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PROSTAGLANDIN E2 BLADDER INSTILLATION FOR THE TREATMENT OF HEMORRHAGIC CYSTITIS AFTER ALLOGENEIC BONE MARROW TRANSPLANTATION

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ABSTRACT

Background. **Hemorrhagic cystitis (HC) is a major complication of high-dose cyclophosphamide therapy used in the preparative regimen for allogeneic or autologous bone marrow transplantation. Several viruses (adenovirus, cytomegalovirus and polyomavirus BK), have also been implicated in the etiology of HC. No one established method of treatment is as yet available.**

Materials and Methods. **HC developed in 10 patients after allogeneic bone marrow transplantation and was BK viruria-associated in all cases. All patients were treated with instillations of prostaglandin E2 (PGE2) directly into the bladder.**

Results. **A complete resolution of hematuria within a short time (5±1 days) was observed in all cases; in 4/10 patients urine cleared within 24 hours of the initial treatment. Intravesical PGE2 therapy caused no systemic circulatory or respiratory problems, although bladder spasms occurred in all patients.**

Conclusions. **Intravesical prostaglandin E2 instillation appears to be an effective treatment for hemorrhagic cystitis in bone marrow transplant patients; further studies are required to assess the actual role of BK virus in the pathogenesis of HC in bone marrow transplant patients.**

Key words: bone marrow transplantation, hemorrhagic cystitis, polyomavirus BK, prostaglandin E2 therapy

Hemorrhagic cystitis (HC) is a well-known complication of bone marrow transplantation (BMT) and is normally attributed to the use of high-dose cyclophosphamide in the preparative regimen.[1] Several viruses have also been implicated in the etiology of HC, in particular adenovirus (especially type 11),[2] cytomegalovirus[3] and polyomavirus BK.[4] Although HC may be controlled in most cases by forced diuresis and continuous saline bladder irrigation only, intractable hematuria requires more aggressive treatment, but standard approach is not as yet available; some authors have suggested intravesical instillation of drugs such as formalin,[5] silver nitrate,[6] aluminum[7] and prostaglandin E2 (PGE2).[8]

The results of some previous reports[8-10] seemed to suggest that PGE2 might be beneficial for treating bleeding from the bladder epithelium, but no prospective study had ever been published. The mechanism of action of PGE2 in controlling HC is currently unknown; however, PGE2 has been shown to have a variety of effects on vascular epithelium and it may actually encourage platelet aggregation and induce vasoconstriction. It has also been hypothesized that PGE2 controls bleeding by causing smooth muscle contractions in mucosa and submucosa blood vessels.[11] Early hemostatic alterations may aggravate HC.[12]

We report 10 consecutive cases of BK virus-associated HC in patients submitted to allogeneic BMT, in whom treatment with PGE2 was followed by a dramatic response.

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Patients and Methods

All allogeneic BMT patients who developed HC were enrolled in a prospective study aimed at evaluating the efficacy of PGE2 instillation as first line therapy. Ten of the 130 patients transplanted in our Unit between January 1991 and December 1994 entered the study.

Patient characteristics are outlined in Table 1. All patients were given an individual patient number (IPN). There were 6 acute non lymphocytic leukemias (ANLL), 3 acute lymphocytic leukemias (ALL), and 1 chronic myelogenous leukemia (CML). The conditioning regimens employed were the following: BU/CY, busulphan 4 mg/kg/day orally on days –9 to –6 and cyclophosphamide 50 mg/kg/day i.v. on days –5 to –2; BU/VP/CY, busulphan 4 mg/kg/day orally on days –9 to –6, etoposide 12.5 mg/kg/day twice a day i.v. on days –5 and –4 and cyclophosphamide 60 mg/kg/day i.v. on days –3 and –2; TBI/CY, hyperfractioned total body irradiation (TBI) on days –7 to –4 and cyclophosphamide 60 mg/kg i.v. on days –3 and –2. TBI was performed by delivering eleven 120-cGy fractions in four days, with a 300-cGy anterior and posterior electron boost; total dose was 1320 cGy, with a dose rate of 18-19 cGy/min; TBI/VP/CY corresponds to BU/VP/CY with the substitution of TBI for busulphan.

Table 1. Patient characteristics.

