SUCCESSFUL TREATMENT OF HEMORRHAGIC CYSTITIS SECONDARY TO CYCLOPHOSPHAMIDE CHEMOTHERAPY WITH INTRAVESICAL INSTILLATION OF PROSTAGLANDIN F_2ALPHA

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The treatment of cyclophosphamide-induced hemorrhagic cystitis is difficult. We report a successful case of severe cyclophosphamide-induced hemorrhagic cystitis treated with intravesical instillation of prostaglandin F_2alpha. A 32-year-old woman underwent high-dose cyclophosphamide conditioning before the autologous bone marrow transplantation. She developed clot retention which required continuous irrigation with normal saline. The patient had failed to respond to continuous bladder irrigation with saline and intravesical administration of 1% alum. Fifty ml of prostaglandin F_2alpha solution (1 mg in 100 ml normal saline) was instilled into the bladder, with a dwelling time of 60 minutes, three times a day for 5 days. The hematuria cleared completely 3 days after therapy. The only adverse effect was bladder spasm which was controlled with oxybutynin chloride. The success of this therapy suggests that prostaglandin F_2alpha is a safe and useful therapy for hemorrhagic cystitis secondary to cyclophosphamide chemotherapy.

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Key wors: Prostaglandin F_2alpha, Hemorrhagic cystitis, Bladder instillation

INTRODUCTION

Cyclophosphamide is a carcinostatic agent that is used in the treatment of solid tumors, lymphoproliferative disorders, immune related disorders, nephrotic syndrome, rheumatoid arthritis and acute transplant rejection[1,2]. One of the most common and nuisant complications of cyclophosphamide is hemorrhagic cystitis[3].

The exact mechanism of bladder mucosal damage by cyclophosphamide remains undefined. However, it seems to be associated with acrolein, a urotoxic byproduct of microsomal metabolism of cyclophosphamide which is excreted in the urine[4]. It has been postulated that the urothelium is destructed by direct contract with acro lein causing edema, inflammation, increased permeability, hemorrhage and necrosis[5]. Recently, Mesna (2-mercaptoethane sulfonate) was developed specifically to bind acrolein and was proved to be an effective uroprotective agent when administered parenterally[6]. However, once hemorrhagic cystitis is established, its treatment is very difficult with overall poor results. More recently, intravesical instillation of prostaglandins has been shown to be an effective alternative for the treatment of cyclophosphamide-induced hemorrhagic cystitis[4,7].

We report a case of intractable cyclophosphamide-induced hemorrhagic cystitis and the good response of the patient to intravesical instillation of a prostaglandin F_2alpha.

CASE REPORT

A 32-year-old woman was admitted to the Hematology-Oncology Service for autologous bone marrow transplantation because of malignant lymphoma. The patient underwent high-dose cyclophosphamide (13.2 g) conditioning before the transplantation. On hospital day 25, she developed clot retention which required bladder irrigation at the bedside and continuous blad-

der irrigation with saline. Intravesical administration of 1% alum started, but it readily clogged the catheter and required frequent catheter replacement. After evacuation of the clots, 100 ml of 1 mg % prostaglandin F_2alpha was instilled. Because of severe bladder spasms, the volume was reduced to 50 ml and allowed to remain for 1 hour. The bladder was drained and another 50 ml was instilled for 1 hour. After this 2-hour treatment, the patient was started on continuous bladder irrigation with normal saline for 2 hours and this regimen was repeated three times a day for 5 days. Oxybutynin chloride (3 mg three times daily) was administered to control the bladder spasms. The hematuria cleared completely 3 days after completion of prostaglandin therapy. Her urine has remained clear for 6 months. The patient did not receive sodium 2-mercaptoethane sulfonate (Mesna) as prophylaxis for cyclophosphamide-induced cystitis because this was not part of the protocol used, nor was it approved for this use. No systemic adverse effects of the prostaglandin were observed on blood pressure, temperature, or heart rate, all of which were monitored every 15 minutes during the intravesical therapy.

