Elderly Woman with Triple-negative Metastatic Breast Cancer Successfully Treated with Metronomic Capecitabine

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Abstract. *Triple-negative breast cancer phenotype (estrogen receptor-, progesterone receptor- and human epidermal growth receptor 2-negative) is one of the most aggressive molecular subtypes, accounting for 15-20% of all breast tumors. There is no standard treatment for this setting of patients except anthracyclines and taxanes, but not all elderly patients can tolerate these kinds of agents. We describe the case of an elderly woman affected by triple-negative breast cancer with bone and brain metastases who has been treated for five years with metronomic capecitabine. At the moment, the patient has stable disease and enjoys good quality of life. She had initially been diagnosed with a poor Karnofsky index, which has actually improved from 50 to 90. Metronomic capecitabine treatment has clearly improved her quality of life, as documented by the results of the Functional Assessment of Cancer Therapy Breast.*

Breast cancer is the most frequent cause of cancer death among women, and despite the wide range of new chemotherapeutic drugs, the advanced forms of this disease remain essentially incurable. The options of treatment are based on many factors, including patient characteristics (age, menopausal status and performance status), tumor features (hormone receptor status, human epidermal growth factor receptor-2 (HER2) status, extent and site of metastases) and overall quality of life. In addition, the response to previous treatments and the disease-free interval from diagnosis or from another treatment should be considered (1, 2). Gene expression studies have identified multiple subtypes of breast cancer (3); among all, triple-negative breast cancer (estrogen- and progesterone receptor- and HER2-negative) accounts for 15-20%. Triple-negative breast tumor usually exhibits an aggressive behavior and carries a poor prognosis; it is characterized by a distinct metastatic pattern, which spreads preferentially to the brain. Yet there is no targeted-therapy that can improve the outcome of this tumor, and chemotherapy is the only choice of treatment for patients with triple-negative breast cancer. Capecitabine is usually used as a first-line therapy for metastatic triple-negative breast cancer and may represent a valid therapeutic option for patients in whom combination therapy is not appropriate (4). Capecitabine is an oral cytotoxic drug; this group of pharmaceutical agents are cost-saving and contribute to quality of life (QoL) by reducing the impact on daily activities.

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Key Words: T-negative breast cancer, capecitabine, metronomic chemotherapy, bone metastasis, brain metastasis, stereotactic radiosurgery, quality of life, FACT-B.

Case Report

A 80-year-old woman with severe osteoporosis was admitted to our Department in August 2009 complaining of a palpable lump located in her right breast and of severe pain to the back. The Visual Analog Scale (VAS) for pain score was 7 throughout the waking hours. Upon physical examination, a firm mass in the lower quadrant of the right breast was found. No evident axillary lymphadenopathy was present. All vital signs, as well as blood and urine analysis and chest X-ray, were normal. Plasmatic tumor marker analysis revealed that Cancer Antigen 15-3 (CA 15-3) and Carcino-Embryonic Antigen (CEA) levels were both within normal limits. Mammography was performed and indicated the presence of a mass of 2.2 cm in diameter, with abnormal borders located close to the axillary process of the right breast, accompanied by an affected regional lymph node of 1 cm in diameter.

Thoracic computerized tomographic (CT) examination confirmed the presence of a lesion in the right breast and of an homolateral lymph node, while it did not reveal any pathology in the lung parenchyma or mediastinum (Figure 1).

The bone scintigraphy described a diffuse bone metastasis with extensive involvement of the spine, hemithorax, skull, pelvis, humerus, femoral segments bilaterally (Figure 2).

A core biopsy of the breast mass was performed and the histopathological examination diagnosed a ductal carcinoma. Immuohistochemical analysis of the bioptic tissue for estrogen and progesterone receptors, and for HER2 was performed, and all three were negative. The Ki67 index was 28%. The tumor was classified as grade 3, according to the nuclear grading system.

The total body CT scan confirmed multiple bone metastases and showed a lesion of 1 cm in the cortico-subcortical parenchyma of the left frontal lobe with local edhema (Figure 3), so the patient underwent stereotactic radiosurgery (SRS), with a total dose of 25 Gy.

Considering her age, the Karnofsky performance status (the score was 50, because the patient required considerable assistance) and the willingness of the patient, a metronomic schedule with capecitabine at 1,500 mg daily was proposed.

