

## ORIGINAL ARTICLE

# Treatment of post-hematopoietic stem cell transplantation hemorrhagic cystitis with intravesicular sodium hyaluronate

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**Hemorrhagic cystitis (HC) is a well-known complication of HSCT. Its overall incidence has been reported to vary from 7–68%. The spectrum of clinical presentation varies from asymptomatic microhematuria to life-threatening bleeding. Sodium hyaluronate is a glycosaminoglycan present on the bladder mucosa, which serves as an important protective substance against uroepithelial damage. Preparations of this component have been shown to be effective in the treatment of interstitial cystitis. We report our experience in the treatment of post-transplant HC with intravesical instillation of sodium hyaluronate. Five out of the seven patients included in this study achieved complete response, while one patient had only partial response. Sodium hyaluronate administration was not associated with any local or systemic adverse effects. We consider that the results of our study are promising and the efficacy of sodium hyaluronate in the treatment of post-transplant HC should be tested in larger cohorts of patients.**

*Bone Marrow Transplantation* (2006) **38**, 507–511.  
doi:10.1038/sj.bmt.1705474; published online 21 August 2006

**Keywords:** allogeneic bone marrow transplantation; sodium hyaluronate; hemorrhagic cystitis

## Introduction

Hemorrhagic cystitis (HC) is a relatively common and potentially severe complication observed after high-dose chemoradiotherapy, especially in conjunction with hematopoietic stem cell transplantation (HSCT). Differences in definition criteria are in part responsible for the wide range of reported incidence, which depends upon such factors as the conditioning regimen, type of transplant and the presence of acute graft-versus-host disease (GVHD).<sup>1,2</sup>

The spectrum of clinical presentations varies from asymptomatic microhematuria to life-threatening bleeding. Moreover, the formation of blood clots can lead to hydronephrosis and renal failure.<sup>3</sup> Early presentation of HC is mainly caused by direct toxicity of the conditioning regimen to the uroepithelium, while viral reactivation contributes to the pathogenesis of late onset HC.<sup>4,5</sup> Many therapeutic modalities have been tested in the treatment of established HC refractory to supportive measures, but none of them has been proved to be effective to date. Sodium hyaluronate is a glycosaminoglycan present on the bladder mucosa, which serves as an important protective substance against uroepithelial damage. Preparations of this component have been shown to be effective in the treatment of interstitial cystitis<sup>6,7</sup> including post-chemoradiotherapy induced interstitial cystitis.<sup>8</sup>

In this study, we tested the efficacy and safety of sodium hyaluronate in a cohort of seven patients with post-transplant HC.

## Patients and methods

### *Patient characteristics*

All the patients who underwent HSCT between December 2004 and November 2005 at the Department of Bone Marrow Transplantation of Hadassah – Hebrew University Hospital and developed HC grade  $\geq 2$ , were included in this study. All patients or their guardians signed an approved informed consent. Patient characteristics are shown in Table 1. Two of the patients had undergone a previous HSCT, and one of them had a previous episode of HC. Patients transplanted from haploidentical family members received T-cell depleted grafts. Unmanipulated graft and post-transplant anti-GVHD prophylaxis with cyclosporine alone (3 mg/kg/day) was used in all patients transplanted from matched siblings. Patients treated with cyclophosphamide during conditioning received HC prophylaxis, which consisted of: hyperhydration, forced diuresis and mesna. Before transplantation, all patients received, acyclovir (500 mg/m<sup>2</sup>  $\times$  3/day) from days –8 until day +100. Cytomegalovirus (CMV) reactivation (diagnosed by two successive positive PCRs or one positive CMV pp65 antigenemia) were treated with ganciclovir 10 mg/kg/day.

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Received 23 May 2006; revised 11 July 2006; accepted 13 July 2006; published online 21 August 2006

**Table 1** Patients characteristics

Patient	UPN	Age	Sex	Disease	Donor	Source of stem cells	Conditioning	ANC engraftment (days)	Platelet engraftment (days)	aGVHD grade	Platelet count at onset ( $10^9/l$ )	Needs for platelet transfusions <sup>a</sup>
1	1992	28	F	CLL	Auto	PBSC	Thio, VP-16, ARA-C, Mel, Cy	39	50	NA	4	72 units
2	1995	16	F	AML	Haplo	BM	TBI, Mel, mabcampath	17	34	2	10	315 units
3	1980	14	M	ALL	MSD	PBSC	Flu, Bu, VP-16, ATG	14	13	4	98	25 units
4	1972	31	M	MDS	MSD	PBSC	Flu, Bu, Thio	19	21	2	329	None
5	2023	13	M	ALL	Haplo	PBSC	Cy, Flu, Bu, VP-16	15	13	1	36	12 units
6	2050	27	M	ALL	Haplo	PBSC	TBI, Cy, Flu, Bu, mabcampath	22	81	No	24	214 units
7	2061	29	F	AML	MSD	PBSC	Flu, TBI, Thio	11	13	1	26	302 units

