

# Circulating Tumor Cell Data: Integration with Imaging and Serum Tumor Markers for Metastatic Breast Cancer Patient Management

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## Key Words

Decision making · Circulating tumor cells · Breast cancer

## Abstract

Management of metastatic breast cancer is critical to maximizing survival with good quality of life. Circulating tumor cell (CTC) levels in the peripheral blood hold promise for enabling improved patient care. We describe a case of a 47-year-old female with infiltrating ductal carcinoma who developed metastatic disease. Serum tumor markers were discordant with imaging studies at several time points. CTC levels were used to support decision making in light of the discordant data. The use of this tool enabled prompt changes in therapy with progressive disease and supported suspending therapy to enable recovery from treatment adverse effects when a significant response was detected by imaging and CTCs were absent from the peripheral circulation. The additional information provided by CTC enumeration helped clarify disease status and provided support for treatment decisions.

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## Introduction

Metastatic breast cancer continues to be almost uniformly fatal; however, improvements in survival in developed countries have been documented [1]. This improvement can be attributed to better therapeutic and diagnostic tools for disease management. Yet, there is a limited array of tools for a noninvasive assessment of metastatic breast cancer, which includes imaging [computed tomography (CT) scans, bone scintigraphy, positron emission

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tomography (PET), and magnetic resonance imaging] and measurement of serum tumor marker concentration in the peripheral blood. Additional tools for managing metastatic breast cancer are needed. One challenge to the introduction of new clinical tools is to determine their best use in clinical decision making. In other words, facilitating the integration of clinical information from these new assessments into the clinical workflow and decision making is critical.

Circulating tumor cells (CTCs) are useful as an indicator of prognosis both initially and after therapy [2]. Multiple studies have shown that patients with  $\geq 5$  CTCs/7.5 ml of peripheral blood have a worse prognosis for survival than patients with  $< 5$ /7.5 ml. The concentration of CTCs shed by solid tumors and detected in the peripheral circulation correlates with relapse and survival in multiple types of cancer [3–8]. A system for measuring CTC concentration in peripheral blood to monitor metastatic breast, colon, and prostate cancer has been cleared by the United States Food and Drug Administration and is now commercially available for clinical use (CELLSEARCH®, Janssen Diagnostics, LLC). However, how to best integrate this new information on disease status with existing measurements of disease prognosis and progression in clinical decision making remains empiric. Here we present a case of metastatic breast cancer in which CTC information was used to help resolve discrepancies between more conventional assessments to improve patient care.

### Case Presentation

The patient was a 47-year-old Caucasian female. She was diagnosed with infiltrating ductal carcinoma of the right breast in 1994. The tumor was staged as T1N0M0. Pathology demonstrated estrogen-receptor-positive and progesterone-receptor-positive disease. At that time, she was treated with breast-conserving surgery, followed by radiation therapy. The patient refused adjuvant tamoxifen therapy.

In March 1998, the patient was diagnosed with distant recurrence of her disease localized to the right femur. She was treated with radiation therapy, followed by paclitaxel and doxorubicin. After an initial response, the chemotherapy was discontinued and the patient was placed on maintenance letrozole and pamidronate.

The patient was diagnosed with progressive disease based on imaging done in November 2006. Her therapy was switched to fulvestrant plus zoledronic acid based on the imaging study (table 1). An initial CTC measurement using the CELLSEARCH® System resulted in a determination of 1/7.5 ml (fig. 1). A repeat CTC measurement in February 2007 again returned a value of 1/7.5 ml.

In April 2007, PET/CT imaging revealed metastatic deposits in the liver and bone, suggesting progressive disease; however, based on the low CTC count in February the decision was made to not change treatment. Repeat imaging in July 2007 showed a partial response (PR) in the liver and bone lesions (fig. 1). Thus, although the patient's CTC count had risen to 6/7.5 ml and initial tumor marker measurements were elevated (497 U/ml for CA 27.29 and 58 ng/ml for CEA), therapy with fulvestrant plus zoledronic acid was continued based on a lack of changes in imaging studies and continued good performance status (table 1).

In October 2007, the patient's CTC count remained at 6/7.5 ml, while her CA 27.29 had risen to 520 U/ml. In December 2007, the CTC count had declined to 0 and tumor marker levels were stable. PET/CT imaging demonstrated improvement in the liver lesions and a mixed response in the bone lesions (fig. 1).

The following month, the patient experienced increasing lower back pain. Radiation therapy was given to the metastatic sites identified as active by increased standardized uptake values from the PET/CT imaging in December 2007. The following February, CTC levels remained below 5/7.5 ml and tumor markers were elevated and stable. CTCs were absent from the patient's peripheral blood in a measurement in April 2008.