In November 2009, the patient began the treatment: after orthopantomography and dental evaluation, she started therapy with zoledronic acid (4 mg every 28 days), calcium and vitamin D 10.000 UI/weekly.

Four months later, cerebral magnetic resonance imaging showed the reduction of multiple secondary lesions localized in the skull and in the left cortico-subcortical frontal lobe. In April 2010, the patient described the disappearance of bone pain (VAS 0-2); furthermore, activities of daily living and QoL improved significantly, without the development of any serious adverse effects.

The patient continued therapy until June 2010, when the CT scan showed no more evident secondary localization in the cortico-subcortical region of the left frontal lobe, as a result of radiosurgery, and no signs of edema; furthermore, stability of bone disease and no changes of the breast lesion were described.

She then continued treatment; a whole-body CT scan performed in October 2010 showed reduction of the right breast nodule and stability of bone disease.

Re-evaluation with CT scan has been performed every six months, the last in January 2014, always showing stable disease without any secondary localizations of the tumor (Figure 4). In parallel, there was complete bone pain relief (VAS 0/2).

The patient has actually stopped zoledronic acid treatment and is undergoing a complete revaluation of the oral cavity, in order to avoid osteonecrosis of the jaw. Therapy with capecitabine continues (after a period of five years) without side effects and with significant improvement in the Karnofsky performance status (the score is currently 90), daily activities and QoL. Data for QoL were collected with the Functional Assessment of Cancer Therapy-Breast (FACT-B), a 44-item self-report instrument designed to measure multidimensional QoL in patients with breast cancer. The test was administered to the patient at time 0 and after one year of treatment (November 2009-November 2010). Matched *t*-tests were conducted to discern whether baseline and 12 month tests differed on the quality-of-life indicator ($p<0.05$ was considered significant). Statistical analysis was performed using Graph Pad Prism 5.0 (GraphPad Software Inc., San Diego, CA, USA). The results of this test show a gradual improvement of physical, emotional and functional conditions of our patient in only one year (Table I).

Discussion

We describe the case of an elderly woman diagnosed five years ago with triple-negative metastatic breast cancer, and treated for five years with metronomic capecitabine, with the result of stable disease and an improvement of QoL.

Even now, there is no standard treatment for this setting of patients, except anthracyclines and taxanes, and no targeted therapies have been designed. Despite this, we were able to manage this patient with a capecitabine based-therapy in first line, chosen both due to the age of our patient and her poor performance status.

Therefore, we suggest that capecitabine has great activity as first-line therapy for elderly patients with triple-negative metastatic breast cancer and may represent a valid therapeutic option in patients for whom combination therapy is not appropriate. Capecitabine is an oral prodrug of fluorouracil with antitumor activity as single agent in refractory breast cancer, with response rates of 15-29% and associated with median overall survival of 10.1-15.2 months, as reported by multiple studies (5). The recommended dose and schedule is 2500 mg/m^2 daily on days 1 to 14 every 21 days, but dose interruptions or reductions are necessary in 30% of patients. Starting capecitabine at a lower dose (<1250 mg/m^2 twice daily) can reduce the incidence of adverse events without compromising its efficacy (5). Capecitabine-associated toxicities include hand–foot syndrome, diarrhea and stomatitis. Our patient reported no toxicity, with perfect adherence to the treatment.

Some chemotherapeutic agents have an anti-angiogenic effect when they are administered at low doses on a frequent or continuous schedule, with no extended interruptions (metronomic chemotherapy) (6, 7). Metronomic chemotherapy can induce an anti-angiogenic activity, by inhibiting proliferation and migration or inducing apoptosis of activated endothelial cells; this therapy also increases the expression of the endogenous angiogenesis inhibitor thrombospondin-1, and reduces the number and the viability of bone marrow-derived endothelial progenitor cells (8-11). It has been suggested that the anti-angiogenic effect of metronomic therapy may have better efficacy on triple-negative breast cancer, due to the highly proliferative behavior of this cancer subtype and to the importance of neo-angiogenesis in supporting its progression (12).

