Clinical Case Report

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Highly durable response to capecitabine in patient with metastatic estrogen receptor positive breast cancer

A case report

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Abstract

Rationale: In estrogen receptor-positive HER2-negative (ER+HER2-) metastatic breast cancer, chemotherapy should be offered only to patients who develop endocrine resistance or have a rapid disease progression. However, the correct sequence of chemotherapy administration is still debated.

Patient concerns: We report the case of a 49-year-old woman with ER+ HER2- metastatic breast cancer who experienced an exceptionally long response to capecitabine administered as second-line therapy following a first-line anthracycline-based chemotherapy.

Diagnoses: The patient was diagnosed with ER+ HER2- metastatic breast cancer with massive liver involvement and mediastinal lymph nodes metastasis.

Interventions: This patient was treated with capecitabine 1000 mg/mq bid given intermittently for 14 days within a 21-day cycle as a second-line therapy following a rapid progression on letrozole treatment given as a maintenance therapy.

Outcomes: Our patient experienced a progression-free survival (PFS) >3 years with an exceptionally good quality of life (QoL).

Lessons: In ER+HER2- metastatic breast cancer patients, capecitabine monochemotherapy in second line may be associated with a particularly satisfactory PFS and no impact in terms of QoL. Future studies focused on biomarkers with predictive ability may help select patients who represent the best candidates to this treatment.

Abbreviations: CMF = ciclophosphamide, methotrexate, fluoruracil, ER = estrogen receptor, ER+HER2- = estrogen receptor-positive HER2-negative, ET = endocrine therapy, PFS = progression-free survival, PR = progesterone receptor, QoL = quality of life.

Keywords: capecitabine, chemotherapy, long response, metastatic breast cancer

1. Introduction

Breast cancer is the most common form of cancer in Western Countries.[1] Approximately 5% of patients present with metastatic disease at diagnosis and another 20% of patients with early breast cancer will eventually relapse, thus becoming metastatic.[2]

Several agents are now available for metastatic breast cancer treatment, including chemotherapy, endocrine therapy (ET), and biological agents (ie, CDK 4/6 inhibitors and anti-HER2 agents), both singularly and combined. However, in this setting, palliation still remains the main goal, with the prolongation of overall survival (OS) and improvement of quality of life (QoL) being considered as primary objectives.

In estrogen receptor-positive, HER2-negative tumors (ER+ HER2-) metastatic breast cancer patients, ET is generally considered the first choice, unless visceral crisis or primary endocrine resistance occurs.[3] Therefore, the use of chemotherapy should be restricted to those patients who develop an endocrine resistance or have a rapidly progressing disease.

Here we report the outcome of a 49-year-old, premenopausal woman, who had a extraordinarily prolonged response to a second-line chemotherapy with capecitabine.

2. Case presentation

In April 2009, the patient, a 44-year-old, white, premenopausal woman with no comorbidities and no familiarity for cancer, had a diagnosis of breast cancer based on a core biopsy performed on a 1 cm mass in her left breast. Subsequently, she underwent left mastectomy and ipsilateral axillary dissection. The pathological report described a ductal carcinoma of the breast (1 cm) extended to 3 of 11 axillary lymph nodes dissected. Biological factors were

