Case Report

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Metastatic Breast Cancer: Clinical Relevance of Metastatic Sampling and Therapeutic Targets

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ABSTRACT

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Introduction

Advanced breast cancer (ABC) remains a virtually incurable disease with median overall survival of three years and a five-year survival rate close to 25%. ABC comprises both inoperable locally advanced breast cancer (LABC) and metastatic breast cancer (MBC), being a treatable disease with several available treatment options [1]. Patients with MBC demand a more tailored therapeutic approach regarding preferences, pretreatments, response to previous therapies, symptoms, tumour biology and burden [2]. Regarding tumour biology, disease progression to MBC should be confirmed by biopsy of metastatic lesion and biological markers reassessed at least once in metastatic setting [1]. BRAC germ-line mutation status, reassessment of human epidermal growth receptor 2 (ERBB2) status, as well as analysis of PIK3CA tumor somatic mutation, estrogen receptor-positive (ER+) and programmed death-ligand 1 (PD-L1) are important factors to define whether targeted therapies can be used. The present case report aims to illustrate the clinical challenges associated to MBC and the relevance of tissue sampling when facing disease progression to metastatic spread.

Case Report

A 49-years old Caucasian woman, ECOG 0 with familial history of lung, gastric and pancreatic cancer, was diagnosed with multicentric ductal invasive breast carcinoma in 2012. Staged as T2N2(4+) M0 with immunohistochemistry showing 100% positivity for hormonal receptors and negative for ERBB2. Total left mastectomy with axillary node dissection was performed followed by adjuvant chemoradiotherapy with 3 cycles of FEC-T (5-fluorouracil, epirubicin, cyclophosphamide) plus docetaxel and hormone therapy with goserelin plus tamoxifen for two years, maintaining monotherapy with tamoxifen until three years were completed. Complains of lower backpain, with no trauma associated, led to a thoraco-abdominopelvic CT-scan and bone scintigraphy to rule out disease progression. CT-scan showed "de novo" pulmonary micronodules with bone scintigraphy indicating a new hyper fixating lesion on the sacroiliac joint. Bone biopsy was performed and histological analysis inconclusive. CT-scan lung images were revised in Multidisciplinary Team with Pneumology and decided against performing micronodule biopsy due to technical issues.

Facing the possibility of metastatic spread to lung and bone, goserelin plus exemestane were re-introduced after hormonal assessment compatible with premenopausal status. After three years of stable disease under a luteinizing hormone-releasing hormone (LHRH) agonist plus an aromatose inhibitor, reassessment CT-scan showed increase in size of pulmonary micronodules and new mediastinal lymph node involvement, despite negative tumoral markers. PET-Scan with 18Fluorodeoxyglucose confirmed presence of multiple hyper fixating lesions compatible with both lung and lymph node lesions. Regarding an increment in size inferior to 20%, persistent negative tumoral markers and bad anatomy for lung biopsy, patient agreed on maintaining treatment with goserelin plus exemestane. Two years later, due to pulmonary disease progression with over 20% increase of some lesions, nodule biopsy was performed with histological analysis showing presence of breast cancer metastasis positive for hormonal receptors (HR) and ERBB2 (3+). Sequencing of BRCA gene was performed due to family history and availability of targeted drug in this context of disease [3]. BRCA2 mutation was present and patient referred to Genetic Counselling.

Having confirmed a stage IV breast cancer with lung metastasis positive for HR plus ERBB2, treatment with LHRH agonist and exemestane was discontinued and patient initiated on palliative chemotherapy with docetaxel and targeted therapy with Trastuzumab plus Pertuzumab [4]. After six cycles of Docetaxel, follow-up CT-Scan revealed stable disease and anastrozole (post-menopausal status confirmed) added to the dual ERBB2 blockade, being kept for three months until new progression was documented. This led to treatment regimen change to ado-trastuzumab emtansine [5] (TDM-1) in October/2020. With an overall survival of eight years, patient remained fully active without any adverse effect reported after four months of TDM-1.

Discussion

Breast cancer can be categorized into 3 different types based on the expression or absence of human epidermal growth factor 2 (ERBB2) and estrogen or progesterone receptors: Luminal A/B (hormone receptor positive/ERBB2 negative); ERBB2+ and basal-like (triple negative). The division according to the presence or absence of hormonal receptors and ERBB2 is of paramount importance to define treatment strategy and prognosis both in non-metastatic and metastatic settings. Regarding MBC, median overall survival for HR+/ERBB2- is 4 to 5 years, five years for EBB2+ and 10 to 13 months for triple negative. Tumour and patient-related factors with prognostic relevance are presence of visceral metastases, brain metastases and multiple metastatic sites, all conferring worst prognosis. Factors associated with better prognosis are better performance status, younger age at diagnosis, bone-only metastases and longer disease-free interval between diagnosis and metastatic progression [6]. To anti-ERBB2 naïve patients with ERBB2+ MBC, it should be offered anti-ERBB2 therapy as first-line. In this setting, combination of chemotherapy (ChT) plus trastuzumab and pertuzumab is the standard of care [4]. Moreover, BRCA germinative mutation also offers a therapeutic target for poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors, such as Olaparib or Talazoparib [3,7].

Here we report a young woman with an early breast cancer HR+/ERBB2- that progressed to MBC after adjuvant treatment with ChT plus anti-estrogen receptor combined with a LHRH agonist. Facing this progression, biopsy of a metastatic lesion was obtained to reassess hormonal receptor and ERBB2 status and define the best palliative treatment. The re-staging revealed a shift on tumour's biology, with metastatic disease being ERBB2 positive. There is no scientific evidence supporting which status should be used to define treatment when tumour biology differs between primary tumour and metastatic disease. However, it is recommended the use of targeted therapy when receptors are positive in at least one sample [1]. Despite the presence of a mutated BRCA gene, the use of PARP inhibitors was not possible regarding the positivity for ERBB-2. Being anti-ERBB2 naive and not having any contra-indication, ChT plus trastuzumab and pertuzumab was the therapy chosen. Although presenting a positive response to anti-ERBB2 treatment with stable disease, progression under this regimen led to discontinuation of anti-ERBB2 and prescription of TDM-1, based on its superior efficacy as second-line when compared to other anti-ERBB2 therapies [1,5].

Conclusion

The case reported illustrates the relevance of metastatic tissue sampling in the presence of metastatic breast cancer. Biopsy should be performed, if anatomically possible, to confirm diagnosis and reassess hormonal receptors and ERBB2 status. Although no evidence exists supporting which receptor status should be preferred, when primary tumour and metastatic disease diverge, targeted therapy should be considered when possible. Moreover, this case highlights the clinical relevance of further clinical trials using PARP inhibitors in ERBB2 positive MBC, to assess its efficacy and define whether could be a valid therapeutic option.

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