

ORIGINAL ARTICLE

Estrogen as treatment of hemorrhagic cystitis in children and adolescents undergoing bone marrow transplantation

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Hemorrhagic cystitis (HC) after allogeneic hematopoietic stem cell transplantation (HSCT) can cause significant morbidity and mortality. Previous reports have suggested a role for estrogen in the control of HC in adult patients. Here, we describe the clinical courses of 10 children and adolescents treated with estrogen for HC following HSCT. Eight patients (80%) experienced a significant improvement in their hematuria following the commencement of therapy, with six (60%) undergoing resolution of macroscopic hematuria, without any recurrences. The treatment was well tolerated by the majority of patients, with only one patient needing to interrupt treatment (hepatotoxicity). We conclude that estrogen is well tolerated and often effective, and should be considered as an adjunctive treatment option in children and adolescents with HC following HSCT.

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Introduction

Hemorrhagic cystitis (HC) is a well-recognized complication of hematopoietic stem cell transplantation (HSCT) in children and adolescents. The etiology is often multifactorial and includes cyclophosphamide toxicity, irradiation, acute graft-versus-host disease (GvHD) and viruses (adenovirus, polyoma BK virus and cytomegalovirus).¹ In addition, the event is often precipitated and exacerbated by thrombocytopenia. Clinically, its severity ranges from asymptomatic micro-hematuria to macro-hematuria with clots, painful bladder spasm and even urinary tract obstruction. The time course varies from a mild, transient

condition to a chronic debilitating problem with significant medical and psychological impacts. Unfortunately, despite many different therapies being described, no definitive treatment has been established. Recently, encouraging results using conjugated estrogens have been described in adults.² We describe our use of this modality in children and adolescents suffering HC following HSCT.

Patients and methods

Ten cases of HC following high-dose chemotherapy and HSCT in children and adolescents treated at the Children's Cancer Centre, Royal Children's Hospital between 1 January 1998 and 1 January 2004 are reported. The clinical characteristics of the patients are listed in Table 1. All patients had received cyclophosphamide (120 mg/m²) with mesna as part of their conditioning regimen. The majority of patients (all except cases 7 and 9) had also received total body irradiation (12 Gy). The severity of HC was graded according to the previously reported Bearman scale.³ A summary of the patients' status at the time of presentation with hematuria is listed in Table 2. Patients who suffered HC were routinely hyper-hydrated and transfused platelets to maintain the platelet count above $50 \times 10^9/l$. Patients were required to have a serum bilirubin less than 100 $\mu M/l$ prior to the commencement of estrogen. The conjugated estrogen product used was Premarin (Ayerst Laboratories). All patients receiving estrogen were assessed clinically for potential side effects/toxicities daily, and had their liver function assessed at least every 48 h.

Results

Seven male and three female patients aged between 8 and 19 years of age were treated. There were three related and seven unrelated HSCT: two antigen-mismatched cord blood transplants and eight matched BMT. Most patients also suffered associated abdominal pain, dysuria and polyuria. All patients were thrombocytopenic at the onset of symptoms (range $10\text{--}26 \times 10^9/l$). Despite this, four patients developed clots and in two this resulted in urinary tract obstruction. Five patients were suffering acute GvHD at the onset of their symptoms. Urinary viral cultures were

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Table 1 Clinical characteristics of the children and adolescents

No.	Age (years)	Sex	Diagnosis	Clinical status	Therapy	Outcome post-BMT (years)
1	8	Male	ALL	CR3	Unrelated cord	Died; GvHD (0.25)
2	11	Male	ALL	CR3	Unrelated BMT	Alive (6)
3	13	Female	ALL	CR2	Unrelated cord (2 Ag mismatch)	Died; relapse (0.5)
4	16	Male	Myelofibrosis		Unrelated BMT	Died; GvHD (0.20)
5	13	Female	CML/ALL	CR2	Unrelated cord (2 Ag mismatch)	Died; infection (0.25)
6	14	Male	ALL	CR3	Unrelated BMT	Died; CMV (0.25)
7	17	Male	Aplastic anemia		Related BMT	Alive (3)
8	10	Female	ALL	CR2	Related BMT	Died; relapse (0.33)
9	15	Female	AML	CR2	Related BMT	Died; relapse (2)
10	19	Male	ALL	CR2	Related BMT	Died; GvHD (2)

CML = chronic myeloid leukemia; CMV = cytomegalovirus; AML = acute myeloid leukemia; BMT = bone marrow transplantation; GvHD = graft-versus-host disease; ALL = acute lymphoblastic leukemia.

Table 2 Presentations of hemorrhagic cystitis

No.	Onset (days post BMT)	Symptoms	Grade (I–IV) (Bearman ³)	Platelets ($\times 10^9/l$)	GvHD (I–IV) (sites/severity)	Virus study	Ultrasound	
1	33	Hematuria Dysuria Polyuria	IV	26	Skin	I	BK virus	Normal
2	95	Hematuria	III	20			Negative	Normal
3	46	Hematuria Clot retention	III	10			CMV ^a	Multiple clots
4	3	Hematuria	II	16	Skin, liver, GIT	IV	BK virus	
5	36	Hematuria Clot retention	IV	11	Skin, GIT	II	Adeno ^b , BK virus, CMV ^c	Multiple clots
6	15	Hematuria	IV	14	Skin, liver	II	BK virus	Multiple clots
7	1	Hematuria Dysuria	III	37			Negative	
8	10	Hematuria Dysuria ^d	IV	10			Negative	Multiple clots Retention
9	50	Hematuria Dysuria	IV	10			BK virus, CMV	Normal
10	14	Hematuria	IV	11			Negative	Normal

BMT = bone marrow transplantation; CMV = cytomegalovirus; GvHD = graft-versus-host disease.

