Severe rhabdomyolysis associated with pemetrexed-based chemotherapy

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Pemetrexed is an antifolate metabolite that inhibits several enzymes involved in the folate pathway. It has activity against various solid tumours, and has been approved for treatment of malignant pleural mesothelioma on the basis of findings from a randomised phase III trial.[1] The main toxic effects noted for pemetrexed have been rash, myelosuppression, diarrhoea, mucositis, and reversible elevation of liver enzymes—effects that are preventable partly by vitamin supplementation.[1]

A 68-year-old man with malignant pleural mesothelioma had extrapleural pneumonectomy followed by external mediastinal radiotherapy (50 Gy total dose, completed in March, 2003). Because of distant disease progression involving supradiaphragmatic and infradiaphragmatic lymph nodes and a biopsy-confirmed metastatic nodule in the mammary gland, he received 500 mg/m² pemetrexed, given as an intravenous infusion over 10 min followed at least 45 min later by carboplatin (AUC [area under the curve] 5, given as an intravenous infusion over 60 min) in the setting of an expanded access trial in January, 2004. As requested per protocol, he was given full vitamin supplementation (ie, 400 µg folic acid a day orally and 1 mg vitamin B12 as one intramuscular injection every 9 weeks), starting 14 days before first trial treatment. The patient was given 4 mg dexamethasone twice a day intramuscularly on the day before chemotherapy and the day after chemotherapy; on the day of chemotherapy, he received 16 mg dexamethasone, 50 mg ranitidine, and 8 mg ondansetron intravenously. No acute toxic effects were reported.

On day 2 after chemotherapy, he developed severe and gradually worsening myalgias, weakness of the arms and legs, and abdominal tenderness. On day 4 after chemotherapy, he was therefore admitted to the accident and emergency department. Physical examination showed a severely ill patient with weakness in both arms and both legs. Laboratory tests on admission showed substantially increased serum concentrations of creatine kinase (21530 U/L), myoglobin (3000 µg/L), aspartate aminotransferase (453 U/L), and alanine aminotransferase (159 U/L); serum electrolytes and renal-function tests were normal. The patient was diagnosed with rhabdomyolysis. The patient was treated with vigorous fluid replacement with the addition of sodium bicarbonate, methylprednisolone, and furosemide. On the third day in hospital, concentration of creatine kinase decreased to 1835 U/L, and the weakness improved slowly during the following weeks. However, the patient was unable to do his normal daily activities, and 1 month later he was transferred to a long-term hospital clinic for muscular rehabilitation, at which stage serum concentrations of creatine kinase and transaminases were normal.

Drug-induced rhabdomyolysis is a fairly common and potentially life-threatening syndrome associated with several drugs, including chemotherapeutic agents.[2] In patients with cancer, rhabdomyolysis has been reported in association with exposure to high-dose interferon alfa,[3] vancomycin after high-dose chemotherapy with peripheral-blood stem-cell transplantation,[4] and the combination of cyproterone and statins.[5] To our knowledge, this is the first report of severe and life-threatening rhabdomyolysis during pemetrexed-based chemotherapy. Moreover, to our knowledge, no cases of rhabdomyolysis have been reported as a consequence of exposure to other structurally related drugs such as methotrexate and raltitrexed.

The causal association of rhabdomyolysis with pemetrexed in our patient is suggested by a temporal relation and by the absence of concomitant exposure to any other drugs potentially involved with this clinical syndrome, including statins. Although to our knowledge no cases of rhabdomyolysis have been reported with carboplatin-based regimens, with the exception of a patient with a testicular germ-cell tumour given high-dose ifosfamide, carboplatin, and etoposide and peripheral-blood stem-cell transplantation,[6] we cannot presently rule out its involvement in the pathogenesis of this particular patient. Nevertheless, we think that clinicians should be aware of this possible, although rare, complication of pemetrexed-based treatment to recognise promptly and treat successfully the potentially life-threatening disorder of rhabdomyolysis.

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Conflicts of interest

We declare no conflicts of interest.

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