Ifosfamide-induced encephalopathy in a patient with metastatic fibrosarcoma

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ABSTRACT

Ifosfamide is a cytostatic drug commonly used in chemotherapy. One of the common adverse effects resulting from the treatment with ifosfamide is encephalopathy. This paper describes a case study of a 64-year-old patient who suffered from a full-blown encephalopathy as a result of chemotherapy administered during the treatment of fibrosarcoma of the femur. It provides a hypothesis of the mechanism behind toxic effects of ifosfamide on the central nervous system and elaborates on a number of documented ways of preventing aforementioned complications.

KEY WORDS: ifosfamide, fibrosarcoma, encephalopathy, methylene blue, thiamine

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INTRODUCTION

Ifosfamide is a cytotoxic drug of the alkylating agent group, specifically a nitrogen mustard derivative. According to the summary of product characteristics, it may be used to treat advanced testicular, ovarian, cervical and lung cancer, blood cancer, including malignant non-Hodgkin's lymphoma and Hodgkin's lymphoma, as well as sarcoma.

Like other cytotoxic drugs, ifosfamide may produce a number of adverse events, including: myelotoxicity, alopecia, nausea and vomiting, mucositis and cardiac complications. Other adverse effects include haemorrhagic cystitis and, less frequently, nervous system disorders, of which the most common is encephalopathy. The patient may develop a mild encephalopathy which presents with sluggishness and sleepiness. However, its symptoms may also include impaired memory, disorientation as well agitation and confusion. Some patients experience rare, albeit disturbing, symptoms such as fits and coma. They are of transient nature. According to some reports, methylene blue (MB) or thiamine may be used to reverse encephalopathy faster.

CASE REPORT

In December 2012, a 64-year old female patient presented at the Greater Poland Cancer Centre in Poznań, with suspected recurrence of right distal femur fibrosarcoma, previously treated with surgical methods. The patient underwent two surgical procedures (in April and August 2012). A follow-up thoracic computed tomography (CT) scan revealed lesions suspected to be metastases. A biopsy was performed which confirmed a metastasized sarcoma. As the lesions were inoperable, the patient was referred for palliative chemotherapy. The patient's medical history was as follows: status post-surgery (total mastectomy) and adjuvant chemotherapy for left breast cancer in 1999 and status post-surgery of left kidney tumour (angiomyolipoma) in January 2012. In addition, the patient was receiving anti-hypertensive treatment with a satisfactory outcome.

The patient was referred for cytostatic treatment. She was initiated on monotherapy with ifosfamide administered intravenously. The doxorubicin regimen was not considered for that patient as she had received that drug as adjuvant therapy for breast cancer in 1999. During the patient's hospital stay, an X-ray exam of the skull showed osteolytic lesions of metastatic nature (in the frontal, parietal and occipital bones), while an ultrasound scan of the right thigh showed multiple nodular masses, suggestive of a local recurrence, accompanied by significantly enlarged lymph nodes.

Given that the treatment was palliative and the patient was scheduled for radiotherapy of the local recurrence, the dose of the first course of chemotherapy was reduced (total dose of 5 g administered by a 24-hour infusion). No signs of early toxicity were observed. Subsequently, the cytostatic treatment was extended to 7 days (1700 mg/m^2 BSA/24 h over 7 days) while the dose was reduced by 50%.

In August 2013, the patient was admitted on the ward to receive further treatment. The eighth course of chemotherapy was initiated in which full ifosfamide dose was used, that is 1700 mg/m^2 BSA/24 h (3043 mg of absolute dose/24 h).

The results of Complete Blood Count (CBC) performed upon admission was as follows: leukocytes – 7.12 g/l (4.00–10.00), neutrocytes – 4.99 g/l (1.6–6.1), haemoglobin – 7.00 mmol/l (7.6–10) (grade 1 anaemia according to the NCI), platelet count – 255.0 g/l (150–370), serum creatinine – 1.20 mg/dl (0.5–1.2), total bilirubin – 0.28 mg/dl (0.20–1.00), alanine transaminase – 17 U/l (0–41) and aspartate transaminase – 18 U/l (0–35). On the following days, the level of albumins and electrolytes (sodium, potassium) was monitored and remained within the normal range. On the fourth day of cytostatic treatment by infusion, the patient reported anxiety. Based on the interview and physical examination, no significant abnormalities were identified and the treatment was continued. On the following day of infusion, the patient's status deteriorated considerably. She was confused and motor agitated, and her verbal response was illogical. On a Glasgow Coma Scale, the patient scored 8. The cytostatic drug was discontinued. The patient was initiated on fluid therapy, antioedematous drugs and symptomatic treatment. A head CT scan and a neurological consultation were ordered. The head CT scan did not show any significant lesions in the central nervous system (CNS). On the following day, the patient's general condition did not significantly improve. She was still illogical and temporarily drowsy. In addition, she did not respond to verbal contact but was responsive to pain. Antioedematous medication, infusion liquids and symptomatic treatment were continued. On the third day after ifosfamide had been discontinued, the patient's status started improving gradually. The patient was still weak and drowsy, but she was able to maintain a logical verbal contact. On the following days, the patient's status kept improving gradually until her neurological status returned to normal on the sixth day.

