CASE REPORT

A CASE REPORT OF IFOSFAMIDE INDUCED ENCEPHALOPATHY IN THE MANAGEMENT OF METASTATIC VULVAR LEIOMYOSARCOMA IN NATIONAL HOSPITAL ABUJA

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ABSTRACT

Introduction: Ifosfamide induced encephalopathy (IIE) is not a common phenomenon and is under reported in our context. Its incidence ranges between 10 to 40% in developed settings. It comprises of a range of neuropsychiatric conditions such as confusion, disorientation, somnolence, agitation, hallucinations, lethargy, and seizures. With the extensive use of ifosfamide in oncology in the management of sarcomas, lymphomas and gynaecologic malignancies, its toxicity may present a challenge to the management of patients with cancer.

Case Presentation: Here we report a case of metastatic recurrent vulvar leiomyosarcoma in a 48-year-old woman, with no family history of cancer. She was referred after the histopathological assessment of a recurrent lesion in her vulvar associated with abdominal distension, a solitary subcutaneous scalp lesion and multiple subcutaneous metastatic nodular lesions at her back. She was investigated and found to be fit for chemotherapy. She was placed on oral dexamethasone, a proton pump inhibitor and antacids and planned to commence systemic chemotherapy using the Ifosfamide based MAID regimen. On the Day 2 chemotherapy infusion, she developed confusion, loss of consciousness and mutism which she recovered completely from 6 hours after suspension of the chemotherapy and institution of emergency medications.

Conclusion: Clinical practitioners are often unable to identify high-risk patients prior to treatment and the unanticipated development of neurologic symptoms may cause treatment delay, treatment discontinuation, and subsequent disruption of treatment plans. Therefore, a high index of suspicion is important to prevent, identify and manage this condition.

Keywords: Leiomyosarcoma, vulvar, ifosfamide, encephalopathy, central nervous toxicity, confusion, hypoalbuminaemia, methylene blue, thiamine

INTRODUCTION

Ifosfamide, a cytotoxic agent, also an oxazaphosphorine that acts as an alkylating agent is widely used in the treatment of wide range of malignant diseases (including sarcomas, lymphomas, and gynecologic diseases) at several doses and frequencies of administration. Approximately 50-80% of

intravenous ifosfamide is oxidized by hepatic enzymes into its active forms (4-hydroxyifosfamide and aldofosfamide) and into other inactive dechloroethylated and carboxy metabolites. Most metabolites are excreted by the kidneys, with the dechloroethylated and carboxy metabolites accounting for 50% of the drug excreted in urine. Hemorrhagic cystitis is a common adverse effect of ifosfamide that is related to one of its metabolites, acrolein. This is prevented by administering 2-mercaptoethane sulfonate sodium (mesna).

Cases of ifosfamide-related encephalopathy have often been observed in clinical practice. Its symptoms include neuropsychiatric conditions such as confusion, disorientation, somnolence, agitation, hallucinations, lethargy, and seizures. These symptoms usually manifest within 48 hours of initiation, and recovery occurs within 48 to 72 hours after the withdrawal of ifosfamide. The reported incidence of ifosfamide-related encephalopathy varies from 15% to 40%. Although the exact etiology of this condition is unknown, inactive metabolites of ifosfamide (including chloroacetaldehyde) may be involved. Methylene blue, thiamine, and albumin have been studied as reversing agents for this condition. With the widespread use of ifosfamide in oncology, its toxicity may pose a challenge to the treatment of patients with cancer. Clinical practitioners are often unable to identify high-risk patients prior to treatment and the unexpected development of neurologic symptoms may cause treatment delay, treatment discontinuation, and subsequent disruption of treatment plans. Although toxicity is reversible in most cases, severe long-term complications (including coma and death) have been reported. Previously proposed risk factors included history of cisplatin use, poor Eastern Cooperative Oncology Group (ECOG) performance status (PS), renal dysfunction, high cumulative dose, history of brain metastasis, and hypoalbuminemia.[1-7]

CASE REPORT

The patient was a 44-year-old, separated, Igbo, Christian, trader who resides at Karshi, Nassarawa State. She presented to our clinic on referral on account of a recurrent right vulvar growth which had developed over 3 months with associated pain and discomfort. She presented at the University of Abuja Teaching Hospital where she underwent an excision procedure, and she was told it was a benign lesion (leiomyoma). She was discharged and did not follow up at the hospital. Five months later, she developed another growth at the same site, which made her return to the hospital and another biopsy was done which revealed leiomyosarcoma. At this point, she had developed insidious onset abdominal distension, progressive weight loss, easy fatigability, intermittent cough, loss of appetite, single nodular lesion in the frontal aspect of her scalp and multiple subcutaneous lumps in her back. She had no family history or prior history of managing any cancer, no history suggestive of exposure to any form of radiation or chemotherapy. She was retroviral disease negative and was in a discordant relationship prior to her separation.