Abbreviations: MSD = matched sibling donor; TBI = total body irradiation; Mel = melphalan; Cy = cyclophosphamide; Flu = fludarabine; Bu = busulfan; VP-16 = etoposide; Thio = thiotepa; ARA-C = cytarabine; ATG = anti-thymocyte globulin.

<sup>a</sup>Including single donor and random donor platelet units.

### Definitions

HC was defined as the presence of macroscopic hematuria in the absence of other conditions such as gynecological-related bleeding, nephrolithiasis and/or bacterial or fungal infection of the lower urinary tract.<sup>1</sup> HC was classified as early-onset if the symptoms appeared during the first week after transplantation, while HC was characterized as late-onset if the symptoms appeared after the first 7 days. Urine cultures for bacterial and fungal pathogens were obtained from all patients during the episode of hematuria.

Severity of HC was graded according to the following criteria: I: microscopic hematuria. II: macroscopic hematuria. III: macroscopic hematuria with the presence of clots and/or decrease in hemoglobin levels necessitating blood transfusions. IV: life-threatening bleeding, not responding to treatment and necessitating surgical intervention.<sup>9</sup>

Response to treatment was defined as follows: initial response was defined as the day upon amelioration of symptoms appeared; complete response was defined as the day in which disappearance of all symptoms including macroscopic hematuria, dysuria, etc. Disappearance of clots with decrease in blood transfusion requirements but with persistence of macroscopic hematuria was defined as partial response (PR). Any other response was considered as no response.

### HC treatment

All patients who developed hematuria were initially managed with hyperhydration and forced diuresis. When indicated, continuous bladder irrigation with saline was performed for prevention of clotting formation. Irradiated leuko-depleted red blood cell and platelet transfusion were given to maintain the hemoglobin level and platelet count above 8 g/l and  $40 \times 10^9/l$ , respectively.

### Sodium hyaluronate treatment program

Sodium hyaluronate (Cystistat, Bioniche Teo, ON, Canada) was a gift from Medison Pharma Ltd, Israel.

Method of sodium hyaluronate administration: 40 mg of sodium hyaluronate in 50 ml (one container) was slowly instilled into the bladder through a Foley catheter. When all the solution had been instilled the catheter was clamped and the sodium hyaluronate was kept in place for a

minimum of 20 min as performed in interstitial cystitis treatment. In the event of no response 7 days after the first instillation of sodium hyaluronate, a second course of treatment was given. Bladder irrigation (if performed) was usually resumed following drug administration only when urine excretion was decreased due to clot formation.

### Results

#### Incidence of cystitis

Seven out of a total of 123 patients who underwent HSCT at our institution during the study period, developed clinically significant hemorrhagic cystitis and were included in this study. The median time to onset of the HC was 30 days, range (4–66) after transplantation. One patient developed early onset HC (day 4 after HSCT), while six developed late-onset HC (range, 12–66 days after HSCT). All the seven patients developed moderate to severe (grade III) HC. Urine cultures for detection of adenovirus were performed in three patients and were negative in all three of them. Details are shown in Table 2.

#### Treatment before sodium hyaluronate

All the patients were initially treated with hyperhydration, forced diuresis and red cell and platelet transfusion support. Three out of seven patients needed continuous bladder irrigation because of massive clot formation and urine retention. The urine cultures for bacterial or fungus were negative in all the cases. Details are shown in Table 2.

#### Treatment with sodium hyaluronate

Sodium hyaluronate instillation was initiated at a median of 3 days, range (2–7) after development of the symptoms of HC. Three out of seven patients received a second course of treatment because of inadequate response 7 days after the first instillation of sodium hyaluronate. None of the patients developed local or systemic adverse reactions attributable to the treatment.

