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Risk factors and treatment of hemorrhagic cystitis in children who underwent hematopoietic stem cell transplantation

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Summary

A retrospective cohort of 163 children with 171 hematopoietic stem cell transplantation (HSCT) performed during Mar. 1992–Dec. 2005 were analyzed to evaluate the incidence, risk factors, management, and outcome of hemorrhagic cystitis (HC). Fourteen patients (8.2%) developed HC (6 boys, median age 6.6 years) at 0–166 days after HSCT (median 25 days), and lasted for 3–96 days (median 26 days). Older age at transplant (median 11.0 vs. 6.4 years, $P = 0.013$), allogeneic transplant (OR = 4.4, $P = 0.02$), cyclophosphamide-containing conditioning (OR = 4.87, $P = 0.008$), moderate-to-severe acute graft-versus-host disease (GVHD) (OR = 3.56, $P = 0.025$) and hepatic GVHD (OR = 3.62, $P = 0.017$) were associated with higher risks of HC in univariate but not multivariate analyses. While estrogen was ineffective in most patients, intravesical formalin, which was used in five patients, was found to be a very effective yet safe treatment for intractable HC. Patients with HC had longer hospital stay (median 175 vs. 88 days, $P = 0.004$). HC resolved after treatments in all cases but eight of the 14 patients subsequently died of other complications of HSCT. In conclusion, HC is a serious complication of allogeneic HSCT. Treatment with intravesical formalin appears effective and safe and can be considered early in severe HC to reduce the risk of morbidity and mortality.

Introduction

Hemorrhagic cystitis (HC) is one of the important complications of hematopoietic stem cell transplant (HSCT) in children. Its incidence ranges from 3.6% to 25% in this group of patients [1–7]. Causes of HC include chemotherapeutic agents such as oxazaphosphorines (cyclophosphamide and ifosfamide) or busulfan [8,9], and viral infections such as polyomaviruses [3,10,11], adenovirus [12] or cytomegalovirus (CMV) [13]. In many cases, no obvious cause could be identified but a number of risk factors have been reported in the literature that may predispose these patients to develop HC. While many cases of mild HC resolve spontaneously without complications, those with moderate-to-severe HC may result in significant morbidity or even mortality. The management of HC is mainly supportive, including hydration to maintain good urine output, bladder irrigation to prevent urinary tract obstruction, and surgical treatment to secure hemostasis. Antiviral agents [13,14] and estrogen [15,16] have been tried with some success. Other treatments such as intravesical alum or formalin are sometimes considered in difficult cases [17]. As there is limited number of studies on HC after HSCT in pediatric population, we would like to evaluate the incidence of HC, its risk factors, management, and outcomes in children after HSCT in our center.

Patients and methods

Study design and participants

This was a retrospective review of all pediatric HSCT performed in Queen Mary Hospital, a University-affiliated quaternary referral center in Hong Kong, over the past

13 years (Mar. 1992 to Dec. 2005). The patients' data on demographic and clinical characteristics, progress in the post-HSCT period including occurrence and treatment of HC, and final outcomes were extracted. Apart from centrally stored hospital records, patients' information was retrieved and verified from our Hematology–Oncology–Immunology database through our Departmental Computer Server. For patients admitted in or after 1997, relevant clinical information including laboratory results can also be retrieved by the Clinical Management System of the Hospital Authority Server through the desk computers in the wards. The incidence of HC was determined and the patients with HC were compared with other patients to identify risk factors of HC. The management and outcomes of patients with HC were described.

Definitions

Hemorrhagic cystitis was defined as the presence of sustained gross hematuria and symptoms of bladder irritability such as dysuria, frequency or urgency, in the absence of urinary tract infection. The urine of patients with HC was sent for bacterial and viral cultures and electron microscopy for polyomavirus. HC was graded into three levels: grade 1, gross hematuria without clots; grade 2, gross hematuria with clots; grade 3, gross hematuria with clots and urethral obstruction [18]. Resolution of HC was defined as clearance of gross hematuria after discontinuation of treatment. Acute graft-versus-host disease (GVHD) was graded according to the Seattle grading system [19]. Neutrophil engraftment was defined as neutrophil count rising from trough to 0.5×10^9/l or above for three consecutive days. Platelet engraftment was defined as platelet count consistently and spontaneously rising above 20×10^9/l.

