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# Pegylated Liposomal Doxorubicin-Induced Acute Transient Encephalopathy in a Patient with Breast Cancer: A Case Report

Michelle Baker<sup>a</sup> Maurie Markman<sup>c,d</sup> Jiaxin Niu<sup>b</sup>

Departments of <sup>a</sup>Pharmacy and <sup>b</sup>Medical Oncology, Western Regional Medical Center at Cancer Treatment Centers of America, Goodyear, Ariz., and <sup>c</sup>Department of Medical Oncology, Cancer Treatment Centers of America, and <sup>d</sup>Drexel University College of Medicine, Philadelphia, Pa., USA

## Key Words

Breast cancer · Encephalopathy · Pegylated liposomal doxorubicin · Blood-brain barrier · Brain metastasis

## Abstract

**Background:** Pegylated liposomal doxorubicin (PLD) has a unique pharmacokinetic profile and is widely used to treat a variety of malignancies, alone or in combination with other agents. **Case Report:** A 57-year-old female patient with metastatic breast cancer developed dural metastases to the brain and underwent craniotomy and whole-brain radiation. She continued to receive chemotherapy with carboplatin without any serious complications. Four months later, there was evidence of progression leading to the institution of PLD. During the first course of PLD, there was evidence of acute encephalopathy which resolved after 18 h with discontinuation of this agent. Interestingly, she did well when she was rechallenged with conventional doxorubicin in the following cycles. **Conclusion:** We hereby report, to the best of our knowledge, the first case of acute transient encephalopathy induced by PLD. We postulate that partial disruption of the blood-brain barrier may have been responsible for PLD-induced encephalopathy.

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Jiaxin Niu, MD, PhD  
Department of Medical Oncology, Western Regional Medical Center at Cancer  
Treatment Centers of America  
14200 W. Celebrate Life Way, Goodyear, AZ 85338 (USA)  
E-Mail [jiaxin.niu@ctca-hope.com](mailto:jiaxin.niu@ctca-hope.com)

## Introduction

Anthracyclines are active agents in the treatment of a wide variety of malignancies. For decades, the conventional anthracyclines have arguably been the most active agents against breast cancer in both the adjuvant and metastatic settings. However, the use of anthracyclines has been limited due to cumulative dose-related cardiotoxicity, in particular in the metastatic setting where a substantial proportion of patients have previously received an anthracycline as adjuvant chemotherapy in the modern era.

Pegylated liposomal doxorubicin (PLD) is doxorubicin encapsulated in liposomes and sterically stabilized by the binding of methoxy polyethylene glycol to the surface. As a result, it has a different pharmacokinetic profile than conventional doxorubicin [1]. Both prospective studies and a retrospective analysis have demonstrated that PLD has equivalent efficacy, but a significantly lower risk for cardiotoxicity in women with metastatic breast cancer [2, 3]. Thus, PLD is commonly used to treat women with metastatic breast cancer, even in the setting of a previous anthracycline exposure, without substantially increasing the risk for cardiotoxicity.

As compared with conventional doxorubicin, PLD is associated with an increased incidence of hand-foot syndrome and stomatitis.

Here we report a case of a 57-year-old woman who developed acute transient encephalopathy during the course of receiving the very first dose of PLD. Fortunately, prompt discontinuation of PLD infusion resulted in complete recovery of her encephalopathy. Interestingly, she tolerated conventional doxorubicin well without any neurological symptoms in the following cycles of anthracycline therapy. To our knowledge, this is the first reported case of acute encephalopathy induced by PLD.

