Case Report
Open Access
CrossMark

Alpelisib monotherapy in PIK3ca-mutated efficacy on triple-negative metastatic breast cancer in subsequent lines: a case report

Abstract

We report a case of a female patient with breast cancer, emphasizing the importance of a new biopsy of the metastases with the evolution of the disease and the response to alpelisib monotherapy in subsequent lines for triple negative breast cancer (TNBC) with PI3K gene mutation, histological subtype historically with poor outcome and limited treatment options.

Keywords: Triple-negative breast cancer, PI3KCA gene mutation

Volume 11 Issue 1 - 2023

Moisés de Sousa Martins Lopes, Emili Galvani de Menezes Ayoub, Flávia Viecili Tarcha, Taciana Sousa Mutão
Hospital Alemão Oswaldo Cruz, São Paulo-SP, Brazil

Correspondence: Taciana Sousa Mutão, Hospital Alemão Oswaldo Cruz, São Paulo-SP, Brazil, Email taci0@hotmail.com

Received: January 12, 2023 | **Published:** January 24, 2023

Introduction

Breast cancer is a heterogeneous disease with distinct behaviors. The heterogeneity of this cancer can be observed by clinical and morphological manifestations, different genetic signatures and consequent differences in therapeutic responses. Treatment for localized or metastatic disease is complex and multidisciplinary. May involve surgery, radiotherapy, and systemic treatment with chemotherapy, endocrine therapy, and biological treatments. Treatment selection is based on prognosis and predictive factors such as tumor histology, clinical and pathological characteristics, the presence or absence of hormonal receptors (RH) (estrogen (RE) and progesterone (PR)) HER2 (human epidermal growth factor receptor 2), Ki67% and multigenic tests. The patient's condition such as age, comorbidities and menopausal profile are also relevant in the choice of treatment.[1]

More than 70% of breast cancers are hormone-positive and HER2-negative receptors.[2] Endocrine therapy, with or without the use of a cyclin-dependent kinase 4 and 6 inhibitors (iCDK4/6), is the standard treatment for patients with advanced HR-positive and HER2-negative breast cancer. Approximately 40% of positive HR and HER2 negative patients have activating mutations in the PIK3CA alpha subunit of phosphatidyldilositol 3-kinase), inducing hyperactivation of the alpha isoform (p110α) of PI3K (phosphatidylinositol 3-kinase).[2] However, the frequency of these mutations may vary according to the molecular subtypes of breast cancer, around 30% in those HER2 positive and between 12.5 and 25% in triple negative subgroups (TNBC).[3–5]

The PI3K signaling pathway regulates several cellular functions, including cell proliferation, survival, translational regulation of protein synthesis, glucose metabolism, cell migration, and angiogenesis. Pik3CA gene activating somatic mutations that increase pi3Kα protein kinase activity have been identified in tumor tissues and associated with cell transformation in various types of human cancer, especially in breast cancer with positive hormone receptor, but the role of this signaling pathway has become increasingly important in HER2+ and TNBC.[3,6]

Alpelisib is a PI3K inhibitor, of oral bioavailability, specific alpha that selectively inhibits p110α approximately 50 times stronger than other isoforms. Initially, in pre-clinical and phase I studies, alpelisib combined with fulvestrant demonstrated synergistic antitumor activity in estrogen receptor tumors with PIK3CA mutation. The most frequent grade 3 or 4 adverse events that have been reported with alpelisib were hyperglycemia and maculopapular eruption.[6,7]

In 2019, the FDA (Food and Drug Administration) and ANVISA (National Health Surveillance Agency) approved alpelisib in combination with fulvestrant in patients with advanced hormonal breast cancer with pik3CA mutation, through progression during or after endocrine regimen. Approval was based on a phase III -SOLAR-1 study.[2] Also demonstrated in the BYLieve study.[3,8–10] 15 to 20% of breast cancers are triple negative (i.e. RH and HER2 negative), and their treatment still remains a challenge, being an aggressive disease with high recurrence. Only recently has the clinical development of PI3K inhibitors begun to show some evidence of activity for targeted therapies on TNBC.[11,12] Various types of chemotherapy used in TNBC may induce PI3K/AKT activation.[13] This activation can causes a possible resistance to taxanes.[14] In addition, inactivation of the PTEN tumor suppressor gene may result in abnormal activation of the PI3K pathway through function loss mutations, gene dissections, or negative transcription regulation.[13] Therefore, some studies are underway to evaluate activity in this scenario.

Case report

A 39-year-old woman (in 2005), was diagnosed with early breast cancer in the left breast. She underwent quadrantectomy and sentinel lymph node research, with evidence of RE and PR positives tumor, HER2 2+, KI67 5%, anatomical staging IA (AJCC 8th edition, 2017). He continued with local radiotherapy treatment and adjuvant hormone therapy with Tamoxifen for 5 years. In the first year of adjuvant treatment, she was diagnosed with Acute Myeloid Leukemia (AML), requiring chemotherapy and trans-retinoic acid (ATRA).

