Strong and Sustained Response to Treatment with Carboplatin plus Nab-Paclitaxel in a Patient with Metastatic, Triple-Negative, BRCA1-Positive Breast Cancer

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Key Words

Triple-negative breast cancer · Nab-paclitaxel · BRCA1-positive breast cancer · HER2-negative breast cancer · Estrogen receptor-negative breast cancer · Progesterone receptor-negative breast cancer · Carboplatin

Abstract

Our case describes a 51-year-old female, diagnosed in April 2008 with a triple-negative, BRCA1-positive, infiltrating ductal carcinoma of the left breast. Initial platinum-based therapy resulted in a complete regression until November 2009, when a recurrence of the disease was detected. As no evidence of metastasis was found, a dose-dense regimen of doxorubicin plus cyclophosphamide was administered, followed by paclitaxel. The patient was actively monitored until March 2012, when brain metastases were discovered and successfully treated with whole-brain radiation therapy. Three months later, the patient experienced severe abdominal pain, and CT scans revealed extensive metastatic disease, including a large mass in the abdomen and more than 20 bilateral pulmonary metastases. Treatment commenced with carboplatin plus nab-paclitaxel. However, carboplatin was stopped after 4 cycles due to persistent neutropenia, and nab-paclitaxel was continued as monotherapy. Whole-body CT scans performed in October 2012 and March 2013 revealed a significant response to therapy, and the patient reported feeling well and being fully mobile. No treatment-related adverse events were observed. A routine brain MRI scan carried out on April 18, 2013, revealed a recurrence of brain metastases; however, CT scans confirmed that disease progression was not systemic, but confined to the central nervous system. Despite

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the initiation of treatment with irinotecan plus temozolomide on April 24, the patient died on July 2, 2013. The author believes that this case is the first report of a robust response to nab-paclitaxel monotherapy in triple-negative BRCA1-positive breast cancer, and that it supports further studies of nab-paclitaxel in this aggressive indication.

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Introduction

Triple-negative breast cancer (TNBC) accounts for approximately 15% of all breast tumors [1–3]. It is characterized by a lack of expression of the estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2) [1, 3]. Due to the absence of expression of these receptors, targeted regimens using hormonal or anti-HER2 therapy are ineffective, and treatment options are generally restricted to systemic chemotherapies [3]. Despite initial responses to standard cytotoxic therapies, relapse is common, and TNBC is associated with an aggressive clinical course. This is reflected by a high rate of visceral metastases, notably including the brain, rapid progression on systemic treatment, and poor survival times [1–3].

Around 5% of all breast cancer tumors are associated with *BRCA1* mutations [3]. Substantial overlap exists between BRCA1-positive breast cancer and TNBC, in terms of a number of shared clinical and pathological features; in addition, both frequently exhibit high histologic grade tumors and aggressive courses [3]. Although not all patients with TNBC exhibit *BRCA1* mutations, a considerable proportion of *BRCA1* carriers do develop this condition [3].

There is an urgent need for new treatment options in TNBC, particularly for those patients who are also BRCA1 positive. In the US, no targeted therapies are currently approved for women with TNBC, and cytotoxic chemotherapy remains the standard of care for such patients, including those with *BRCA1* mutations [3]. The angiogenesis inhibitor bevacizumab is one of a number of targeted therapies currently being evaluated in clinical trials. Promising results with bevacizumab plus chemotherapy have been reported in patients with TNBC being treated in neoadjuvant, first-, and second-line settings [4–7]; however, no benefit has yet been demonstrated in the adjuvant setting [8].

Recently, a novel regimen of bevacizumab combined with carboplatin, as well as nanoparticle albumin-bound paclitaxel particles (nab-paclitaxel), has produced high response rates in phase II trials of patients with TNBC in neoadjuvant [9] and first-line settings [10]. While the individual contribution of each of the experimental agents in these trials is difficult to determine, the studies suggest that carboplatin plus nab-paclitaxel may be an active cytotoxic combination in patients with TNBC. The case study reported here describes a patient with previously treated triple-negative BRCA1-positive breast cancer, who showed a strong response to nab-paclitaxel, first in combination with carboplatin and subsequently as monotherapy, after presenting to the author's clinic with severe metastatic disease. The patient gave her informed consent for the publication of her case details.

Case Report

A 51-year-old Caucasian woman was admitted with significant abdominal pain in June 2012. The patient had been diagnosed with cancer of the left breast at a private clinic in April 2008, and the tumor was initially thought to be a small-cell carcinoma. Following the initial diagnosis, the patient was treated with 4 cycles of carboplatin and etoposide (VP-16);

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unfortunately, dosing information is not available for either drug. This regimen was completed by September 2008 and, at that time, the patient had not received any radiation or systemic therapy other than the initial treatment of carboplatin plus etoposide. The patient's response to this regimen was excellent, with complete regression of the disease. Following completion of the initial treatment, a review of the pathology findings established that the tumor was consistent with infiltrating ductal carcinoma, and that it was triple negative.

