Hemorrhagic Cystitis in a Cohort of Pediatric Transplantations: Incidence, Treatment, Outcome, and Risk Factors

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A B S T R A C T

Hemorrhagic cystitis (HC) can be a severe complication in hematopoietic stem cell transplantation (HSCT). To identify risk factors and etiology and to improve treatment, a number of factors were analyzed retrospectively in a cohort of 74 consecutive pediatric HSCTs between 2007 and 2009 in a single institution. The 74 transplantations were done in 67 children. Potential risk factors for HC were age, gender, underlying disease, ablative conditioning, graft-versus-host disease prophylaxis, unrelated donor, stem cell source, conditioning regime, acute graft-versus-host disease and cytomegalovirus reactivation.

Fourteen patients developed HC (19%). In all but 4 cases (71%), HC appeared after engraftment. Severity was assessed as grade 1 in 1, grade 2 in 8, and grade 3 in 5 cases. In 79% of the patients with HC, urine samples showed BK virus. This may provide guidance for future prevention policies. In 11 children, treatment included forced hydration, spasmolytics, and bladder irrigation. Three children required cystoscopy, intravesical therapy and/or antiviral therapy. Statistical analysis revealed age over six years to be a risk factor for the development of HC.

We conclude that current conditioning regimens lead to a still considerable incidence of HC in pediatric HSCT, necessitating the evaluation of screening protocols and preventive measures.

INTRODUCTION

Hemorrhagic cystitis (HC) has been reported to be a frequent complication of allogeneic hematopoietic stem cell transplantation in children. In the literature, the incidence is found to vary among different studies between 10% and 70%. This partly depends on the definitions and classification used [1]. Symptoms vary from microscopic to macroscopic hematuria with clots, urinary obstruction, and renal and/or bladder damage. Early-onset HC, occurring before engraftment, is seen as a complication of the conditioning regimen with cyclophosphamide, busulfan and/or etoposide as potential risk factors [1-3]. There is still an ongoing debate about total body irradiation as a risk factor for HC [4-6]. Late-onset HC is associated mainly with BK virus as well as with JC virus, adenovirus, and cytomegalovirus (CMV) virus [3,7-9]. In this study, the influence of donor, recipient, and transplantation-specific variables on hemorrhagic cystitis in a cohort of pediatric transplantations was analyzed.

PATIENTS AND METHODS

Patients

All children in our center who underwent an allogeneic stem cell transplantation between 2007 and 2009 were included in this retrospective analysis. All patients gave informed consent to analyze their clinical data. The informed consent procedure was approved by the ethics committee of the hospital.

The charts of these children were reviewed to identify the characteristics defined in Table 1.

Definitions

The symptoms of HC are classified as follows: grade 1 shows microscopic hematuria; grade 2, macroscopic hematuria; grade 3, macroscopic hematuria with clots, and grade 4, macroscopic hematuria with clots, urinary obstruction, kidney damage, and bladder damage [1-3,7].

There was no screening on microscopic hematuria; all patients showing symptoms were evaluated. *Hemorrhagic cystitis* was defined as microscopic or macroscopic hematuria and dysuria with a negative bacterial culture in the urine and no other hemorrhagic conditions [2]. A patient was considered recovered when complaints disappeared; urine samples were no longer monitored for hematuria. PCR was applied to diagnose possible viruria and/or viremia with BK, adeno and JC viruses.

Engraftment was defined as neutrophil count over $.5 \times 10^9$/L for three consecutive days [9,10]. Graft-versus-host disease (GvHD) classification was according to Glucksberg, and GvHD > grade 1 was evaluated as a potential risk factor.

Statistical Methods

To determine the risk factors for the occurrence of HC, we used a Cox regression analysis for the constant variables; for the transplantation-related factors a logistic regression was used. In this analysis the hazard ratio and the *P* value were calculated. When the *P* value was less than .01, the variable was considered significant.

The constant variables were age, gender, underlying disease, Fanconi adapted conditioning versus ablative conditioning, GvHD prophylaxis, serotherapy, related/unrelated donor, stem cell source and conditioning regime [2,8,9,11,12]. The median age was 6 years. This variable was grouped as 0 to 6 years and > 6 years. The stem cell sources peripheral blood stem cells (PBSC) and bone marrow (BM) were combined as PBSC was only used in three cases. The transplantation-related factors were acute GvHD (> grade 1) and a reactivation of CMV (> 1000 copies) [2,9,11].

Statistical Analysis

Data were analyzed in SPSS 15.0.