## Case Report

A 57-year-old Caucasian woman was originally diagnosed with invasive ductal carcinoma in her right breast in February 2011 (ER-positive, PR-positive and HER2-negative). She was also diagnosed as carrying a mutation of BRCA 2. The patient underwent bilateral mastectomy and right-sided sentinel lymph node biopsy with 1 of 6 lymph nodes being found to be positive for metastasis. Unfortunately, she declined adjuvant chemotherapy and radiation recommended by her treating physicians, but only received adjuvant hormonal therapy with letrozole. In February 2012, she presented with renal failure and severe bony pain, and was found to have hypercalcemia with extensive osseous metastasis. CT-guided biopsy of one of the pelvic lesions revealed metastatic adenocarcinoma, consistent with her ER-positive primary breast cancer. The patient received aggressive hydration and denosumab for hypercalcemia. She also received radiation to her sacrum and bilateral sacroiliac joints to palliate her pain. The patient was enrolled in a clinical trial, receiving hormonal therapy with the combination of tamoxifen and metformin. Her monthly denosumab injection for bone metastasis was also continued. Unfortunately, her disease continued to progress, and she was found to have extensive lymphadenopathy involving the cervical, mediastinal and pelvic area. In January 2013, the patient was transferred to our center.

As breast cancer in BRCA mutation carriers has been previously shown to respond to platinum-based chemotherapy [4], treatment with single-agent carboplatin (AUC 5) was initiated. Three days after starting carboplatin, the patient developed a severe headache and projectile vomiting. An MRI of her brain revealed a large, dura-based, contrast-enhancing extra-axial mass, approximately 3.3 × 4.3 cm in size, causing severe vasogenic edema in the

right frontotemporal region, resulting in a significant midline shift. She was seen by a neurosurgeon, and an emergent decompressive craniotomy was performed. The pathology of the resected mass was consistent with metastatic breast cancer. Postoperative brain MRI showed marked improvement, but unfortunately it also demonstrated some small dura-based masses over the left cerebral hemispheres. The patient recovered quickly and subsequently received whole-brain radiation therapy to treat dural metastases. Despite the delay of systemic therapy for almost 2 months due to craniotomy and radiation, her extracranial disease responded well radiographically to the first dose of carboplatin, and thus this agent was continued until June 2013.

At this time, PET-CT showed a progression of the disease in the cervical, mediastinal and retroperitoneal lymph nodes. Carboplatin was discontinued and PLD was initiated as a second-line chemotherapy. For the first cycle, a total of 85 mg (40 mg/m<sup>2</sup>) of liposomal doxorubicin in 250 ml of D5W (5% glucose solution) was prescribed with the same premedications used for the prior carboplatin. PLD was infused at a rate of 1 mg/min for the first 20 min. As no infusion-related adverse effects were observed, the rate was increased to 1.6 mg/min in order to complete the infusion over 1 hour according to our standard protocol. Twenty minutes later (approximately 50 mg PLD in total was given), the patient was noted to develop confusion. She had some tangential thoughts, started to make nonsensical comments to the people around her and began to tell stories from the past. The infusion was held and she was observed for 30 min, but her symptoms did not improve. An on-call physician was contacted to assess her. She was found to be alert and oriented and also able to answer questions appropriately. There were no neurological deficits. As the patient had an MRI earlier that day, no further imaging studies were performed. The infusion was discontinued due to the mental status change, and the patient was observed closely. Her symptoms persisted for 18 h and then resolved spontaneously. The patient's acute transient encephalopathy was deemed secondary to PLD. When she returned for the second cycle of chemotherapy, she was not rechallenged with PLD; instead, she was being administered conventional doxorubicin. This agent was tolerated well without any mental status change for another 5 months. Unfortunately, the patient developed a disease progression, requiring further palliative therapy with an eventual transfer to a hospice service, where she died 2 months later.

## Discussion

Hand-foot syndrome, stomatitis and myelosuppression are the most common side effects of PLD, whereas, to the best of our knowledge, CNS toxicity induced by PLD has not been reported previously.

Drug-induced CNS toxicity is a well-recognized but uncommon adverse effect of cancer therapy due to the presence of the blood-brain barrier (BBB), which separates the brain from the circulation, both physically and functionally. Physically, the BBB is essentially formed by special tight junctions between the epithelial cells that surround the brain tissue to prevent larger molecules from passing through. Functionally, the barrier actively excludes, effluxes and metabolizes potential neurotoxic compounds such as cytokines, antibodies, drugs, etc. [5]. Consequently, only small and hydrophilic molecules such as glucose can easily cross the BBB. Under physiological conditions, the BBB protects the brain's internal milieu against the toxic substances. Conversely, the very same mechanism significantly impairs the delivery of many chemotherapeutic agents to treat primary or secondary brain tumors [6]. Other than the permeability of the BBB, the efficacious drug

delivery in the CNS also depends on the fraction free of plasma protein binding and the extent of active efflux transport from the brain [6].