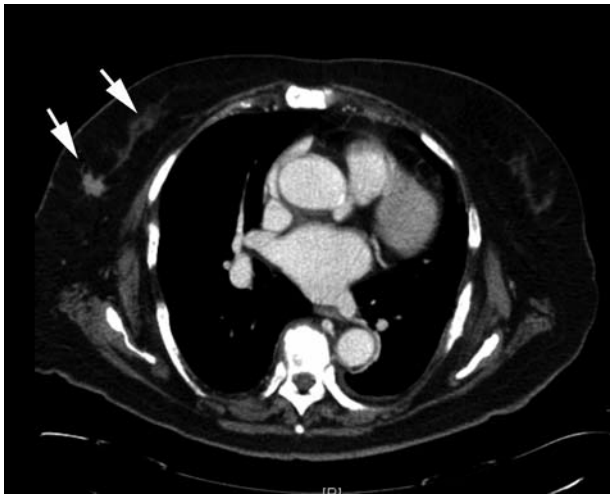

Figure 1. *Thoracic computed tomographic examination showing a mass in the right breast of 2.2 cm in diameter (arrow), with abnormal borders and an homolateral pathologic lymph node (arrow). No secondary lesions were seen in the lung.*

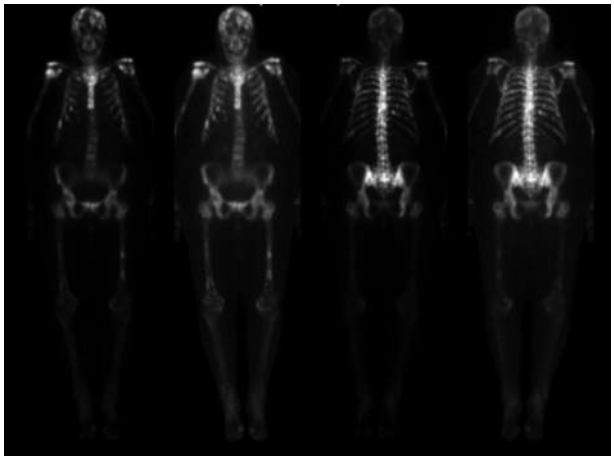

Figure 2. *Bone scintigraphy showing multiple bone metastases.*

Figure 3. *Computed tomographic scan showing a left frontal lobe lesion with local edema.*

Table I. *Functional Assessment of Cancer Therapy-Breast (FACT B) test to evaluate quality of life. After one year of treatment, there was a significant improvement of physical, emotional and functional scores.*

Variable	Descriptive data on quality of life Quality of life FACT B				*p*-Value
	Baseline		After 1 year		
	Mean	SD	Mean	SD	
Physical	13.95	1.32	16.30	1.70	0.0003
Social	19.75	0.50	20.30	2.10	0.18
Relation to physician	5.75	1.20	6.80	1.20	0.02
Emotional	15.00	1.69	16.70	1.71	0.005
Functional	16.55	1.80	18.20	1.70	0.002

Furthermore, metronomic capecitabine is a valid option for elderly patients because of both its efficacy and its tolerability (13).

Age is usually a risk factor for increase of chemotherapy toxicity and for the consequent decrease of chemotherapy tolerance. The decision whether or not to perform cytotoxic chemotherapy for advanced cancer in each elderly patient is a balance between the potential benefits and the adverse effects. The response rates to aggressive chemotherapy are similar in younger and older patients; disease-related survival is often similar, although the older age group has more deaths due to comorbid illnesses (14). Loss of organ function can affect cytotoxic drug metabolism: changes in kidney or liver function or bone marrow deficit are particularly problematic when giving standard chemotherapy. For example, our patient had many comorbidities and would not

