Bone Marrow Transplantation (2012) **47**, 1095 – 1098

www.nature.com/bmt

ORIGINAL ARTICLE

Clinical effectiveness of hyperbaric oxygen therapy for BK-virus-associated hemorrhagic cystitis after allogeneic bone marrow transplantation

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Late-onset hemorrhagic cystitis (HC) after allogeneic hematopoietic stem cell transplantation (HSCT) has been associated with BK virus (BKV). Antiviral drugs are of limited efficacy and the optimal treatment for HC has not yet been established. Hyperbaric oxygen (HBO) may benefit these patients. We, therefore, retrospectively evaluated the effectiveness of HBO therapy in 16 patients with HC after allogeneic HSCT. All 16 patients had macroscopic hematuria and BKV infection. Patients received 100% oxygen in a hyperbaric chamber at 2.1 atmospheres for 90 min, 5 days per week, with a median 13 treatments (range, 4–84). Fifteen patients (94%) showed complete resolution of hematuria. Median urinary DNA BKV titers declined after HBO ($P<0.05$). Patients started on HBO earlier after diagnosis of HC responded sooner ($P<0.05$). HBO was generally well tolerated and proved to be a reliable option for this difficult to manage condition.

Bone Marrow Transplantation (2012) **47,** 1095–1098; doi:10.1038/bmt.2011.228; published online 14 November 2011

Keywords: hyperbaric oxygen therapy; BK-virus; hemorrhagic cystitis; allogeneic transplantation

INTRODUCTION

Hemorrhagic cystitis (HC) is a common and major cause of morbidity in patients who undergo allogeneic hematopoietic stem cell transplantation (HSCT).[1] Its incidence ranges from 7 to 52%, and its manifestations range from painless microscopic hematuria to severe bladder hemorrhage, leading to clot formation within the urinary tract and potential obstructive renal failure.[2] Early onset HC, occurring within one week of the conditioning regimen, has become rare owing to hyperhydration, urine alkalization and the frequent use of Mesna, a uroprotective agent that inactivates acrolein, the toxic metabolite of cyclophosphamide.[3] Late-onset HC has been associated with reactivation of viruses, including polyoma BK and JC viruses, adenovirus types I and II, and cytomegalovirus.[4] Other potential risk factors include acute GvHD, use of busulfan or total-body irradiation in preparative regimens and older age.[2]

Many patients with HC can be treated with hyperhydration and platelet transfusions,[5] but those refractory to these treatments may require further measures, including the administration of prostaglandins, alum, formalin, estrogens, epidermal growth factor, and recombinant human granulocyte-macrophage colony-stimulating factor.[6–9] Patients with viral infection may be treated with anti-viral agents, but their efficacy is limited.[8,9]

Hyperbaric oxygen (HBO) may benefit patients with BK virus (BKV) -associated HC after HSCT.[5,10–16] HBO has been shown effective in the treatment of radiation-induced HC,[17–19] by promoting fibroblast proliferation and capillary angiogenesis, decreasing edema and facilitating damaged hypoxic urothelium.[11,20] We describe our experience with HBO in patients with BKV-associated HC following allogeneic HSCT.

PATIENTS AND METHODS

A retrospective search of our records identified 338 patients who underwent allogeneic HSCT at our institution between January 2005 and January 2010. Of these, 16 patients were diagnosed with HC and treated with HBO therapy. Their clinical characteristics, primary indications for HSCT, clinical status, conditioning regimen, sources of allogeneic HSCT and types of GvHD prophylaxis are shown in Table 1.

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.[21] The severity of hematuria was graded according to the common terminology criteria for adverse events.[22] Symptomatic hematuria, requiring a urinary catheter or bladder irrigation and limiting instrumental activities of daily life (ADL), was classified as grade 2. Gross hematuria requiring transfusions, IV medications, hospitalization, and/or elective endoscopic, radiologic or surgical interventions and limiting self-care ADL was defined as grade 3.