In May 2008, PET/CT imaging revealed progressive disease, both in the liver and bone. Her CTC level had risen from 0 in April to 9/7.5 ml, and CA 27.29 had risen to 1,371 U/ml, confirming progressive disease (fig. 1). The CEA level was up slightly from February. Biopsy of the liver lesions confirmed progressive metastatic breast cancer. The patient's therapy was switched to Abraxane® plus bevacizumab (table 1).

In July 2008, after two rounds of chemotherapy with the new agents, her CTC level had again dropped to 0. Repeat PET/CT imaging at the end of July confirmed a PR to therapy. Over the summer, the patient experienced significant bevacizumab toxicity. Based on the positive response observed with imaging and CTC levels, the decision was made to discontinue treatment with the bevacizumab component of her treatment regimen. Her CTC level remained at 0 upon repeat measurement in September 2008. Based on PR on imaging and negative CTC counts, in September the decision was made to discontinue all chemotherapy due to progressive toxicity experienced by the patient, including new onset neuropathy (table 1).

## Discussion

Assessment of tumor activity in this case was difficult using conventional tumor markers and PET/CT imaging due to a lack of concordance between these assessments, which ordinarily would diminish confidence in treatment decisions. The use of CTC enumeration information to support clinical decision making in a setting of conflicting assessments has been suggested previously [9]. The specificity and responsiveness of the serum tumor markers, CEA and CA 27.29, are reported to be fairly low [10]. Radiographic assessment may have interreader variability and may not reflect changes in disease status in a timely manner [11]. CTC concentration has been reported to be specific for cancer and to respond to changes in disease state promptly [11, 12] and so may compliment other assessments.

The initial response of CTC counts to therapy was complex. In the months after the initiation of fulvestrant plus pamidronic acid therapy in November 2006, the patient's CTC count rose to 6/7.5 ml, then stabilized. Although the CTC count had risen, imaging studies showed response to treatment and the patient's performance status was good, so therapy was continued. By December 2007, the CTC count had reached 0, which brought it into agreement with the PET/CT imaging studies. In contrast, the serum tumor markers remained elevated. Based on the imaging studies in July and December showing response to therapy and the absence of CTCs, the decision was made to continue therapy with fulvestrant and pamidronic acid. In this example, CTCs may have been more reflective of disease state than the serum tumor markers.

At the May 2008 visit, both CTC and CA 27.29 levels were elevated, which supported imaging results that suggested progressive disease. CEA concentration was unchanged. This was an unusual instance, where all assessments were in agreement. The decision was made to start a new line of therapy with Abraxane plus bevacizumab. The patient responded to this change in therapy as assessed by CTC concentration in July 2008, which decreased to 0. The response was confirmed by imaging, which showed a PR.

Although CTC count often responds to changes in disease state fairly quickly, in some instances, changes may not be seen in the first measurement [unpubl. observations, 2]. In this case, the CTC count increased in the first half of 2007 following initiation of fulvestrant plus zoledronic acid therapy, while imaging suggested a PR. The CTC count stabilized at 6/7.5 ml from the July and October measurements, then decreased by the third measurement in December 2007. In our experience, CTC count responses following hormonal therapy in breast cancer may require 3–4 months or more to show a significant change. In contrast, the decrease in CTC concentration observed in the first measurement following change in therapy to Abraxane plus bevacizumab in July 2008 closely tracked the PR determined by imaging, which is typical in our experience for response of CTC counts to chemotherapy. Despite the differences in time to response, in both of these examples from this case the CTC count was ultimately concordant with imaging.

The specificity of CTCs for breast cancer [13] was important in considering the use of CTC enumeration information in this case. The patient experienced adverse effects attributed to bevacizumab [14] in the summer of 2008, and the decision to discontinue bevacizumab was supported by the favorable imaging results and negative CTC levels following the change in therapy. Subsequent negative tests for CTCs in July 2008 and September 2008 gave us additional confidence that a discontinuation of paclitaxel therapy could be allowed so that the patient could recover from its adverse effects, using CTC tests as an option to monitor for disease progression. The use of CTC information in this context is consistent with recommendations to limit the use of imaging to monitor for cancer recurrence [15].

Management of metastatic breast cancer is challenging under any circumstances. This case illustrates how CTC assessments can corroborate imaging and clinical data. In addition, the type of therapy may influence the time to see a CTC response in breast cancer, with hormonal therapy often taking longer than chemotherapy. Finally, in this instance, we found CTC measurement a useful adjunct to imaging for monitoring for disease recurrence to give the patient a needed drug holiday.

