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SHORT COMMUNICATION

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5-Fluorouracil can cross brain–blood barrier and cause encephalopathy: should we expect the same from capecitabine? A case report on capecitabine-induced central neurotoxicity progressing to coma

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Abstract *Purpose*: Capecitabine is a relatively new oral fluoropyrimidine currently licensed for the treatment of colorectal and breast cancer. *Results*: It has the advantage of oral administration with good tolerability and comparable activity to intravenous 5-fluorouracil. Central neurotoxicity has been described in 5-fluorouracil-treated patients but there is little data regarding capecitabine. We report here a case of reversible capecitabine-induced encephalopathy progressing to coma. *Discussion*: Literature on fluoropyrimidine-related neurotoxicity will also be reviewed and possible mechanisms of the drug or its metabolites crossing the blood–brain barrier will be discussed.

Keywords 5-Fluorouracil · Encephalopathy · Capecitabine

Case report

A 46-year-old woman was admitted to the hospital with worsening mental confusion and disorientation. She had been diagnosed with a Duke's B pT4pN0 adenocarcinoma of the ascending colon 5 months before, for which she underwent a right hemicolectomy, and, because of the presence of high-risk features, proceeded to adjuvant chemotherapy with capecitabine 2,000 mg/m^2 daily for two consecutive weeks every 21 days and oxaliplatin 130 mg/m^2 every 3 weeks. Her past medical history included transitional cell carcinoma of the bladder diagnosed 18 months before, successfully and uneventfully treated with a total cystectomy and postoperative chemotherapy with gemcitabine and carboplatin.

The first three cycles of capecitabine/oxaliplatin were completed in 80 days. Toxicities included grade 4 anaemia, grade 3 thrombocytopenia, grade 2 leucopoenia, grade 1 peripheral neuropathy and urinary tract infection, all of which recovered after standard management. Oxaliplatin was reduced by 25% after the second cycle for haematological toxicity. Within 1 week of commencing cycle 4, she experienced progressive deterioration of her neurocognitive function and ataxia that required hospitalization. On admission she was disorientated, had a severely ataxic gait and exhibited intermittent jerking movements of her upper extremities. She was afebrile and did not have signs of meningismus. She demonstrated diffuse hyper-reflexia, and hypertonia along with bilateral up going plantar reflexes. Her Glasgow Coma Scale (GCS) on admission was 14/15. Within a few hours she became increasingly unresponsive and progressed to a coma with a GCS of 7/15. She was transferred to the intensive care unit and intubated. Routine haematological and biochemical studies, plasma ammonia levels, CRP and cerebrospinal fluid examination for microbiological, cytological and biochemical abnormalities were all unremarkable. Minimal low-attenuation white matter changes in the occipital lobe were found on magnetic resonance imaging (MRI) of the brain, but they were considered non-specific and not consistent with the patient's symptomatology. Capecitabine was stopped, and antiviral therapy and broad spectrum antibiotics were started. After 48 h intubation she progressively improved and came out of her coma. In the following days her clinical condition normalized and she was discharged within 1 week. Adjuvant treatment was changed to raltritexed/oxaliplatin. No further neurological toxicity occurred.

Discussion

Capecitabine is an oral antineoplastic drug with proven activity in breast and colorectal cancer. Chemically it is a fluoropyrimidine carbamate which is metabolized to its only active product 5-fluorouracil (5FU) through three activation steps. In the liver, a carboxylester-

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ase converts capecitabine to 5′-deoxy-5-fluorocytidine (5′-DFCR). Cytidine deaminase, an enzyme found ubiquitously and at high levels in liver, plasma and tumour tissues, subsequently metabolizes 5′-DFCR to 5′-deoxy-5-fluorouridine (5′-DFUR), and finally the enzyme thymidine phosphorylase hydrolyses 5′-DFUR to 5FU. Thymidine phosphorylase is present at higher levels in tumour tissue when compared with normal tissue, so that the drug may be selectively activated in the tumour with less systemic toxicity.