#### Response to treatment

Four out of seven patients achieved an initial response during the first 7 days after treatment with sodium

**Table 2** Details of HC and response to treatment

Patient	Onset/day	Grade	Previous treatments	Days from onset to treatment	Day of IR	Day of CR
1	Late/12	3	Hyperhydration, blood transfusions, bladder irrigation	5 and 11	12	23
2	Early/4	3	Hyperhydration, blood transfusions, bladder irrigation	7 and 15	23	No
3	Late/62	3	Hyperhydration, blood transfusions	3	5	12
4	Late/62	3	Hyperhydration	2	2	12
5	Late/66	3	Hyperhydration, blood transfusions	4	2	7
6	Late/30	3	Hyperhydration, blood transfusions	3	2	9
7	Late/26	3	Hyperhydration, blood transfusions, bladder irrigation	2 and 9	No	No

Abbreviation: HC = hemorrhagic cystitis.

hyaluronate. Three patients who did not respond received a second course of treatment, and two of them achieved an initial response later. Overall, six out of seven patients achieved an initial response at a median of 3.5 days, range (2–23). Five out of seven patients achieved a complete response at a median of 12 days, range (7–23). One patient who achieved PR on day +23 post-treatment had recurrence of HC. One out of seven patients did not have any response to treatment and died from septic shock and persistent HC 17 days after initiation of treatment. Details are shown in Table 2.

## Discussion

Hemorrhagic cystitis, characterized by the presence of hematuria due to diffuse inflammation of the bladder mucosa, is a well-known complication of HSCT.<sup>4</sup> The overall incidence of HC has been reported with a wide range of 7–68%.<sup>1</sup> The clinical manifestations of this disorder vary from microscopic hematuria to severe hemorrhage with clot formation and urinary tract obstruction, leading to hydronephrosis and acute renal failure. HC may result in prolonged hospitalization after HSCT, and can be associated with severe morbidity and mortality.<sup>3,9</sup> Several factors have been associated with an increased incidence of HC, such as male sex, inclusion of cyclophosphamide and/or busulfan in the conditioning regimen, previous bladder irradiation, allogeneic (vs autologous) SCT, matched unrelated donor transplantation and development of grade II–IV acute GVHD.<sup>2,10,11</sup> Depending on the time of presentation, HC can be divided into early-onset (which occurs mainly during the first week after transplantation) and late-onset. Early-onset HC is usually the result of the uroepithelial damage caused by the conditioning regimen, and in most cases is a transient and self-limiting disorder. High-dose cyclophosphamide is a well-known risk factor associated with the development of HC. It is believed that the uroepithelial damage following cyclophosphamide administration is mainly induced by acrolein which is a metabolic product of cyclophosphamide.<sup>12</sup> In contrast, late-onset HC can be a severe, protracted and potentially life-threatening disorder, and is usually provoked by other triggers, including reactivation of different viruses such as polyoma virus BK, adenovirus, etc.<sup>13,14</sup> However, the exact pathogenetic mechanisms that result in the development of HC remain largely unknown. In a recent review, Leung *et al.*, classified HC in

pre-engraftment and post-engraftment subtypes. They suggested that immune reactions play a significant role in the pathogenesis of post-engraftment BK-associated HC. Initially, the toxicity to the uroepithelium and the immunosuppression caused by the conditioning regimen provide suitable conditions for BK viral replication. Finally, hematopoietic reconstitution leads to immunological reaction against viral antigens expressed on the uroepithelium, causing extensive mucosal damage and hemorrhage.<sup>4</sup>

Even though HC is a frequent and potentially life-threatening complication of HSCT, no effective treatment currently exists. Episodes of mild hematuria are usually treated with fluid administration and forced diuresis. When the course is complicated by the formation of clots, intermittent or continuous bladder irrigation may be required. In cases of severe persistent HC many different treatment modalities have been tested. However, the accumulated experience is based on a limited number of patients.<sup>15</sup> Intravesical 1% alumin irrigation represents an effective and a rather well-tolerated treatment for patients with HC associated with bladder carcinoma and irradiation. However, the available data on the use of alumin for patients with post-transplant HC are limited. Moreover, systemic accumulation of alumin in patients with renal failure may provoke severe neurotoxicity (encephalopathy, dementia, convulsions). Also, it is known that alumin salts can cause severe allergic reactions in susceptible individuals even after topical use.<sup>16,17</sup> Formalin instillation, one of the most effective treatments for severe HC, requires general anesthesia and is associated with important long-term complications including fibrosis of the bladder, urinary incontinence, papillary necrosis, vesicourethral reflux and urinary tract obstruction with hydronephrosis.<sup>18,19</sup> Prostaglandins have been reported to have some beneficial effects when administered intravesically. However, prostaglandin administration has been tested in small groups of patients and may cause severe bladder spasm.<sup>20–22</sup> Intravenous or intravesical administration of cidofovir has been used in cases of adenovirus associated HC. However, the efficacy of this antiviral agent against HC needs to be further investigated.<sup>23,24</sup> Hyperbaric oxygen therapy has been shown to be effective for HC due to chemotherapy and/or radiation therapy, and two cases of life-threatening late-onset HC after allogeneic BMT in children, which resolved after treatment with hyperbaric oxygen have been reported.<sup>25</sup> Surgical interventions such as cystectomy, nephrostomy, ureterostomy are associated with high rates of morbidity and mortality and are indicated for life-

threatening episodes of HC.<sup>26</sup> Vascular embolization is an option for patients with severe refractory HC, who are clinically unstable and are not eligible for more invasive procedures.<sup>27,28</sup>

