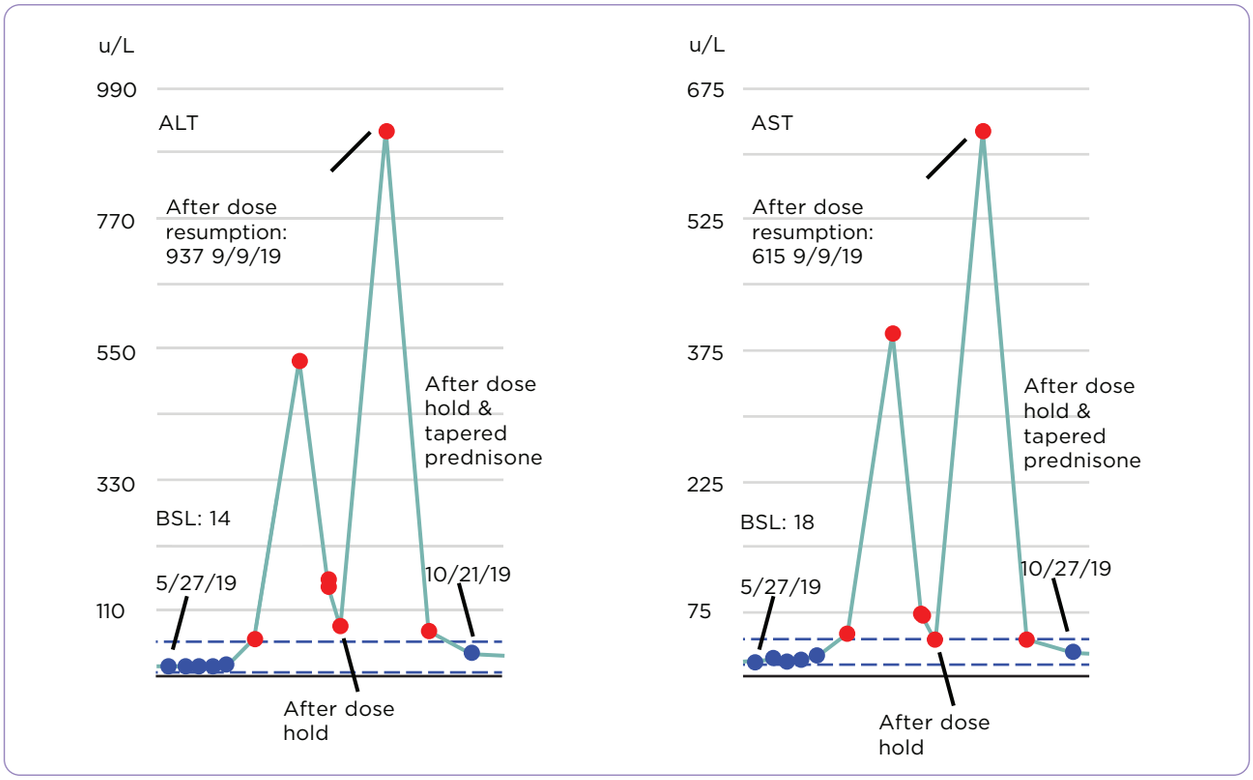

Figure 2. Management of elevated liver enzymes while on treatment with sotorasib.

mg after AST and ALT improved to grade 1 or normal. The following day, the patient was again found to have grade 3 AST/ALT elevation, prompting another hold on sotorasib and further dose reduction in cycle 6 to 360 mg. At the same time, he was initiated on 60 mg of prednisone daily with a taper schedule over 6 weeks provided by the advanced practice registered nurse (APRN). Ultimately, the patient was able to dose escalate back to the full dose of 960 mg daily by cycle 8 day 1 and had no further increase in AST or ALT. The patient completed his last dose of prednisone 10 mg daily on December 14, 2019 (cycle 8 day 11). There were no further derangements in his liver enzymes from cycles 8 to 17. All laboratory studies remained within normal limits until the time he was taken off treatment due to progressive disease in the primary tumor after 13 months on the study.

KRAS was originally identified in 1982 and has historically been considered "undruggable." *RAS* mutations account for about 30% of all cancer mutations and are typically associated with poor prognosis. In patients with non–small cell lung cancer (NSCLC), *KRAS* mutations are present in 30% of patients, with 13% harboring the G12C mutation. Decades have passed without effective or approved therapies to target *KRAS* until sotorasib reached the clinic and extended progression-free survival by 6.3 months. This has led to improved quality of life and effective treatment in this specific subset of patients, with the main toxicities being diarrhea and nausea.

This case is the only known grade 4 increase in ALT (frequency 0.8%), which as outlined previously, quickly returned to normal with dose reduction and initiation of corticosteroids with a tapering schedule. In the phase I clinical trial of 129 patients, 2.3% had a grade 3 increase in AST and 4.7% had a grade 3 increase in ALT. Very little is known about the pathophysiology of altered liver function tests on sotorasib, as this was the

first-in-human trial. While transaminitis can be a common toxicity for patients on immune checkpoint inhibitors, sotorasib is not of the same class to cause such a similar event. Of note, the patient presented with liver dysfunction 9 weeks into the trial, which is in the same range (6 to 14 weeks) as the development of immune-mediated hepatitis or a raised level of transaminase after initiation of an immune checkpoint inhibitor (Spain et al., 2016). In any case, the patient was managed similarly to patients who receive immune checkpoint inhibitors, with a corticosteroid dosed at 1 to 2 mg/kg/day tapered over 4 to 6 weeks, as outlined in the NCCN Guidelines for the management of immune-related adverse events (Darnell et al., 2020). Remarkably, the patient responded well to the administration of prednisone and did not have any further liver enzyme derangement.

Patients on phase I clinical trials require close monitoring by an APRN and collaborative team. For example, alteration in blood levels requires prompt attention for patient safety, and APRNs can quickly identify abnormalities, intervene, and prescribe appropriate treatment. In this case, the initiation of a corticosteroid (prednisone) improved AST/ALT levels, enabling the patient to resume the full dose of sotorasib for a total of 13 months. This patient did not experience adverse events affecting performance status, with Eastern Cooperative Oncology Group (ECOG) performance status remaining at 0 during the duration of treatment.

In addition to quick intervention for adverse events, APRNs can also provide comprehensive patient assessments in collaboration with the clinical pharmacist and physician. Such assessments are vital to patient safety and overall outcomes, as concomitant medications, social habits, or other alternative medications that patients could be consuming may also contribute to observed lab abnormalities, although the trial medication is typically the sole or major focus of attributing lab abnormalities.

A third major role of APRNs in cancer care is ordering molecular testing to identify specific mutations that can lead to initiation of targeted therapy. This can ultimately increase survival and improve quality of life for patients with metastatic disease who have exhausted all standard therapies. In addition, targeted therapies often have less toxicity than standard chemotherapy, and patients tend to feel better while on these types of treatment.

Disclosure

The author has no conflict of interest to disclose.

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