As with its antineoplastic properties, the toxicities of capecitabine also seem to be related to the final conversion to 5FU. Side effects of capecitabine appear to be similar to those seen in 5FU-treated patients, but with a more favourable profile [3]. Central neurotoxicity involving nystagmus, ataxia, dysarthria or epilepsy is a rare but well-defined side effect of 5-fluorouracil. On the contrary, the frequency of capecitabine-induced central neurotoxicity is reported as 0.1–0.5% in the Package Insert information [10] and only two cases have been reported in the literature [4, 7].

The first case occurred in a patient who was re-challenged with capecitabine 1 year after her first capecitabine-based regimen [7]. Within 6 days of the re-challenge, epilepsy-like symptoms consisting of repeated painful and prolonged spasms of her throat and mandibular muscles appeared. Brain MRI showed diffuse subcortical white matter alterations. Capecitabine was stopped and symptoms resolved after 2 days. MRI, a month later, showed complete regression of pathological findings. The other case occurred in a patient who was initially uneventfully treated with both neoadjuvant and adjuvant 5FU [4]. Neurological symptoms appeared on day 2 of treatment with capecitabine for relapsed metastatic disease. They consisted of painful trismus causing inability to speak and swallow. She also exhibited left-sided neglect. Brain MRI showed diffuse white matter hyperintensity and EEG revealed diffuse background slowing. The symptoms spontaneously resolved within 4 days of capecitabine discontinuation. In our patient, central neurotoxicity presented as a rapid deterioration of consciousness to a comatose state, associated with an ataxic gait, diffuse hypertonicity and bilateral up going plantar reflexes. Unlike previously described cases, alterations on MRI imaging found in our patient were minimal and thought to be non-specific. Neurotoxicity appeared during cycle 4 and the patient was fluoropyrimidine naïve. Moreover, the clinical manifestation in our patient was life threatening, with coma requiring intubation, despite the absence of significant alterations on brain imaging.

The three above-described cases are similar to the central nervous system toxicities reported in patients treated with 5-fluorouracil. Two main clinical patterns of 5FU-induced encephalopathy are recognized. The first presents with ataxia, mental confusion and generalized seizures which may progress to a comatose state. It is usually of acute onset and occurs early in 5FU-based treatment. It tends to resolve completely within days, but can sometimes require months of rehabilitation. It can be associated with hyperammonaemia, and radiological studies are usually normal. These cases may be related to a dihydropyrimidine dehydrogenase (DPD) deficiency and usually present in association with other major toxicities like mucositis, myelosuppression and palmar–plantar erythrodysaesthesia (PPE) [11, 12]. The other variant is associated with an inflammatory leukoencephalopathy, manifesting as ataxia, diplopia, dysartria, focal symptoms (such as localized seizure and muscle spasms) and subacute neurocognitive degeneration [8]. It is usually of delayed onset. It has characteristically been seen in patients receiving 5FU in combination with levamisole, with levamisole probably having the major role. Radiologically, it appears as focal white matter alterations and recovery is not guaranteed. Histopathologically, the lesions are characterized by active demyelination similar to that seen in acute multiple sclerosis, with macrophage-predominant inflammatory infiltrate.

Regression of brain metastases in patients treated with either capecitabine or 5FU has been reported in literature [9, 14]. Although this can be considered as an evidence of their ability to cross the blood–brain barrier (BBB), it is difficult to rule out tumour-induced alterations in the BBB permeability as a contributing factor. On the contrary, central neurotoxicity in the absence of brain metastases may well indicate that these compounds can pass BBB in normal conditions. Nucleosides (like capecitabine circulating metabolites 5′-DFCR and 5′-DFUR) have been shown to be transported through the BBB by in vivo brain uptake index (BUI) and brain perfusion methods as well as in vitro isolated capillary and cultured endothelial cells [13]. On the other hand, transport mechanisms for nucleobases (such as 5FU) are less well understood, although there is some evidence that 5FU crosses the BBB by simple diffusion [2].

The main way capecitabine crosses biological membranes seems to be in the form of 5′-DFUR via the hCNT1 transporter [6]. On the other hand, 5FU is not a substrate of hCNT1, suggesting that different transporters may be implicated for this compound. hCNT1 has been demonstrated to be present in the BBB in a rat model [1], although it has not yet been demonstrated in human brain tissue. Therefore a possible mechanism for capecitabine to cross the BBB could be in the form of 5′-DFUR via hCNT1. In the brain, 5′-FDUR could easily be transformed to 5FU due to the relatively high expression of thymidine phosphorylase in normal glial cells [5].

