Bladder Cancer after Cyclophosphamide Therapy for Lupus Nephritis

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Dear Sir,

Bladder toxicity is a serious side effect of cyclophosphamide therapy. Not only can acute hemorrhagic cystitis develop [1], but later bladder fibrosis and carcinoma have been noted [2]. Bladder cancer has been reported mainly in patients who received cyclophosphamide for neoplastic diseases [4, 5], but several patients had a non-neoplastic underlying disorder [6-9]. We report the case of a patient who developed a transitional cell bladder cancer 19 years after receiving low-dose cyclophosphamide for lupus nephritis.

A 51-year-old woman had systemic lupus erythematosus diagnosed in 1967. Manifestations included arthritis, diffuse proliferative glomerulonephritis, pericarditis and central nervous system symptoms. She was treated with corticosteroids, chlorambucil, azathioprine and chloroquine. From December 1970 to September 1971, she received a total dose of 14 g of cyclophosphamide without any evidence of cystitis, but the drug was discontinued because of poor hematological tolerance.

In 1990, she complained of a 3-month history of dysuria, polyuria and lumbar pain. Immunosuppressive medication at this time consisted of azathioprine 50 mg/day, and creatinine clearance was 50 ml/min. A renal ultrasound disclosed right-side hydro-nephrosis. Cystoscopy revealed a bladder tumor. Biopsy specimens showed poorly differentiated transitional cell carcinoma with squamous metaplasia (fig. 1). She underwent total cystectomy with ureterosigmoidostomy. There were no other risk factors for bladder cancer.

Fig. 1. Transitional cell carcinoma invading smooth muscle of bladder. HE.

Bladder cancer associated with cyclophosphamide was first noted in 1971 [3]. Since then, at least 65 cases have been reported in the world literature [4-6]. Four of these had underlying systemic lupus erythematosus and 1 was a renal transplant recipient [7-9]. The relative risk of bladder cancer in patients with malignancy has been estimated to be 6.8-7.9 [4, 5], and there is no apparent plateau for the cumulative risk curve, indicating that the risk may increase further with time [4]. There is much less information about bladder cancer in patients with benign diseases, and controlled studies are needed. The total cyclophosphamide dose associated with cancer has been as low as 3.8 g, although usually it exceeds 100 g [6, 9]. Cyclophosphamide was maintained from a few days, as in the case of

the renal transplant recipient, to 20 years [6,9], and there is no relation between bladder cancer and previous hemorrhagic cystitis [4, 6]. Most tumors are transitional cell carcinomas, although the incidence of the squamous cell type may be increased [6]. They are frequently highly malignant and cause death [4, 6].

Acrolein and other toxic metabolites seem to be responsible for the bladder toxicity of cyclophosphamide. Sodium 2-mercaptoethane sulfonate (mesna) can inactivate acrolein and reduce the risk of hemorrhagic cystitis in patients [10] and the incidence of carcinoma of the bladder in rats treated with cyclophosphamide [11]. Further studies are warranted to examine the ability of mesna to prevent bladder cancer in humans.

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In conclusion, bladder cancer may be a late complication of cyclophosphamide therapy, even when low doses were used and in the absence of previous bladder toxicity. Physicians caring for patients with nonmalignant diseases should be aware of this fact when prescribing the drug. Routine follow-up is recommended for individuals who have received the drug, even if the dose was relatively low, as in this patient. The widespread use of cyclophosphamide for lupus nephritis and the prolonged survival achieved may increase the occurrence of this complication.

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