7 years after the diagnosis of breast cancer (in 2012), in the biopsy of the lesion of the same breast, previously treated with conservative surgery, invasive ductal carcinoma (ICD), HER2 negative, RE and PR positive, KI67 15% were evidenced. She was referred for left mastectomy and axillary resection. In the pathological product of surgery, an invasive lobular carcinoma (CLI), pT3pN2M0 (AJCC 8th edition, 2017) was evidenced. Surgical treatment was followed by chemotherapy, 4 cycles of cyclophosphamide and docetaxel, followed by adjuvant radiotherapy and tamoxifen.

After 2 years, in the presence of hormone therapy, she presented skin infiltration in the left breast. Identified a ductal carcinoma with luminal A molecular profile. She was treated with fulvestrant for approximately 3 years, when she evolved with progression of the disease to liver and bone. Osthelysis inhibitor and chemotherapy with paclitaxel, associated with anti-VEGFR for 6 cycles were prescribed, followed by aromatase inhibitor, letrozol. After approximately 8 months, it evolved with a new progression of disease to liver and bone. The new hormone line was exposed with ribociclib and exemestane for 3 months, when it evolved with a new progression and chemotherapy was initiated combined with docetaxel and xeloda. Capecitabine was discontinued for limiting toxicity after 3 cycles and kept docetaxel for 14 cycles at a reduced dose. At the time, a new liver biopsy was requested to confirm the histology of the breast tumor in Sep/2019. The new biopsy revealed triple negative breast cancer and the material was forwarded for genetic research by next-generation sequencing (NGS), which presented as a discovery, the E545G mutation in the PI3KCA gene, indicating the use of alpelisib. Treatment with alpelisib (monotherapy) was started in June 2020 after disease progression with docetaxel and was maintained until December 2020. During the 6 months of treatment, nausea, diarrhea, inappetence, fatigue and mucositis, all of grade 1 and handling, were adverse events.

The medication was suspended after further liver progression and the patient was exposed to 4 more lines of chemotherapy, namely gemcitabine with cisplatin, eribulin, CMF (cyclophosphamide, methotrexate, fluororacil), and vinorelbine. All medications after alpelisibre had a poor response and significant disease progression. Thus, after palliative care was instituted, the patient died in Sep/2021 after approximately 16 years of illness.

Discussion

In women with recurrent or metastatic breast cancer, evaluation with history, physical examination, hematimetric profile, liver function, chest tomography, MRI or CT of the abdomen, bone screening with bone scintigraphy, and targeted imaging of suspicious bone lesions is recommended. Biopsy documentation of metastatic disease at initial presentation or first recurrence is recommended whenever possible. This strategy ensures confirmation of metastatic or recurrent disease, tumor histology and allows for the determination of biomarkers and selection of appropriate treatment.

The hormone receptor, ER, and PR profile can be false negative or false positive and there may be disagreement between the primary tumor and the metastasis. The reason for the disagreement may be related to the biological changes of the disease, the effect of the treatment on the clones, tumor heterogeneity, or the limited accuracy and reproducibility of the analyses. The discordance rates for triple-receptor expression between the primary tumor and recurrence varies between studies, rates ranging from 3.4% to 60% for ER-negative to positive tumors and 7.2% to 31% for ER-positive to negative. Common among studies is that discordant cases have poor survival, probably due to inappropriate use of targeted therapies.[15,16]

A new biopsy in relapsed disease should be obtained especially in cases where the biomarker profile is previously unknown, originally negative or not overexpressed, and in cases of solitary metastasis or unusual clinical course of the underlying disease. The new biopsy is also well indicated when the objective is to obtain tissue for molecular analysis.[16,17]

The exposed patient was diagnosed with hormone receptor positive breast cancer at age 39 and maintained histology at local recurrence 7 years later. Over time, at least 14 years after, the tumor presented as triple negative, possibly due to heterogeneity and/or resistance to treatment. Although the prevalence of PIK3CA mutations is higher in hormonal tumors, it is known that it is also present in other subgroups. In triple negative breast cancer, this occurs in 12-25% of cases.[3] The new biopsy for molecular investigation, presents as a discovery, the alteration of the E545G PI3KCA gene, than provided a possibility of oral target treatment.

Even though this medication is still used off-label in this scenario, it was chosen for use based on the NGS exam. Also, patient was exhausted from undergoing chemotherapy treatments, so she would like to try. She had good tolerance to the treatment, with Alpelisib monotherapy, and in the first two months she used fexofenadine as a premedication, preventing rash. It presented grade 1 toxicity, for nausea, diarrhea, fatigue and mucositis, all of which were manageable. It did not show the most common effects of alpelisib such as rash and hyperglycemia.