The occurrence of the abovementioned symptoms during therapy based on increased (full) dose of ifosfamide, no visible lesions on the CT scan of the CNS, no underlying cause of the symp-

toms identified on the basis of the neurological examination, a relatively quick resolution of symptoms and recovery of the nervous system led to a hypothesis that the patient's status was the result of the toxic effect of ifosfamide on the CNS.

DISCUSSION

CNS complications induced by ifosfamide are experienced by approx. 10–20% patients. They occur most often in the first to sixth day of treatment and usually resolve spontaneously within two or three days after the treatment is discontinued, although there are reports of patients in whom the symptoms persisted for up to 29 days. The most frequently reported symptoms of ifosfamide toxicity on the CNS include: delirium, torpor, sleepiness, disorientation, hallucinations, stupor, change of personality, muteness and muscle tremor [1–4].

According to the summary of product characteristics, adverse events associated with ifosfamide occur with the following frequency: encephalopathy and sluggishness – > 1/10; hallucinations, psychosis, disorientation, confusion, motor anxiety, sleepiness, impaired memory and vertigo – > 1/1000, < 1/100; cerebellar disorders – > 1/10000, < 1/1000; coma and convulsions – < 1/10000.

The neurotoxicity of ifosfamide in large doses has not been fully explained. The existing publications propose a hypothesis that toxicity is caused by aminoethyl chloride which is one of ifosfamide metabolites. This substance, when combined with cysteine, forms S-aminoethyl-L-cysteine (thialysine) which may be metabolised to thialysine ketimine. This compound inhibits the electron transport chain in the mitochondria, impairing the NAD-to-NADH ratio. This results in accumulation of NADH in cells which, in turn, distorts the reduction and oxidation reactions [2, 5].

The rate of complications associated with ifosfamide treatment which manifest as neurotoxicity depends on the route of administration and is higher in case of oral administration. This is due to the higher level of active ifosfamide metabolites in the serum resulting from the oral route, which follows from the effect of first pass through the liver [6, 7].

However, there is a number of other factors which increase the risk of ifosfamide toxicity. According to the summary of product characteristic, CNS toxicity occurs more often in case of: renal failure (creatinine level above 1.5 mg/dl), prior nephrotoxic treatment (e.g. by cisplatin), low serum albumin and bicarbonate levels, acidosis, liver failure, pelvic tumour, alcohol abuse and old age. Simultaneous use of drugs such as opioid analgesics, antihistamines and some antiemetics may also lead to, or exacerbate, encephalopathy induced by ifosfamide.

Publications suggest that the number of complications, including neurological complications, associated with simultaneous use of ifosfamide and the antiemetic drug aprepitant (neurokinin 1 receptor blocker) is growing. Aprepitant, a relatively new and efficacious drug, is used to prevent delayed chemotherapy-induced nausea and vomiting. It is delivered with cytostatic treatment that has a medium or high emetogenic potential, such as ifosfamide therapy. The drug inhibits CYP3A4, an enzyme responsible for metabolising a number of medications, including ifosfamide. Inhibition of CYP3A4 and a concurrent use of ifosfamide result in a greater build-up of ifosfamide metabolites, which in turn may explain a higher risk of encephalopathy and other adverse events such as haemorrhagic cystitis and neutropenia [8, 9].

A study has been published which indicates that the total bilirubin and haemoglobin levels and body mass may have a potential effect on the risk of developing encephalopathy in the course of ifosfamide treatment. The study enrolled 19 patients receiving high doses of ifosfamide. Eight of them (42%) experienced symptoms of encephalopathy. This group was demonstrated to have a statistically significant lower level of haemoglobin (10.5 ± 1.5 g/dl vs. 12.4 ± 1.7 g/dl) and bilirubin (0.5 ± 0.2 mg/dl vs. 0.8 ± 0.3 mg/dl) and a higher ratio of body mass to standard mass (1.4 ± 0.3 vs 1.1 ±0,2). Importantly, the study showed a significantly higher incidence of symptoms among the female patients (87.5%) [10].

A large retrospective analysis has been published which studies risk factors for CNS toxicity in therapeutic use of ifosfamide. It includes a report on 337 patients of which 38 (11%) developed encephalopathy. The analysis demonstrated a significant role of the patient's overall status (the risk for ECOG PS 2–4 was 5.15 times higher relative to ECOG PS 0–1), serum creatinine level (a 1 mg/dl increase augmented the risk 15.42-fold) and serum albumin level (a 1 g/dl increase reduced the risk by 67%) on the risk of developing encephalopathy. At the same time, the analysis did not show a significant association (or the association was statistically insignificant) between the dose of ifosfamide, patient's age, bilirubin level, alanine (ALT) and aspartate (AST) transaminase activity and the presence/absence of CNS metastases [11].

