Hemorrhagic cystitis following allogeneic hematopoietic stem cell transplantation: experience in a pediatric oncological institution

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ABSTRACT

Objective. To analyze the risk factors associated with hemorrhagic cystitis (HC) severity and the treatment strategies available in HC patients following allogeneic hematopoietic stem cell transplantation (AHSCT).

Materials and methods. A retrospective study of medical records was carried out. Patients with HC following AHSCT treated from 2017 to 2021 were divided into two groups according to severity –mild and severe. Demographic data, disease-specific characteristics, urological sequelae, and overall mortality were compared between both groups. The hospital's protocol was used for patient management.

Results. 33 episodes of HC were collected in 27 patients, 72.7% of whom were male. HC incidence following AHSCT was 23.4% (33/141). 51.5% of HCs were severe (grades III-IV). Severe graft host disease (GHD) (grades III-IV) and thrombopenia at HC onset were associated with severe HC (p= 0.043 and p= 0.039, respectively). This group had longer hematuria times (p< 0.001) and required more platelet transfusions (p= 0.003). In addition, 70.6% required bladder catheterization, but only 1 case needed percutaneous cystostomy. None of the patients with mild HC required catheterization. No differences were found in terms of urological sequelae or overall mortality.

Conclusions. Severe HC could be predicted thanks to the presence of severe GHD or thrombopenia at HC onset. Severe HC can be managed with bladder catheterization in most of these patients. A standardized protocol may help reduce the need for invasive procedures in patients with mild HC.

KEY WORDS: Cystitis; Allogeneic hematopoietic stem cell transplantation; Child.

CISTITIS HEMORRÁGICA TRAS TRASPLANTE ALOGÉNICO DE PROGENITORES HEMATOPOYÉTICOS: EXPERIENCIA EN UN CENTRO ONCOLÓGICO PEDIÁTRICO

RESUMEN

Objetivos. Analizar factores de riesgo asociados a la gravedad de la cistitis hemorrágica (CH) y estrategias de tratamiento en pacientes con CH tras trasplante alogénico de progenitores hematopoyéticos (TAPH).

Material y métodos. Estudio retrospectivo de historias clínicas. Los pacientes con CH tras TAPH tratados entre 2017 y 2021 se dividieron en dos grupos según la gravedad del cuadro (leve y grave). Se compararon datos demográficos, características específicas de la enfermedad, secuelas urológicas y mortalidad global entre ambos grupos. Se utilizó el protocolo del hospital para el manejo de los pacientes.

Resultados. Se recogieron 33 episodios de CH en 27 pacientes, de los cuales el 72,7% fueron varones. La incidencia de CH tras TAPH fue del 23,4% (33/141). El 51,5% de las CH fueron graves (grados III-IV). La enfermedad de injerto contra huésped (EICH) grave (grados III-IV) y la trombopenia al inicio se asociaron a CH grave (p= 0,043 y p= 0,039, respectivamente). Este grupo tuvo mayor tiempo de hematuria (p< 0,001) y necesitó más transfusiones de plaquetas (p= 0,003). Además, el 70,6% precisó sondaje vesical, pero solo un caso cistostomía percutánea. Ningún paciente con CH leve precisó sondaje. No hubo diferencias en las secuelas urológicas ni en la mortalidad global.

Conclusiones. Una CH más grave podría predecirse por la presencia de EICH grave o trombopenia al inicio del cuadro. La CH grave puede manejarse con sondaje vesical en la mayoría de estos pacientes. Seguir un protocolo estandarizado puede reducir la necesidad de procedimientos invasivos en pacientes con CH leve.

PALABRAS CLAVE: Cistitis hemorrágica; Trasplante alogénico progenitores hematopoyéticos; Infancia.

INTRODUCTION

Hemorrhagic cystitis (HC) is characterized by diffuse bladder bleeding due to the alteration of the tissue struc-

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ture of the urothelium and the blood vessels. This condition may occur following bladder exposure to various agents –chemotherapy, radiotherapy, infections…– and represents a frequent complication in patients undergoing allogeneic hematopoietic stem cell transplantation (AHSCT), with an incidence of 6-27%[1]. The increase in this type of transplantations, as well as the significant comorbidity associated with this complication in severe cases –need for urinary diversion or occurrence of urological sequelae –, demonstrate that pediatric urologists have a key role in the cross-disciplinary treatment of these patients[2].

