Gemcitabine-Induced Reversible Posterior Leukoencephalopathy Syndrome: A Case Report and Review of the Literature

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the clinical and radiologic manifestations of RPLS.
2. Define agents or inciting risk factors that have been implicated in the development of RPLS.
3. Describe the treatment and outcome of RPLS, emphasizing supportive care and urgent discontinuation of the offending agent.

ABSTRACT

Gemcitabine is a commonly used chemotherapeutic agent for a variety of tumor types. Although this nucleoside analogue antineoplastic agent is similar in structure to cytarabine, central nervous system toxicities have rarely been attributed to gemcitabine. Reversible posterior leukoencephalopathy syndrome (RPLS) is a rare but increasingly identifiable clinicoradiologic process in cancer patients associated with cytotoxic and immunosuppressive agents. The syndrome is characterized by acute to subacute onset of headache, nausea, vomiting, altered mental status, seizures, stupor, and visual disturbances. The pathophysiology of RPLS continues to remain controversial but likely involves loss of cerebrovascular autoregulation leading to arteriole leakage. Radiologically, posterior occipital white matter edema is noted, with characteristic findings on magnetic resonance imaging. Often the syndrome is reversible with treatment of concurrent hypertension or removal of the causative agent; however, failure to quickly recognize the syndrome and discontinue the offending agent may result in profound and permanent central nervous system dysfunction or death. This article describes a case of RPLS attributed to gemcitabine use for pancreatic cancer. Such a descriptive case serves as a platform for the discussion of the syndrome, proposed mechanisms of central nervous system damage, and review of the currently available literature on the topic. With increased awareness of RPLS by oncologists and other medical providers, cancer patient care may be improved and further insight into this complication of therapy through continued research may be gained. The Oncologist 2007;12:1332–1335


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INTRODUCTION

Gemcitabine (Gemzar®; Eli Lilly, Indianapolis, IN) is a nucleoside analogue antineoplastic agent structurally similar to cytarabine (ara-C; Bedford Laboratories, Bedford, OH) that is approved by the U.S. Food and Drug Administration for use in non-small cell lung, breast, ovarian, and pancreatic cancers [1–5]. In the latter, it has been shown to be more effective than 5-fluorouracil (5-FU; Abraxis Pharmaceutical Products, Schaumburg, IL) in alleviation of disease-related symptoms and modestly improves survival [1]. The combination of gemcitabine and erlotinib (Tarceva®; Genentech Inc, San Francisco, CA), an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, provides statistically significantly longer survival than with gemcitabine alone [6]. Central nervous system (CNS) toxicities are uncommon with gemcitabine, yet are well documented with ara-C. We present a case report and review of the literature of CNS effects that suggest gemcitabine-related neurotoxicity, specifically the clinicoradiographic syndrome of reversible posterior leukoencephalopathy syndrome (RPLS).

CASE

B.H. was a 65-year-old white woman with a history of gastroesophageal reflux, hypothyroidism, hyperlipidemia, and hypertension who was diagnosed with locally advanced, unresectable pancreatic adenocarcinoma (clinical stage III, T4N1M0). Her initial serum cancer antigen (CA) 19–9 was 20,920 U/ml (normal, 0–35 U/ml). Combined modality therapy was begun with 5-FU (500 mg/m² per day i.v. on days 1–3 and 29–31) concurrent with daily fractions of radiation therapy (1.8 Gy per day) to a total of 54 Gy. Treatment was completed without complications, yet her cancer remained unresectable and nonmetastatic with a reduction in CA19–9 to 4,282 U/ml. Palliative systemic chemotherapy was initiated with gemcitabine (1,000 mg/m² on days 1 and 15 of each 28-day cycle) and erlotinib (100 mg orally daily). Her performance status remained excellent with a CA 19–9 nadir reaching 1,543 U/ml.

Ten days after the third cycle of chemotherapy, she sustained a fall and was admitted for altered mental status and a subacute decline in performance status. On presentation, her vital signs were normal and a neurologic exam revealed a flattened affect, somnolence, disorientation, and decreased interaction but was without focal deficits otherwise. All CNS depressant medications were avoided and her blood pressure ranged from 120–150/60–90 mmHg throughout the hospital stay. A head computed tomography, lumbar puncture, transthoracic echocardiogram with bubble study, and magnetic resonance arteriography were each within normal limits. Brain magnetic resonance imaging (MRI) (T2 and fluid-attenuated inversion recovery [FLAIR] image sequences) revealed multiple areas of abnormal enhancement involving the posterior circulation, including the bilateral occipital lobes, the thalamus, and the cerebellum (Figs. 1 and 2). The clinicoradiographic diagnosis was consistent with RPLS given exclusion of other processes. With supportive care and avoidance of further gemcitabine, her mental status gradually returned to near baseline. Erlotinib was subsequently discontinued late in the hospitalization. Despite cognitive improvement, she ultimately died while hospitalized from respiratory failure in the setting of poor overall performance and nutritional status. Given the clinicoradiographic findings, the presenting...
symptoms could be attributed to neurotoxic side effects from gemcitabine-induced RPLS.