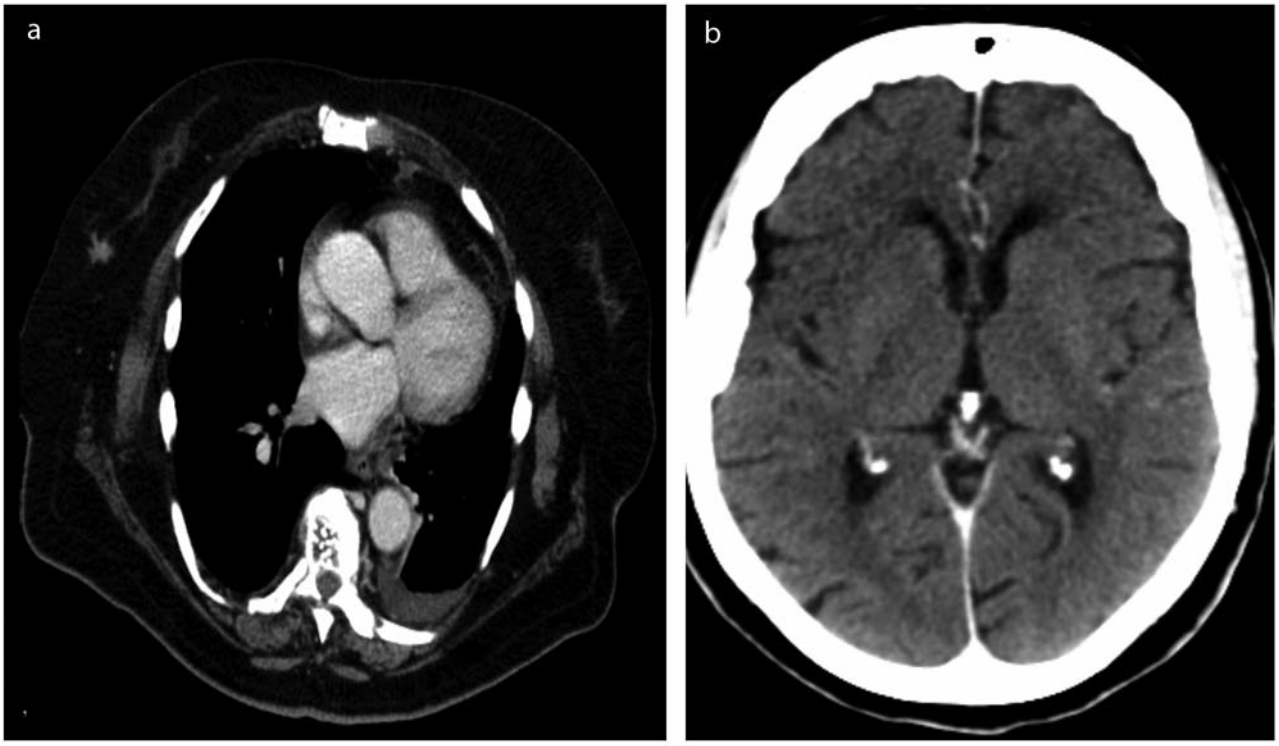

Figure 4. *Computed tomographic scan showing stable disease of the lesion in the right breast (a) and no lesions in the cortico-subcortical region of the left frontal lobe, with no signs of edema (b).*

tolerate an aggressive therapy, neither physically nor psychologically. Metronomic capecitabine therapy determined a significative reduction of her disease, and at the same time, an improvement of her QoL. Taking into consideration the presence of the breast cancer and the risk of ulceration, we also proposed excision of the nodule in the right breast to our patient, but she refused.

The response duration in triple-negative breast cancer is usually short, with rapid relapse in the first two to three years after surgery, and is associated with a median survival of about 13 months in metastatic disease (15-17). However, our patient, although having a metastatic onset of breast cancer, is still alive, maintaining stable disease after five years of therapy.

Brain metastases are usually the major cause of morbidity and mortality, affecting neurocognition, speech, coordination, behavior, and QoL in oncological patients: our patient also had a brain metastasis. The current standard of care for patients with brain metastases is whole-brain radiotherapy, with or without surgery, or SRS. SRS offers good local control and prolonged survival in selected patients (18, 19). Our patient underwent SRS five years ago, and there is no evidence of relapse in the brain, as confirmed by the last CT scan of January 2014.

Advanced triple-negative breast cancer has a poorer prognosis than other breast cancer subtypes, but our patient is still alive after 5 years and is continuing therapy with capecitabine and zoledronic acid, with stable disease of breast and bone.

Conclusion

Our patient is now 85 years old, she has no more bone pain (VAS 0), her QoL and compliance are optimal. She was diagnosed with a poor Karnofsky index before the treatment; the Karnofsky score has actually improved from 50 to 90, therefore we can state that a combined therapy of zolecronic acid and capecitabine has improved her QoL. Furthermore, the metastatic disease is stable and perfectly controlled by metronomic capecitabine-based chemotherapy.

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Received April 4, 2014
Revised May 29, 2014
Accepted May 30, 2014