According to when HC occurs from transplantation, it can be divided into two groups[3,4]. One is early HC, which occurs before or a few days following transplantation and often resolves spontaneously. It is associated with the use of alkylating agents such as cyclophosphamide (CPM) and ifosfamide (IFM) at high doses, or busulfan in the conditioning phase[3,5-7]. Incidence and severity have decreased in the last decades as a result of shorter, less intense conditioning regimens, the lesser use of CPM and IFM, and the use of sodium 2-mercaptoethane sulfonate (MESNA) for HC prophylaxis during the administration of these alkylating agents[4,8,9]. The other group is late HC, which typically occurs from week 3 following AHSCT. It is more severe, with greater associated comorbidity. Even though etiology has not been so well defined, potential risk factors, such as graft host disease (GHD), polyomavirus BK, adenovirus, or cytomegalovirus infections, and lymphocyte depletion[5-7,10-13], have been described.

Over almost 30 years, more than 650 AHSCTs have been carried out in the Oncological Hematology and Hematopoietic Stem Cell Transplantation Department from our institution. Today, 40-50 AHSCTs are conducting annually. It is a reference institution in Spain, and it has been internationally endorsed (ONT-CAT-JACIE).

The objective of our study was to analyze potential risk factors associated with greater HC severity and the treatment strategies used according to severity in patients presenting with this complication following AHSCT.

MATERIALS AND METHODS

A single-center, observational, descriptive, retrospective study of patients under 18 years of age diagnosed with HC following AHSCT from January 2018 to December 2021 was carried out. HC was defined as the occurrence of voiding signs –dysuria, pollakiuria, vesical tenesmus– associated with hematuria without infection data. According to severity, episodes were categorized as mild or severe using Droller's classification[14]. Patients with positive urinary culture, patients not requiring hospital admission, and patients diagnosed and treated in another institution were excluded. Two HC episodes in a single patient were considered different when the healing period between both was at least one month. Data was collected by reviewing electronic medical records.

Demographic variables such as sex and age at AHSCT, as well as transplantation-related variables such as baseline pathology, graft lymphocyte depletion, conditioning regimen, and presence of acute GHD –along with GHD severity and use of prophylaxis (ciclosporin combined with thymoglobulin or mofetil mycophenolate)–, were collected. Severe acute GHD was defined as grade III or higher GHD according to the European Group for Blood and Marrow Transplantation's classification[15]. HC severity related variables, such as onset time following transplantation, duration, presence of acute renal insufficiency (ARI, with creatinine levels above the normal higher limit and/or glomerular filtration rate < 60 ml/min/1.73 m^2), thrombocytopenia at clinical onset, and need for platelet or blood derivative transfusion, were also collected. The presence of poliomavirus BK, cytomegalovirus, and adenovirus was analyzed through urine PCR.

Ultrasound variables such as blood clots –and their size–, bladder mucosa thickness, and upper urinary tract dilatation were recorded. Therapeutic variables such as need for bladder catheterization (BC), administration of intravesical therapies, and surgical procedures –cystostomy, nephrostomy, or cystoscopy– were also collected.

The specific HC treatment protocol from our institution was used for patient management. General measures included intravenous hyperhydration, diuretics (furosemide), analgesics (metamizole, opioids), and/or anticholinergics. Triple lumen, 16Fr catheters were used for ongoing bladder lavage with saline solution. In younger patients, double lumen, thinner catheters were used, with manual lavage every 8 hours or cystostomy when lavage was not effective. Regarding bladder therapies, intravesical cidofovir was indicated in patients with positive urine PCR for polyomavirus BK or adenovirus.

Urological sequelae were defined as ultrasound disorders –hydronephrosis, bladder mucosa thickening…– persisting after HC healing.

