The management of haemorrhagic cystitis with sodium pentosan polysulphate

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Accepted for publication 18 June 2004

OBJECTIVE

To assess the use of sodium pentosan polysulphate (SPP) for haemorrhagic cystitis (HC), a potentially life-threatening side-effect in patients treated with pelvic radiotherapy or cyclophosphamide, and which can be difficult to manage as patients often have significant comorbidity.

PATIENTS AND METHODS

Between September 1991 and December 2000, 60 consecutive patients (24 women and 36 men) with haemorrhagic cystitis were primarily treated with SPP; 53 patients had had radical radiotherapy for pelvic malignancy and seven systemic cyclophosphamide. All patients were screened for blood dyscrasia and residual/primary urothelial malignancy with imaging, urine cytology and cystoscopy.

RESULTS

In all, 51 patients were available for follow-up; the median (range) interval between completing treatment and developing haematuria was 4.5 (0.08–39.4) years, the duration of treatment 180 (21–1745) days and patients were followed for 450 (19–4526) days from the onset of haematuria. All patients were started on SPP at an initial dose of 100 mg three times daily. In 21 patients the dose was gradually reduced to a maintenance dose of 100 mg and in 10 further patients SPP was stopped because the haematuria stopped completely. Twenty patients died while on treatment from causes not directly related to their haematuria.

CONCLUSION

We recommend the use of SPP as the primary method of managing haemorrhagic cystitis associated with pelvic radiotherapy or systemic chemotherapy.

KEYWORDS

haemorrhagic cystitis, radiotherapy, cyclophosphamide, sodium pentosan polysulphate

INTRODUCTION

Haemorrhagic cystitis (HC) can be an unwelcome sequel when treating patients with malignancy; it has several causes, including pelvic radiation or systemic treatment with oxazophosphorine alkylating agents (cyclophosphamide). The incidence of HC was reported as 6.5% in a series of 1784 patients with carcinoma of the cervix treated with both intracavitary and external beam radiotherapy; the median interval to developing haematuria after completing therapy was 35.5 months [1]. After treatment with cyclophosphamide the incidence of haematuria was as high as 68%, with a mortality of 4% from uncontrolled haemorrhage, but the routine use of sodium 2-mercaptoethanesulphonate has reduced it considerably [2].

Several treatments have been proposed for HC, including clot evacuation and continuous bladder irrigation [1], oral aminocaproic acid [3], oestrogens [4], endoscopic laser coagulation [5,6], intramural orgotein (free radical scavenger) [7], intravesical regimens of alum [8], formalin [9], placental extract [10] or prostaglandin [11], embolization [12], Helmstein's hydrostatic distension, hyperbaric oxygen [13], urinary diversion [14] and even cystectomy [15]. For a more detailed review of the management of HC, see [16–18].

Two reports with a small series advocated the use of sodium pentosan polysulphate (SPP) for managing HC [15,19]; thus we retrospectively reviewed the efficacy of this treatment in our institution.

PATIENTS AND METHODS

SPP is not licensed for general prescribing in the UK and can only be supplied for a named patient (from IVAX Pharmaceuticals UK, Ltd, London). The pharmacy records for the use of this drug were reviewed; it had been prescribed and dispensed to 60 patients (24 women and 36 men) with HC between September 1991 and December 2000. Fifty-three patients had radical radiotherapy for pelvic malignancy, TCC of the bladder (27), gynaecological malignancy (21), carcinoma of the prostate (two), and one each with adenocarcinoma of the bladder, small-cell carcinoma of the bladder, and adenocarcinoma of the colon. Seven patients had received cyclophosphamide.

All patients were screened for blood dyscrasia and residual/primary urothelial malignancy, with imaging, urine cytology and cystoscopy. HC was diagnosed from the characteristic appearance of telangectasia in the bladder and the absence of other bladder disease.

RESULTS

In all, 51 patients were available for follow-up; the median (range) interval between completing treatment and developing haematuria was 4.5 (0.08–39.4) years, the duration of treatment 180 (21–1745) days, and the follow-up 450 (19–4526) days from the onset of haematuria. Fifteen patients required admission and irrigation for a median of 14 (7–56) days and 14 required a transfusion of 6 (2–25) units of blood. Further supportive management in the form of

bladder irrigation under general anaesthetic was required in five patients, with one having a laparotomy to repair an iatrogenic bladder perforation.

The patients were started on SPP at an initial dose of 100 mg three times daily and this was gradually reduced to a maintenance dose of 100 mg (21 patients); in 10 the SPP was stopped because there was complete and sustained cessation of haematuria. Twenty patients died on treatment from causes not directly related to their haematuria.

DISCUSSION

Radiation results in both acute and chronic bladder injuries; HC is a result of the chronic phase of the radiation-induced insult. The site of damage for chronic radiation therapy is the submucosa, resulting in necrosis of the vascular endothelium, vessel wall thickening and eventually obliterative endarteritis. This results in hypoxia, hypovascularity and ischaemia. The response of the bladder to ischaemia is neovascularization, but these new vessels are fragile and prone to bleed [20].

Cyclophosphamide itself does not cause haematuria, but its toxic urinary metabolite, acrolein, does; it causes transmural oedema, hyperaemia, mucosal ulceration, epithelial necrosis, haemorrhage and eventually irreversible changes to the bladder [21]. Several patients treated with cyclophosphamide have subsequently developed TCC tumours of the bladder [22].

Of oral SPP, 3–5% is excreted in the urine [23]; the mechanism of action of SPP is unclear, but it has been extensively used for managing interstitial cystitis [24]. It has been proposed that epithelial permeability, as determined by the potassium leak test, is increased in patients with interstitial cystitis. SPP replaces surface glycosaminoglycans which have been lost, and so reverses the damage to the surface [25]. In addition, the bladder epithelium is less susceptible to bacterial adherence and so triggers for haematuria are decreased [26].

Recent work also implicated a role for SPP as an anti-inflammatory agent. SPP is an inhibitor of mast cell stimulation [27], and decreases the production of nuclear factor κB, a mediator of the inflammatory response, in transitional epithelium [28].

Oral SPP was used as the first-line treatment for HC in the present patients; it was even used in severe cases of HC requiring continuous bladder irrigation and washouts. In our experience SPP can take 1–8 weeks to have an effect. There were no side-effects with SPP requiring discontinuation; this is particularly pertinent, as the other possible treatments cause severe toxicity, especially intravesical formalin. In our practice SPP has removed the need for therapeutic surgical intervention for HC in most patients and none has required cystectomy for HC at our institution since introducing SPP treatment.

This study provides long-term data on the efficacy of SPP in managing HC, and with the two previous studies [15,19], provides a strong rationale for this to be the primary treatment in this debilitating condition.

In conclusion, we recommend SPP as the treatment of choice for managing HC secondary to radiotherapy or chemotherapy. It requires no anaesthetic or specialized equipment, and in this study was completely and durably successful.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **SPP**, sodium pentosan polysulphate; **HC**, haemorrhagic cystitis.