CYCLOPHOSPHAMIDE INDUCED HAEMORRHAGIC CYSTITIS

(A Case Report)

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Introduction

Acute haemorrhagic cystitis is a troublesome complication of high dose cyclophosphamide administration. Bladder toxicity has been reported in 4-36 per cent of patients receiving this drug [1]. Acute cystitis - the commonest form of bladder toxicity, is characterized by dysuria, frequency and haematuria, in absence of bacteriuria. Cystitis usually develops within 24 to 48 hours after drug exposure and lasts for 5-7 days [2]. Severe cases manifest with frank haematuria, passage of clots which can lead to obstructive uropathy [2,3].

Case Report

A 15-year-old boy presented in Mar 95 with one week history of fever and generalized bodyache. On examination, he was found to have pallor, generalized lymphadenopathy and hepatosplenomegaly. There was no bony tenderness or bleeding manifestations. On the basis of clinical profile peripheral smear and bone marrow aspiration studies, he was diagnosed as a case of acute lymphocytic leukemia - L1. He received 2 cycles of induction chemotherapy with daunorubicin, vincristine and L-asparaginase. Two months later, consolidation phase of chemotherapy was started with inj cyclophosphamide 1 gm IV infusion on day 1 and 15 besides vincristine, cytosine arabinoside and 6 - mercaptopurine.

Ten days after the second dose of cyclophosphamide, patient developed pain in suprapubic region, dysuria and haematuria. Clinical examination did not reveal any additional findings and there were no other bleeding manifestations.

Investigation revealed haemoglobin of 6.4 gm/dL. Total leucocyte count was 5000/cmm - polymorphs 65 per cent lymphocytes 30 per cent, monocytes 2 per cent and eosinophils 3 per cent. His platelet count was 40,000/cmm. Bleeding time, clotting time and prothrombin time were normal. There was macroscopic haematuria, routine urinalysis showed 2+ proteins and numerous RBCs. Urine culture on 3 occasions was sterile. Ultrasonography of abdomen revealed normal sized kidneys with no features of obstruction; however, there were multiple clots in the bladder. His blood urea was 35 mg/dL and serum creatinine 0.8 mg/dL. Cystoscopy revealed diffuse hyperaemia of the bladder mucosa with multiple areas of petechial lesions ranging in size from 1 to 5 mm which were actively bleeding.

Patient was diagnosed to have cyclophosphamide induced haemorrhagic cystitis. Though the patient had thrombocytopenia, but there were no bleeding manifestations, hence, it was not suspected as the cause of haematuria. Over the next one week, platelet count rose to over 100,000/cmm, however, gross haematuria continued. For one month, patient remained on continuous bladder irrigation and received 5 units of blood transfusion. After 5 weeks, haematuria gradually subsided.

Discussion

Cyclophosphamide, an alkylating agent, is widely used in malignant and a variety of inflammatory diseases. Adverse effects of cyclophosphamide therapy include bone marrow suppression, haemorrhagic cystitis, alopecia, pulmonary fibrosis, infertility and carcinogenesis. Bladder complications besides acute haemorrhagic cystitis include bladder fibrosis and carcinoma [4].

Acute haemorrhagic cystitis occurs in 30 per cent of patients receiving high dose cyclophosphamide [1]. The toxicity is probably dose related as most of reports of haemorrhagic cystitis are following high dose/prolonged use of cyclophosphamide [2,3]. Bladder damage is due to *acrolein* a metabolite of cyclophosphamide, which has a direct toxic effect on the mucosa [3]. Though cystitis occurs within 24-48 hours, but late occurrences upto a month after stoppage of the drug are not rare [2,5].

In mild cases, symptoms subside in 5-7 days and no active treatment is required but in severe cases, management is troublesome and frustrating at times. On cystoscopy, one finds diffuse hyperaemia, ecchymoses, and petechiae which are actively bleeding.

During cyclophosphamide treatment, plenty of oral fluids, bladder irrigation and frequent voiding are recommended since these reduce the time of contact of acrolein with the bladder mucosa, thereby minimising the chances of cystitis. It is recommended that if haemorrhagic cystitis develops, the drug should be

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temporarily stopped. Patients with severe haemorrhage frequently pass clots, require repeated blood transfusion and at times, electrocautery, cryosurgery or formaldehyde irrigation. 2 mercaptoethane sulphone sodium (MESNA) prophylaxis is recommended especially in patients receiving high dose cyclophosphamide. This drug combines with acrolein and detoxifies it, hence reducing the chances of bladder toxicity. MESNA has been found to be superior to bladder irrigation alone [3,5].

The case highlights that late and severe haemorrhagic cystitis can develop even when cyclophosphamide has not been given in high doses.

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DRUG TOXICITY

Delayed severe hypertriglyceridemia from tamoxifen

The effects of estrogen replacement therapy on lipid metabolism - mainly, a reduction in levels of low density lipoprotein (LDL) and modest increases in triglycerides and high density lipoproteins (HDL) have been well documented. However, estrogens may prove harmful in women with underlying hypertriglyceridemia, leading to profoundly high triglyceride levels and ensuing pancreatitis. What is less widely known is that tamoxifen, used clinically for its antiestrogenic properties, may have a paradoxical estrogenic effect on lipid metabolism, with the same potential complication. Doctors at university of pittsburgh medical centre. Pittsburgh, USA in *N Engl*

J Med (Vol 337 No. 4) have reported 3 cases of severe hypertriglyceridemia due to tamoxifen therapy, each patient had previously had hypertriglyceridemia. Although 2 patients recovered with tamoxifen withdrawal, diet and medication (gemfibrozil and clofibrate), the third patient had fulminant pancreatitis and died of multi organ failure, with a peak triglyceride level of 3673 mg/dL; tamoxifen induces hypertriglyceridemia by stimulating the endogenous production of triglycerides, which overloads serum clearance by lipoprotein lipase and hepatic triglyceride lipase. Substantial build up occurs only when these enzymes are already saturated. Tamoxifen should be used cautiously in patients who have hypertriglyceridemia in the fasting state before treatment is begun.