In this specific case, we show the importance of molecular investigation in subsequent lines, enabling a well-tolerated treatment option, which offered progression-free survival of 6 months and mainteining quality of life, in a patient with metastatic and polytreated breast cancer. For an aggressive cancer profile and that there is a more rapid loss of performance status making it difficult to maintain long-term cytotoxic treatment regime. The use of alpelisib was the most lasting treatment, compared to the next lines used.

Conclusion

To date, there are no robust data reported on alpelisib monotherapy in metastatic triple-negative breast cancer and PIK3CA mutated. However, the case reported above demonstrates that it may be an effective and well tolerated treatment option even in subsequent lines, slowing or avoiding cytotoxic therapies. Evolution of the molecular area has allowed therapies that increase progression-free survival and maintaining quality of life, but further studies will help to identify implications of the PI3KCA mutation in breast cancer and to determine which patients benefit from PI3K inhibitors.

Acknowledgments

None.

Conflicts of interest

The authors have declared no relevant conflicts of interest related to this work.

Funding declaration

The authors have received no funds for the development of this work.

References

1. Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA). Cancer de mama Rio de Janeiro: INCA. 2022.
2. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-Mutated, Hormone Receptor–Positive Advanced Breast Cancer. *N Eng J Med.* 2019;380(20):1929–1940.
3. Martínez-Sáez O, Chic N, Pascual T, et al. Frequency and spectrum of PIK3CA somatic mutations in breast cancer. *Breast Cancer Res.* 2020;22(1):45.
4. Cizkova M, Susini A, Vacher S, et al. PIK3CA mutation impact on survival in breast cancer patients and in ERa, PR and ERBB2-based subgroups. *Breast Cancer Res.* 2012;14(1):R28.

5. Gonzalez-Angulo A, Ferrer-Lozano J, Stemke-Hale K, et al. PI3K Pathway Mutations and PTEN Levels in Primary and Metastatic Breast Cancer. *Mol Cancer Ther*. 2011;10(6):1093–1011.
6. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumors. *Nature.* 2012;490(7418):61–70.
7. Juric D, Rodon J, Tabernero J, et al. Phosphatidylinositol 3-kinase α-selective inhibition with alpelisib (BYL719) in PIK3CA-altered solid tumors: results from the first-in-human study. *J Clin Oncol*. 2018;36(14):1291–1299.
8. Rugo HS, Borrego MR, Chia SKL, et al. Alpelisib (ALP) + endocrine therapy (ET) in patients (pts) with PIK3CA-mutated hormone receptor-positive (HR+), human epidermal growth factor-2-negative (HER2-) advanced breast cancer (ABC): First interim BYLieve study results. *Journal of Clinical Oncology.* 2019;37(15):1040.
9. Rugo HS, Lerebours F, Ciruelos E, et al. Alpelisib plus fulvestrant in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): one cohort of a phase 2, multicentre, open-label, non-comparative study. *Lancet Oncol.* 2021;22(4):489–498.
10. Bosch A, Li Z, Bergamaschi A, et al. PI3K inhibition results in enhanced estrogen receptor function and dependence in hormone receptor-positive breast cancer. *Sci Transl Med*. 2015;7(283):283ra51.
11. Juric D, Janku F, Rodón J, et al. Alpelisib Plus Fulvestrant in PIK-3CA-altered and PIK3CA-wild-type estrogen receptor–positive advanced breast cancer. *JAMA Oncol*. 2019;5(2):e184475.
12. Pascual J, Turner NC. Targeting the PI3-kinase pathway in triple-negative breast cancer. *Ann Oncol.* 2019;30(7):1051–1060.
13. Huang WC, Hung MC. Induction of Akt activity by chemotherapy confers acquired resistance. *J Formos Med Assoc.* 2009;108(3):180–194.
14. Zhang W, CAi J, Xheng X, et al. Paclitaxel resistance in MCF-7/PTX cells is reversed by paeonol through suppression of the SET/phosphatidylinositol 3-kinase/Akt pathway. *Molecular Medicine Reports.* 2015;12:1506–1514.
15. Liedtke C, Broglio K, Moulder S, et al. Prognostic impact of discordance between triple-receptor measurements in primary and recurrent breast cancer. *Ann Oncol.* 2009;20(12):1953–1958.
16. Pusztai L, Viale G, Kelly CM, et al. Estrogen and HER 2 receptor discordance between primary breast cancer and metastasis. *Oncologist.* 2010;15(11):1164–1168.
17. Arslan C, Sari E, Aksoy S, et al. Variation in hormone receptor and HER 2 status between primary and metastatic breast cancer: review of the literature. *Expert Opin Ther Targets.* 2011;15(1):21–30.

Citation: Lopes MSM, Ayoub EGM, Tarcha FV, et al. Alpelisib monotherapy in PIK3ca-mutated efficacy on triple-negative metastatic breast cancer in subsequent lines: a case report. *MOJ Surg.* 2023;11(1):7–9. DOI: 10.15406/mojs.2023.11.00210