Routine follow-up appointments took place, and, in November 2009, the patient was diagnosed with a recurrent infiltrating carcinoma of the left breast at the same clinic that had initially diagnosed and treated her. Pathology tests performed at this time revealed a grade III, 2.5-cm carcinoma, although neither of the 2 sentinel lymph nodes showed involvement. In addition, the patient's *BRCA1* status was tested, and she was identified as a mutation carrier. Treatment for the carcinoma recurrence took place at Loyola University, Chicago, from March to July 2010. The patient received neoadjuvant dose-dense doxorubicin at 60 mg/m² plus cyclophosphamide at 600 mg/m² once every 2 weeks for 4 cycles. In addition, pegfilgrastim was administered at a dose of 6 mg on the second day of each cycle to stimulate neutrophil production. As there was no evidence of metastasis, this regimen was followed by treatment with paclitaxel at 175 mg/m² for 4 cycles.

The patient continued to be actively monitored and, in March 2012, she presented with expressive aphasia. Upon further investigation, diffuse brain metastases were discovered, and treatment commenced with whole-brain radiation therapy (30 Gy in 10 fractions) at Loyola University. This resulted in a significant improvement of the patient's symptoms and regression of the brain metastases.

Follow-up continued at Loyola University until June 2012 when, during a routine clinic visit, the patient experienced severe abdominal pain and was admitted to the author's clinic. A CT scan of the abdomen and pelvis performed on the day of admission revealed a large mixed cystic and solid mass in the region of the porta hepatis, posterior to the uncinate process of the pancreas. This scan also revealed worrying signs of metastasis, namely necrotic adenopathy; celiac, retroperitoneal, and left iliac chain adenopathy; multiple tiny hypodensities in the liver, and right renal nodules of abnormal appearance. The following day, a separate CT scan of the chest found more than 20 diffuse, bilateral, pulmonary metastases. [Figure 1](#) shows abdominal and chest CT scans of the patient taken prior to treatment.

Urgent radiation therapy to the abdomen commenced that day, as the patient had reported a maximum score of 10 on a rating scale for her abdominal pain. In view of the patient's history, the underlying cause was suspected to be metastatic breast cancer. A biopsy of the left lung mass was performed on the third day of admission, and a general pathologist identified non-small cell carcinoma. After discussing the pathology findings, it was agreed that the cancer was very poorly differentiated and high grade, and, although it was likely to be of lung origin, it was difficult to exclude other cancers, including malignancies of the breast or abdomen.

The patient elected to continue treatment at the author's clinic and, on June 12, 2012, she started a carboplatin plus nab-paclitaxel regimen. The dosing schedule was carboplatin 450 mg (area under the curve = 5) once every 3 weeks, plus nab-paclitaxel at 100 mg/m² once a week for 3 weeks in a 4-week cycle. Despite filgrastim injections to stimulate neutrophil production, carboplatin was removed from the regimen after 4 cycles of treatment due to the persistent occurrence of neutropenia, which resulted in frequent dose delays (see [table 1](#)).

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The patient continued to receive nab-paclitaxel monotherapy. However, from the end of August 2012, the dose was reduced to 90 mg/m² once a week for 3 weeks in a 4-week cycle, due to a decrease in body weight, body mass index, and body surface area. Whole-body CT scans, including brain imaging, were scheduled to be performed on a regular basis, along with assessments of bone scans, laboratory results, and tumor markers. In this regard, a whole-body CT scan performed in October 2012 revealed that the patient had responded significantly to the therapy, as evidenced by a reduction of at least 50% in bulky tumor burden. The patient also reported decreased abdominal pain and shortness of breath. The positive response to nab-paclitaxel monotherapy was confirmed by a repeat whole-body CT scan in February 2013. The number of metastases in the lung appeared to have reduced to 1, and the large abdominal mass had decreased in size. [Figure 2](#) shows abdominal and chest CT scans taken after treatment with nab-paclitaxel.

At follow-up in March 2013, the patient was continuing to receive nab-paclitaxel and confirmed that the treatment had been well tolerated, with no treatment-related adverse events. The patient reported feeling well and was fully mobile. This contrasted significantly with her original presentation to the author's clinic, when she was bedridden with severe disease and related symptoms.

A brain MRI scan carried out on April 18, 2013, as part of routine tumor surveillance, revealed a recurrence of the brain metastases. However, whole-body CT scans carried out 5 days later confirmed that the patient's response to nab-paclitaxel was still being maintained in all areas other than the CNS. On April 24, treatment was initiated with temozolomide 100 mg/m² daily on days 1–7 and 15–21 of each 28-day cycle, plus irinotecan administered at a dose of 125 mg/m² once every 2 weeks. Unfortunately, the patient's condition deteriorated and she died on July 2, 2013.