Another relatively large retrospective study was conducted which enrolled 200 patients receiving ifosfamide (with patients

diagnosed with sarcoma and lymphoma in equal proportions). The study demonstrated that the risk of encephalopathy depends on the primary diagnosis. In the group of 200 patients, encephalopathy symptoms occurred in 29 patients, of which 24 patients (83%) received treatment due to sarcoma and only 5 (17%) were treated for lymphoma. The above conclusion may be explained by a hypothesis that sarcomas occur more frequently in the pelvis and the retroperitoneal space, which is linked to kidney function and was previously mentioned as a potential risk factor for ifosfamide-induced encephalopathy. Moreover, the report confirms a correlation between CNS disorders occurring during therapeutic use of ifosfamide and the level of albumin (low level increases the risk), creatinine (high level increases the risk), simultaneous use of opioids and a previous treatment by cisplatin. It is important to note that this study, unlike the smaller-scale retrospective analyses mentioned before, shows a link between the higher risk of CNS complications and an elevated level of haemoglobin and finds no such link with a concomitant use of CYP3A4 inhibitors such as the previously mentioned aprepitant [12].

Essential aspects of encephalopathy induced by toxicity of ifosfamide metabolites are its prevention and treatment with MB. Reports about MB efficacy in resolving the CNS disorder are not conclusive. Publications only include a few reports of spectacular effects achieved in the treatment of encephalopathy induced by the toxic effect of ifosfamide. One of them is a case presented by Küpfer et al. in 1994. According to the report, encephalopathy was seen to resolve after 30 minutes from intravenous administration of 50 mg MB [2, 13]. However, there is another report which says that a patient suffered the symptoms for 8 days despite MB treatment which means the symptoms persisted statistically longer than the average duration reported in the literature [2, 14].

One of the retrospective studies included 52 patients who received ifosfamide in large doses. During treatment, 12 (23%) patients experienced encephalopathy symptoms. As soon as CNS toxicity was discovered, 8 patients were initiated on intravenous MB in a dose of 50 mg 6 times a day. Following MB administration, symptoms resolved within one hour in one patient, within 12 hours in three other patients and in 24 hours in another patient. The remaining patients were relieved of the symptoms within 48 hours (2 patients) and 72 hours (2 patients). It is important to note that 3 of those patients received further cycles of ifosfamide with concomitant intravenous administration of MB in a preventive dose of 50 mg 4 times a day. Two of the patients experienced symptoms of toxicity to a lesser extent than before, and one patient did not have any symptoms of toxicity at all. There were 4 patients who developed encephalopathy but were not treated with MB. They were relieved of the symptoms after 48 hours. Despite the fact that this study demonstrated MB efficacy in treatment and prevention, one must note that it enrolled a small number of patients and did not randomise the participants [2].

There are also reports on good outcomes achieved by thiamine (vitamin B_1) when used to resolve ifosfamide-induced encephalopathy. In one of the reports, the authors propose to start the patient on thiamine when he or she does not improve on MB. A description of a female patient is provided who experienced CNS toxicity when receiving chemotherapy based on ifosfamide. The patient did not improve for 36 hours despite interruption of the cytostatic treatment and initiation of MB in usual doses. She received thiamine 100 mg dissolved in 100 ml saline every 4 hours. Her status improved after 7 doses of thiamine [15].

Another report presents ten patients with CNS toxicity experienced due to ifosfamide exposure. Unlike described above, the first line of treatment used was thiamine 100 mg dissolved in 100 ml saline every 4 hours. MB was reserved as a further line of treatment in case previous strategies failed. According to the author, all patients completely responded to treatment within 8 to 72 hours (median: 36 hours). One of the patients regained orientation within 5 hours from the first dose of thiamine. Another patient experienced disappearance of such symptoms as dysphasia, sleepiness and asterixis (tremor of the hand characteristic of liver failure) within 30 minutes. Three patients continued ifosfamide therapy, and received intravenous thiamine 100 mg every 6 hours or oral thiamine 300 mg every 12 hours to prevent encephalopathy. None of the patients experienced any more symptoms of toxicity [16].

SUMMARY

The patient described at the beginning of this paper had typical symptoms of neurological disorders which may occur as a result of ifosfamide treatment. According to some publications, factors which increase the risk of CNS toxicity in that patient include: age (65 years), female sex, use of opioid analgesics, low (but within a normal range) bilirubin level and increased BMI (body mass index) = 27 kg/m^2. Other predictive factors described above, including an elevated creatinine level, prior treatment by cisplatin, lower albumin level, acidosis, liver failure, pelvic tumour and alcohol abuse did not apply to that patient. Despite absence of hard evidence for MB or thiamine efficacy in resolving ifosfamide-induced encephalopathy, such treatment may be considered for patients.

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