

Hepatic encephalopathy after treatment with temozolomide

Annemarie Goldbecker · Anita Blanka Tryc ·
Peter Raab · Hans Worthmann · Julian Herrmann ·
Karin Weissenborn

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Abstract Temozolomide in combination with radiation has been in use for more than 5 years for the therapy of glioblastoma. Known adverse effects concerning the gastrointestinal system are elevation of liver enzymes. We present the case of a patient treated with temozolomide who developed severe cholestatic liver damage and consecutive hepatic encephalopathy. Neurological symptoms were mistaken as being caused by focal brain damage for more than 9 months. After the correct diagnosis had been made and the treatment had been started, the patient's condition ameliorated. In conclusion, neurological deficits in patients with known brain lesion should not be attributed automatically to the pre-existing damage even if it is progressive but should be examined carefully, also including toxic and metabolic encephalopathies into the differential diagnosis. Furthermore, new side effects of drugs have to be considered. At least this case might lead to a closer monitoring of liver enzymes during temozolomide therapy.

Keywords Temozolomide · Hepatotoxicity · Cholestasis · Glioblastoma multiforme · Hepatic encephalopathy

Introduction

Temozolomide, an imidazotriazene, is an oral chemotherapeutic drug with a cytotoxic effect due to alkylation and depletion of DNA-repairing enzymes [1]. Temozolomide is spontaneously hydrolyzed to its active species and eliminated mainly renally [2]. Its main adverse effect is bone marrow suppression with neutropenia and thrombopenia. Adverse effects affecting the gastrointestinal system mentioned by the German SMPC (summary of product characteristics) for temozolomide are constipation, nausea, vomiting, stomatitis, diarrhoea, dyspepsia, dysphagia as well as other unspecific symptoms. The serum ALT (alanine aminotransferase) level is increased frequently ($\geq 1/100$, $< 1/10$) under therapy, other liver enzymes are only affected in 0.1–1% of all cases. Severe liver injury is not mentioned as a possible side effect of temozolomide therapy in the SMPC. The SMPC says that dose has not to be changed in patients with mild or moderate liver dysfunction, and according to pharmacokinetic studies, there are no hints that the dose has to be adjusted in patients with severe liver dysfunction.

Case description

A 66-year-old woman, who had been of good health so far, attracted attention by reduced language production, psychomotor slowing and reduced motivation in summer 2007. Finally, she stopped eating. Weight at this time was 55 kg (height 170 cm). Cerebral computer (CCT) and magnetic resonance tomography (MRI) revealed a left-frontal tumour (ca. $5 \times 5 \times 4$ cm) with oedema and middle line shift. Examination at the time of admission to a local neurosurgery clinic revealed global aphasia and slight paresis of the right leg. A craniotomy was carried out in

A. Goldbecker (✉) · A. B. Tryc · H. Worthmann ·
J. Herrmann · K. Weissenborn
Department of Neurology and Clinical Neurophysiology,
Hannover Medical School, 30623 Hannover, Germany
e-mail: goldbecker.annemarie@mh-hannover.de

P. Raab
Institute for Diagnostic and Interventional Neuroradiology,
Hannover Medical School, 30623 Hannover, Germany

July 2007 and the tumour was removed totally according to macroscopic criteria. Histology showed a glioblastoma WHO grade IV. After surgery, the neurological deficits vanished except for a mild gait disturbance. Medication at the time of discharge from hospital was magnesium, pantoprazole, dexamethasone, candesartan, hydrochlorothiazide and a combination of dyhydrogesterone and estradiol. Combined radio-chemotherapy with temozolomide 100 mg per day started in August 2007. At this time, liver enzymes were within the normal range.