In conclusion, we have described the first case of capecitabine-induced neurotoxicity progressing to a comatose state. This presented in a similar fashion to the acute encephalopathy previously described with 5-fluorouracil. Our case suggests that at least one of the metabolites of capecitabine has the ability to cross BBB and cause central neurotoxicity, we suggest a possible mechanism for this. Clinicians should be aware of this potentially life-threatening side effect.

References

1. Anderson CM, Xiong W, Young JD, Cass CE, Parkinson FE (1996) Demonstration of the existence of mRNAs encoding N1/cif and N2/cit sodium/ nucleoside cotransporters in rat brain. Mol Brain Res 42:358–361
2. Bourke RS, West CR, Chheda G, Tower DB (1973) Kinetics of entry and distribution of 5-fluorouracil in cerebrospinal fluid and brain following intravenous injection in a primate. Cancer Res 33:1735–1746
3. Cassidy J, Twelves C, Van Cutsem E, Hoff P, Bajetta E, Boyer M, Bugat R, Burger U, Garin A, Graeven U, McKendric J, Maroun J, Marshall J, Osterwalder B, Perez-Manga G, Rosso R, Rougier P, Schilsky RL, Capecitabine Colorectal Cancer Study Group (2002) First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. Ann Oncol 13:566–575
4. Couch LS, Groteluschen DL, Stewart JA, Mulkerin DL (2003) Capecitabine-related neurotoxicity presenting as trismus. Clin Colorectal Cancer 3:121–123
5. Fox SB, Moghaddam A, Westwood M, Turley H, Bicknell R, Gatter KC, Harris AL (1995) Platelet-derived endothelial cell growth factor/thymidine phosphorylase expression in normal tissues: an immunohistochemical study. J Pathol 176:183–190
6. Mata JF, Garcia-Manteiga JM, Lostao MP, Fernandez-Veledo S, Guillen-Gomez E, Larrayoz IM, Lloberas J, Casado FJ, Pastor-Anglada M (2001) Role of the human concentrative nucleoside transporter (hCNT1) in the cytotoxic action of 5′-deoxy-5-fluorouridine, an active intermediate metabolite of capecitabine, a novel oral anticancer drug. Mol Pharmacol 59:1542–1548
7. Niemann B, Rochlitz C, Herrmann R, Pless M (2004) Toxic encephalopathy induced by capecitabine. Oncology 66:331–335
8. [No authors listed] (1999) Case records of the Massachusetts General Hospital. weekly clinicopathological exercises. Case 24–1999. Neurologic disorder in a 65-year-old man after treatment of colon cancer. N Engl J Med 341:512–519
9. Phuphanich S, Jacobs M, Spiers A (1994) Response of recurrent brain metastases in malignant melanoma to 5-fluorouracil and interferon-alpha therapy. J Neuroimaging 4:114–116
10. Roche Xeloda (capecitabine) data sheet
11. Shehata N, Pater A, Tang SC (1999) Prolonged severe 5-fluorouracil-associated neurotoxicity in a patient with dihydropyrimidine dehydrogenase deficiency. Cancer Invest 17:201–205
12. Takimoto CH, Lu ZH, Zhang R, Liang MD, Larson LV, Cantilena LR Jr, Grem JL, Allegra CJ, Diasio RB, Chu E (1996) Severe neurotoxicity following 5-fluorouracil-based chemotherapy in a patient with dihydropyrimidine dehydrogenase deficiency. Clin Cancer Res 2:477–481
13. Tamai I, Tsuji A (2000) Transporter-mediated permeation of drugs across the blood–brain barrier. J Pharm Sci 89:1371–1388
14. Wang ML, Yung WK, Royce ME, Schomer DF, Theriault RL (2001) Capecitabine for 5-fluorouracil-resistant brain metastases from breast cancer. Am J Clin Oncol 24:421–424