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Reduction in Circulating Tumor Cell Count following Therapy with *nab*[®]-Paclitaxel plus Carboplatin in a Patient with Leptomeningeal Carcinomatosis from Breast Cancer

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Key Words

Abraxane[®] · Chemotherapy · Circulating tumor cell count · Metastases · *nab*[®]-Paclitaxel · Taxanes

Abstract

This case study reports on a 56-year-old woman with breast adenocarcinoma and leptomeningeal metastases. After initial chemotherapy with a dose-dense regimen of doxorubicin/cyclophosphamide followed by 3 cycles of docetaxel (100 mg/m²), a lumpectomy was performed that revealed invasive ductal carcinoma with lymph node involvement. Because of the extent of the disease, she underwent a mastectomy. Two months after the completion of initial chemotherapy, leptomeningeal metastases were detected on December 13, 2006. After completion of whole-brain radiation therapy, she received systemic chemotherapy with a novel albumin-bound 130-nm formulation of paclitaxel (*nab*[®]-paclitaxel) at 100 mg/m² combined with carboplatin AUC = 6, both given weekly. Clinical response was prompt, with a reduction in the circulating tumor cell (CTC) count from 63 before treatment to 2 after the first treatment cycle. While undergoing treatment with *nab*-paclitaxel plus carboplatin, she reported an improvement in neurologic symptoms, including a decrease in headaches, improved cognition and balance, and an overall improved quality of life. Before the third treatment cycle, she had a CTC count of 2. Without treatment, the median survival of patients diagnosed with leptomeningeal metastases is 4–6 weeks. However, this patient survived for 4 months after the diagnosis of leptomeningeal carcinomatosis. Treatment was discontinued because of complications of urosepsis, and the patient died on April 7, 2007. Our case shows that additional treatment with weekly *nab*-paclitaxel combined with carboplatin (AUC6) can prolong life for some patients with leptomeningeal carcinomatosis from breast cancer.

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Introduction

Leptomeningeal carcinomatosis (LC), also known as leptomeningeal metastases, is a devastating complication of neoplastic disease. The overall incidence is estimated at 3–8% of cancer patients, usually occurring late in the disease course [1]. The predominant histology arising from solid tumors is adenocarcinoma, and the most common sites of primary tumors giving rise to leptomeningeal metastases are breast, lung, and melanoma [2, 3]. Although small-cell lung cancer and melanoma have the highest rates of leptomeningeal metastases, breast cancer, at a 5% rate of metastases, accounts for most case evaluations of LC because of the high incidence of breast cancer itself [2, 4]. Symptoms most frequently associated with LC include pain, cognitive changes, headache, weakness, and paresthesias [3, 5]. LC is diagnosed based on the presence of malignant cells in the cerebrospinal fluid (CSF) and confirmed by magnetic resonance imaging (MRI) scans of the brain and/or spine [2, 6].

Treatment options for patients with LC include radiation therapy to sites of symptomatic bulky disease and/or the administration of intraventricular, intrathecal, or systemic chemotherapy to eradicate detectable tumor cells in the CSF [1]. However, the optimum treatment route and regimen have not yet been established. This study reports on a patient with LC from breast cancer who received systemic chemotherapy consisting of a novel albumin-bound 130-nm formulation of paclitaxel [*nab*®-paclitaxel (Abraxane®); Celgene Corp.] plus carboplatin.