Sodium hyaluronate (a member of glycosaminoglycans), is a major component of the extracellular matrix of most tissues. High concentration of glucosaminoglycans are present in the uroepithelium, and constitute a protective barrier against irritating agents that can potentially cause damage to epithelium.<sup>29,30</sup> Sodium hyaluronate has been developed to temporarily replenish the deficient glycosaminoglycan layer of the bladder mucosa. It has been used in the treatment of patients with interstitial cystitis with beneficial results.<sup>6</sup> The mechanisms of action of sodium hyaluronate in this setting are not well understood. Sodium hyaluronate has many biological activities, which include inhibition of immune complexes, adherence to polymorphonuclear cells, inhibition of leukocyte migration, regulation of fibroblast and endothelial cell proliferation, enhancement of connective tissue healing, etc.<sup>31</sup> Based on the different mechanisms of action of sodium hyaluronate, and the known efficacy in the setting of interstitial cystitis, we decided to test the efficacy of a similar approach in patients with post-transplant HC.

We consider that the results of our study are promising and the efficacy of sodium hyaluronate in the treatment of post-transplant HC should be further investigated in larger cohorts of patients.

## References

- El-Zimaity M, Saliba R, Chan K, Shahjahan M, Carrasco A, Khorshid O *et al*. Hemorrhagic cystitis after hematopoietic stem cell transplantation: donor type matters. *Blood* 2004; **103**: 4674–4679.
- Cesaro S, Brugiolo A, Faraci M, Uderzo C, Rondelli R, Favre C *et al*. Incidence and treatment of hemorrhagic cystitis in children given hematopoietic stem cell transplantation: a survey from the Italian association of pediatric hematology oncology – bone marrow transplantation group. *Bone Marrow Transplant* 2003; **32**: 925–931.
- Hale GA, Rochester RJ, Heslop HE, Krance RA, Gingrich JR, Benaim E *et al*. Hemorrhagic cystitis after allogeneic bone marrow transplantation in children: clinical characteristics and outcome. *Biol Blood Marrow Transplant* 2003; **9**: 698–705.
- Leung AYH, Yue KY, Kwong YL. Polyoma BK virus and hemorrhagic cystitis in hematopoietic stem cell transplantation: a changing paradigm. *Bone Marrow Transplant* 2005; **36**: 929–937.
- Tsuboi K, Kishi K, Ohmachi K, Yasuda Y, Shimizu T, Inoue H *et al*. Multivariate analysis of risk factors for hemorrhagic cystitis after hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2003; **32**: 903–907.
- Morales A, Emerson L, Nickel JC, Lundie M. Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. *J Urol* 1996; **156**: 45–48.
- Kallestrup EB, Jorgensen SS, Nordling J, Hald T. Treatment of interstitial cystitis with Cystistat: a hyaluronic acid product. *Scand J Urol Nephrol* 2005; **39**: 143–147.
- Diamantopoulos J, Kapsalis Z, Pliotas G, Koliarakis N, Antonadou T, Karagiorgis P. Use of sodium hyaluronate solution in patients suffering from post-radiation cystitis. *Radiother Oncol* 2004; **7** (Suppl 1): S461.
- Brugeries L, Hartmann O, Travagli JP, Benhamou E, Pico JL, Valteau D *et al*. Hemorrhagic cystitis following high dose chemotherapy and bone marrow transplantation in children with malignancies: incidence, clinical course, and outcome. *J Clin Oncol* 1989; **7**: 194–197.
- Seber A, Shu XO, Defor T, Sencer S, Ramsay N. Risk factors for severe hemorrhagic cystitis following BMT. *Bone Marrow Transplant* 1999; **23**: 35–40.
- Asano Y, Kanda Y, Ogana N, Sakata-Yanagimoto M, Nakagawa M, Kawazu M *et al*. Male predominance among Japanese adult patients with late-onset hemorrhagic cystitis after hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2003; **32**: 1175–1179.
