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Metastatic triple-negative breast cancer successfully treated with bicalutamide

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Abstract

Triple-negative breast cancer (TNBC) is considered the group with the worst prognosis among the four molecular subtypes of breast cancer. The current treatment of metastatic TNBC is traditionally limited to chemotherapy. Androgenic receptors (AR) are an emerging target with therapeutic potential in TNBC refractory to chemotherapy. We present the case of a 66-year-old woman diagnosed with TNBC who had failed to 2 lines of chemotherapy after a diagnosis of recurrence. Immunohistochemistry was requested for the determination of AR, which was positive without specifying the percentage of AR expression. We started bicalutamide 50 mg QD, achieving disease control. At 50 months from the start of this treatment, the patient remains in stable disease, without any toxicity associated with treatment. Androgenic blockade could represent another management option for patients with advanced TNBC. The drug of choice and the dose to be used in this setting remains controversial. Furthermore, there is no consensus on the percentage of tumoral expression of AR to be considered a candidate for this treatment.

Introduction

Breast cancer (BC) represents the most common type of cancer in the female population, worldwide, it ranks second in incidence and fourth in mortality [1]. BC is a very heterogeneous disease; 4 molecular subtypes are currently recognized according to their expression of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor 2 (HER2) receptors. The triple-negative breast cancer (TNBC) subtype does not express any of these 3 receptors and is considered the group with the worst prognosis [2]. Androgenic receptors (AR) are an emerging marker with therapeutic potential in BC [3]. To date, studies are inconsistent in showing a clear relationship between the increase in circulating levels of androgens and the risk of BC, so it is not considered a risk factor [4]. AR are expressed in 90% of luminal-A tumors, and their expression is related to a better prognosis. This receptor stimulates or inhibits cell proliferation, in addition to promoting metastasis or resistance to various drugs [5]. Antiandrogen therapy (AT) has been used to inhibit tumor growth in advanced BC, especially in tamoxifen-resistant ER-positive tumors and TNBC [4]. Because of the lack of high-quality evidence, AT is not considered a standard option in advanced TNBC, with only a few cases reporting a clinical benefit in this difficult setting. We present a case of TNBC refractory to chemotherapy, who subsequently initiated AT based on bicalutamide, achieving a very long progression-free survival.

Patient and observation

A 66-year-old woman went to the breast tumor unit of our center after being diagnosed with left-sided BC by excisional biopsy and having undergone a modified radical mastectomy. The histopathological report revealed a moderately differentiated infiltrating ductal adenocarcinoma of 3.5 x 1.5 cm in diameter, with extensive angiolymphatic invasion and surgical resection margins free of neoplasia; 1 of 14 dissected axillary nodes was positive for neoplasia. Immunohistochemical analysis revealed negativity for ER, PR, and HER2, being classified as TNBC. Initial imaging studies did not reveal distant metastatic disease. After evaluating the case by a multidisciplinary team, it was decided to administer adjuvant treatment based on anthracyclines and taxanes at standard doses, as well as radiotherapy. One year after the end of the treatment, recurrence of the disease characterized by neoplastic infiltration of the femoral head and T5 and T7 vertebrae was demonstrated by bone scan, as well as a metastatic lesion in segment V of the right hepatic lobe of 2.6 x 1.9 cm by tomography. We started systemic treatment based on gemcitabine and zoledronic acid due to bone disease. After 5 cycles of this regimen, a disease progression characterized by an increase in the initial target hepatic lesion was observed, as well as a new metastatic lesion in the right kidney. We then

initiated second-line chemotherapy with capecitabine at a standard dose. After 1 cycle, our team decided to suspend this drug based on toxicity characterized by G3 mucositis. Immunohistochemistry was requested for the determination of AR, which was positive without specifying the percentage of AR expression. We started AT with bicalutamide at a dose of 50 mg daily, achieving disease control. At 50 months from the start of this treatment, the patient remains in stable disease, without any toxicity associated with AT.

Discussion

We described the clinical course of a patient with TNBC in treatment with an antiandrogen (bicalutamide) after having disease progression to two chemotherapy lines. To the best of our knowledge, this is the longest progression-free survival reported with bicalutamide in this setting. TNBC accounts for 15% of all cases of BC, and due to the absence of targeted treatments, chemotherapy continues to be the standard therapy; with an average overall survival of approximately 13 months [6]. Lehmann *et al*. identified 6 molecular subtypes of TNBC according to their genetic profile: basal-like 1, basal-like 2, immunomodulator, mesenchymal, mesenchymal stem cell-like, and the androgenic receptor luminal (ARL) [7]. This last subtype is enriched with hormonal regulatory pathways and is dependent on the stimulus of AR. Although this can be expressed in any TNBC subtype, the ARL subtype has the highest expression of AR [8]. ARs are expressed in 12-55% of cases of TNBC. Preclinical studies demonstrated clinical benefit with only 1% of AR expression, however, at higher AR expression, this benefit seems to be more pronounced. The evidence supporting AT in TNBC is scarce, with very few prospective studies in this regard. Phase II studies on the treatment of advanced TNBC with AT are summarized in Table 1. In the phase II study by Gucalp *et al.* among women treated with bicalutamide after a median of 1 cycle of chemotherapy, none achieved a complete response (CR) or a partial response (PR); and only one achieved a response duration on stable disease of 6 months [9]. Traina *et al*. described one patient with a CR and five with a PR among those women with a tumoral expression of AR of 10% or greater after treatment with enzalutamide [10]. The drug of choice and the dose to be used in this setting remains controversial. Furthermore, there is no consensus on the percentage of tumoral expression of AR to be considered a candidate for treatment with AT.

Conclusion

TNBC represents the most aggressive form of presentation of BC, and the one with the worst prognosis. The standard treatment in advanced-stage tumors continues to be chemotherapy. In patients who have manifested disease progression from one to several lines of treatment, androgenic blockade could represent another management option, seeking to improve the outcome in these patients without greatly compromising their quality of life.

Competing interests

The authors declare no competing interests.

Authors' contributions

All authors participated equally in the production of this manuscript: Carlos Eduardo Salazar-Mejía (writing of the manuscript), María Elena García-Gutiérrez (revision of the text), Carlos Javier Rodríguez-Álvarez (revision of the text), Miguel Ángel Flores-Caballero (table editing), Blanca Otilia Wimer-Castillo (revision of the text), Oscar Vidal-Gutiérrez (revision of the text). All the authors' have read and approved the final version of this manuscript.

Table

Table 1: phase II studies on the treatment of advanced TNBC with antiandrogen therapy

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Table 1: phase II studies on the treatment of advanced TNBC with antiandrogen therapy				
Author/year	**Patients**	**Treatment**	**Clinical benefit**	**PFS, median**
Gucalp et al 2013	26 patients	Bicalutamide 150 mg QD	19% at 6 months	12 weeks
Traina et al 2015	78 patients	Enzalutamide 160 mg QD	25% at 4 months	13 weeks
TNBC: triple-negative breast cancer; QD: quaque die (latin)				