These variables were compared between the mild HC and the severe HC groups. Qualitative variables were expressed as frequencies and percentages, whereas quantitative variables were expressed as medians and interquartile ranges (IQR). The χ^2 test and Fisher's exact test when expected levels were below 5 were used to compare qualitative variables, whereas Mann-Whitney's U test was employed to compare quantitative variables. Statistical significance was established at $p < 0.05$. For statistical analysis, the IBM SPSS software, version 17, was used.

The study was approved by the Niño Jesús Pediatric University Hospital's Drug Research Ethics Committee (C.I.R-0038/22).

Table 1. **HC types according to severity using Droller et al.'s classification.**

Grade		*Droller et al.'s definition*	*Frequency (%)*
Mild	I	Microhematuria	4/33 (12.1%)
	II	Macrohematuria without blood clots	12/33 (36.4%)
Severe	III	Macrohematuria with small blood clots	7/33 (21.1%)
	IV	Large blood clots causing urinary tract obstruction and requiring instruments	10/33 (30.3%)

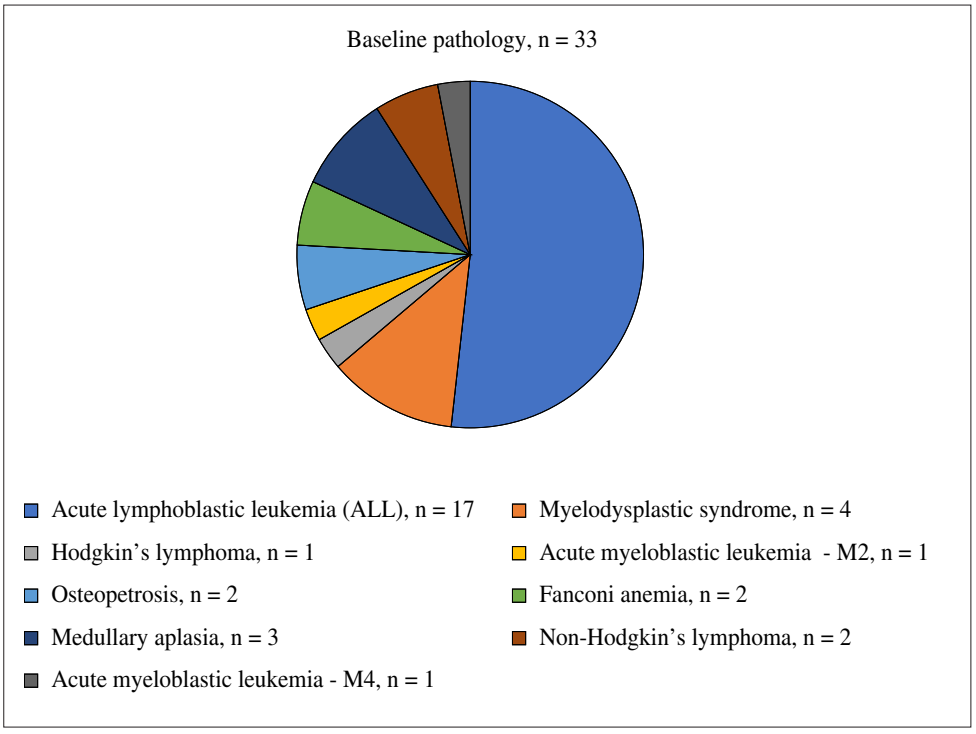

Figure 1. Baseline hemato-oncological pathologies in HC episodes.

RESULTS

A total of 141 AHSCTs were conducted in 125 patients. 33 episodes of HC were recorded in 27 patients who received haploidentical AHSCT in the study period, with an incidence of 23.4%. Of the 33 episodes, 17 were severe HC and 16 were mild HC (Table 1). 72.7% of cases occurred in male patients, with a median age at AHSCT of 12.3 years (IQR: 7.2-15.3). HC onset time from transplantation was 41.5 days (IQR: 16.5-90.25), with episodes having a duration of 8 days (IQR: 3.5-26.5).

