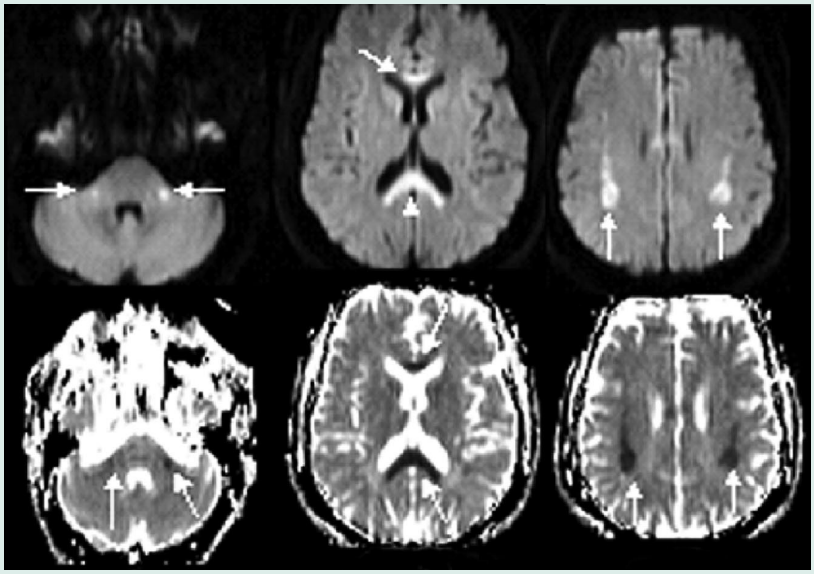
Capecitabine-induced multifocal leukoencephalopathy



Areas of restricted diffusion with corresponding ADC map hypointensity in the brachium pontis, corpus callosum, and posterior centrum semiovale.

In the Videnovic et al. report on capecitabine-induced leukoencephalopathy, manifestations included nausea, confusion, short-term memory loss, headaches, vertigo, ataxia, dysarthria, and body shaking/stiffening. Distinctive multifocal MRI abnormalities including involvement of the splenium of the corpus callosum were present in all cases.

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Neurotoxicity is second only to myelosuppression as a cause of chemotherapy dose reduction or termination in patients under treatment for cancer. Capecitabine is an oral pro-drug that is rapidly converted to 5-flurouracil (5-FU) in the liver. It achieves protracted serum levels of 5-FU that result in higher tumor response rates than are typically seen after IV administration of 5-FU. This change in formulation resulted in a hitherto unappreciated toxicity associated with capecitabine.

In the Videnovic et al. report five patients had a subacute encephalopathy associated with white matter changes on diffusion-weighted MRI. All patients had complete, or near complete, clinical and radiographic resolution over several days after discontinuation of the drug. Patients were not re-challenged at a lower dose, and the development of this encephalopathy may be an absolute contraindication to re-treatment with capecitabine or 5-FU. This complication has been described rarely and may occur with acute neuromuscular toxicity.[1] Two patients in this report had received whole brain radiotherapy or stereotactic radiosurgery for brain metastases. Perhaps radiotherapy predisposed these patients to a toxic leukoencephalopathy, but clearly radiotherapy was not required. The mechanism of capecitabine leukoencephalopathy is unknown. The rapid appearance and resolution has no temporal correlation with myelin turnover even though the radiographic abnormalities were confined to white matter. Given the diffusion-weighted MRI abnormalities, one might hypothesize localized edema that resolved with drug withdrawal.

Identification of this new CNS reaction is a sobering reminder of the potential for new toxicities to emerge when old drugs are reformulated and the pharmacokinetics and pharmacodynamics of an agent change. Capecitabine neurotoxicity is a relatively rare event, but is one more concern when evaluating such patients. Furthermore, capecitabine has efficacy in the treatment of CNS metastasis,[2] suggesting we may use this drug more and see this reaction with increasing frequency.

References

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2. Rogers LR, Remer SE, Tejwani S. Durable response of breast cancer leptomeningeal metastasis to capecitabine monotherapy. Neuro-oncology 2004;6:63–64.

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Neurology 2005;65;1685
DOI 10.1212/01.wnl.0000192632.21789.31