Original Study

Posterior Reversible Encephalopathy Syndrome Associated With Dose-adjusted EPOCH (Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin) Chemotherapy

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Abstract

The purpose of our study was to identify risk factors for the development of posterior reversible encephalopathy syndrome (PRES) after administration of dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin (DA-EPOCH). Of 44 patients receiving DA-EPOCH at our institution, 3 (7%) developed PRES. The patients who developed PRES were more likely to have a pre-existing central nervous system insult, fluid status or electrolytes abnormalities, and hypertension.

Introduction: The purpose of our study was to identify the key risk factors for the development of posterior reversible encephalopathy syndrome (PRES) after administration of the combination chemotherapy regimen, DA-EPOCH (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin). **Materials and Methods:** We performed a retrospective medical record review of patients receiving DA-EPOCH with or without rituximab (DA-EPOCH ± R) at our institution from July 2012 to September 2014. The patients were screened for evidence of severe neurotoxicity through identification of requests for neurology consultations or neuroimaging studies. Patients with evidence of central nervous system (CNS) neurotoxicity were reviewed in detail to identify documented cases of PRES. The key risk factors assessed included rituximab administration sequence, and the presence of CNS insults, fluid status or electrolyte abnormalities, organ dysfunction, and hypertension. **Results:** A total of 44 patients received DA-EPOCH ± R at our institution from July 2012 to September 2014. Of these 44 patients, 3 (7%) were diagnosed with PRES. The patients who developed PRES were more likely to have a pre-existing CNS insult, fluid status or electrolytes abnormalities, and hypertension. **Conclusion:** To the best of our knowledge, the present study is the first description of PRES associated with DA-EPOCH. The key risk factors for the development of PRES identified in our study included hypertension, fluid imbalance, electrolyte abnormalities, baseline organ dysfunction, a high tumor burden, and the presence of pre-existing CNS insults during chemotherapy, such as CNS infection. Patients with these risk factors appear to have a greater risk of developing PRES and should be monitored closely during treatment.

Clinical Lymphoma, Myeloma & Leukemia, Vol. ■, No. ■, ■-■
Keywords: Antineoplastic, Infection, Intrathecal, Neurotoxicity, Risk factor

Introduction

The combination chemotherapy regimen EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) has been used for the treatment of non-Hodgkin lymphoma since the 1990s. When administered as a continuous 96-hour infusion, with intercycle adjustments in dosing according to the depth of the hematologic nadir, this regimen, termed dose-adjusted EPOCH (DA-EPOCH), is thought to overcome drug resistance through

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Submitted: Oct 13, 2016; Revised: Nov 22, 2016; Accepted: Dec 6, 2016

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2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2016.12.004

optimized pharmacokinetics and dose intensity.[1] The addition of rituximab to DA-EPOCH (DA-EPOCH-R) in the early 2000s further improved the efficacy of this regimen for B-cell lymphomas.[2] DA-EPOCH with or without the addition of rituximab (DA-EPOCH ± R) is relatively well tolerated, with the most common toxicities hematologic in nature. In the larger prospective studies performed to date, no significant neurotoxicity associated with DA-EPOCH ± R, other than vincristine-associated sensory neuropathy, has been reported.[1-5]

Posterior reversible encephalopathy syndrome (PRES) is a neurologic condition characterized by vasogenic cerebral edema.[6] Historically, several different terms have been used to describe the disorder, including hypertensive encephalopathy, reversible posterior leukoencephalopathy syndrome, reversible posterior cerebral edema syndrome, and brain capillary leak syndrome. The term PRES is somewhat misleading, because the syndrome is not always reversible nor always confined to the posterior regions of the brain.[6-12] Although the precise mechanism of PRES is unclear, 2 elements are essential for the syndrome to develop: (1) relative hypertension and (2) endothelial dysfunction, leading to disruption of the blood–brain barrier.[6] The exact incidence of PRES is largely unknown, and the reported incidence rates have varied depending on the clinical setting. An early review from 2 major metropolitan hospitals reported 15 cases during 7 years.[13] The clinical presentation can vary greatly, but the most common symptoms reported have been headache, seizure, visual disturbances, and altered mental status.[6,11,12] The development of PRES has been associated with a variety of conditions, including eclampsia, solid organ transplantation, and chemotherapy.[6,11,12]