- de Vries CR, Freiha FS. Hemorrhagic cystitis: a review. *J Urol* 1990; **143**: 1–9.
- Akiyama H, Kurosu T, Sakashita C, Inoue T, Mori SI, Ohashi K *et al*. Adenovirus is a key pathogen in hemorrhagic cystitis associated with bone marrow transplantation. *Clin Infect Dis* 2001; **32**: 1325–1330.
- Azzi A, Cesaro S, Laszlo D, Zakrzewska K, Ciappi S, De Santis R *et al*. Human polyomavirus BK (BKV) load and hemorrhagic cystitis in bone marrow transplantation patients. *J Clin Virol* 1999; **14**: 79–86.
- Choong SK, Walkden M, Kirby R. The management of intractable haematuria. *Brit J Urol* 2000; **86**: 951–959.
- Kennedy C, Snell ME, Witherow RO. Use of alum to control intractable vesical hemorrhage. *Brit J Urol* 1984; **56**: 673–675.
- Kavoussi LR, Gelstein LD, Andriole GL. Encephalopathy and an elevated serum aluminium level in a patient receiving intravesical alum irrigation for severe urinary hemorrhage. *J Urol* 1986; **136**: 665–667.
- Kumar S, Rosen P, Grabstald H. Intravesical formalin for the control of intractable bladder hemorrhage secondary to cystitis or cancer. *J Urol* 1975; **114**: 540–543.
- Fair WR. Formalin in the treatment of massive bladder hemorrhage. Techniques, results and complications. *Urology* 1974; **3**: 573–576.
- Trigg ME, O'Reilly J, Rumelhart S, Morgan D, Holidia M, de Alarcon P. Prostaglandin E1 bladder instillations to control severe hemorrhagic cystitis. *J Urol* 1990; **143**: 92–94.
- Levine LA, Jarrard DF. Treatment of cyclophosphamide induced hemorrhagic cystitis with intravesical carboprost tromethamine. *J Urol* 1993; **149**: 719–723.
- Ippoliti C, Przepiorka D, Mehra R, Neumann J, Wood J, Claxton D *et al*. Intravesicular carboprost for the treatment of hemorrhagic cystitis after marrow transplantation. *Urology* 1995; **46**: 811–815.
- Nagafuji K, Aoki K, Henzan H, Kato K, Miyamoto T, Eto T *et al*. Cidofovir for treating adenoviral haemorrhagic cystitis in hematopoietic stem cell transplant recipients. *Bone Marrow Transplant* 2004; **34**: 909–914.
- Fanourgiakis P, Georgala A, Vekemans M, Triffet A, De Bruyn JM, Duchateau V *et al*. Intravesical instillation of cidofovir in the treatment of hemorrhagic cystitis caused by adenovirus type 11 in a bone marrow transplant recipient. *Clin Infect Dis* 2005; **40**: 199–201.
- Hattori K, Yabe M, Matsumoto M, Kudo Y, Yasuda Y, Inoue H *et al*. Successful hyperbaric oxygen treatment of life-threatening hemorrhagic cystitis after allogeneic bone marrow transplantation. *Bone Marrow Transplant* 2001; **27**: 1315–1317.
- Garderet L, Bittencourt H, Sebe P, Kaliski A, Claisse JP, Esperou H *et al*. Cystectomy for severe hemorrhagic cystitis in allogeneic stem cell transplant recipients. *Transplantation* 2000; **70**: 1807–1811.
- Gine E, Rovira M, Real I, Burrel M, Montana J, Carreras E *et al*. Successful treatment of severe hemorrhagic cystitis after hematopoietic cell transplantation by selective embolization of

- the vesical arteries. *Bone Marrow Transplant* 2003; **31**: 923–925.
- 28 Paladri F, Bonifazi F, Rossi C, Falcioni S, Arpinati M, Giannini MB *et al*. Successful treatment of severe haemorrhagic cystitis with selective vesical artery embolization. *Bone Marrow Transplant* 2005; **35**: 529–530.
- 29 Hurst RE, Rhodes SW, Adamson PB, Parsons CL, Roy JB. Functional and structural characteristics of the glycosaminoglycans of the bladder luminal surface. *J Urol* 1987; **138**: 433–437.
- 30 Parsons CL. The therapeutic role of sulfated polysaccharides in urinary bladder. *Urol Clin North Am* 1994; **21**: 93–100.
- 31 Goldberg RL, Tole BP. Hyaluronate inhibition of cell proliferation. *Arthritis Rheum* 1987; **30**: 769–778.