

PI3K Inhibitors and Adverse Events

Optimizing patient care for the treatment of advanced breast cancer

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BACKGROUND: Excessive activation of the PI3K pathway has been associated with malignant transformation and resistance to treatment in various cancer types. Various PI3K inhibitors have been evaluated in phase 3 clinical trials; however, most have been associated with modest clinical improvement and poor tolerability. The safety profile of PI3K inhibitors poses new challenges in treatment monitoring and management of common adverse events (AEs).

OBJECTIVES: The purpose of this article is to provide an overview of AEs associated with PI3K inhibitors, with a focus on alpelisib, as well as guidance on the prevention and management of AEs.

METHODS: The literature and results from phase 3 trials evaluating the efficacy and safety of endocrine therapy plus PI3K inhibitors in patients with advanced breast cancer were reviewed.

FINDINGS: AEs associated with PI3K inhibitors include hyperglycemia, diarrhea, nausea, rash, and decreased appetite. Prevention strategies are recommended to avoid the development or decrease the severity of these AEs. Patient education and multidisciplinary care are necessary for the optimal care of these patients.

KEYWORDS

advanced breast cancer; PI3K inhibitors; endocrine therapy; adverse events

DIGITAL OBJECT IDENTIFIER

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BREAST CANCER IS THE MOST FREQUENTLY DIAGNOSED CANCER among females and a leading cause of death worldwide (Bray et al., 2018). In the United States, 279,100 new cases of invasive breast cancer and more than 42,690 breast cancer-related deaths are estimated for 2020 (American Cancer Society, 2020a). The poorest outcomes are observed in patients with metastatic-stage breast cancer, which presents a five-year relative survival rate of 27%. About 70% of advanced breast cancers (comprising locally advanced and metastatic breast cancers) are hormone receptor (HR) positive and human epidermal growth factor receptor 2 (HER2) negative (Wood et al., 2017). Endocrine-based therapeutic regimens, typically used in combination with targeted therapies such as cyclin-dependent kinase 4/6 or mammalian target of rapamycin inhibitors, are systemic treatments for HR-positive, HER2-negative advanced breast cancer (National Comprehensive Cancer Network [NCCN], 2020b). However, the majority of HR-positive advanced breast cancers eventually acquire resistance to endocrine therapy, which highlights the need for new and effective treatment options (Cardoso et al., 2018; Sobhani et al., 2018).

Phosphatidylinositol 3-kinase (PI3K) inhibitors became part of the advanced breast cancer treatment landscape with the U.S. Food and Drug Administration's approval of alpelisib plus fulvestrant for the treatment of postmenopausal women and men with phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha-mutated HR-positive, HER2-negative advanced breast cancer following progression on or after endocrine therapy (Novartis Pharmaceuticals, 2019). Currently, alpelisib is the only PI3K inhibitor approved for treatment of advanced breast cancer in combination with fulvestrant. In the future, alpelisib may also be used in combination with other endocrine treatments, such as aromatase inhibitors. Interim analyses from the BYLieve trial show that alpelisib plus aromatase inhibitor regimens have a similar efficacy and safety profile as alpelisib plus fulvestrant regimens (Rugo, Ruiz Borrego, et al., 2019). There are also numerous other PI3K inhibitor-based regimens being investigated in early-phase clinical trials in HR-positive, HER2-negative advanced breast cancer (Sobhani et al., 2018). Despite the unique safety profile of PI3K inhibitors, their associated adverse events are generally manageable and reversible with monitoring, medical intervention, and patient education.