The diagnosis of PRES is typically determined from the clinical presentation and neuroimaging findings. Magnetic resonance imaging (MRI) is recommended over computed tomography because the characteristic findings of cerebral edema with bilateral and symmetric involvement of the occipital and parietal regions are most easily demonstrated by MRI.[6,12] The affected brain regions are best identified using the MRI fluid-attenuated inversion recovery (FLAIR) sequence showing conspicuous hyperintensity.[11] MRI diffusion-weighted imaging can be used to distinguish cytotoxic edema of infarction (hyperintensity) from the vasogenic edema (iso- or hypointensity) associated with PRES. MRI further assists in differentiating alternative causes (eg, parenchymal brain metastases). The MRI findings of PRES are characteristic and often used to confirm the diagnosis of PRES. However, in many clinically convincing cases, the MRI findings will be normal. Consequently, normal MRI findings cannot exclude a diagnosis of PRES.

PRES is a rare, but serious, neurologic complication not infrequently encountered in the oncology setting. Multiple conditions have been previously identified that are commonly seen in oncology patients associated with PRES, including immunosuppression, hypertension, renal dysfunction, and tumor lysis syndrome. The various medications used in the management of oncologic disorders, including chemotherapy, immunosuppressive agents, targeted therapy, corticosteroids, and growth factors, have all been implicated in the development of PRES.[6,11,12] Chemotherapy represents an important class of drugs associated with PRES, most notably high-dose, multidrug regimens, such as those used for pediatric acute lymphoblastic leukemia. Although the individual chemotherapeutic agents of doxorubicin, cyclophosphamide, and vinca alkaloids have all been associated with PRES development, currently, no published data have described PRES in association with the treatment regimen DA-EPOCH. However, after observing 3 such cases at our institution, we sought to identify the potential common themes or risk factors associated with this severe neurologic complication.

Materials and Methods

A retrospective medical record review was conducted under an institutional review board-approved protocol. We identified patients receiving DA-EPOCH ± R at our institution from July 2012 to September 2014. The patients were screened for evidence of severe neurotoxicity through the identification of requests for neurology consultations or neuroimaging studies. The medical records of patients with evidence of central nervous system (CNS) neurotoxicity were reviewed in more detail to identify documented cases of PRES. The key risk factors assessed included rituximab administration sequence, the presence of pre-existing CNS insults (eg, intrathecal chemotherapy, CNS infection), fluid imbalance, electrolyte abnormalities, renal dysfunction, hepatic dysfunction, and hypertension. The incidence rates of risk factors in patients with and without PRES were compared using Fisher's exact test, with a 2-tailed *P* value.

Results

A total of 44 patients had received DA-EPOCH ± R at our institution from July 2012 to September 2014. The median age at diagnosis was 60 years (range, 30-79 years), and 64% of the patients were men. The most common diagnoses were diffuse large B-cell lymphoma (DLBCL) (57%), B-cell lymphoma unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (18%), anaplastic large cell lymphoma (7%), Burkitt lymphoma (5%), and peripheral T-cell lymphoma (2%). Of these 44 patients, 6 required neurology consultations, 11 underwent brain neuroimaging, and 3 (7%) were diagnosed with PRES. Of the 3 cases, 2 had classic radiographic and clinical features consistent with PRES, and the third case was complicated by a later diagnosis of progressive multifocal encephalopathy (PML). A summary of the baseline patient characteristics is provided in Table 1. A thorough review of each documented case of PRES is provided.

Case 1

A 62-year-old man was admitted to our hospital for treatment with DA-EPOCH-R for *MYC*, *BCL2*, and *BCL6* co-rearranged ("triple-hit") B-cell lymphoma unclassifiable. Rituximab was given on day 5, and intrathecal methotrexate was administered for CNS prophylaxis 2 days before the initiation of systemic chemotherapy. Cerebrospinal fluid (CSF) subsequently tested negative for disease. The patient tolerated his first cycle of chemotherapy well, except for some moderate fluid retention that was likely secondary to aggressive hydration to prevent tumor lysis syndrome.

Approximately 2 days after discharge, the patient reported increasing neck pain, headache, confusion, and gait disturbance. Soon after reporting these symptoms, he experienced a witnessed generalized seizure at home and was readmitted to the hospital. On admission, he was noted to have elevated blood pressure (range, 140-150/80-90 mm Hg compared with 120/70 mm Hg at baseline)