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ORIGINAL

Presence of PIK3CA mutation in patients with stage IV luminal breast cancer and its relationship with rapid progression

Presencia de mutación del PIK3CA en pacientes con cáncer de mama luminales estadio IV y su relación con la rápida progresión

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ABSTRACT

Introduction: breast cancer is a disease of the mammary gland in which its cells grow and multiply abnormally. In Argentina, there were around 131 000 new cases of cancer, of which approximately 22 000 cases were of breast origin (2020). Although survival is increasing and its mortality rate is constantly decreasing due to great advances, in this work we will mention certain aspects related to rapid progression, increased mortality and lack of response to treatments that are associated with specific genetic mutations. We will address the PIK3CA pathway; one of the most active pathways in breast cancer, its relationship with the prognosis of the disease, resistance mechanisms and response to current treatments.
Method: we will rely on academic literature, publications and our own experiences regarding this pathology, taking 23 patients with stage IV luminal breast cancer from the Lucen Clinic and the Marie Curie Hospital between 1998 and 2001.
Results: 10 of them had the mutation in the PIK3CA pathway (43 %) and 13 did not (57 %). In addition to this, we will evaluate the survival time of the patients by comparing both groups; obtaining results that those who had this mutation had a lower average survival time, around 5-6 months, details that will be analyzed later.
Conclusions: therefore, we will conclude that metastatic breast cancer in stages IV that have the mutation of this gene will have a worse prognosis in terms of their quality of life, due to the chemoresistance generated by having the mutated PIK3CA pathway.

Keywords: Breast Cancer; Specify Mutations; Mortality; PIK3CA; Resistance Mechanisms.

RESUMEN

Introducción: el cáncer de mama es una enfermedad de la glándula mamaria en el cual sus células crecen y se multiplican de manera anormal. En Argentina ocurrieron alrededor de 131 000 casos nuevos de cáncer de los cuales aproximadamente 22 000 casos fueron de origen mamario (año 2020). Si bien la supervivencia está en aumento y su tasa de mortalidad está en baja constante debido a los grandes avances, en este trabajo mencionaremos ciertos aspectos relacionados a la rápida progresión, al aumento de la mortalidad y a la falta de respuesta a los tratamientos que se asocian a las mutaciones genéticas específicas. Abordaremos la vía del PIK3CA; una de las vías más activas en cáncer de mama, su relacion con el pronóstico de la enfermedad, mecanismos de resistencia y la respuesta a tratamientos actuales.
Método: nos basaremos en bibliografía académica, publicaciones y experiencias propias en cuanto a esta patología, tomando 23 pacientes con cáncer de mama luminal estadio IV de la Clínica Lucen y el Hospital Marie Curie entre.
Resultados: 10 de ellos presentaron la mutación en la vía del PIK3CA (43 %) y 13 no (57 %). Además de esto,

evaluaremos el tiempo de sobrevida de los pacientes poniendo en comparación ambos grupos; obteniendo resultados de que aquellos que presentaban esta mutación, tenían un menor promedio de sobrevida, alrededor de 5-6 meses, detalles que se analizaran más adelante.
Conclusiones: por ende, llegaremos a la conclusión de que los cánceres de mama metastásico en estadios IV que cuenten con la mutación de este gen, van a tener un peor pronóstico en cuanto a su calidad de vida, debido a la quimioresistencia que genera contar con la vía del PIK3CA mutada.

Palabras clave: Cáncer de Mama, Mutaciones Genéticas; PIK3CA; Mortalidad; Mecanismos de Resistencia.

INTRODUCTION

Cancer, regardless of its type, begins with transforming a cell or group of cells and ends with the cure or death of the patient suffering from the disease. Cancer cells have the power to survive, proliferate, differentiate, and express many specific functions. Still, their inability to regulate these functions ultimately leads to a phenotypic alteration with subsequent malignant transformation. In addition to local tumor growth, i.e., carcinoma in situ, the process of metastasis begins in parallel. This phenomenon occurs because cells migrate from the primary tumor to another site where they can survive and proliferate.[1,2]

Breast cancer is the most common malignant neoplasm as a cause of death, second only to lung cancer in women. Nowadays, its systematic detection through complementary imaging studies such as ultrasounds, MRIs, and mammograms is a fundamental tool for this pathology, with microcalcifications or densities in pathological breasts being the main sign.[3]