**PHARMACOLOGY AND NEUROTOXICITY OF GEMCITABINE**

Gemcitabine, much like ara-C, is a synthetic pyrimidine nucleoside analogue that has a structure similar to the naturally occurring nucleoside deoxycytidine. Phosphorylation of these agents to triphosphate forms by deoxycytidine kinase is required for direct inhibition of DNA synthesis by incorporation with resultant chain termination [7]. Ara-C rapidly distributes i.v. and concentrations in cerebrospinal fluid may reach 20%–50% of plasma levels [8]. Although more lipophilic, it is unclear if gemcitabine can cross the blood–brain barrier [9]. Both agents are rapidly metabolized by cytidine deaminase, which is absent in the CNS [8].

Neurologic toxicity (acute cerebellar syndrome) associated with high doses of ara-C is well documented and manifests as dysarthria, dysmetria, ataxia, and dysdiadochokinesia. Simultaneous cerebral impairment may occur, including somnolence, encephalopathy, memory loss, psychosis, and headache, with resolution typically within 5 days of drug discontinuation. However 30% of patients may have persistent neurologic dysfunction [9]. Both i.v. and intrathecal ara-C have been associated with RPLS, although the mechanism is not known [10].

Neurologic toxicities with gemcitabine are uncommon and include peripheral neuropathy and somnolence in 3% and 9% of patients, respectively [11]. Davis et al. [12] reported a patient with lung adenocarcinoma and a single brain metastasis in whom, after treatment with cisplatin and gemcitabine, imaging revealed response of the primary despite progression within the CNS. The authors concluded that gemcitabine likely does not cross the blood–brain barrier [12]. Russell et al. [13] identified the first suspected case of gemcitabine-induced RPLS in a patient with lung cancer after six courses of gemcitabine. Chemotherapy was held with resolution of most MRI and clinical findings within 2 weeks. Similarly, Larsen and Hansen illustrate three cases of separate malignancies in which gemcitabine was administered with cisplatin and/or paclitaxel (Taxol®; Mead Johnson and Co. Sub Bristol Myers Co., Princeton, NJ) [14]. CNS symptoms in all three patients and radiographic evidence of leukoencephalopathy in one patient were observed with symptom provocation after readministration of gemcitabine.

**RPLS**

RPLS was first described in 1996 as a syndrome diagnosed on clinical and radiographic findings [15]. Several factors, including hypertensive encephalopathy, pre-eclampsia/eclampsia, renal failure, general anesthesia, and cytotoxic or immunosuppressant agents, have been implicated (Table 1) [16–23]. The clinicoradiologic findings are typically indistinguishable amongst cases of RPLS, regardless of the underlying cause. Patients have a variety of acute to subacute neurologic symptoms including headache, nausea, vomiting, altered mental status, seizures, stupor, and visual disturbances [16]. Focal neurologic deficits are uncommon.

The pathophysiology of RPLS remains poorly understood, but it is theorized to be a result of vasospasm or loss of cerebrovascular autoregulation leading to arteriole leakage and vasogenic edema [17]. Originally reported in association with abrupt and severe hypertensive encephalopathy, RPLS has recently been observed with little to no hypertension [18]. RPLS primarily affects white matter, with typical imaging revealing involvement of the bilateral parietal-occipital lobes and occasionally the basal ganglia, brainstem, and cerebellum. FLAIR sequence MRI identifies the vasogenic edema of RPLS as hyperintense lesions that are more conspicuous than on T2-weighted imaging [16]. Posterior cerebral circulation has less sympathetic adrenergic innervation, and therefore is potentially more susceptible to hypertension. Radiographic and clinical findings are typically reversible within 2 weeks after correction of the precipitating event. Otherwise, persistent neurologic defects may occur with progression to infarction, hemorrhage, or death.

No single antineoplastic class or agent has been consis-
tently associated with RPLS, although implicated drugs include those listed in Table 1 [19–23]. The mechanism of toxicity for many of these agents is theorized to be hypertension or direct CNS microvascular injury. To our knowledge, there have been no published reports of RPLS or significant neurotoxicity associated with erlotinib or other EGFR tyrosine kinase inhibitors; however, erlotinib alone or with gemcitabine may be associated with RPLS.

**CONCLUSION**

Increasing awareness of RPLS in adult oncology patients is an important recent development and does not appear limited to a specific clinical setting, condition, or antineoplastic agent. As the name implies, RPLS is potentially reversible; however, failure to recognize the syndrome and correct the underlying cause may result in catastrophic CNS injury or death. Similar to ara-C, gemcitabine may result in CNS toxicities including RPLS in excess of that previously appreciated. The increased clinical reporting of RPLS warrants further investigations into the mechanism of toxicity, risk factors for development, and education of those providers caring for oncology patients.

**REFERENCES**