Review Article

AlpelisibEfficacy in Advanced Breast Cancer

ABSTRACT

Breast cancer is one of the popular problems related to the medical field. The incidence rate keeps increasing and this indicates the slow progression of the disease. Breast cancer develops silently without medical attention, and most cases are discovered during a routine clinic visit. While other cases may accidentally discover breast lumps, changes in breast shape or size, and nipple discharge. Breast cancer highly affects women worldwide. Mortality rates of breast cancer are improving, but still, the survival rate in the advanced stage is decreasing. Nowadays, Chemotherapy is considered the gold-standard approach for most cancer types and a modest improvement in both survival rates and toxicity reduction. Therefore, this article aims to focus on the use of one of the modest drugs that treat advanced breast cancer, which is Alpelisib, and highlight the mechanism of action, indication, contraindication, pharmacodynamic, pharmacokinetic, dose, and its side effects.

Keywords: Advanced Breast Cancer, Alpelisib, PIK3CA Mutation.

1. INTRODUCTION

Breast cancer is one of the main problems related to healthcare providers and one of the top research preferences among other medical research. Breast cancer become more aggressive, and the incidence rate keeps increasing yearly. Each year there are one million and seven hundred thousand new cases that get worse. Most probably the incidence rate will increase significantly in the next 5–10 years. These rates indicate the slow progress of this disease (1-3). Breast cancer develops silently without medical attention, and most cases are discovered by the physician on routine clinic screening while other cases may be discovered with an accidentally discovered breast lump, change in breast shape or size, and sometimes it comes with nipple discharge. Breast cancer mostly affects women worldwide. Mortality rates of women who have already been diagnosed with breast cancer have improved, but still, the survival rate in the metastatic stage has decreased (3). Nowadays, Chemotherapy is considered the gold-standard approach for most cancer types and a modest improvement in both survival rates and toxicity reduction (4, 5). Therefore, this article aims to focus on the use of one of the modest drugs that treat advanced breast cancer, which is Alpelisib, and highlight the mechanism of action, indication, contraindication, pharmacodynamic, pharmacokinetic, dose, and its side effects.

2. DISCOVERY

Alpelisib is being developed by Novartis, which is a global healthcare company. The first clinical trials started in Oct 2010. It was approved in the USA on May 24th, 2019(6).

3. MECHANISM OF ACTION

Alpelisib works by inhibiting the phosphatidylinositol 3-kinase (PI3K) which leads to inhibiting the activation of some signaling pathways such as PI3K/AKT/mTOR. This will lead to inhibit the tumor cell growth and survival in patients with tumor cells with PIK3CA mutation (7).

4. USES

Alpelisib is used in combination with fulvestrant to treat advanced breast cancer in postmenopausal women with PIK3CA-mutated and HR-positive or HER2-negative (6).

5. FDA AND DCGI APPROVAL STATUS

Alpelisib got approval on May 24th, 2019 by the FDA in the USA for use in combination with fulvestrant to treat some medical conditions such as postmenopausal women with HR-positive, HER2- negative, PIK3CA-mutated, and advanced or metastatic breast cancer (6).

6. DOSE AND ADMINISTRATION INSTRUCTION

The main dose of Alpelisib is 300mg once daily. While it can be decreased to 250mg or 200mg once daily. Fulvestrant is administered 500mg intramuscularly on days 1, 15, and 29 and one monthly (8).

7. COMMON TOXICITIES

The main side effects of Alpelisib are hyperglycemia, diarrhea, and Severe cutaneous reactions such as Stevens-Johnson syndrome (SJS) and erythema multiforme. Also, it may cause pneumonitis in rare conditions (8).

8. ONGOING LANDMARK CLINICAL TRIALS

1. (NCT03207529): This study tested the drug in a patient with metastatic androgen receptor-positive and PTEN-positive breast cancer.
2. (NCT01623349): This study tested the drug in a patient with recurrent triple-negative breast cancer or high-grade serous ovarian cancer.
3. (NCT01872260, NCT02734615): This study tested the drug in a patient with advanced or metastatic estrogen receptor (ER)-positive breast cancer.
4. (NCT01300962, NCT02038010, NCT02167854): This study tested the drug in a patient with HER2-positive metastatic breast cancer.
5. (NCT02379247): This study tested the drug in a patient with locally recurrent or metastatic HER-2-negative breast cancer.

9. COST-EFFECTIVENESS

In the USA, patients who were treated with Alpelisib with fulvestrant gained 0.43 quality-adjusted life years (QALYs) compared with a patient who was treated by fulvestrant alone. The cost of adding Alpelisib to fulvestrant therapy was around two hundred and seventy-five thousand dollars, resulting in an incremental cost-effectiveness ratio (ICER) of six hundred and forty-eight thousand dollars/QALY, assuming patients progress to treatment with everolimus plus exemestane or palbociclib plus fulvestrant (9).

10. PI3K/AKT/MTOR PATHWAY AND BREAST CANCER

The PI3K/AKT/mTOR pathway plays an important role in the regulation of cell proliferation, growth, and survival, especially in advanced breast cancer. In breast cancer, modest chemotherapy mainly works by targeting these three important sites of this pathway (10).

11. PHARMACODYNAMIC AND PHARMACOKINETIC

11.1 PHARMACODYNAMIC

Alpelisib inhibits the most common PIK3CA somatic mutations (H1047R and E545 K), But it had less efficacy against the distinct lipid kinase PIK4β (11).

11.2 PHARMACOKINETIC

The pharmacokinetic profile shows that the Alpelisib was rapidly absorbed into the bloodstream, with a mean transit time to the absorption compartment of 1.28 hours. The volume of distribution estimates was 10 L/h. The elimination half-life from plasma was 13.7 h. Around 38% of Alpelisib was excreted as an unchanged or inactive metabolite. 79.8% of excreted metabolites leave with the feces and 13.1% leave with urine. Alpelisib has limited drug-drug interactions (12).

12. MECHANISM OF RESISTANCE

There are several ways of resistance to PI3K inhibitors. The effect of isoform-specific PI3K inhibitors, such as Alpelisib, can be circumvented by activating other isoforms and promoting downstream signaling of the PI3K/AKT/mTOR pathway (10).

13. TAKE-HOME POINTS

- Alpelisib is a selective inhibitor of Phosphatidylinositol 3-Kinase (PI3K).
- Alpelisib is used in combination with fulvestrant to treat advanced breast cancer.
- Alpelisib getsapprovedinIndiaonJanuary 3rd,2020,by theCentral Drugs Standard Control organization.
- The main dose of Alpelisib is 300mg once daily, while it can be decreased to 200mg Once daily. The dose of Fulvestrant is 500mg on days 1, 15, and 29.

14. CONCLUSION

Patients harboring PIK3CA gene mutations mainly have a poor prognosis. A new drug that targets the PI3K pathway such as Alpelisib may increase the survival rate for those patients. Alpelisib shows a new therapeutic option in these patients with limited ways of treatment. However, the treatment decision should follow a thorough benefit-risk assessment, as recommended by the 5th ESO-ESMO international consensus guidelines for advanced breast cancer (13).

ABBREVIATION

BC; BREAST CANCER. **QALYS**; QUALITY-ADJUSTED LIFE YEAR.

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