Most of these neoplasms are adenomatous and express estrogen, progesterone, and HER2 receptors. Therefore, we can say that this type of cancer has abnormal cell proliferation with multiple genetic aberrations, which influence estrogen expression and inherited genes in a certain way.[4] These cancers that have estrogen receptors are called luminal cancers and can be divided into different groups, the most common being type A.[5]

We should also mention the PIK3CA gene, an essential component of growth factor receptors' distal signal transduction pathways. Aberrant activation of this gene plays a vital role in carcinogenesis, presenting distinctive characteristics such as cell proliferation, autophagy, apoptosis, angiogenesis, and chemoresistance.[6,7]

Finally, mutations and amplifications of this pathway are the most frequently occurring events in cancer, and its abnormal activity is a transformative event in the disease process. It has, therefore, been described as one of the most commonly disrupted pathways in cancer, making it an attractive candidate for therapeutic intervention. Thanks to this, we will be able to identify which patients have this mutation and which do not, and thereby assess which patients are most vulnerable and which progress more rapidly in their disease, depending on the presence of the mutation in this pathway.[8,9]

This pathway is considered one of the most affected by genetic alterations compared to any other. Breast cancer is a significant health problem in Argentina, as it is the leading cause of death from tumors in women. Every year, there are 6100 deaths from this disease, and it is estimated that there will be more than 22 000 new cases per year, representing 32,1 % of the total incidence of cancer in Argentina.[10,11] In 2022, there were 5750 deaths in women from breast cancer, corresponding to a crude rate of 24,4 deaths per 100 000 women.[12] As a result, we will learn, through the application of scientific and experimental knowledge, the relationship between patients with the characteristics above, the presence or absence of the PIC3KA genetic mutation, and the treatments applied to them. Therefore, we will ultimately obtain a statistical result of which patients are most vulnerable and have the worst progression of the disease, depending on the presence of this genetic mutation.[13]

Today, due to the high incidence of breast cancer and the tremendous technological advances in medicine, specifically in oncology, this study will enable us to identify the optimal treatments and clinical status of patients in the terminal stages of the disease. In addition, it will provide us with valuable information on state-of-the-art therapies such as PIC3KA inhibitors, a therapeutic option for the patients we will discuss in this paper, as this study aims to demonstrate that patients with this gene mutation will have a worse disease progression and lower survival rates.

METHOD

The main objective of this study is to demonstrate the importance of a gene in this disease and how, by developing optimal technologies, results can be obtained for the well-being of a large part of the population. At the same time, we will compare two study groups depending on whether or not they have the PIK3CA mutation to show who will progress faster and in what way.

To this end, information obtained from the medical records of patients with luminal breast cancer with or without the PIK3CA gene mutation will be used. Databases such as PubMed and Mayo Clinic were also accessed

to expand the information. As a result, through a systematic review of medical records, we will find a way to identify which patients will progress more rapidly in terms of their disease, depending on the presence of this gene mutation.

The study focuses mainly on one group of patients: "menopausal women diagnosed with stage IV luminal breast cancer with or without the PIK3CA mutation."

An observational study method will be used to observe and record the variables of interest without interfering in their development. These patients were selected using a non-probabilistic sampling method. This means that the researcher chooses the sample subjectively and not randomly based on the medical records of patients in the clinical oncology department of the Marie Curie Hospital and Lucena Clinic.

Patients are selected by applying specific inclusion and exclusion criteria, which are listed below:

Inclusion criteria

- Patients with a confirmed diagnosis of breast adenocarcinoma, documented histologically or cytologically.
- Patients with metastatic or locally advanced disease that is not amenable to curative resection.
- Postmenopausal women over 60 years of age or women under 60 years of age with 12 months of amenorrhea, plus plasma or serum estradiol and FSH levels within the postmenopausal ranges according to local laboratories, without taking contraceptives or hormone replacement therapy.
- Negative for HER2.
- Positive for hormone receptors, both progesterone and estrogen.
- Patients who are in good clinical condition and whose vital signs are within normal parameters: Heart rate 80-100 bpm, respiratory rate 16-20 bpm, blood pressure 100-130.
- Patients with a sample for PIK3CA mutation testing in a paraffin block.