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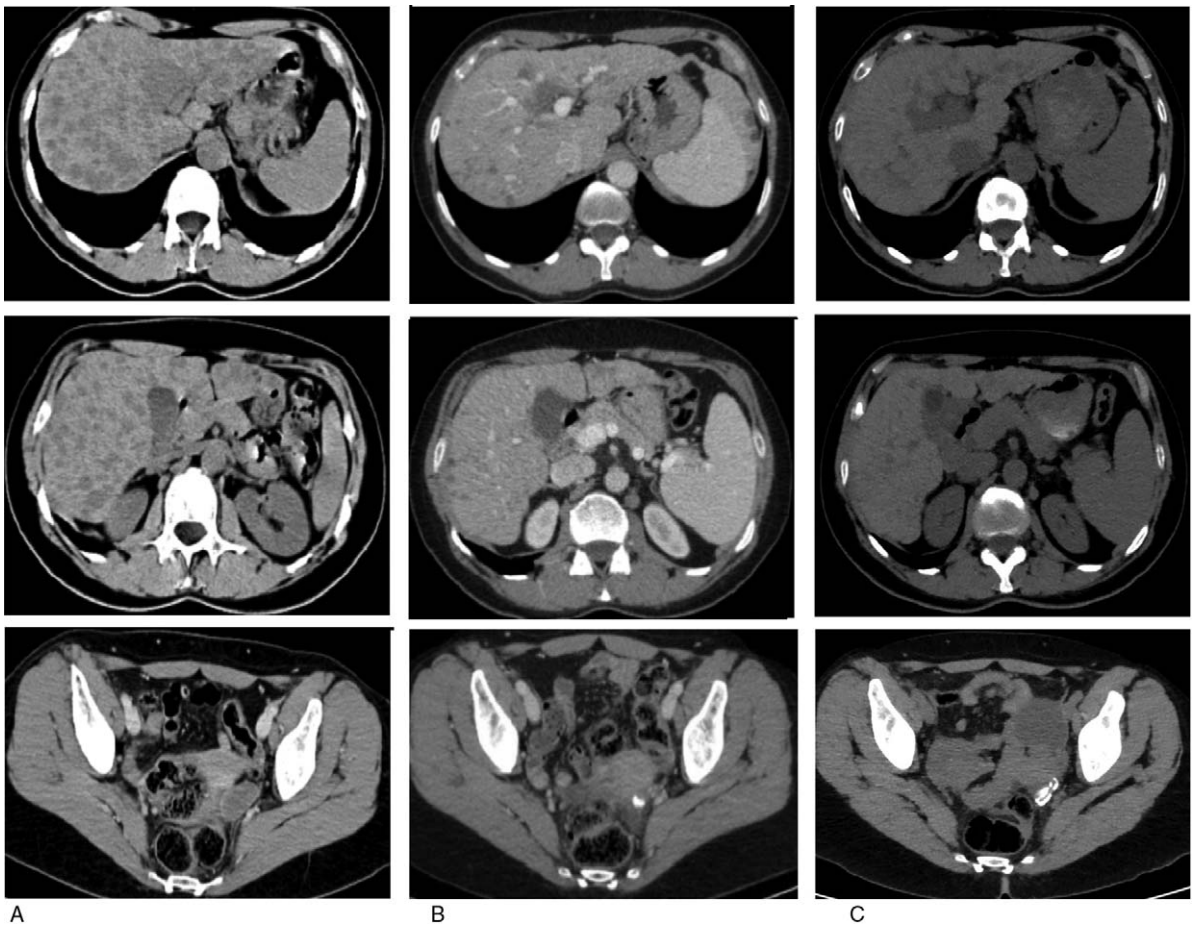

Figure 1. Computed tomography scan at the time of the first progression (A); best response with capecitabine (B); progression to capecitabine (C).

as follows: estrogen receptor (ER) 80%, progesteron receptor (PR) 80%, ki67 20%, HER-2-negative. Staging: pT1b (1 cm) pN1a (3/11) stage IIA. She was treated with adjuvant chemotherapy (6 cycles of docetaxel-cyclophosphamide), followed by radiation therapy. In addition, adjuvant ET (tamoxifen plus LHRH analogous) was planned for 5 years.

Starting from January 2013, we observed a progressive increase of CA 15.3 serum levels, which continued till May 2013, when the patient performed a positron emission tomography scan and computed tomography (CT) scan which showed metastatic involvement of multiple mediastinal lymph node and liver disease (Fig. 1A).

Given the initial alteration of liver function and the extent of disease, we chose to administer an anthracycline-based chemotherapy. The patient refused an alopecia-inducing chemotherapy, so 6 cycles of nonpegylated liposomal doxorubicin and cyclophosphamide were administered from June to September 2013, with a good clinical and instrumental response. Subsequently, she started a maintenance therapy with letrozole 2.5 mg once daily, which continued until February 2014, when a significant worsening of liver function and increase of tumor markers occurred. Considering the rapid clinical and biochemical progression and endocrine resistance, we decided to switch from ET to chemotherapy, thus prescribing capecitabine. From March 2013 To June 2017, the patient received 53 cycles of capecitabine 1000 mg/mq bid, given intermittently for 14 days on a 21-day cycle.[4] During the first 2 years of treatment, CT scans documented a response relatively to the liver lesions and mediastinal lymph nodes, classified as partial response according to RECIST criteria (Fig. 1B), whereas blood test analysis showed a progressive normalization of liver function. This surprising result was followed by an extraordinarily prolonged instrumental disease stability. No relevant side effects were reported. The patient conserved a good QoL and maintained her working activity and social life during the whole treatment.