On examination, she was ill looking, cachectic, pale, with abdominal distention, frontal scalp lesion and multiple subcutaneous lesions 2 x 2cm in the left and right groin regions at the back. Her performance status was Eastern Cooperative Oncology Group (ECOG) 1. On vaginal examination she had a right vulvar warty exophytic lesion measuring 6 x 10cm flat surfaced with an extension into the perianal

region which bleeds on contact. There was pinkish serosanguinous discharge with an adjoining hypopigmented right labia majora (Figure 1).

Figure 1: Vulvar lesion on examination

MANAGEMENT AND OUTCOME

Chest and Abdominopelvic CT scan revealed lymphangitis carcinomatosis and multiple metastatic lesions in the liver. Head and neck CT scan revealed subcutaneous frontal scalp metastatic lesion with no signs of skull bone invasion and no brain metastases. ECG done showed sinus rhythm. Full blood count, liver function, albumin and serum electrolyte, urea and creatinine results were within normal reference ranges.

She was commenced on systemic chemotherapy with Ifosfamide 2g/m^2, mesna 800mg 0hr, 1600mg continuous infusion, doxorubicin and dacarbazine Days 1-3 regimen. Her condition deteriorated on the 2nd day while on ifosfamide chemotherapy. She developed reduced consciousness with confusion and mutism which was alerted at the chemotherapy suite. The ifosfamide infusion was stopped while she was placed on supportive care including intravenous fluid hydration with IV Dextrose saline infusion alternated with Normal saline, mesna which lasted 12 hours after the suspension of chemotherapy and oral steroids. IV methylene blue, IV thiamine or IV salt poor albumin were not accessible. She recovered fully after 6 hours. Blood samples for serum electrolyte, urea and creatinine were immediately taken and results were within reference ranges. No history of blood in urine, suprapubic pains or dysuria 48 hours after the incidence.

DISCUSSION

Several studies have revealed risk factors that lead to IIE which include history of cisplatin use, poor Eastern Cooperative Oncology Group (ECOG) performance status (PS), renal dysfunction with high serum creatinine levels, high levels of haemoglobin, high cumulative dose, history of brain metastasis, and hypoalbuminemia.[1,2,3,4,5,7] Others include the use of opioids and aprepitant.[5,6] This patient was placed on syrup morphine few days before commencement of chemotherapy due to severe pains which was not relieved by the initially prescribed dihydrocodeine DFF118 60mg tid prescription. Having a raised index of suspicion in patients with these myriad of risk factors could raise suspicion in predicting such patients prior to treatment. Unfortunately, this is the classical picture of most cancer cases in Nigeria, late presentation worsened by advanced disease stage, malnutrition, other psychosocial issues, severe financial toxicity which restricts treatment decisions, swift availability of investigations, supportive care and other appropriate interventions.

CONCLUSION

Caution should be applied when prescribing ifosfamide based chemotherapy regimen for the management of malignancies, ensuring that the carrier fluid which is usually 0.9% Sodium chloride (NaCl) normal saline is at least 1 litre. The level of serum albumin should be assayed during the prechemotherapy preparatory tests and noted. Serum levels less than or equal to 3.5g/dl of albumin increase the risk of CNS toxicity. There should be increased on-the-job, step-down training to strengthen the capacity of oncology healthcare workers, along with sustained advocacy for continuous education on the management of chemotherapy infusion-related adverse effects There should be drug revolving fund arrangements in chemotherapy suites to ensure continuous and sustainable supply of emergency medications and antidotes at the chemotherapy suites or wards for immediate use when the need arises. IV Methylene Blue, IV Thiamine and IV salt poor albumin should be included in the list of emergency drugs for the chemotherapy suite to be available at all times.

DECLARATIONS

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