Exclusion criteria

- Patients who have received prior treatment in the metastatic or locally advanced stage with any PIK3CA inhibitor or any inhibitor of that pathway.
- Patients unable or unwilling to swallow pills.
- Patients with malabsorption syndrome or other conditions that interfere with enteral absorption.
- Patients with active inflammatory bowel disease or a history thereof.
- Presence of liver disease.
- Presence of clinically significant heart disease such as uncontrolled hypertension, history of stroke, history of heart attack, heart failure, or severe arrhythmia.
- Patients requiring daily oxygen.
- Patients with active symptomatic lung disease.
- Presence of active eye conditions.
- Positive HIV tests.
- Patients on chronic corticosteroid therapy.
- Pregnancy or breastfeeding.

The study considers variables based on the criteria mentioned above for collecting medical records. These variables include the presence of the PIK3CA genetic mutation, active breast cancer, stage IV, luminal patients, and the time of disease progression to the last line of treatment.

This study is being conducted in public and private clinical oncology practices in Buenos Aires.

The necessary information will be obtained through a literature search using PubMed, the Mayo Clinic, the Argentine Society of Oncology, and a review of medical records from the Marie Curie Hospital and the Lucena Clinic. Patient data will be collected from February 2022 to June 2024, with a 10-hour study. Weekly systematic review of medical records from June 2024 to date.

RESULTS

Now, do patients with the PIK3CA gene mutation progress earlier than patients who do not have this mutation?

The results were collected from 23 patients' medical records at the Marie Curie Hospital and the Lucena Clinic.

Through biopsy and the shipment of paraffin blocks of tumor material for genetic study, 10 patients were found to have specific mutations for the PIK3CA gene, and the remaining 13 did not. Most of the patients were in a similar age range, around 40-60 years old, and had no relevant medical history. All patients had a diagnosis of adenocarcinoma confirmed by a histopathological sample.

Of the 23 patients included in this study (100 %), 13 did not have the mutation (57 %) and 10 did (43 %).

Of these 10 patients, only 4 (40 %) had a survival rate of 6 months, while the rest (60 %) did not survive beyond 5 months. In the group of patients who did not have the mutation, it was observed that they had a

minimum survival rate of 12 months, with some reaching a year and a half (18 months).

It is essential to mention that the time to progression of neoplastic disease in a cancer patient is defined as the time during which the patient remains stable, with a partial or complete response to a line of treatment. Therefore, this variable is used to measure the time that patients receive each therapy, regardless of whether or not they have the PIK3CA mutation. Disease progression is defined as new metastatic lesions or a 20 % increase in the diameter of existing lesions.

It was, therefore, evident that patients with specific mutations had a worse prognosis and faster disease progression.

DISCUSSION

As we all know, Argentina ranks second in terms of risk of death from this disease. Knowing the risk factors, being alert to early symptoms, and being well informed about treatments and their responses are key for society.

However, regarding this study, we cannot guarantee that all patients received the indicated treatments in a timely manner, as they have different access to cancer medication, nor can we guarantee that the medication was taken correctly.

Another limitation is the sample size. Access to the PIK3CA study was not the same for all patients, and the vast majority of them did not participate, so they could not be included in our study sample.

The findings are comparable with the medical information analyzed, showing higher mortality in the mutated PIK3CA branch. Therefore, the PIK3CA status tool provides us with prognostic and predictive information in Argentina. To date, the mutated PIK3CA status is a negative prognostic factor, and we do not know its predictive value, as it will depend on access to therapies that modulate the pathway of this gene, which is currently heterogeneous in Argentina due to differences in the healthcare system.

In the future, it will be important that all breast cancer patients have access to this test from the onset of metastatic disease, as we now have specific targeted therapies available.

CONCLUSIONS

This study showed that the presence of the PIK3CA gene mutation in patients with stage IV luminal breast cancer is associated with more rapid disease progression and shorter survival compared to patients who do not have this mutation. The results reinforce the negative prognostic value of PIK3CA mutation status, positioning it as a relevant genetic marker when evaluating the clinical evolution of these patients. Although the small sample size and differences in access to treatment represent limitations, the findings are consistent with the international literature and support the need to implement systematic testing for this mutation in the diagnosis of advanced disease. In this regard, equitable access to molecular studies and targeted therapies is a priority objective for improving the personalized approach to breast cancer in our country. Early identification of this genetic alteration will optimize therapeutic selection and enhance affected patients' quality of life and prognosis.

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FINANCING

None.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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