Case report

Permanent lesion to the corticospinal tract after therapy with capecitabine

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SUMMARY

Capecitabine is an oral fluoropyrimidine used to treat solid tumours such as colorectal and breast cancer. A rare but severe side effect is capecitabine-induced leukoencephalopathy, including bilateral lesion to the corticospinal tract. However, neurological symptoms due to capecitabine treatment are usually reported to be reversible after discontinuation of capecitabine. Here, we present the case of a patient with bilateral degeneration of the corticospinal tract and progressive spastic tetraplegia after chemotherapy with capecitabine mimicking primary lateral sclerosis. Although therapy with capecitabine was ended, symptoms substantially worsened over the following years and the patient finally died from aspiration pneumonia almost 3 years after the application of capecitabine.

BACKGROUND

Capecitabine is a prodrug of 5-fluorouracil (5-FU) used to treat colorectal and breast cancer. Toxic encephalopathy induced by capecitabine is a rare but severe side effect that has consistently been reported over the last 15 years.^{1–7} Involvement of the bilateral corticospinal tract in capecitabine-induced leukoencephalopathy has also been described.⁸ However, neurological symptoms due to capecitabine treatment usually are reported to be reversible after discontinuation of capecitabine.^{5–8}

CASE PRESENTATION

A 63-year-old male patient was admitted to hospital in November 2017 because of progressive gait disturbance, from which he had suffered for about 1–1¼ years. The patient had been treated with capecitabine chemotherapy due to rectum carcinoma from June to September 2016. R0 resection of the carcinoma was performed in October 2016. Further capecitabine therapy was not administered. Case history included deep vein thrombosis in January 2017. The patient had no pre-existing neurological condition.

Clinical examination showed dysarthria and spastic tetraplegia. Neuropsychological testing revealed impaired executive functioning. Neither clinical nor electrophysiological involvement of the lower motor neuron was detected. The patient was treated symptomatically with baclofen and could be discharged to his home.

INVESTIGATIONS

MR imaging as well as MR tractography were conducted, which revealed bilateral degeneration of the corticospinal tract (figure 1). Imaging of the corticospinal tract via diffusion tensor imaging has been used for assessing microstructural pathological abnormalities in patients with amyotrophic lateral sclerosis and other motor neuron diseases.^{9–11}

DIFFERENTIAL DIAGNOSIS

The patient showed progressive spastic tetraplegia without impairment of the lower motor neuron. Thus, the diagnosis of primary lateral sclerosis (PLS) was considered. PLS is a rare motor neuron disease which almost exclusively affects upper motor neurons, although there are different concepts about the clinical presentation of PLS and the condition may be considered as a variant of amyotrophic lateral sclerosis.¹²

However, PLS is a motor neuron disease considered to have a comparatively benign prognosis with a rarely lethal course. Importantly, in the case of our patient, neurological symptoms first occurred directly after administration of capecitabine chemotherapy. Given the rare occurrence of PLS (and administration of capecitabine), an association of the patient's leukoencephalopathy and lesion to the corticospinal tract with capecitabine therapy is most likely.

As a second differential diagnosis, pathology of the cervical spinal cord was considered. Cervical MR imaging showed intervertebral disc protrusion at C4/C5 with relative cervical spinal canal stenosis (figure 2). Neurosurgical nucleotomy at C4/C5 and C5/C6 with implantation of two polyetheretherketone (PEEK) cages was performed elsewhere in March 2017. However, spastic tetraplegia further worsened after the operation. This, and the fact that the patient showed bulbar speech, ruled out that the disc protrusion was responsible for the patient's condition.

OUTCOME AND FOLLOW-UP

Although therapy with capecitabine had been ended in September 2016, symptoms progressively worsened. In June 2018, the patient was again admitted to the hospital, now wheelchair-bound. As oral baclofen in a dosage of 135 mg/d was not sufficient to control spasticity, intrathecal baclofen pump therapy was initiated.

However, the disease further progressed within the following months. The patient was finally

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Figure 1 Transversal cerebral MR imaging reveals abnormal fluid-attenuated inversion recovery signal and abnormal T2-weighted signal secondary to corticospinal tract degeneration, as indicated by arrows (top left and top right, respectively). Sagittal cerebral MR tractography showing reduction of corticospinal tract fibres (bottom).

bed-ridden and not able to swallow. He succumbed to aspiration pneumonia in March 2019.

DISCUSSION

Toxic leukoencephalopathy and lesion to the corticospinal tract is a severe side effect of chemotherapy with fluoropyrimidine capecitabine, which is used to treat colorectal and breast cancer.^{1–8}

We report a case of permanent and progressive lesion to the corticospinal tract, which was not reversible after discontinuation of capecitabine therapy. Our patient showed progressive spastic tetraplegia, bulbar speech and dysphagia, and finally died at home almost 3 years after administration of capecitabine.

A co-concomitant neurodegenerative disorder such as PLS has to be considered as the differential diagnosis. However, as neurological symptoms first occurred directly after capecitabine administration and as the clinical (lethal) course of the disease in the case of our patient does not match the comparatively benign prognosis of PLS, a causal association of capecitabine treatment and lesion to the corticospinal tract seems most likely.

Capecitabine is a prodrug metabolised to 5-FU, which acts via inhibition of thymidine synthesis and DNA replication. Thymidine phosphorylase catalyses the metabolism to 5-FU and is predominantly located in white-matter tracts.¹³ Studies in mice have demonstrated that systemic application of 5-FU leads to both acute and progressively worsening delayed damage to white-matter tracts.¹⁴ Whereas vascular damage and inflammatory reactions were observed only at short intervals after 5-FU treatment, delayed oligodendrocyte death and a loss of

Figure 2 Sagittal cervical T2-weighted MR imaging showing intervertebral disc protrusion at C4/C5 with relative cervical spinal canal stenosis but no pathological signal in the spinal cord.

the progenitor cell populations required for replacement might represent the mechanism that causes progressive delayed leukoencephalopathy and damage to white-matter tracts after 5-FU administration.¹⁴ The slowly progressive clinical course of the disease in the case of our patient is consistent with this observed delayed degenerative damage to the rodent central nervous system after 5-FU administration.

Thus, it is plausible that chemotherapy with the 5-FU derivative capecitabine can lead not only—as previously reported—to acute encephalopathy, but also—as in the case of our patient—to permanent and progressive leukoencephalopathy and lesion to the corticospinal tract.

Learning points

- Chemotherapy with capecitabine can cause leukoencephalopathy and damage to the corticospinal tract.
- Although neurological symptoms due to capecitabine treatment previously have been reported to be reversible after discontinuation of capecitabine, our case shows that capecitabine-induced lesions can be permanent and progressive.
- Evidence from animal studies provides a possible model for progressive delayed leukoencephalopathy and damage to white-matter tracts after 5-fluorouracil administration due to oligodendrocyte and myelin pathology.

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