Prevention and treatment of HC

All patients who received cyclophosphamide as part of conditioning regimen would be given adequate prehydration and sodium 2-mercaptoethanesulphonate (mesna) for bladder mucosal protection. Mesna was given before cyclophosphamide as a bolus injection, and during and after cyclophosphamide as a continuous infusion for a total of 17 h. When HC was diagnosed, patients would be given hydration fluid to maintain a good urine output to prevent clot formation and resultant urinary tract obstruction. Patients who developed haematuria while receiving cyclophspamide or shortly afterwards would be given additional mesna. All patients were given intensive platelet transfusion to maintain platelet counts above 50×10^9/l and any coagulopathy was corrected with fresh frozen plasma to maintain international normalized ratio (INR) below 1.5 and activated partial thromboplastin time (APTT) below 1.5 times upper limit of normal. Bladder irrigation would be started if clots were detected. Other adjunctive treatments such as estrogen, antiviral agents, cystoscopy, intravesicular alum, or formalin instillation were administered at the discretion of the clinicians, as there was no universally accepted guideline. In patients treated with intravesical formalin, cystogram would be performed beforehand to exclude vesicoureteric reflux. If reflux was identified, Fogarty catheter would be used to block the vesicoureteric orifice before instillation of formalin to prevent reflux of formalin.

Statistical analyses

The risk factors of HC were determined by univariate and multivariate analyses of various clinical and transplant factors of patients with and without HC. In univariate analyses, Chi-squared tests or Fisher's exact tests were used for categorical variables where appropriate and odds ratios were determined. Mann–Whitney U-test was used for continuous variables. Logistic regression was used for multivariate analysis, which included factors found to be significant in univariate analyses. A P-value <0.05 was considered statistically significant. All statistical analyses were carried out by the SPSS 11.0 software (SPSS, Inc., Chicago, IL, USA). This study has been approved by the Institutional Review Board of the Hospital Authority of Hong Kong, which complies with the Declaration of Helsinki.

Results

From 1992 to 2005, we had a total of 171 transplants performed in 163 patients. Ninety-three were boys and 70 were girls. The median age at transplant was 6.6 years (range: 0.2–18.7 years). Allogeneic transplants constituted 73.1% and the rest were autologous transplants. The types of underlying disease, donor, hematopoietic stem cell source, conditioning and GVHD prophylaxis regimen were tabulated in Table 1.

Hemorrhagic cystitis occurred in 14 of all transplants (8.2%). Three patients had grade 1 (21.4%), four patients had grade 2 (28.6%) and the remaining seven patients had grade 3 disease (50%). The characteristics of these patients were tabulated in Table 2. The most frequent cause of HC was viral infections, which occurred in six patients (42.9%). Four of these were polyomaviruses, one was cytomegalovirus and one was adenovirus. Two cases (14.3%) occurred within 48 h of completion of conditioning and were probably related to cyclophosphamide. In the remaining six cases, no specific cause could be identified and these cases were likely multifactorial. Patients with HC were older at the time of transplant

Table 1. Demographic and clinical characteristics of all HSCT patients.

	Number	(%)
Underlying diseases		
Leukemia	57	(33.3)
Solid tumor	41	(24.0)
Benign hematological disease	40	(23.4)
Autoimmune disease	6	(3.5)
Primary immunodeficiency	23	(13.5)
Inborn errors of metabolisms	4	(2.3)
Type of transplants		
Autologous	46	(26.9)
Allogeneic	125	(73.1)
Type of donors		
Autologous	46	(26.9)
Matched sibling	75	(43.9)
Mismatched sibling	5	(2.9)
Haploidentical	12	(7.0)
Matched unrelated donor	25	(14.6)
Mismatched unrelated donor	8	(4.7)
Type of stem cell source		
Bone marrow	119	(69.6)
Peripheral blood stem cell	35	(20.5)
Cord blood	17	(9.9)
Conditioning		
Cyclophosphamide + busulphan ± others	76	(44.4)
Cyclophosphamide + others	15	(8.8)
Busulphan + others	4	(2.3)
TBI + cyclophosphamide ± others	29	(17.0)
TBI + others	7	(4.1)
Other chemotherapeutic agents	40	(23.4)
T-cell depletion of grafts		
Yes	19	(11.1)
No	152	(88.9)
Graft-versus-host disease prophylaxis*		
ATG + cyclosporine A + MTx	60	(48.0)
ATG ± others	6	(4.8)
Cyclosporine A + MTx	55	(44.0)
Cyclosporine A ± others	4	(3.2)

*Allogeneic transplants only ($n = 125$); TBI, total body irradiation; ATG, anti-thymocyte globulin.