The patient's condition remained well until October 2007. Then the patient developed nausea, vomiting and painless jaundice. At this time, 27 cycles of radiation had been applied combined with continuous temozolomide therapy. Radio-chemotherapy was stopped and she was admitted to the hospital. There, bilirubin was found to be elevated to 20.8 mg/dl (0.2–1.0), aspartate aminotransferase (AST) to 380 U/l (0–31), ALT to 410 U/l (0–34), alkaline phosphatase (ALP) to 2,009 U/l (38–126), gamma glutamyl transpeptidase (GGT) to 368 U/l (0–38), lactate dehydrogenase (LDH) to 430 U/l (0–247), amylase to 335 U/l (0–46) and C-reactive protein (CRP) to 2.00 mg/dl (0.00–0.75) (normal ranges are given in parentheses). Cholinesterase was lowered to 5,043 U/l (5,859–13,600). Blood count, electrolytes, international normalized ratio (INR) and partial thromboplastin time (PTT) were normal. Serology for hepatitis B and C was negative. Endoscopic retrograde cholangiopancreatography (ERCP) revealed ulcerous papillitis, and a temporary stenting was performed. Liver biopsy showed massive cholestasis, fatty degeneration of about 50% of the parenchyma, few areas of liver cell necrosis and slight reactive hepatitis. The aetiology was suspected to be drug-toxic, most probably due to temozolomide. The patient was discharged 1 month later. Radio-chemotherapy was not re-started. Liver enzymes at this time had slightly decreased but in particular cholestatic enzymes were still massively elevated. The patient had developed anaemia, hyponatraemia and hypokalaemia. Medication at this time had been potassium, esomeprazole, thyroxine and dexamethasone. Liver enzymes remained elevated to a lower extent in the following months. But in March 2008, Quick value decreased to 33% (70–100) (INR at this time 2.0) and albumine fraction to 46.1% in the serum electrophoresis, reflecting a disturbance of liver synthesis.

At beginning of July 2008, the patient was admitted to the medical clinic of our hospital. The patient was cachectic (41.8 kg bodyweight). Medication at this time was pantoprazole, vitamine K, pancreatine and ursodesoxycholic acid. Immunologic diagnostic was without pathological results. All together, with the former results, the diagnosis of drug-toxic liver damage was confirmed. Therapy with a high caloric diet, ursodesoxycholic acid and

vitamin K was started. On 12 July, the patient had a first tonic-clonic seizure. CCT showed a left frontal lesion after glioblastoma surgery, but no indication of tumour growth. A neurologist was involved and antiepileptic therapy with levetiracetam 1,000 mg daily was started. At the first contact with the neurologist, the patient's husband reported that last year, besides jaundice, the patient had developed fatigue and that her handwriting had changed. The patient herself complained that she had problems to classify the days of the week correctly at the moment. Examination revealed psychomotor slowing, disorientation, bilateral dysidiadochokinesis, asterixis in all limbs, a loss of the lower limb reflexes, reduced pallesthesia of the distal lower limb, and gait and posture ataxia. Hepatic encephalopathy grade 2 was diagnosed in addition to slight polyneuropathy. The patient was transferred to the neurological clinic. The patient's sum score of the PSE-Syndrome-Test (PHES) [3] at admission was -9 (≥ -4) (Fig. 1). EEG showed a normal alpha rhythm. Somatosensory evoked potentials of the tibial nerve were normal, while amplitude and speed of conduction of the right N. suralis were reduced. T1-weighted MRI showed new bilateral hyperintensity of the pallidum (compared to images from January 2008) (Fig. 2) as frequently seen in patients with chronic severe liver dysfunction. Furthermore, MRI detected a slight increase of contrast enhancement in the former resection area with a small solid component (Fig. 3). As recurrence of the glioblastoma could not clearly be excluded, magnetic resonance spectroscopy was also performed. Metabolite ratios in the tumour region were compared to those in the left parietal subcortex. Choline, as a marker for cell membrane turnover, and creatine, as a

