Pseudocirrhosis after the Use of Taxanes and Bevacizumab in Metastatic Breast Cancer: Case Reports

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Abstract: Currently, multiple lines of cytotoxic chemotherapy for treatment of metastatic breast cancer are available, and Taxanes, used as monotherapy or in combination with anti-angiogenic drugs, such as Bevacizumab, are one of the most used schemes in clinical practice. These drugs have different side effects and the liver is one of the most affected organs. The objective of this paper is to report three cases of metastatic breast cancer with positive expression of hormone receptors and without amplification of HER-2 protein that were treated with Taxane and Bevacizumab, developed pseudocirrhosis probably caused by these drugs and died due to liver failure. It can be drawn from the study that liver failure, as a pseudocirrhosis evolution, is an unusual but lethal event that may occur during the treatment of metastatic breast cancer with Taxanes and Bevacizumab. This warns the importance of diagnostic suspicion of this pathology.

Key words: Breast cancer, Taxanes, Bevacizumab, Pseudocirrhosis, liver failure.

1. Introduction

Breast cancer is the most common cancer among women, with 57,960 new cases estimated in Brazil in 2016 [1]. Despite several advances in the treatment of early disease, this is still considered an incurable cancer in the metastatic setting and the treatment goal should be prolonging survival with adequate control of symptoms in order to preserve patient’s quality of life [2].

Nowadays, there are multiple systemic treatments for metastatic disease; Anthracyclines and Taxanes are the most used cytotoxic drugs as initial therapy because they have high objective response rates with acceptable toxicity. Taxanes offer similar efficacy to anthracyclines, and usually, it is not observed cross-resistance among these drugs, making them possible options as sequential strategies. It is described various adverse effects in the medical literature with the use of Paclitaxel and Docetaxel, and the liver is one of the most affected organs with such chemotherapies [3].

In order to provide higher response rates, chemotherapy combinations have been widely studied but they are more toxic and do not provide any gain in survival when compared to monotherapy [3]. Bevacizumab is a humanized monoclonal antibody anti-VEGFA, and is used in other cancers besides breast cancer. Its addition to an anti-neoplastic agent in metastatic disease appears to be associated with an increased treatment response and extended progression-free survival compared to monotherapy. Although the prospective studies did not report an increase in overall survival, this strategy offers a more tolerable side effect profile than the cytotoxic chemotherapy doublets [4, 5].
The objective of this paper is to report three cases of metastatic breast cancer treated with Taxanes and Bevacizumab and developed pseudocirrhosis after the systemic treatment.

2. Case Reports

2.1 Case 1

MCLN, female, 40 years old, previously healthy, was diagnosed with left breast ductal invasive carcinoma on May 28, 2009. She underwent a radical mastectomy with axillary lymphadenectomy and immediate breast reconstruction. The pathological exam revealed a tumor of 2.5 cm with 4 of 20 lymph nodes compromised. Immunohistochemistry revealed: ER + 100%, PR + 90%, Her-2 negative and Ki-67 75%. She received adjuvant chemotherapy with Doxorubicin + Cyclophosphamide + Paclitaxel for six cycles, followed by radiotherapy and hormonal therapy.

The patient developed bone metastasis in November 2011 and her first treatment was hormonal therapy until further disease progression in February 2013, when an abdominal CT (computed tomography) scan showed liver metastasis. She received then palliative treatment with Paclitaxel and Bevacizumab until August 2013 (Paclitaxel was suspended after reaching maximum benefit).

After two months, a new abdominal CT scan was done (Fig. 1) and it showed a heterogeneous liver with important subcapsular retraction, compatible with pseudocirrhosis. Following her treatment, she underwent four different chemotherapy lines for subsequent disease progression, all in combination with Bevacizumab.

In February 2014, the patient evolved with hypoalbuminemia, elevated transaminases and DHL (lactate dehydrogenase) levels, as well as ascites and symptomatic esophageal varices. Her images revealed worsening of bone disease, with stable liver injury (however, with more parenchymal retraction). The patient showed unsatisfactory clinical progress despite the optimization of measures to portal hypertension, and died due to liver failure in June 2014.

2.2 Case 2

COVG, a 44-year-old female, previously healthy, was diagnosed with breast ductal invasive carcinoma in 2007. The tumor immunohistochemistry revealed: ER + 80%, PR + 60% and Her-2 negative. She was treated with quadrantectomy and adjuvant chemotherapy based on Doxorubicyn + Cyclophosphamid followed by weekly paclitaxel and hormonal therapy with Tamoxifen.

Fig. 1 Abdominal CT scan showing the evolution to pseudocirrhosis with an heterogeneous and lobulated liver: (a) from November 2011; (b) from April 2014.
In October 2009, she complained of nausea and a palpable mass in the right upper quadrant of her abdomen (Fig. 2). A CT scan showed multiple liver lesions and she started first line treatment with the combination of Docetaxel and Bevacizumab, with excellent clinical and imaging responses (by RECIST Version 1.1).

She followed successive disease progression, always treated with systemic therapy combined with Bevacizumab, and after reached stable disease in the fifth chemotherapy line, she remained using oral metronomic chemotherapy with Cyclophosphamide and Methotrexate + Bevacizumab until February 2013, when presented with ascites, portal hypertension (periesophageal and perigastric varices) and reduced hepatic parenchyma in CT scans, compatible with pseudocirrhosis.

After clinical optimization of her liver disease and elastic ligature of esophageal varices in February 2013, she received an additional line of chemotherapy based on infusional 5-fluorouracil due to the progression disease in bone and liver, reaching only stable disease by RECIST. However, she had a new and severe deterioration of liver function with ascites, jaundice and high digestive bleeding by portal hypertension, evolving to death in May 2013.