^aTreated with IV ganciclovir.

^bTreated with IV riboviran.

^cTreated with IV acyclovir.

^dTreated with intravesical bupivacaine and IV oxybutinin.

positive in six patients, five with polyoma BK virus, two with CMV and one with adenovirus.

A summary of treatments and response to episodes of HC are summarized in Table 3. Patients were usually started on intravenous estrogen and transferred to oral estrogen after 2 or 3 days. The duration of estrogen administration varied from 5 to 23 days. Eight of the 10 patients had a significant reduction in their symptoms coincident with the first commencement of estrogen. Furthermore, there was complete resolution of macroscopic hematuria in the one patient with mild HC (100%) and five of the seven with severe HC (71%). In general, estrogen therapy was very well tolerated, with no episodes of flushing, hypertension, thrombosis or feminization in males recorded. One patient (patient five), who suffered from grade III liver GvHD at the commencement of estrogen therapy, had treatment ceased because of a rise in serum bilirubin. With resolution of the GvHD, this eventually returned to normal.

Discussion

HC continues to be a major problem for children and adolescents undergoing HSCT. The reported incidence in institutional series ranges from 15 to 40%.⁴ Direct urothelial toxicity resulting from exposure to high levels of acrocytin, a metabolite of cyclophosphamide, appears to be the most common mechanism. Additional contributing factors include exposure to viruses (adeno, CMV and polyoma BK virus in particular), radiation and acute GvHD. All of these toxicities are likely to be exacerbated by the presence of either thrombocytopenia or coagulation disorders, both of which are quite common in this patient cohort. Many different treatment options have been described previously. Initially, increased fluids and forced diuresis, together with platelet transfusions and correction of any coagulopathy, are usually instituted. Most patients also require analgesia and spasmolytic drugs. Other non-invasive measures have included hyperbaric oxygen,⁵

Table 3 Responses to treatment with conjugated estrogens

No.	Prior therapy	Estrogen therapy	Response (time)	Side effects	Further therapy
1		12.5 mg i.v. b.i.d. × 12 days 5 mg p.o. b.i.d. × 6 days	Complete (21 days)	None	
2		2.5 mg p.o. b.i.d. × 3 days 12.5 mg i.v. b.i.d. × 2 days 5 mg p.o. b.i.d. × 7 days 2.5 mg p.o. b.i.d. × 3 days	Complete (9 days)	None	
3	Bladder washouts Suprapubic catheter	50 mg i.v. b.i.d. × 2 days 5 mg p.o. b.i.d. × 5 days	No	None	Cauterization of mucosa
4		25 mg i.v. b.i.d. × 2 days 5 mg p.o. b.i.d. × 3 days 50 mg i.v. b.i.d. × 3 days	Complete (5 days)	None	
5	Bladder washouts	5 mg p.o. b.i.d. × 20 days 50 mg i.v. b.i.d. × 2 days	Complete (21 days)	Hyperbilirubinemia (46–159 μmol/l)	
6		5 mg p.o. b.i.d. × 10 days 50 mg i.v. b.i.d. × 2 days 5 mg p.o. b.i.d. × 21 days	Partial (microscopic hematuria)	Hyperbilirubinemia (30–250 μmol/l)	Bladder washouts
7		50 mg i.v. b.i.d. × 3 days 5 mg p.o. b.i.d. × 12 days	Complete (21 days)	None	
8	Bladder washouts Suprapubic catheter Intravesical PGF2 α	5 mg i.v. b.i.d. × 7 days 35 mg i.v. b.i.d. × 3 days	Complete (6 days) Complete (14 days)	None None	
9		5 mg p.o. b.i.d. × 21 days 5 mg p.o. q.d. × 7 days 25 mg i.v. b.i.d. × 3 days 5 mg p.o. q.d. × 14 days	Complete (9 days)	None	
10	Bladder washouts Intravesical PGF2 α	25 mg i.v. b.i.d. × 1 days 5 mg p.o. t.d.s. × 11 days	No	None	Suprapubic catheter

i.v. = intravenous; p.o. = post os; b.i.d. = twice daily; q.d. = four times daily; t.d.s. = thrice daily.

prostaglandins⁶ and estrogens.^{2,7–9} Where blood clots are being passed or where urinary tract obstruction is suspected, bladder washouts may also be required. Endoscopy examination of the bladder lining with cauterization of bleeding mucosa may also be of benefit. More invasive techniques, such as installation of formalin or use of a pressure balloon, may be effective, but carry an increased risk of bladder retraction and incontinence.¹⁰ In rare cases, cystostomy or cystectomy has been required.¹¹

The mechanism by which estrogens are thought to act is stabilization or micro-vasculature. A number of previous investigators have documented limited experience of estrogens in the treatment of HC in HSCT. Liu *et al.*⁷ reported five adults who responded to both intravenous and oral estrogen without complication, and Miller *et al.*⁹ documented a successful outcome in six of seven adults (86%). Most recently, an encouraging report of a positive effect in seven of 10 adult patients (70%) was published.² Our results suggest that a similar efficacy can be expected in children and adolescents. There has been a single case report of treatment failure, notably in a case of severe bleeding.⁹ Like all treatments, failure to respond is an indication to examine alternative interventions.

All patients tolerated the therapy without incident. The potential adverse effects of estrogen administration, which include liver dysfunction, hypercoagulability, hypertension and malignant transformation, were not observed. One patient had a rapid elevation in serum bilirubin, but this was in the context of grade III liver GvHD and sepsis and resolved without long-term problems.

In conclusion, we believe that estrogen is a worthwhile therapeutic option in the treatment of HC in children and adolescents following HSCT. Our data demonstrate the feasibility, safety and efficacy of this intervention. A larger multi-center trial is needed to confirm these preliminary results.

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