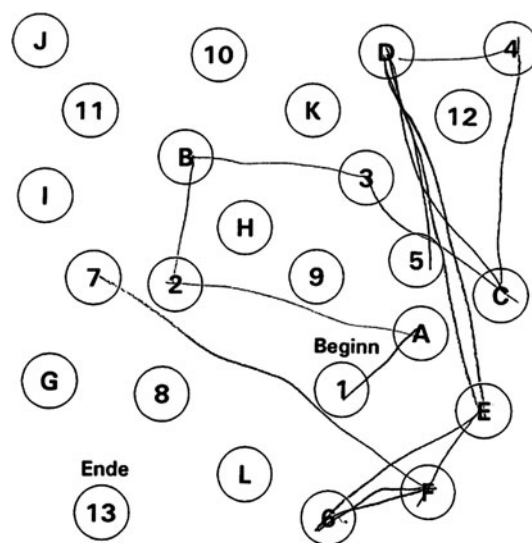


Fig. 1 Result of the number connection test B—a sub-test of the PSE-Syndrome-Test. The patient was not able to connect numbers and letters in alternating order

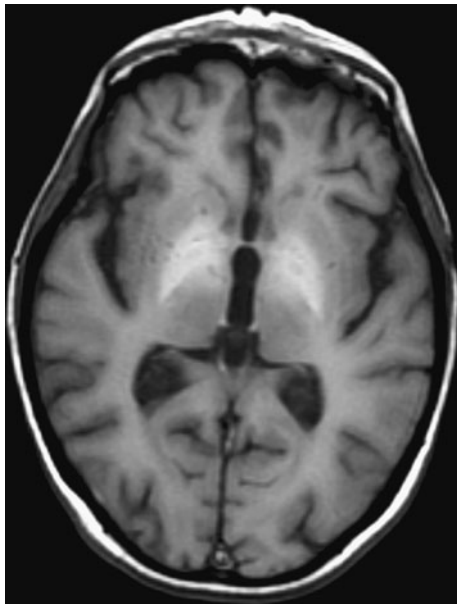


Fig. 2 Transaxial T1-weighted magnetic resonance imaging with pallidal hyperintensity

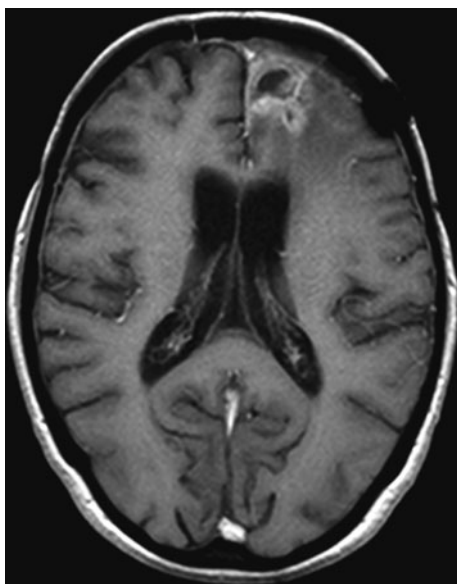


Fig. 3 Transverse T1-flash-sequence (TE 4,76 ms, TR 105 ms) post-Gadolinium-injection. Status post-resection of a left frontal glioblastoma and radiation therapy. Image shows linear and partly blurry enhancement at the resection site

marker for energy metabolism, were lower in the lesion than in the normal subcortex. The regional cerebral blood volume was increased in some areas near the frontal cranium, but not in the areas with contrast enhancement. Thus, taking all findings together, a recurrence of the tumour could not be diagnosed at this point of time. Vitamins B1 and E were normal; vitamin A was in the lower normal range (210 µg/l, 200–1,200), vitamin B6 was below

1.5 µg/l (3.6–18). Manganese, measured in EDTA-blood, was increased to 33.8 µg/l (normal <14, biological tolerance value <20 µg/l). Plasma ammonia was increased to 56 µmol/l (12–38). TSH was lowered to 0.27 µU/ml (0.3–4.0), while the peripheral thyroid hormones were normal.

Treatment with lactulose, L-ornithine-aspartate and long-chain amino acids was started; furthermore, the patient received a combination of vitamins. Orientation, asterixis and gait disturbance improved, and she was discharged.