(median age 11.0 years vs. 6.4 years with and without HC, $P = 0.013$). All cases of HC occurred in patients who underwent allogeneic transplant and none occurred after autologous transplant. Among allogeneic transplant, haploidentical transplant seemed to carry the highest risk, as 16.7% of these transplants resulted in HC, compared with 12% of matched sibling transplant and 12% of matched unrelated donor (MUD) transplant. Documented viral, bacterial and fungal infections occurred in 42% of haploidentical transplants, compared with 33% of matched sibling transplants and 48% of MUD transplants. All patients with HC had cyclophosphamide as part of the conditioning regime, disregarding whether the HC were early or late onset. Patients with grades 3 or 4 acute

Table 2. Clinical characteristics and therapies of patients with hemorrhagic cystitis.

Patient no.	Sex	Age (years)	Diagnosis	Donor	Stem cell source	Grade of acute graft-versus-host disease	Cause of hemorrhagic cystitis (HC)	Grade of HC	Onset of HC	Therapy of HC	Time to resolution of HC	Outcome on follow-up
1	F	0.9	SCID	Mother	BM	4	Polyomavirus	3	D11	Hydration, irrigation, cystoscopy, formalin	32 days	Well at 14.3 years
2	M	4.7	WAS	Mother	BM	4	Unknown	1	D26	Hydration alone	11 days	Well at 12.7 years
3	F	9.7	Thal major	MS	BM	3	Cytomegalovirus	3	D26	Hydration, irrigation, cystoscopy, alum	50 days	Died at D82
4	M	15.6	Lymphoma	MS	BM	Nil	Polyomavirus	3	D13	Hydration, irrigation, premarin, cystoscopy, alum, formalin	15 days	Died at D585
5	M	4.5	JMML	MS	PBSC	Nil	Cyclophosphamide	1	D1	Hydration, mesna, premarin	3 days	Died at D196
6	M	6.4	Aplastic anemia	MS	BM	Nil	Polyomavirus	3	D20	Hydration, irrigation, premarin, ribavirin, cystoscopy	27 days	Died at D64
7	M	9.9	ALL	MUD	CB	Nil	Adenovirus	2	D47	Hydration, irrigation, premarin, ribavirin	47 days	Died at D208
8	M	15.5	CML	MUD	BM	4	Polyomavirus	2	D166	Hydration, irrigation, premarin, cystoscopy	50 days	Well at 7.6 years
9	F	16.4	Thal major	MS	BM	Nil	Unknown	3	D78	Hydration, irrigation, premarin, cystoscopy, alum, formalin	96 days	Well at 7.6 years
10	F	12.0	CVID	MUD	BM	4	Unknown	1	D24	Hydration alone	7 days	Died at D312
11	F	8.7	Thal major	MS	BM	3	Unknown	3	D90	Hydration, irrigation, cystoscopy, formalin	14 days	Died at D187
12	F	14.2	Thal major	MS	BM	Nil	Unknown	3	D24	Hydration, irrigation, cystoscopy, formalin	90 days	Well at 4 years
13	F	14.0	Fanconi anemia	MS	BM	Nil	Cyclophosphamide	2	D0	Hydration, mesna	7 days	Well at 2.7 years
14	F	16.2	AML	MS	BM	Nil	Unknown	2	D34	Hydration, irrigation	23 days	Died at D61

SCID, severe combined immunodeficiency; WAS, Wiskott Aldrich syndrome; MS, matched sibling; JMML, juvenile myelomonocytic leukemia; MUD, matched unrelated donor; CVID, common variable immunodeficiency; PBSC, peripheral blood stem cell.

GVHD, especially those with moderate-to-severe hepatic GVHD, were more likely to develop HC. The gender of the patient, the type of underlying diseases, the type of hematopoietic stem cell source, cell dose and engraftment time were not related to the risk of HC (Table 3). In multivariate logistic regression, none of the demographic or transplant factors was significantly associated with HC.