RESULTS

Patient and Treatment Characteristics

Sixty-seven children were included in this study. Of those, five children underwent transplantation twice, and

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Table 1
Characteristics and Univariate analysis for Hemorrhagic Cystitis

Variables	HC n = 14	No HC n = 60	Total n = 74	Hazard ratio	95% CI	*P* Value
Age, yr						
0 to 6	3	37	40			
> 6	11	23	34	4.748	1.324 to 17.025	.017
Gender						
Male	10	38	48	1.427	.448 to 4.551	.548
Female	4	22	26			
Underlying disease						
Malignant	10	40	50	1.190	.448 to 4.551	.769
Nonmalignant	4	20	24			
Conditioning						
Ablative	13	53	66	1.717	.225 to 13.130	.602
Nonablative	1	7	8			
GvHD prophylaxis						
CsA	1	30	31			
CsA and MTX	5	18	23	.111	.007 to 1.791	.121
CsA and prednisone	7	11	18	.283	.042 to 3.103	.353
Other*	1	1	2	.360	.033 to 2.436	.250
Serotherapy						
Yes	12	44	56	2.169	.485 to 9.697	.311
No	2	16	18			
Donor						
Related	2	17	19			
Unrelated	12	43	55	2.353	.526 to 10.521	.263
CMV reactivation†						
Yes	3	7	10	2.429	.528 to 11.181	.225
No	11	53	64			
Stem cell source						
Bone marrow +						
PBSCT	7	30	37	1.173	.0684 to 2.012	.562
Cord blood	7	30	37			
Conditioning regimen						
Cy + Bu (Mel)	5 (0)	16(3)	21 (3)			
TBI + VP-16	3	13	16			
Bu + Flu	1	11	12			
Cy + Flu	0	5				
Other‡	5	12	17			
aGvHD§						
Yes	1	13	14	.348	.041 to 2.972	.335
No	13	47	60			

CsA indicates cyclosporine; HC, hemorrhagic cystitis; PBSCT, peripheral blood stem cell transplantation; Cy, cyclophosphamide; Bu, busulfan; CMV, cytomegalovirus; TBI, total body irradiation; MTX, methotrexate; Eto, etoposide; Flu, fludarabine; Mel, melphalan; aGvHD, acute graft-versus-host disease.

* includes methotrexate or tacrolimus and prednisone.

† CMV reactivation defined as viral load > 1000 copies.

‡ includes Cy+Bu+VP-16 or Flu+treosulfan or TBI+VP16+thiotepa or Cy+Bu+Flu or TBI or Flu+thiotepa or Flu+Mel+treosulfan or treosulfan or Flu or Cy+TBI+thiotepa.

§ indicates GvHD > grade 1.

one child underwent transplantation three times, resulting in 74 transplantations. Four children died before day 56 after transplantation [9].

All patients who received cyclophosphamide were prophylactically treated with Mesna (2-Mercaptoethane sulfonate sodium)[13] in a daily dose equal to the cyclophosphamide dose, divided in 6 doses, up to 24 hours past the last cyclophosphamide dose, according to the institutional protocol.

Hyperhydration was also according to institutional protocol with 3 L/m^2/day.

Seven patients with Fanconi anemia had conditioning regimens, adapted to the underlying condition.

According to institutional protocols, IgG levels were checked regularly and i.v. IgG was supplemented in case levels fell below 4 g/L.

Treatment of hemorrhagic cystitis was according to local standard operating procedures, depending on severity [1-3,7]. Treatment consisted of conservative measures, such as forced hydration, spasmolytics, and analgesics. In severe cases (grades 2 and 3 HC), complimentary options were used, such as optimization of the hematological homeostasis, bladder irrigation, cystoscopy, intravesical therapy with pentosanpolysulphate, heparin, granulocyte-macrophage colony stimulating factor (GM-CSF) and intravenous cidofovir [1,7,14,15].

Incidence of Hemorrhagic Cystitis

The incidence of hemorrhagic cystitis was 19% (14 of 74 patients). In total, four patients died before 56 days after transplantation [9]. Two of those patients developed HC. One patient had grade 2 HC and died 22 days after transplantation of respiratory insufficiency and multiple infections during aplasia. There was no recovery from HC. The other patient died 52 days after transplantation of progressive neurological complications, having recovered from HC grade 3.

The median time to HC was 27 days (range, 0 to 76 days) after stem cell transplantation and persisted for a median of 38 days (range, 6 to 18 days). Neutrophil engraftment occurred after a median time of 24 days (range, 15 to 74 days). One patient showed HC symptoms two days before