IPN	*Sex/age*	*Disease status*	*Conditioning regimens*	*Mesna*
74	F/42	ANLL 3° cr	TBI/VP/CY	120%
88	F/15	ALL 2° cr	BU/CY 200	120%
96	F/52	CML 1° cp	BU/CY 200	120%
151	M/41	ANLL 2° cr	BU/VP/CY	180%
152	M/19	ANLLnr	BU/VP/CY	180%
155	F/22	ANLL 1° cr	BU/CY 200	180%
171	M/25	ALL 1° cr	TBI/CY	180%
180	M/29	ANLL 1° cr	BU/CY 200	120%
183	F/42	ALL nr	TBI/VP/CY	120%
188	F/24	ANLL 1° cr	BU/CY 200	120%

ANLL = acute non-lymphocytic leukemia; ALL= acute lymphocytic leukemia; CML= chronic myelogenous leukemia; cr= complete remission; cp= chronic phase; nr= not in remission. For conditioning regimens, see text.

All patients had a central venous catheter implanted and were treated until discharge in private, positive-pressure rooms with Hepa-filtered air. Decontamination procedures for patients and the nursing ward were performed. All patients received a single dose of polyspecific immunoglobulins (IVIG) at a dosage of 500 mg/kg ten days before bone marrow infusion and then 200 mg/kg weekly until discharge, mainly for prevention of CMV infections. As a GVHD prophylaxis cyclosporin A (CsA; 3 mg/kg) was given starting on day –1, while methotrexate was given on days +1, +3, +6, and +11, according to Storb *et al.*[13]

HC prevention

In order to prevent cyclophosphamide-induced HC, all patients were subjected to hyperhydration and received mesna during cyclophosphamide infusion; four patients (IPN 151, 152, 155, and 171) were given a mesna dose equal to 180% of the cyclophosphamide dose, while the remaining six got a mesna dose equivalent to 120% of the cyclophosphamide dose. Mesna was always delivered by continuous daily infusion. Urine output was maintained by infusion of furosemide (40 mg/m^2 over 24h), and patients were asked to void as soon as they felt the stimulus.

Urinary monitoring

Microscopic urinalysis was performed on the first morning urine sample from the day before the first dose of cyclophosphamide to 5 days after the last dose of this drug. The presence of microhematuria was also assessed three times daily by dip-stick urinalysis, beginning on the day prior to the first infusion of cyclophosphamide and continuing until 7 days after the last one. Subsequently, this procedure was performed once a day for the following 21 days. Nursing staff and patients were asked to note all urinary symptoms, the presence of clots in urine and the occurrence of menstrual bleeding.

Urine and serum specimens

Specimens for BK virus monitoring were collected at least once a week during the hospital stay (for 30-40 days) and later during clinic vis-

its. Samples were collected on alternate days during episodes of HC. The urine specimens (10-50 mL) were centrifuged at 1500 g for 15 min and the supernatants and the pellets were stored separately at –70 °C.

Viral assay

Urine specimens were analyzed for BK virus by DNA hybridization assay and polymerase chain reaction (PCR) as previously reported.[14]

Diagnosis and classification of HC

A diagnosis of HC was made when macroscopic hematuria occurred in the absence of a generalized hemorrhagic diathesis. It was graded according to Brugieres *et al.*[15]

Treatment

All patients received platelet transfusion when they demonstrated thrombocytopenia (Plt < 20×10^9/L) and aggressive fluid hydration to obtain forced diuresis. PGE2 instillations were given as first-choice therapy within 1 or 2 days of onset of hematuria; only cases IPN 88 and IPN 96 delayed this specific therapy because they were temporarily being treated in other departments. Packed cell transfusions were administered as required to maintain hemoglobin levels >7 g/L.

Method of PGE2 administration

Before starting the procedure, a sedative (morphine) was given to relax the patient and reduce the pain associated with the instillations. Prostaglandin E2 (Dinoprostone) 0.75 mg in 200 mL of normal saline was instilled slowly into the bladder *via* a Foley catheter; when all of the PGE2 had been instilled the catheter was clamped and the PGE2 was left *in situ* for 4 hours. This treatment was repeated daily for 4 days, or until macroscopic hematuria resolved.

Results

HC appeared from day 15 to day 71 post bone marrow transplantation, with a median of 33 days except in one case (IPN 180) in whom it developed acutely two days before transplant, just at the end of cyclophosphamide administration. Moreover, one patient (IPN 188) had two attacks of HC nine days apart.