### Disclosure Statement

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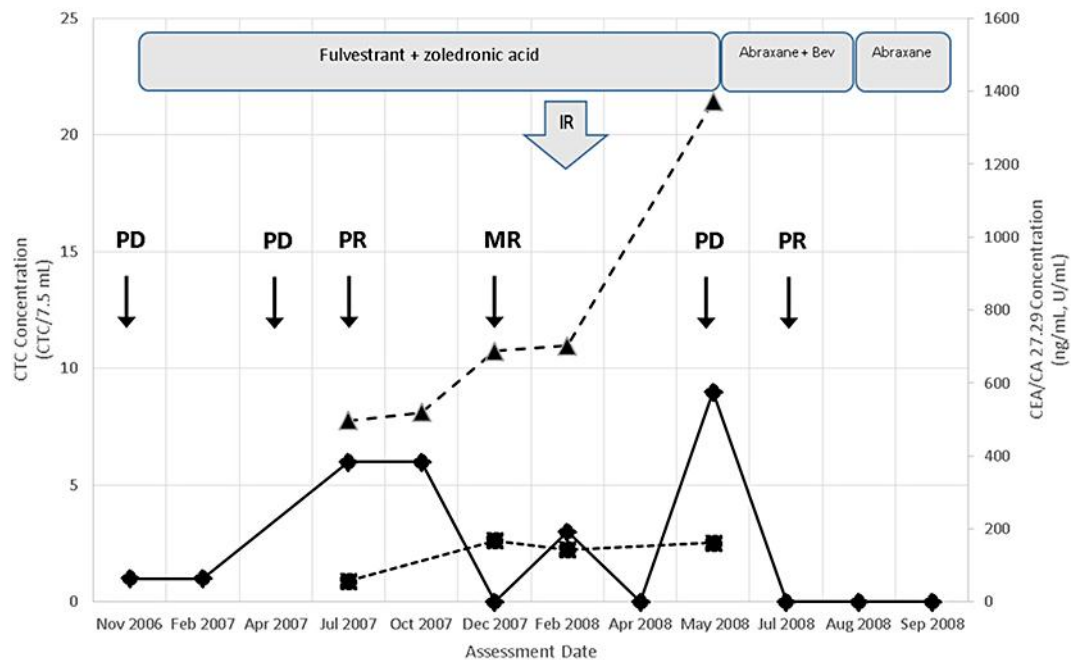
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**Table 1.** Summary of assessments and clinical decisions

Time frame	Clinical decision	Assessments	Commentary
November 2006	Therapy switch to fulvestrant plus zoledronic acid	Imaging – PD [CTC] – low	– Decision to switch therapy based on imaging that showed PD in November 2006
July 2007	Continuation of fulvestrant plus zoledronic acid treatment	Imaging – PR Clinical – performance status: good [CTC] – marginal [CEA] – elevated, stable [CA 27.29] – elevated, stable	– Marginal [CTC] agreed with good performance status – Continued fulvestrant plus zoledronic acid therapy – Imaging showed equivocal response
December 2007	Continuation of fulvestrant plus zoledronic acid treatment	Imaging – MR Clinical – performance status: good [CTC] – absent [CEA] – elevated, stable [CA 27.29] – elevated	– Imaging response, performance status, and absence of CTCs indicate good prognosis – Continued treatment
February 2008	Continuation of fulvestrant plus zoledronic acid treatment	Clinical – performance status: reporting increasing pain [CTC] – low [CEA] – elevated, stable [CA 27.29] – increasing	– Clinical symptoms and increased [CTC] suggest progression – Treated with radiation
May 2008	Therapy switch to Abraxane plus bevacizumab	Imaging – PD [CTC] – elevated [CEA] – elevated [CA 27.29] – elevated	– All assessments suggesting progression – Therapy switched to Abraxane plus bevacizumab
August 2008	Discontinue bevacizumab	Clinical – ulceration on foot [CTC] – absent	– Stably absent CTCs agree with prior PR on imaging – Bevacizumab discontinued to address treatment-related AEs
September 2008	Discontinue Abraxane	Clinical – neuropathy [CTC] – stably absent	– Continued absence of CTCs – Drug holiday to address treatment-related AEs

PD = Progressive disease; PR = partial response; MR = mixed response; [CTC] = CTC concentration; [CEA] = CEA concentration; [CA 27.29] = CA 27.29 concentration; AE = adverse effect.



**Fig. 1.** Integrated display of therapy and assessments performed. The various assessments used in managing this case are displayed. Each symbol represents an assessment:  $\blacklozenge$  = CTC count;  $\blacktriangle$  = CA 27.29 determination;  $\blacksquare$  = CEA determinations. The time point of each PET/CT imaging assessment is shown as a two-letter code with an arrow below: PD = progressive disease; PR = partial response; MR = mixed response. Boxes representing the duration of each treatment are shown across the top of the graph with the name of the therapeutic regimen. The arrow labeled IR indicates the time frame when radiation treatment was given. Bev = Bevacizumab.