One strategy to improve the delivery of chemotherapeutic agents to the CNS is to encapsulate the small-molecule drugs in liposomes to circumvent the BBB [7]. Liposomes are artificially prepared vesicles with an aqueous core, surrounded by a lipid bilayer which confers more resistance of doxorubicin to hydrolysis [8]. Polyethylene glycol coating (pegylation) causes sterical hindrance for the uptake by the reticuloendothelial system, avoids interaction with plasma components and reduces renal filtration.

As a result, PLD has a circulation half-life of approximately 74 h, whereas the conventional doxorubicin has a half-life of less than 10 min [2]. These pharmacokinetic properties including prolonged circulation and extended extravasation through leaky vasculature of the tumor certainly facilitate the delivery of PLD to cross the BBB. Indeed, it was reported that there was up to a 30-fold higher accumulation of PLD in the cerebrospinal fluid and a 9- to 14-fold increased level in the tumors of rats bearing an inoculated brain sarcoma as compared to the concentration achieved with its counterpart, conventional doxorubicin [9]. Interestingly, in patients with metastatic brain tumors, the accumulation of PLD was 7–13 times higher in the metastatic lesions than in the normal brain tissue, suggesting a more effective delivery of PLD via a partially disrupted BBB [10].

It is generally believed that the BBB is selectively disrupted at the sites of malignant tumors, and radiation may further enhance this effect. In a study of 14 patients with primary brain tumors, it was demonstrated that the perilesion permeability was 22% higher than the adjacent normal brain tissue, and it increased to 76% after 30–40 Gy of radiation. Radiation also increased the permeability of normal brain tissue by 25% [11]. This concept is also supported by the fact that brain metastases have been reported to respond to systemic chemotherapy, although the response rate is much lower than that of the primary tumor or the extracranial metastatic sites [12, 13].

It can be difficult to sort out a cause and effect relationship between a chemotherapeutic agent and mental status change since many metabolic abnormalities could lead to altered mental status. Further, a large percentage of patients receive regimens comprised of multiple chemotherapeutic agents, making it difficult to indict a particular drug.

However, the temporal association with PLD and a lack of known precipitant factors for encephalopathy supports our hypothesis that PLD indeed induced acute transient encephalopathy in this case. Moreover, that retreatment with a conventional doxorubicin with exactly the same premedications did not induce a mental status change seems to further lend support for this hypothesis.

A Medline search found no other reports associating this drug with mental status change, and to the best of our knowledge, this case appears to represent the first report of this kind. In our case, the development of encephalopathy was rather acute. Infusion of PLD (the only chemotherapy agent administered) resulted in a transient encephalopathy, which resolved gradually by discontinuation of PLD. Therefore, the cause and effect are quite evident. PLD has been studied quite extensively in multiple clinical trials, yet no mental status change has been reported as a direct side effect of PLD.

As discussed above, PLD does not cross the intact BBB effectively to reach the normal brain tissue, but rather accumulates at a very high concentration in the metastatic tumor, suggesting at least a partial disruption of the BBB is required for the effective delivery of PLD. Our patient had developed dural masses, requiring surgical intervention and whole-brain radiation before she was treated with PLD. We postulate that all these 3 factors could have collectively contributed to the partial disruption of the BBB, with a unique pharmaco-

kinetic profile, PLD rapidly accumulated in normal brain tissue, resulting in acute encephalopathy.

## Conclusion

In summary, to our knowledge, we report here the first case of PLD-induced acute transient encephalopathy so that clinicians can be made aware of this potential side effect, particularly in patients who have received whole-brain radiation for brain metastasis.

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