Regarding the baseline pathology, all cases were hemato-oncological conditions (Fig. 1), with acute lymphoblastic leukemia (ALL, 17/33) being the most frequent one, followed by myelodysplastic syndrome. All patients received chemotherapy conditioning prior to AHSCT. The most common regimen was combined fludarabine, busulfan, and thiotepa (FBT). In 5 cases, cyclophosphamide was added, with hyperhydration-based HC prophylaxis (3 liters/m^2) and administration of MESNA. 51.5% of HC episodes occurred in patients who had undergone lymphocyte depletion.

Even though all patients received GHD prophylaxis, 18 out of the 33 cases occurred in patients with acute GHD, 66.7% of whom had severe acute GHD. When comparing the mild HC and severe HC groups, no differences were found in terms of sex (p= 0.71), age at AHSCT (p= 0.76), onset time from AHSCT (p= 0.6), baseline pathology (comparing ALL with the other hematological conditions; p= 0.6), conditioning regimen (FBT vs. cyclophosphamide regimens; p= 0.6), lymphocyte depletion (p= 0.39), or presence of acute GHD (p= 0.61).

However, severe HC was associated in a statistically significant fashion with longer durations –25 days (IQR: 10-39.5) in severe HC vs. 3.5 days (IQR: 2.25-5.75) in mild HC (p < 0.0001)– and with the presence of severe acute GHD (p= 0.043) (Table 2).

Even though the presence of concomitant poliomavirus BK infection was greater in the severe HC group (86.7%

Table 2. Transplantation- and HC-related demographic and clinical/analytical variables.

	Total HC n = 33	*Mild HC n = 16 (48.5%)*	*Severe HC n = 17 (51.5%)*	*p*
Demographic				
Male sex, n (%)	24 (72.7)	11 (68.8)	13 (76.5)	0.71
Age at AHSCT, years, median (IQR)	12.3 (7.2-15.3)	12.3 (7-16.5)	12.5 (7.2-15)	0.76
Transplantation-related				
Baseline pathology, n (%)				0.6
ALL, n (%)	17 (51.5)	9 (56.3)	8 (47.1)	
Other conditions	16 (48.5)	7 (43.8)	9 (52.9)	
Conditioning regimen, n (%)				0.65
FBT	28 (84.8)	13 (81.3)	15 (88.2)	
Cyclophosphamide + others	5 (15.1)	3 (43.8)	2 (11.8)	
Lymphocyte depletion, n (%)	17 (51.5)	7 (43.8)	10 (58.8)	0.39
Acute GHD, n (%)	18 (54.5)	8 (50)	10 (58.8)	0.6
Severity of acute GHD, n (%)				**0.04**
Mild acute GHD (grade I - II)	6/18 (33.3)	3/8 (44.4)	1/10 (10)	
Severe acute GHD (grade III or +)	12/18 (66.7)	5/8 (62.5)	9/10 (90)	
HC-related				
HC onset time from AHSCT, days, median (IQR)	41 (16-85)	26 (15-90)	42 (20.5-93)	0.6
HC duration, days, median (IQR)	8 (3.5-26.5)	3.5 (2.2-5.7)	25 (10-39.5)	**0.001**
Polyomavirus BK, n (%)	19/26 (73.1)	6/11 (54.5)	13/15 (86.5)	0.09
Cytomegalovirus, n (%)	3/28 (10.7)	0/13	3/15 (20)	0.2
Adenovirus, n (%)	6/28 (21.4)	1/13 (7.7)	5/15 (33.3)	0.2
ARI during HC, n (%)	11 (33.3)	3 (18.8)	8 (47.1)	0.08
Thrombopenia at HC onset, n (%)	26 (78.8)	10 (62.5)	16 (94.1)	**0.04**
Platelet transfusion, n (%)	19 (57.6)	5 (31.3)	14 (82.4)	**0.003**
Blood derivative transfusion, n (%)	15 (45.5)	5 (31.3)	10 (58.8)	0.1

in severe HC vs. 54.5% in mild HC), no significant differences were found regarding the presence of viral infections. There were no differences either in terms of ARI rate between both groups (p= 0.085).