Discussion

It is well established that TNBC is associated with a particularly aggressive clinical course [1, 3]. Therapeutic options are limited, and standard cytotoxic chemotherapy remains the mainstay of treatment, despite the disease progressing quickly in the majority of women [1–3]. Prognosis is poor. In patients with advanced or metastatic disease, median survival times of around 1 year have been reported along with a median duration of response to first-line therapy of just 12 weeks [2]. There is an urgent need for the development of novel treatment strategies that will significantly increase survival times.

Nab-paclitaxel is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nm [11]. It is able to target delivery of paclitaxel to tumors by interacting with albumin receptors involved in drug transport [11]. Nab-paclitaxel displays an improved therapeutic index compared with standard solvent-based paclitaxel, allowing the safe infusion of higher doses in a shorter time span with no requirement for premedication [11]. In addition, nab-paclitaxel demonstrates a more favorable safety profile [11].

Nab-paclitaxel is currently approved for the treatment of breast cancer after either failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy [12]. Recent reports have shown the potential for nab-paclitaxel to be used in the treatment of TNBC. For example, a Japanese case study reported a complete response in a patient with TNBC and lymph node metastases who received 8 cycles of adjuvant nab-paclitaxel therapy following surgery [13]. However, the majority of ongoing research with nab-paclitaxel in TNBC is in combination with bevacizumab, which itself has

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provided modest improvements in efficacy versus chemotherapy alone in neoadjuvant, first-, and second-line settings [4–7].

Two phase II studies have recently reported promising activity with the combination of nab-paclitaxel, bevacizumab, and carboplatin in first-line [10] and neoadjuvant [9] treatment of patients with TNBC, and the combination was deemed to be well tolerated. Another phase II study examined the efficacy and safety of nab-paclitaxel administered in combination with bevacizumab and gemcitabine as first-line treatment for HER2-negative, metastatic breast cancer [14]. A subset of 13 patients was identified as having TNBC, and this cohort demonstrated a clinical benefit rate – defined as complete response, partial response, or stable disease – of 85%. A case study has been published of one of the TNBC participants in this trial, who achieved long-term complete remission of almost 2 years and a progression-free survival of just over 2.5 years [15]. As a consequence of these findings, the phase II/III TnAcity trial (www.clinicaltrials.gov NCT01881230) will compare nab-paclitaxel plus gemcitabine with nab-paclitaxel plus carboplatin, and also with gemcitabine plus carboplatin, with the aim of clarifying how to best use existing drugs in patients with TNBC.

The case study described in this paper adds to previous trials and reports indicating the potential efficacy of nab-paclitaxel in TNBC, either as monotherapy in a later-line setting, or in combination with bevacizumab and chemotherapy agents at an earlier stage. To the author's knowledge, this is the first account of a patient with metastatic, triple-negative, BRCA1-positive breast cancer achieving a strong response to treatment with nab-paclitaxel, which was sustained from the first routine whole-body CT scan in October 2012 until the recurrence of brain metastases in April 2013. This case study also suggests that nab-paclitaxel is well tolerated, adding to the argument in favor of further investigations of this agent in metastatic TNBC, particularly in patients who are also BRCA1 positive.

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Table 1. Hematology laboratory results over 4 cycles of carboplatin plus nab-paclitaxel, on day 1 of each cycle

Laboratory parameter	Cycle 1		Cycle 2				Cycle 3		Cycle 4*	
	6/12/12	6/25/12	7/16/12	7/23/12	7/30/12	8/6/12	8/13/12	8/27/12	9/10/12	9/17/12
White blood cells, $\times 10^9/l$	12.80	2.40	1.70	3.50	2.20	1.80	2.20	1.19	2.00	3.70
Red blood cells, $\times 10^6/\mu l$	3.56	3.92	3.31	3.58	3.49	3.40	3.06	2.67	2.43	2.13
Hemoglobin, g/dl	10.9	12.0	10.4	11.3	11.1	10.8	10.2	8.9	8.5	7.7
Platelets, $\times 10^9/l$	472	436	110	210	215	193	97	58	51	100
Neutrophils, %	87.5	43.3	57.0	57.5	48.8	43.2	42.0	35.3	50.1	73.6

* Carboplatin stopped.

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Fig. 1. Abdominal (a) and chest (b, c) CT scans taken prior to treatment in June 2012, showing a 5 × 4 cm complex cystic mass near the porta hepatis posterior to the uncinate process (a), a 2.8-cm left lung mass (b), and a 3.5-cm right lung mass (c).

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Fig. 2. Abdominal (a) and chest (b, c) CT scans taken in February 2013 following treatment with nab-paclitaxel.