STUDENTS' CORNER
LETTER TO THE EDITOR

Sotorasib and Panitumumab: A breakthrough in the treatment of KRAS-mutated mCRC

Muhammad Ahsan, Muhammad Ibrahim Siddique

Dear Editor, Colorectal cancer (CRC) is a prevalent malignancy in Pakistan, ranking as the fourth most common cancer, thus contributing to the cancer-related mortality.[1] It originates from the epithelial cells of the large intestine, particularly the colon and rectum. The metastatic form, metastatic mCRC, is a more advanced stage of CRC, characterised by spread beyond the original site to distant organs, such as the lungs, liver, and peritoneum. Metastasis is a significant concern for patients and clinicians alike due to the stronger association with mortality, causing mass-effect and interfering with normal physiological functions. Moreover, treatment of mCRC is complex, often requiring a combination of surgical, chemotherapeutic, and immunotherapeutic interventions.

The KRAS protein, which is commonly implicated in mCRC, alternates between an inactive and active states. A specific mutation in the KRAS codon 12 mutation impairs GTP hydrolysis, leading to constitutive activation that continuously promotes cell proliferation. Sotorasib is a targetted agent that forms an irreversible covalent bond with a cysteine residue in KRAS G12C mutant protein, locking it in its inactive form, thereby inhibiting cell growth and promoting apoptosis. This specific cysteine residue is not present in wild-type KRAS, which helps to avoid off-target effects.[2]

Sotorasib treatment has been associated with several common side effects. The most frequently reported (≥20%) include gastrointestinal disturbances such as diarrhoea, fatigue, musculoskeletal pain, nausea, hepatotoxicity, and cough. Common laboratory abnormalities (observed in ≥25% of patients) include lymphopenia, anaemia, elevated liver enzymes, hypocalcaemia, elevated alkaline phosphatase, proteinuria, and hyponatraemia.[3]

Panitumumab is a biologic agent and the first full human monoclonal antibody antibody of the IgG2 subclass approved by the US Food and Drug Administration (FDA). It is indicated for the treatment of epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer. Its use is typically reserved for patients who have experienced disease progression despite prior therapies with fluoropyrimidine, oxaliplatin, and irinotecan. Panitumumab inhibits tumour growth by blocking EGFR activity, promoting apoptosis, reducing angiogenic signalling, and inhibiting receptor internalisation.⁴ Notable adverse effects of panitumumab include skin rash, hypomagnesaemia, fatigue, and interstitial lung disease.[4]

A recent phase 3 randomised controlled trial evaluating the efficacy of Sotorasib plus Panitumumab in patients with chemorefractory KRAS G12C-mutated mCRC reported promising results compared with standard care (trifluridine–tipiracil or regorafenib). The combination showed an almost twofold increase in progression-free survival (5.6 vs. 2.0 months) alongside achieving a higher response rate (26.4% vs. 0%), improved disease control (71.7% vs. 46.3%), and a similar incidence of grade 3 or higher adverse events (35.8% vs. 43.1%). Additionally, this combination therapy circumvents resistance mediated by EGFR reactivation, making it a promising option for this patient population. [5]

In conclusion, the sotorasib plus panitumumab combination represents a novel targetted therapy for patients with refractory KRAS G12C-mutated mCRC. While it is not yet commercially available in Pakistan, the available data concerning its safety and efficacy support its potential benefit. Further clinical trials and evaluations are needed to fully establish the role of this combination therapy in clinical practice.

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2nd year MBBS Student, Ziauddin Medical College, Karachi, Pakistan.
Correspondence: M. Ahsan. e-mail: muhammadahsanarif6@gmail.com
ORCID ID: 0009-0008-7137-9077

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