Unfortunately, the patient did not attend our clinic again for a follow-up examination. In September 2008, the patient was again admitted to a local hospital with jaundice, dehydration and loss of vigilance. Bilirubine was 24.1 mg/dl (0.2–1.0). Abdominal ultrasound showed hepatosplenomegaly but no cholestasis. CCT showed recurrence of the tumour. The patient got volume therapy to compensate for dehydration and treatment against hepatic encephalopathy. After initial improvement, she deteriorated again and finally became comatose. A further CCT showed a left frontal intracranial bleeding with access to the ventricular system. The patient rapidly died due to transtentorial herniation.

Discussion

To our knowledge, a case of severe liver damage due to temozolomide has not been described before. Hepatotoxicity has been described for other alkylating substances like busulfan, thiotepa [4] and dacarbazine [5, 6]. But the adverse effect in these cases has not been cholestatic liver disease but veno-occlusive disease with hepatitis. Histopathology in our case did not show abnormalities of the vessels and only mild concomitant hepatitis. Neyns and colleagues reported a case of acute cholestatic hepatitis in a patient with glioblastoma [7]. But besides temozolomide, this patient was treated with valproic acid and liver enzymes normalized after valproic acid therapy had been stopped.

Of the concomitant treatment, proton pump inhibitors as pantoprazole and esomeprazol, which were taken by the patient throughout the period, are known to be hepatotoxic. But they mainly induce elevation of liver enzymes and in rare cases hepatitis. Thus, the development of a severe cholestatic liver disease due to the proton pump inhibitors is unlikely. This is underscored by the fact that the liver enzymes ameliorated temporarily while the therapy with proton pump inhibitors was ongoing. None of the other drugs prescribed to the patient before she developed cholestasis are known to induce severe liver damage. And as they are much more widely used than temozolomide, the

probability of former occurrence of such a side effect is supposed to be higher. Hepatitis B and C and autoimmune disease have been excluded. Other viruses and accumulation diseases have not been examined in detail to our knowledge. But liver biopsy did not show large inflammatory infiltrates as suspected in case of a viral origin, nor fibrosis or cirrhosis, as in most cases of Wilson's disease, or hemosiderin granules, as found in cases of hemochromatosis [8].

In the case of our patient, anamnesis revealed that the patient had developed hepatic encephalopathy simultaneously to the occurrence of jaundice. The patient's husband described a change of handwriting and the patient herself complained about severe psychomotor slowing and confusion. Nevertheless, it took 9 months until the diagnosis was made. Obviously, the neurologic symptoms were attributed to the glioblastoma although she had been nearly free of symptoms after surgery and deteriorated later on. The patient's confusion and motor symptoms would have probably been continuously attributed to the brain lesion due to tumour and operation without the occurrence of a seizure and the consultation of a neurologist. An immediate correct diagnosis, however, would have improved the patient's quality of life significantly since the symptoms ameliorated after the introduction of therapy against hepatic encephalopathy.

Besides the characteristic clinical findings in this case, MRI also hinted at possible neurological problems due to severe liver dysfunction. It showed hyperintense basal ganglia in T1-weighted images as frequently found in cases of liver cirrhosis [9, 10], cholestasis or manganism [11]. These signal alterations are due to manganese deposition in subjects with either increased manganese exposition or decreased manganese excretion. Manganese is normally excreted via the bile. Due to the cholestasis, the manganese concentration measured in EDTA-blood was significantly increased in our patient and exceeded the value tolerated in persons working with manganese (<20 µg/l). Both hypermanganism and hepatic encephalopathy are known to be associated with Parkinson symptoms [12–14]. Accordingly, our patient presented with bradykinesia and micrography.

Conclusion

The presented case suggests three conclusions. (1) Clinical deterioration in patients with known neurological disease may not be attributed automatically to the pre-existing condition but must be examined *lege artis* like a first

manifestation. Thereby, anamnesis of patient and relatives is of great importance. (2) Side effects of drugs must be considered even if they have never been described before. (3) Liver enzymes must be thoroughly monitored during temozolomide therapy since the drug may induce severe liver dysfunction. In particular, patients with known liver disease should be monitored.

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