Thrombocytopenia at HC onset was associated with the development of severe HC (94.1% in severe HC vs. 62.5% in mild HC; p= 0.04). In addition, patients with severe HC required more platelet transfusions than patients with mild HC (82.4% vs. 31.3%; p= 0.003), with no need for further transfusions of other blood derivatives (p= 0.11).

Urinary system ultrasonography was carried out in all severe HC patients and in 11 out of 16 mild HC patients. Median blood clot size was 18 mm (IQR: 11-31). Two mild HC cases had blood clots at ultrasonography. Bladder mucosa thickening was observed in 85.7% of cases, with a median thickness of 8 mm (IQR: 6-10.7). Focal thickening was more frequent than diffuse thickening (15/24), but neither type was associated with more severe HC. Upper urinary tract dilatation was more frequent in severe HC (41.2%) than in mild HC (18%), with no statistical significance (p= 0.25) (Table 3).

All mild HC cases were managed without BC. In severe HC cases, BC was required in 70.6% of the total, with a median BC placement time from HC onset of 9 days (IQR: 0.25-21.5) and a duration of 19.5 days (IQR: 10.75-40). Regarding intravesical therapies, hyaluronic acid was administered in 8 out of the 17 severe HC cases. In three patients with grade IV HC, tranexamic acid was administered to control hematuria. To dissolve blood clots, urokinase was used in 47.1% of severe HC cases. In 64.7% of severe HC cases, intravesical cidofovir was employed.

One patient with significantly large blood clots (Figure 2) required cystostomy as a result of urethro-vesical catheter obstruction. No further surgical procedures were needed (Table 4).

Follow-up time from AHSCT was 12 months (IQR: 5-22). 6 patients had urological sequelae, more frequently in severe HC cases (29.4%), but the difference was not significant (p= 0.17). None of the patients had altered renal function as a result of HC at the end of the follow-up period. Overall mortality was 30%, with no direct association with HC.

Table 3. Ultrasound findings.

	Total 28/33 (84.8%)	*Mild HC n = 16 (48.5%)*	*Severe HC n = 17 (51.5%)*	*p*
Blood clots, n (%)	11 (39.3)	2 (18.2)	9 (52.9)	0.004
Median size, mm (IQR)	18 (11-31)	10.5 (10-11)	18 (15.5-33)	0.09
Bladder mucosa thickening, n (%)	24 (85.7)	9 (81.8)	15 (88.2)	1
Median thickening, mm (IQR)	8 (6-10.7)	6 (5-9)	10 (6-12)	008
Type of thickening				0.68
Focal, n (%)	15 (62.5)	5 (55.6)	10 (66.7)	
Diffuse, n (%)	9 (37.5)	4 (44.4)	5 (33.3)	
Upper urinary tract dilatation, n (%)	9 (32.1)	2 (18.2)	7 (41.2)	0.25

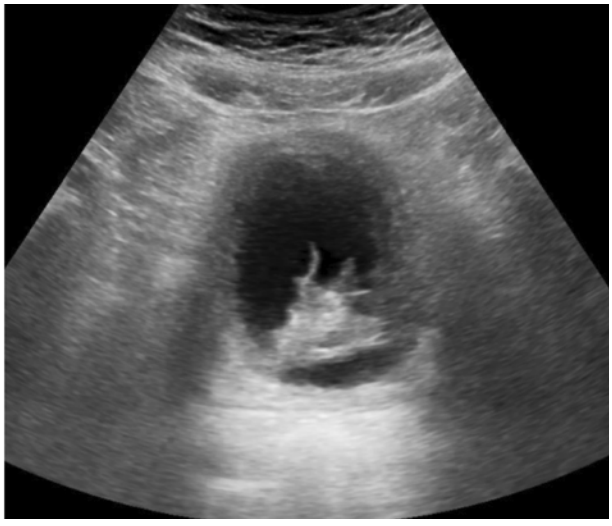

Figure 2. Ultrasound image of a large intravesical blood clot, with 0.7x2.2x4.2 cm diameters (TxAPxCC), causing irreversible urethro-vesical catheter obstruction.

Table 4. Treatments used in the management of severe HC.