DISCUSSION

Hemorrhagic cystitis following cyclophosphamide chemotherapy is not uncommon. Foad and Hess[9] have reported that the incidence of hemorrhagic cystitis associated with cyclophosphamide chemotherapy ranges from 2% to 40% in patients taking long-term, low-dose cyclophosphamide. According to Droller et al., the mortality was 75% in patients with massive hemorrhage who had been treated with high doses of intravenous cyclophosphamide.

The best treatment for cychophosphamide-induced hematuria is detoxification of the acrolein with agent such as 2-mercaptoethane sulfonate. However, once established, treatment depends on the degree of hematuria. In mild cases, hematuria may be treated with continuous irrigation of the bladder to prevent clot retention and allow spontaneous bladder hemostasis. Other therapeutic methods include bladder irrigation with alum[11], silver nitrate[12], or formalin[13].

Recently, preliminary reports suggests that there may be a role for prostaglandins in prevention or treatment of cyclophosphamide cystitis. Mohiuddin et al. successfully controlled cyclophosphamide-induced hemorrhagic cystitis in one case by instillation of prostaglandin E, (dinoprostone). Levine et al. reported that complete resolution of gross hematuria occurred in 9 of 18 consecutive patients who received intravesical prostaglandin F_2alpha for severe hemorrhagic cystitis following cyclophosphamide chemotherapy[8].

The exact mechanism of the action of the prostaglandins in the urinary tract is not known. Levine et al. propose that prostaglandins control bleeding by causing smooth muscle contraction in blood vessels in the mucosa and submucosa. This allows hemostasis by natural physiologic mechanisms as opposed to the fixation of urothelial tissue by formalin and silver nitrate[8]. It appears that prostaglandins have multiple mechanisms by which they can prevent cystitis. They could increase mucus production in the bladder, thus affording protection from contact with the acrolein. They could reduce the inflammatory response by reducing histamine secretion, hydrolases and effectiveness of cell-mediated inflammation.

In conclusion, intravesical instillation of prostaglandin F_2alpha was completely successful in a patient with intractable hemorrhagic cystitis following cyclophosphamide chemotherapy. Further studies to determine the optimum dose of prostaglandin F_2alpha, duration of treatment and the best way for prophylaxis of bladder spasms will be needed. Although the success of therapy in the present case is encouraging, a prospective randomized trial comparing prostaglandin therapy to conventional therapy seems indicated. Obviously, the best treatment of cyclophosphamide-induced hemorrhagic cystitis is prevention of direct contact with acrolein. However,

intravesical instillation of prostaglandin F_2alpha may be a useful therapeutic option for established hemorrhagic cystitis following cyclophosphamide chemotherapy.

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和文抄録

プロスタグランジン$F_2\alpha$膀注療法により治癒した サイクロフォスファマイドによる出血性膀胱炎

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サイクロフォスファマイドによる出血性膀胱炎の治療は困難である．われわれはプロスタグランジン$F_2\alpha$の膀注療法により治癒せしめた1例を経験したので報告する．症例は32歳の女性で，悪性リンパ腫に対し，自家骨髄移植を行う前処置として大量のサイクロフォスファマイドの投与を受けた．その後出血性膀胱炎が出現したため，生理食塩水によるカン流や1%みょうばん水の膀胱内注入などを試みたが，いずれも失敗に終わった．プロスタグランジン$F_2\alpha$（1 mgを100 mlの生食に溶解）を50 ml膀注し，1時間留置した．これを1日3回連続5日間施行した．血尿は治療終了後3日目に消失した．唯一の副作用は膀胱収縮であり，これは塩酸オキシブチニンを使用することにより解消した．今回の治療成功例により，プロスタグランジン$F_2\alpha$はサイクロフォスファマイドによる出血性膀胱炎に対する安全で有用な治療法となることが示唆される．

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