PGE2 bladder instillations resulted in elimination of gross hematuria in all patients (Table 2). In 4/10 cases urine cleared within 24 hours of the initial treatment, and the median time for the whole patient population was 5 days. The mean duration of PGE2 administration was 5 days. Despite the fact that all patients required antispasmodics and analgesics during administration, only one (IPN 183) necessitated stopping PGE2 instillation because of intolerability. Bladder spasms, the commonest side effect encountered, occurred in all patients but were controllable with parenteral antispasmodics and required narcotic analgesics. No systemic side effects were observed.

BK viruria was demonstrated in all patients using a dot blot hybridization assay and PCR; BKV DNA was detectable in the urine before the onset of HC, during the attack and persisted for at least two months after BMT (Table 3).

Discussion

HC is a frequent complication after bone marrow transplantation. The incidence of severe, sometimes life-threatening HC ranges from 6.5%[15] to 52%[16] in various series depending on patient selection, prior therapy administered to the patient and his/her prior toxicity experience, the conditioning regimens employed, the use of

Table 2. Treatment with PGE2: results.

IPN	*Day of onset of HC*	*Grade*	*Day of PGE2 start*	*Resolution of HC*
74	+23	II	+23	+25
88	+56	III	+67	+69
96	+71	II	+76	+83
151	+41	I	+41	+43
152	+21	II	+26	+31
155	+27	II	+29	+37
171	+23	I	+23	+25
180	-2	I	-1	+1
183	+15	II	+16	+27
188	+24/+32	II	+24/+35	+29/+40

Table 3. Monitoring BKV before, during and after 2 months after first BK viruria.

IPN	First urine sample containing BK virus	Day of onset HC	Intermediate urine sample containing BK virus	Resolution of HC	Last urine sample containing BK virus*
74	+17	+23	+24	+25	+77
88	+20	+56	+68	+69	+80
96	+62	+71	+79	+83	+122
151	+42	+41	+42	+43	+102
152	+28	+21	+29	+31	+88
155	+34	+27	+35	+37	+94
171	+24	+23	+24	+25	+84
180	+1	–2	+1	+1	+61
183	+17	+15	+24	+27	+77
188	+26	+24/+32	+25/+37	+29/+40	+86

** 2 months after first BK viruria*

mesna and the frequency of viral infections. In particular, Arthur *et al.*[4] observed that a substantial portion of late-onset HC in BMT patients was associated with BK virus reactivation.

Human polyomavirus BK infects a large percentage of populations.[17] After the primary infection, which usually occurs in childhood and is not associated with serious clinically apparent manifestations, the BK virus becomes latent, persisting indefinitely in the kidney. Reactivations, characterized by viruria, occur in various conditions such as pregnancy[18] and in patients affected by the acquired immunodeficiency syndrome.[19]

In our experience, a strong association between HC and BK viruria was observed; indeed, BK viruria was detected in all patients with HC. Viral reactivation occurred in both patients with postinfection natural antibodies and those treated with IVIg.

Even though HC is a frequent, severe complication of BMT, no one established method of treatment is as yet available. Mild hematuria may require no more than maintaining a high urine output and occasional irrigation, while moderate hematuria requires Foley catheter drainage and vesical irrigation. When these measures fail, several drugs such as formalin, silver nitrate, aluminum and prostaglandins[5-8,20] have been instilled into the vesica on occasion to control the bleeding. Chapman reported recovery from HC in a BMT patient within 7 days of beginning treatment with vidarabine, followed by clearance of the BK virus from the urine within 20 days.[21]

In this study we report our experience with PGE2 treatment for BK virus-associated HC in a series of 10 consecutive patients undergoing allogeneic BMT. Our results confirm on a larger patient population previous reports documenting the effectiveness of this treatment on bladder bleeding.[8-10] Moreover, in these previous studies no information was provided about BK viruria occurrence.

The efficacy of this method of treatment is well illustrated by the experience of one patient (IPN 88) who developed HC requiring hospital recovery on day 56 after BMT; hematuria and clots persisted despite bladder irrigation, hydration and forced diuresis. On day +67 PGE2 was instilled intravesically; this was followed by a prompt reduction in the severity of hematuria and clearing of the urine within 2 days.

Direct instillation of PGE2 into the bladder was not associated with any systemic circulatory or respiratory problems, although bladder spasms requiring narcotic analgesics were recorded in all patients.

The role of BK virus in the pathogenesis of HC in BMT patients remains to be clarified; this report confirms the strong association between HC and BK viruria, but further studies (based on quantitative assay) are required to elucidate this point.

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