Case Report

A 56-year-old Caucasian woman was diagnosed with breast adenocarcinoma in May 2006, five months after a regular, unremarkable screening mammogram. Tumor tissue was triple-negative for estrogen and progesterone receptors and Her2/neu. There was no family history of breast cancer; however, she had presented with endometrial cancer in 2000 and had subsequently undergone a hysterectomy. In June 2006, she received neoadjuvant chemotherapy with a dose-dense regimen of Adriamycin®/Cytosan® (doxorubicin, Pharmacia, Inc.; cyclophosphamide, Bristol-Myers Squibb), followed by a dose-dense regimen of paclitaxel in July. After developing severe neuropathy, she was switched to docetaxel 12 days after initiating treatment with paclitaxel. She remained on docetaxel for a total of 3 cycles until September. Because of a slight decrease in breast-mass size after treatment and as a breast-conserving surgery option, she underwent a lumpectomy in November. However, the biopsy revealed infiltrating ductal carcinoma with lobular features, presence of the tumor at all margins, metastases to 1 of the 2 sentinel nodes, and lymphovascular invasion. Therefore, a mastectomy was performed that showed residual invasive ductal adenocarcinoma with lobular features and metastases to 4 of the 14 lymph nodes. Tumor margins were clear, aside from the inferior surgical margin of 0.1 cm.

While recovering from the mastectomy, she complained of headaches and back pain that radiated down the back of her legs, and she also fell at home several times. A head computed tomography scan was unremarkable. A bone scan showed possible metastatic disease in the right sacroiliac joint, and X-rays of the lumbar spine revealed degenerative changes. In December, an MRI scan of the thoracic and lumbar spine showed only degenerative changes without signs of metastatic disease. However, an MRI scan of the brain showed mild enlargement of the supratentorial ventricular cistern with subtle abnormal leptomeningeal enhancement without discrete nodules (fig. 1a). A lumbar puncture performed 1 day after the MRI scan revealed the presence of malignant cells characteristic of adenocarcinoma, confirming the diagnosis of LC (table 1). Beginning in December, the patient received 5 treatments of whole-brain radiation therapy.

At the end of December 2006, the patient was unable to walk or balance without assistance and complained of increasing headaches and back pain. In January 2007, she began systemic

chemotherapy treatment with *nab*-paclitaxel (100 mg/m², 30-minute infusion) and carboplatin (AUC6, 1-hour infusion on day 1) via a portacath weekly for 3 weeks of a 4-week cycle. Overall, she received 2 treatment cycles, and the treatment regimen was well tolerated, despite chemotherapy-induced neutropenia and anemia (hemoglobin 8.5 g/dl). Blood tests revealed a reduction in the circulating tumor cell (CTC) count from 63 before the first cycle to 2 before the second cycle (table 1).

Additionally, during systemic chemotherapy, the patient showed neurologic improvement with decreased headaches, improved cognition and balance, and overall improved quality of life. For the second treatment cycle (weekly treatment for 3 weeks per cycle), *nab*-paclitaxel was continued at 100 mg/m² weekly; however, the carboplatin dose was reduced to AUC2 because of prolonged neutropenia.

After cycle 2, the patient showed signs of neurologic deterioration with headaches, mental status changes, and vomiting. In February, she was hospitalized with hydrocephalus, and a ventriculoperitoneal shunt was inserted to relieve intracranial pressure. Following the procedure, the patient ceased vomiting and demonstrated a clinical and cognitive improvement. In addition, her CTC count remained at 2, and an MRI showed fewer LC lesions. A follow-up CTC count after the second cycle remained at 2, and a follow-up MRI after the second cycle did not show evidence of focal enhancement suggestive of metastatic disease. Specifically, there was no evidence in the leptomeninges of nodularity or enhancement (fig. 1b). However, the patient continued to have persistent cells in the CSF (table 1).

Before cycle 3, she was hospitalized with urosepsis and received treatment with total parenteral nutrition and antibiotics. She also suffered from incontinence and was catheterized. Treatment was discontinued, and her care was transferred to hospice services. She died from complications resulting from urosepsis in April 2007. The patient had no additional systemic site of disease outside the leptomeninges.

Discussion

Overall, patients with LC from breast cancer have a poor prognosis. Without treatment, the median survival is 4–6 weeks [1, 3]. Treatment of LC has been shown to extend median survival from the time of diagnosis to 3–6 months, with one-year survival rates of 11–25% [2, 3, 7]. The lack of durable remissions may be attributed to the aggressive nature of LC and the difficulty in targeting malignant cells in the subarachnoid space. Furthermore, LC may be resistant to additional therapy because it occurs late in the disease course, when many patients have already been treated with several other agents.