	CH grave N = 17 (51.5%)
Bladder catheterization (BC) for ongoing bladder irrigation, n (%)	12 (70.6)
BC onset from HC onset, days, median (IQR)	9 (0.25-21.5)
BC duration, days, median (IQR)	19.5 (10.7-40)
Intravesical therapies	
Hyaluronic acid, n (%)	8 (47.1)
Tranexamic acid, n (%)	3 (17.6)
Urokinase, n (%)	8 (47.1)
Cidofovir, n (%)	11 64.7)
Surgical procedures	
Cystostomy	1 (5.8)
Others	(–)

DISCUSSION

Pediatric patients undergoing AHSCT are subject to multiple complications, with HC being a significant cause of morbidity as a result of its frequency[4,6]. In our study, HC incidence following AHSCT was similar to that reported in the literature[11,16,17]. Even though some studies have related HC incidence and severity with male sex and older ages[2,11,16,18], similarly to ours, other authors have found no differences[3,10]. The lack of association between conditioning type and HC severity can be explained by the use of the same regimen (FBT) in most patients and the routine use of HC prophylaxis when CPM or IFM were added. Lymphocyte depletion in AHSCT reduces the risk of GHD, but it can favor the occurrence of HC-predisposing viral infections[3,19]. Some authors have observed a relationship between lymphocyte depletion and HC occurrence[5], but similarly to our study, no greater severity was found.

Even though many studies have searched for HC-related risk factors, few of them are focused on foreseeing severity. Severe HC represents a therapeutic challenge and often requires longer treatments[18]. In our study, severe HC was associated with longer durations, severe acute GHD, thrombopenia at HC onset, and greater need for platelet transfusion. Acute GHD can affect the bladder mucosa, thus representing a pathogenic factor of HC following AHSCT. This has been supported by recent retrospective studies with large sample sizes, which identify acute GHD as an HC-independent risk factor following a multivariate analysis[7,18,20-22]. In addition, immunosuppressive therapy based GHD treatment may predispose to opportunistic viral infections which, in turn, can favor or worsen HC[6,11]. Therefore, this could mean greater severity of acute GHD leads to more severe HC, but this hypothesis remains controversial[6,16,17].

Although thrombopenia secondary to conditioning has been considered one of the causes of early onset HC –with HC usually being mild and self-limited–, it was associated with severe HC in our study. Both thrombocytopenia and coagulopathy lead to vulnerability, which could explain why HC is more severe. However, chemotherapy treatment, both acute and chronic GHD, and baseline disease progression could interfere as confusing factors in the need for platelet transfusions. Consequently, it is not prudent to consider it has a linear association with HC severity.

Polyomavirus BK infection has been associated with greater HC severity[23]. In a prospective study, viruria above $1x10^9$ copies/ml was associated with grade II-IV HC[7]. In our study, a trend towards greater polyomavirus BK infection was observed in severe HC.

Regarding ultrasound findings, Zaleska[1] observed a positive clinical and radiological correlation according to episode severity. Severe HC cases had greater risk of sequelae –hydronephrosis, post-inflammatory ureteral stenosis, and fibrosis with reduced bladder capacity– and, secondary to it, altered renal function. Hydronephrosis is usually related to long-lasting and/or severe HC, but it is often self-limited[1,3,24]. Bladder thickening occurs regardless of HC severity, and it typically increases with HC duration[1,24]. In this respect, our study found greater frequency of urological sequelae in severe HC patients, but these differences were probably not significant owing to how little frequent they were. However, no correlation was found between these findings and altered renal function.

This study has certain limitations, including its retrospective nature, a relatively small study population –but significant according to the currant literature–, and the lack of multivariate analysis, which limits statistical power to detect differences between groups and control potential confusion factors.

In conclusion, severe HC can be predicted thanks to the presence of severe acute GHD and thrombopenia at HC onset. Most patients with severe HC can be successfully managed with BC, with ongoing bladder lavage and intravesical therapies, and no surgical procedures required. The use of a specific therapeutic protocol can reduce the need for invasive procedures such as BC in patients with mild HC. Prospective studies with larger sample sizes are required to detect risk factors associated with the occurrence and grade of HC.

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