2.3 Case 3

MHAP, female, 74 years old, regular accompaniment for essential hypertension, was diagnosed in 2004 with breast ductal invasive carcinoma measuring 2.3 cm with 1 axillary lymph node positive for micrometastasis. Immunohistochemistry revealed: ER + 100%, PR + 100% and Her-2 negative. She underwent a quadrantectomy, followed by adjuvant treatment with chemotherapy based on Doxorubicyn + Cyclophosphamide followed by weekly paclitaxel, radiotherapy and hormonal therapy with Letrozole for five years, until January 2010.

In May 2011, an abdominal CT scan (Fig. 3) showed multiple hepatic nodules, whose biopsy confirmed disease recurrence. She received first line treatment with Paclitaxel and Bevacizumab, with excellent clinical and radiological response.

The patient underwent multiple treatment lines of hormonal therapy by subsequent disease progression, until August 2013 when she received Vinorelbine to obtain a higher response. In May 2014, she presented with ascites and a new abdomen CT scan showed heterogeneous liver and lobulated shape (aspect suggestive of pseudocirrhosis). She received Fulvestrant.

Fig. 2 Abdominal CT scan showing an enlarged liver with multiple lesions and the evolution to pseudocirrhosis: (a) from November 2009; (b) from November 2012.
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and then two other lines of palliative chemotherapy, but she evolved with refractory ascites, jaundice, hypercalcemia and hepatic encephalopathy. The patient died in December 2014 due to liver failure.

3. Discussion

Prospective studies in the early 2000s had already shown that the use of combination cytotoxic therapy is effective in providing a higher response rate, reaching approximately 60% of objective response in first line treatment and even with description of 20% of patients achieving complete remission (more commonly observed in patients with metastatic disease confined to the liver). Since the introduction of Taxanes in clinical practice, despite getting better control of the disease and mild increases in survival, it is still common a rapid evolution to liver failure due to tumor progression through the parenchyma, with median survivals ranging from 18 to 27 months [6]. In these cases reports, deaths were not directly related to mechanical complications of neoplastic infiltration, but due to a phenomenon still poorly described in the medical literature caused by the use of cytotoxic agents. Moreover, only one of the three patients had unique liver disease, and this presented the longest clinical course even with metastatic disease in activity.

Bevacizumab had already been widely studied in the setting of metastatic disease in different combinations with cytotoxic chemotherapy, but the more accepted doublet is indeed with Paclitaxel (used in some point of the disease in the three cases reported) [4, 5]. Miller et al. [6] have previously shown the magnitudinal gain in objective response rate and progression free survival with this combination, both considered statistically significant. The results of the study ECOG E2100 were subsequently reviewed and replicated by other groups that also observed the same gains. Despite the implied costs in combination drug (it is recommended to keep the antibody until disease progression or limiting toxicity) and no proven benefit in overall survival, the use of anti-angiogenic is well accepted in visceral crisis scenarios in which there is a clear necessity to obtain important cytoreduction with systemic therapy [6, 7].

Pseudocirrhosis is characterized by radiological changes in the hepatic contour and parenchyma, with development of diffuse nodularity, caudate lobe hypertrophy and capsular shrinkage, but without histopathological evaluation of a cirrhotic liver. It usually evolves similarly to chronic liver disease with portal hypertension and hepatobiliary dysfunction, after use of chemotherapeutic agents in patients with metastatic disease to the liver. The most studied primary cancer in this context is breast cancer, which accounts for 50% of reported cases, but there are also
descriptions of this evolution in patients with pancreatic, stomach, esophagus and thyroid cancer [8].

From the ethiopathogenic point of view, it is possible to find hepatic steatosis, focal hepatitis, portal fibrosis, nodular regenerative hyperplasia and necrosis of hepatocytes without fibrosis of the parenchyma, probably explained by redox mechanisms in the Cytochrome P450 system and high oxygen free radicals that alter the normal function of the cell’s membrane, promoting the release of lysosomes and aldehydes, which leads to hepatocyte dysfunction and apoptosis [7]. Such changes are morphologically translated by classical changes in the liver parenchyma seen in classical cirrhosis and are virtually indistinguishable in imaging exams to the radiologist. It is imperative that the oncologist have a correct temporal correlation between disease progressions and systemic treatments used and the emergence of regenerative changes described to complete this diagnosis, considering that up to 75% of women with metastatic breast cancer receiving chemotherapy have some degree of abnormal liver contour in CT scans [8, 9].

Many antineoplastic agents are recognized as hepatotoxic agents (doxorubicin, 5-fluorouracil, methotrexate, cyclophosphamide, oxaliplatin), however, they do not seem to be implicated in the pathophysiology of pseudocirrhosis. It is hypothesized that chemotherapy causes such a great reduction in tumor volume that promotes the mechanical retraction of the capsule and the development of scar tissues in the surrounding parenchyma of metastases, in addition to nodular hyperplasia caused by direct chemical injury to hepatocytes [8-10]. Another explanation could be a possible effect of extensive desmoplastic infiltration that can occur after exposure to chemotherapy in patients with large volume of metastatic disease [11].

4. Conclusions

Such etiological correlations were impossible to set to our reported patients, in view of the serious complications presented after the exposure to combined therapy of Taxanes and Bevacizumab. The reported cases showed an unusual event, but lethal to patients undergoing treatment for metastatic breast cancer, warning the importance of diagnostic suspicion when the medical oncologist chooses to combine therapeutic strategies in order to obtain higher rates of objective responses. Thus, further work should be conducted in order to guide clinical practice on the management of this serious complication by the use of chemotherapy based on Taxanes with Bevacizumab.

References

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