The onset of HC ranged from 0 to 166 days after HSCT (median 25 days), and lasted for 3–96 days (median 26 days). Those with more severe HC took longer time to resolve (mean duration of HC: 7.0, 32.3 and 47.1 days in grade 2, 3, and 4 HC, respectively). All patients were given intensive platelet transfusion to maintain platelet counts above 50×10^9/l and any coagulopathy was corrected with infusion of fresh frozen plasma to maintain INR below 1.5 and APTT below 1.5 times upper limit of normal. In addition, all patients were given hydration fluid to maintain good urine output. Ten patients (71.4%) also required bladder irrigation. The two patients with cyclophosphamide-related HC were given additional mesna infusions. Two patients (14.3%) with viral infections were given ribavirin but their HC showed no obvious improvement. Estrogen was tried in six patients (42.9%) but there was no significant improvement in most patients and five patients required further treatments for the cystitis. Cystoscopy was required in eight patients (57.1%) for clot removal and alum or formalin treatment. Alum was instituted to the bladder in three patients (21.4%). One patient had good response while the other two required further treatments. In five patients (35.7%), 4% formalin was instilled to the bladder and satisfactory response was noted in all with resolution of HC. Two patients were found to have vesicoureteric reflux and Fogarty catheters were used to block the ureteric orifices to prevent reflux of formalin to the upper urinary tract. Formalin was allowed to stay in the bladder for 10–20 min and then washed out. Four patients had HC resolved after only one treatment. One patient (no. 12 in Table 2) required repeated instillation of formalin for three times within 2 months before bladder hemorrhage completely resolved. She developed acute pyelonephritis 1 month after the first intravesical formalin instillation, which resolved with treatment. The other patients did not experience any adverse effect from intravesical formalin instillation. The three survivors (patient no. 1, 9, 12) are well and do not have bladder symptoms on long-term follow-up for 4–14 years. Their renal function and ultrasound scan of the urinary system were normal.

Patients with HC had a significantly longer hospital stay compared with those without HC (median 175 days vs. 88 days, $P = 0.004$). HC resolved after treatments in all cases. However, eight of the 14 patients subsequently died of other complications of HSCT, including sepsis, severe GVHD, pneumonitis, and intracranial bleeding. Although the cause of death in these patients was not directly related to HC, the risk of death was higher in patients with HC (RR = 1.55) compared with patients without HC, even after exclusion of those who had undergone autologous transplant (RR = 1.71). The remaining six survivors with history of HC recovered without long-term problems related to HC, upon a follow-up of 2.7–14 years.

Table 3. Univariate analysis of risk factors of hemorrhagic cystitis.

Variables	Odds ratio (95% CI)	*P*-values
Age		
>8 years	3.63 (1.09, 12.1)	0.026
≤8 years	1.00	
Gender		
Male	0.53 (0.18, 1.60)	0.25
Female	1.00	
Underlying disease		
Malignant	0.38 (0.12, 1.19)	0.09
Nonmalignant	1.00	
Type of transplant		
Allogeneic	4.40 (1.29, 15.04)	0.02
Autologous	1.00	
Source of stem cells		
Bone marrow	1.71 (0.24, 12.36)	0.59
PBSC	0.49 (0.03, 7.30)	0.60
Cord blood	1.00	
Conditioning		
Cyclophosphamide	4.87 (1.51, 15.72)	0.008
Noncyclophosphamide	1.00	
Acute graft-versus-host disease (GVHD) prophylaxis		
ATG	2.04 (0.68, 6.17)	0.20
Non-ATG	1.00	
Acute GVHD		
Grade ≥3	3.56 (1.11, 10.7)	0.025
Grade ≤2	1.00	
Hepatic aGVHD		
Stage ≥3	3.62 (1.19, 11.0)	0.017
Stage ≤2	1.00	
Gut aGVHD		
Stage ≥3	2.46 (0.71, 8.52)	0.15
Stage ≤2	1.00	
Cutaneous aGVHD		
Stage ≥3	1.93 (0.63, 5.87)	0.24
Stage ≤2	1.00	
Nucleated cell dose		
$> 4 \times 10^8$/l	2.63 (0.56, 12.4)	0.21
$\leq 4 \times 10^8$/l	1.00	
Neutrophil engraftment		
>18 days	0.37 (0.04, 3.29)	0.35
≤18 days	1.00	
Platelet engraftment		
>30 days	2.52 (0.39, 16.3)	0.32
≤30 days	1.00	

PBSC, peripheral blood stem cell.

Table 4. Nonsurgical treatments of intractable hemorrhagic cystitis.