The regimen described here was selected based on activity demonstrated with a docetaxel/carboplatin combination in a patient with multiple brain metastases and LC from breast cancer [8]. After 4 courses of chemotherapy with docetaxel/carboplatin, the patient achieved a complete response and experienced neurologic improvement. However, her disease recurred 4 months afterwards. Because our patient received prior treatment with docetaxel, a different taxane, *nab*-paclitaxel, was used instead.

nab-paclitaxel, which has been approved for the treatment of metastatic breast cancer (MBC), was chosen because, unlike conventional taxanes, it does not require toxic solvents. Additionally, a study in patients with MBC showed significantly higher response rates (33 vs. 19%; $p = 0.001$) and longer time to progression (23 vs. 17 weeks; $p = 0.006$) in patients treated with *nab*-paclitaxel (260 mg/m² intravenous) versus conventional paclitaxel (175 mg/m² intravenous) [9]. Furthermore, compared with conventional paclitaxel, *nab*-paclitaxel was associated with a significantly lower incidence of grade 4 neutropenia (9 vs. 22%; $p < 0.001$), despite a 49% higher dose of

paclitaxel. *nab*-paclitaxel may be administered using higher doses of paclitaxel than those used with conventional paclitaxel, with a shorter infusion duration and no requirement for premedication [10, 11]. Additionally, in a phase II study of patients with MBC, weekly *nab*-paclitaxel at 150 mg/m² demonstrated a significantly longer, independently assessed, progression-free survival compared with docetaxel (12.9 vs. 7.5 months; $p = 0.007$) [12]. Therefore, the demonstrated efficacy of *nab*-paclitaxel over conventional paclitaxel and docetaxel in patients with MBC and the activity of docetaxel/carboplatin in LC presented a logical foundation for this regimen.

The significance of systemic chemotherapy in managing LC is somewhat controversial, based on the presumption that it cannot reach therapeutic levels because of the blood-brain barrier (BBB). However, tumor neovascularization can disrupt the BBB and allow increased penetration of systemic chemotherapy to the entire neuraxis. Furthermore, systemic chemotherapy has demonstrated the potential to treat all areas of disease in patients with LC who generally have widespread incurable systemic disease [13].

This patient and her family provided consent for treatment with the *nab*-paclitaxel/carboplatin chemotherapy regimen in order to prolong survival and improve her quality of life. Although she did not achieve complete resolution of LC, this treatment regimen prolonged survival by 4 months from diagnosis. After the first cycle, her CTC count was reduced from 63 to 2, suggesting a leaky vasculature that allowed chemotherapy to reach the subarachnoid space, hence an eradication of tumor cells. A reduction in CTC count to below 5 during therapy typically indicates response and prolonged survival [14]. The patient discontinued treatment because of urosepsis. Based on lab tests performed when treatment was discontinued, the CTC count remained at 2, suggesting that death may have resulted from a disease complication, in this case urosepsis, rather than the disease itself.

This case study demonstrates that systemic chemotherapy with *nab*-paclitaxel/carboplatin may prolong survival and improve quality of life in patients with LC from breast cancer. Furthermore, the reduction in CTC count demonstrated clinical benefits beyond survival. This case demonstrates improved quality of life of the patient, including reduced neurologic symptoms, during treatment with *nab*-paclitaxel/carboplatin. Further investigation of this and similar therapy combinations in patients with LC is warranted.

Table 1. Results of CSF parameters measured at different intervals

CSF parameters	Lumbar puncture intervals		
	at diagnosis of lepto-meningeal carcinomatosis	after both treatment cycles	during subsequent hospitalization
Protein, mg/dl	44	84	105
Glucose, mg/dl	57	38	72
Serum CTC count	63	2	2

Fig. 1. MRI scans before (a) and after (b) 2 cycles of nab®-paclitaxel and carboplatin.

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