In July 2017, a CT scan showed an increase of the ovarian diameters (Fig. 1C) and the onset of rib bone lytic lesions. Laparoscopic bilateral oophorectomy and multiple peritoneal biopsies were performed. Both the pathological reports confirmed the mammary origin of the lesions. Capecitabine was discontinued and the patient started eribuline, which continued until disease progression, occurred in May 2018. Then she started Fulvestrant + Palbociclib and is currently on treatment with nab-paclitaxel. None of the subsequent treatments reached a progression-free survival (PFS) comparable to capecitabine. Indeed, this patient experienced a PFS >3 years with capecitabine. The patient has provided informed consent for the publication of the case. Being a case report, ethical approval was considered not necessary.

3. Discussion

In the case we presented, we observed an extraordinarily prolonged response to second-line capecitabine monotherapy

in a patient who developed a secondary endocrine resistance and was experiencing an initial visceral crisis condition.

In metastatic ER+HER2- breast cancer patients, several relevant questions may be raised concerning the appropriateness of chemotherapy administration. Most commonly, chemotherapy represents the therapy of choice in ER+HER 2-negative metastatic breast cancer patients with a symptomatic, life-threatening disease or for whom all the available endocrine weapons have been exhausted. However, the correct sequence of chemotherapy treatments has not been clearly identified, and depends also on previous treatments. Capecitabine monotherapy was extensively evaluated in phase II-III trials as first and subsequent chemotherapy lines[5–7] and is currently employed in patient who progressed following anthracycline and taxane chemotherapy regimens. Capecitabine has a favorable safety profile, and it is suitable for long-term administration generally without cumulative toxicity. It is also used as an alternative to taxanes and anthracyclines in patients who wish to avoid alopecia and are concerned about their lifestyle, or in elderly patients. It is also one of the chemotherapy agents which was more thoroughly investigated using metronomic schedules, both as a single therapy or in combination with other drugs such as vinorelbine and cyclophosphamide.[8]

Recently, a systematic review of 8 phase II trials and 2 phase III trials enrolling 1494 patients, of whom 80% had received taxanes and antracyclines, showed an overall response rate of 18%, a median PFS of 4.2 months and a median OS of 13.5 months in patients treated with capecitabine monotherapy.[9] Subsequent trials in which capecitabine was used as control arm showed similar results.[10,11] Compared to those reports, our patient had an outstanding outcome, with a PFS which reached 39 months. However, the reasons responsible for her prolonged response remain unknown. A recent report analyzed the genomic and phosphoproteomic profiles of breast cancers from 6 patients who had exceptional response to capecitabine: 3 patients had functional alteration in DNA repair and chromatin remodeling genes, whereas 3 other patients had variants of unknown significance. No TP53 or PTEN mutations were found, whereas PTEN was positive at immunohistochemistry.[12] Some preclinical data suggest that sensitivity to 5-fluorouracil may be enhanced by deficiencies in chromatin remodeling and homologous recombination genes.[13]

Our work has to be interpreted also in light of its limitation. In strict regard to the study design, that is, case report, the poorly generalizable nature of our results deserves to be mentioned. Indeed, evidence from a single case is generally not representative of a wider population. Another possible limitation consists of the exclusively clinical nature of our work. We did perform only clinical evaluations, while excluding any genomic, transcriptomic, and proteomic profiling, which may have brilliantly integrated a more traditional, clinical-instrumental approach. Such an integrated approach may have helped inform therapeutic decisions and interpret treatment outcomes. Lastly, we must consider the limits stemming from a retrospective approach to the evidence previously described, as medical records were retrieved following occurrence of relevant events, in a patient with a notably long clinical history. This may have caused a partial loss of information.

In metastatic breast cancer, decision-making may be significantly helped by the availability of biomarkers which may inform our decisions. Such biomarkers may derive from different investigational levels, possibly integrating genomic, transcriptomic, and proteomic analyses. The inherent results may also help interpret data on clinical outcome in exceptional responders, possibly exemplified by the case we described, as well as in case of fast progressors. In addition, these data should be always considered and implemented in light of the physician experience, relevant comorbidities, safety profile, and patient preferences and values.[14]

Author contributions

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