Treatment	Reference	Response rate	Complications	Remarks
Intravesical formalin	[21–28,31–33]	80–100%	Bladder rupture, small contracted bladder, urinary incontinence, ureteric strictures, hydroureteronephrosis, acute tubular necrosis, interstitial nephritis, fistulas, myocardial toxicity	General or spinal anaesthesia required
Intravesical alum	[34]	66–100%	Suprapubic pain and spasm, ileus, hypermagnesemia, encephalopathy, metabolic acidosis	
Intravesical silver nitrate	[35]	68%	Renal failure, small fibrotic bladder	Short-lasting effect
Intravesical phenol	[36]	100%	Bladder fibrosis and contracture, methemoglobinemia	General or spinal anaesthesia required, isolated case reports
Intravesical prostaglandin	[37]	50–75%	Bladder spasm	Mainly for cyclophosphamide-induced hemorrhagic cystitis (HC)
Intravesical GM-CSF	[38]	50%	None reported	Small case series, relatively expensive
Intravesical epidermal growth factor	[39]	100%	None reported	Isolated case report, relatively expensive
Hydrostatic pressure	[40]	50–100%	Bladder perforation and rupture, urinary incontinence, vomiting, abdominal pain	General or spinal anaesthesia required
Embolization	[41]	50–92%	Arterial damage, gluteal pain, embolization of lower limbs or aorta, bladder necrosis	
Hyperbaric oxygen	[42]	75–96%	CNS toxicity, decompression sickness	Mainly for radiation-induced HC
Sodium pentosan polysulphate	[43]	100%	None reported	Isolated case report
Estrogen	[15,16]	70–100%	Hyperbilirubinemia, liver dysfunction	Caution in patients with thromboembolic, cardiac or cerebrovascular disease
Antiviral agents (cidofovir, ribavirin, vidarabine)	[14,44,45]	40–89%	Renal impairment (cidofovir), pancytopenia, hemolytic anemia (ribavirin)	Indicated only in viral infections
Clotting factors (FVIIa, FXIII)	[46,47]	75–100%	Thrombosis	Small case series

GM-CSF, granulocyte-macrophage colony stimulating factor; CNS, central nervous system.

Discussion

Hemorrhagic cystitis is an important cause of morbidity and occasionally mortality in HSCT recipients [2,3]. Its incidence varied significantly among different centers, which is partly explained by the different definitions used for HC in different studies. Our review was concentrated on cases with moderate-to-severe HC and found an incidence of 8.2%, which is within the range of those reported in the literature. Similar to a previous report of HC in pediatric patients, we found that older children are more prone to develop HC [7]. However, there was another study reporting that children younger than 8 years were more likely to develop HC [2].

It is noteworthy that all cases of HC occurred in allogeneic transplants, and autologous transplants seemed to carry a very low risk, although cyclophosphamide was also used in a significant proportion of autologous transplants. This finding is in accordance with another large series [2] and might be related to the higher degree of immunosuppression in allogeneic transplants predisposing to various cystitis-associated viral infections. The possibility of GVHD involving bladder mucosa might be another important pathogenetic factor of HC in allogeneic transplants, as supported by the association between GVHD and HC in our study and the study by Russell [5] and Cesaro [2]. The potent immunosuppressive therapies instituted for GVHD might also predispose to viral infections that cause HC [7]. However, the association between GVHD and HC was not evident in the study by Gorczynska [7], who found that children with severe (grades 3 or 4) GVHD had similar incidence of HC as children with mild or no acute GVHD (grades 0–2).

In contrast with previous reports [1,2,7], we found that transplantation from haploidentical parent donor rather than unrelated donor carried the highest risk among allogeneic transplants. This might be related to the 3-antigen mismatch situation predisposing to more severe GVHD or immunosuppression. The relatively higher number of haploidentical transplants performed in our center might have enhanced the detection of association of HC with this factor. Further studies are needed to confirm our finding.

Although cyclophosphamide is the most frequent cause of early onset HC and probably not a direct cause of late onset HC, the prior use of cyclophosphamide may have caused subclinical damage to the bladder mucosa and hence predispose to clinically significant HC when inciting viral agents attack the immunocompromized host later in the post-transplant period. This is supported by the findings from other studies that high-dose chemotherapy increased the risk of polyomavirus-related HC [7], and the association of HC with prior use of cyclophosph-

Table 5. Previous studies on formalin treatment of intractable hemorrhagic cystitis in children.