BKV was measured in urine as indicated by symptomatology and monitored by serial quantification every 3 days. Urinary tract BK load was measured by quantitative PCR, using a previously described method[23] and expressed as number of copies per milliliter of urine. The viral detection threshold was 500 copies/mL.

HBO therapy was started when patients showed grade 2–3 HC. Response to HBO was defined as macroscopic hematuria disappearance within the first 2 weeks; patients without improvement were categorized as having treatment failure. The primary objective of this study was to access complete response to HBO treatment, defined as the disappearance of all symptoms, including macroscopic hematuria. Secondary objectives included a determination of the correlation between the time from hematuria onset to HBO therapy and the time from therapy to hematuria resolution, determined using standard Pearson correlation.

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Received 11 April 2011; revised 27 September 2011; accepted 13 October 2011; published online 14 November 2011

Table 1. Clinical characteristics of the patients

Patient No.	*Age (years)*	*Sex*	*Diagnosis*	*Clinical status*	*Conditioning regimen*	*Source for Allogeneic HSCT*	*GvHD prophylaxis*
1	34	M	CML	CP2	BuCyATG	PBSC, MUD	C, MTX
2	34	F	Aplastic anemia	P	FluBuCyATG	PBSC, MUD	MMF, T
3	18	M	Aplastic anemia	P	FluCyAlentuzumab	PBSC, MUD	Gluc,T
4	39	F	MDS	CR1	BuCy	PBSC, MRD	C, Gluc, MTX
5	33	F	AML	CR1	BuCy	PBSC, MRD	C, MTX
6	1	F	AML	CR1	BuCyATG	CB, MUD	T
7	39	M	AML	CR1	BuCyATG	PBSC, MUD	Gluc, T
8	28	M	CML	CP2	BuCyATG	PBSC, MUD	T
9	18	M	Aplastic anemia	P	FluCyAlentuzumab	BM, MUD	MTX, T
10	34	F	Fanconi anemia	PR	FluCyAlentuzumab	PBSC, MUD	C, MTX
11	30	F	ALL	CR1	BuCyMelph	PBSC, MRD	C, Gluc
12	28	M	ALL	CR1	BuCyMelph	PBSC, MRD	C, MTX
13	14	F	ALL	CR2	BuCyMelphATG	PBSC, MRD	C, MTX
14	37	F	MPS	CR1	BuCy	PBSC, MRD	C, MTX
15	38	M	AML	CR1	BuCy	BM, MRD	C, MTX
16	56	M	MM	CR2	Melph	PBSC, MRD	C, MMF

Abbreviations: ATG = anti-thymocyte globulin; C = cyclosporine; CB = cord blood; CP = chronic phase; Flu = fludarabine; Gluc = glucocorticoids; MDS = myelodysplastic syndrome; Melph = melphalan; MM = multiple myeloma; MMF = mycophenolate mofetil; MPS = myeloproliferative syndrome; MRD = matched related donor; MUD = matched unrelated donor; P = progression; PR = partial response; T = tacrolimus.

Table 2. Clinical presentations of hemorrhagic cystitis in the 16 patients

Patient No.	*Onset (days post BMT)*	*Hematuria (grade)*	*Ultrasound*	*GvHD (type)*	*GvHD (grade)*	*Viruria*	*Antiviral treatment before HBO*
1	13	3	Bladder wall thickening	Cutaneous	II	BKV+ADV	None
2	17	2	Not performed	Cutaneous	II	BKV+ADV+CMV	Ribavirin
3	49	2	Bladder wall thickening	None	II	BKV+ADV	None
4	75	2	Normal	Cutaneous and Gastrointestinal	II	BKV	Cidofovir
5	18	2	Bladder wall thickening	Cutaneous	II	BKV	None
6	68	3	Inconclusive	Cutaneous	II	BKV+ADV	None
7	25	2	Bladder wall thickening	Cutaneous	II	BKV+ADV	Ribavirin
8	37	3	Bladder wall thickening	Cutaneous	II	BKV	None
9	2	2	Bladder wall thickening	Cutaneous	II	BKV+ADV	Ribavirin
10	21	3	Bladder wall thickening	Cutaneous	III	BKV+ADV+CMV	Cidofovir+ Ribavirin
11	61	3	Normal	Cutaneous	II	BKV	None
12	33	2	Bladder wall thickening	Gastrointestinal	II	BKV	None
13	31	2	Not performed	Cutaneous and Gastrointestinal	II	BKV+ADV	Cidofovir+ Ribavirin
14	55	2	Bladder wall thickening	Cutaneous and Gastrointestinal	II	BKV+CMV	Cidofovir
15	16	2	Bladder wall thickening	Cutaneous	II	BKV	None
16	145	2	Bladder wall thickening	Cutaneous	II	BKV	None