Study reference	No. of patients	Age	Grade of hemorrhagic cystitis (HC)	Treatment before formalin	Outcome
[26]	6	NA	3	Cystoscopy and fulguration of bleeding points	Resolution of HC in five patients after one treatment and one patient after two treatments. One patient developed transient anuria after treatment and grades 2–3 hydroureteronephrosis later.
[23]	3	11 months, 17 months, 8 years	3	Bladder irrigation ($n = 3$), vesicotomy ($n = 1$)	Prompt resolution of HC in all patients. No complications.
[22]	1	8 years	2	Cystodiathermy	Resolution of HC after two treatments. Acute oliguric renal failure developed 2 months later with ureteric stenosis and chronic interstitial nephritis.
[21]	1	4 years	3	Bladder irrigation, cystostomy	Resolution of HC after two treatments. No complications.
[24]	1	10 years	3	Bladder irrigation, intravesical silver nitrate, vesicotomy	Prompt resolution of HC. No complications.
[25]	1	15 years		Nil	Prompt resolution of HC. Left hydroureteronephrosis developed 3 months later.

NA, data not available.

amide [5]. Meticulous monitoring of patients who have been exposed to high-dose cyclophosphamide is therefore important to facilitate early recognition and treatment of HC. Maintaining high urine output after cyclophosphamide infusion and prolonging urothelial protection with mesna should be considered in high-risk patients.

Apart from supportive treatments, there are many non-surgical options reported to be useful in the treatment of HC. The reported effectiveness and complications of these treatment options are shown in Table 4. Some of these therapeutic approaches have been tried in pediatric patients. Heath reported that estrogen was quite effective in the treatment of HC in children and adolescents [15]. However, this was not the case in our patients. The relatively higher severity of HC in our cohort may partly explain the difference. As viral infections especially polyomaviruses were potentially important pathogenetic contributors to development of HC, antiviral agents such as ribavirin and cidofovir have been tried in these patients. However, we did not find them to be useful, probably because significant damage to the bladder mucosa has occurred when HC was clinically manifested and viral inhibition at this late stage might be ineffective [20]. It remains to be investigated whether it is beneficial to give antivirals prophylactically to patients who carry polyomavirus or to give antivirals early when viruria occurs before HC develops.

In contrast to estrogen and antiviral agents, intravesical formalin instillation was found to be very effective in our patients, resulting in markedly reduced hemorrhage and fast resolution of HC. There were few reports of using formalin in pediatric patients [21–26] (Table 5). The use of intravesical formalin for the treatment of bladder hemorrhage was first described by Brown in 1969 [27]. Formalin can precipitate cellular proteins of the bladder mucosa [28], and has occluding and fixative actions on telangiectactic tissue and on small capillaries [29]. It has been reported to be particularly useful in severe HC related to cyclophosphamide [21,23]. We have applied this form of treatment in some of our patients with intractable HC and found that it was also useful in late-onset cystitis. However, intravesical instillation of formalin may damage the upper urinary tract when reflux occurs resulting in ureteric stenosis and chronic interstitial nephritis or hydroureteronephrosis [22,25,26]. Therefore, it is important to exclude or prevent vesicoureteric reflux before instillation of formalin, such as using Fogarty catheters to block the ureteric openings [21,24]. Other complications of intravesical formalin include rupture of bladder, small contracted bladder, urinary incontinence, acute tubular necrosis, vesicovaginal or vesicoileal fistulas, and myocardial toxicity [30]. We have not encountered such complications related to formalin treatment in all of our patients, which might be related to the low concentrations of formalin used, as the rate of complications was directly related to the concentrations of formalin [31]. Although it appeared safe and effective in selected patients, prospective clinical trials of intravesical formalin in comparison with other treatments are needed to determine the most effective and safe therapies for moderate-to-severe HC.

Our study had several limitations. Firstly, this is a retrospective review and not a prospective study and is subjected to possible observation and selection biases. Nevertheless, we have included all patients treated in our center to minimize the selection bias and most data were organized and complete in the database of our departmental computer server. Secondly, the sample size is small limiting the statistical power of detecting significant association between HC and transplant variables, and the ability to control for confounding variables in multivariate analyses. However, the present series is already a relatively large one reporting the use of intravesical formalin for treating children with HC after HSCT. Further studies are needed to confirm our findings on the safety and efficacy of intravesical formalin for children with HC.

In conclusion, HC is a serious complication of allogeneic HSCT. Treatment with intravesical formalin appears effective and safe in children and can be considered early in severe HC to reduce the risk of continuous bleeding, urinary tract obstruction and renal impairment.

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