Abbreviations: ADV = adenovirus; BKV = BK virus; MH = macroscopic hematuria.

An independent samples Mann Whitney *U* Test was used to outline the time frame from symptom start to HBO, which made a difference in hematuria resolution. We also compared changes in log BKV load before and after HBO therapy in each patient and for the entire group, as determined by Wilcoxon signed-rank tests.

RESULTS

The median time to onset of HC after HSCT was 32 days (range, 2–145 days). One patient developed early onset HC (2 days after HSCT), whereas the other 15 developed late-onset HC. All 16 patients developed hematuria grade 2 or 3, and 15 developed GvHD, despite prophylactic immunosuppressants. All patients had urinary BKV load above the threshold of detection (500 copies/mL). Eight patients tested positive for adenovirus and 3 for CMV viremia. All 16 were initially treated with hyperhydration, forced diuresis and red cell and/or platelet transfusion. Seven patients received antiviral drugs (ribavirin and/or cidofovir, Table 2), which were not effective, as symptoms, and BK viruria persisted after 7 days of treatment. Onset of hematuria and grade, ultrasound findings, GvHD type and grade, viruria at the time of HC presentation and antiviral treatment before HBO are shown in Table 2.

Patients received 100% oxygen in a hyperbaric chamber at 2.1 atmospheres for 90 min 5 days a week. Fifteen of the 16 (94%) patients achieved a complete response, with hematuria resolution, after a median 13 sessions (range, 4–84 sessions). In addition, there was a strong correlation between the time from hematuria onset to HBO therapy and the time from therapy to hematuria resolution ($r = 0.70$, $P < 0.05$). When patients started HBO at an average of 10 days (standard error of the mean (s.e.m.) = 1) after the diagnosis of cystitis their hematuria resolved in 15 days (s.e.m. = 2) and those who began HBO at an average of 59 days (s.e.m. = 15) responded in 56 days (s.e.m. = 30) ($P < 0.05$). We can therefore conclude that patients who started HBO earlier after the diagnosis of HC responded sooner than those who started HBO later. When we compared the urine BK viral loads before and after HBO (Table 3), we observed significant changes in log BKV load

Table 3. Details of hyperbaric oxygen therapy in the 16 patients

Patient No.	*Period from onset of hematuria to HBO treatment (days)*	*Number of HBO sessions until hematuria resolution*	*Resolution of hematuria after HBO*	*Urine BK viral loads before HBO (copies/mL))*	*Urine BK viral loads after HBO (copies/mL)*	*Complications during HBO*	*Outcome post-BMT (months)*
1	10	11	Yes	$1 \times 10\text{^}3$	$5 \times 10\text{^}8$	Abdominal pain	ANED (33)
2	17	4	Yes	$9 \times 10\text{^}8$	$7 \times 10\text{^}6$	None	Died, bacterial infection (4)
3	11	12	Yes	$9 \times 10\text{^}8$	$5 \times 10\text{^}8$	None	ANED (12)
4	4	15	Yes	$2 \times 10\text{^}9$	$1 \times 10\text{^}7$	None	ANED (28)
5	9	9	Yes	$2 \times 10\text{^}10$	$2 \times 10\text{^}4$	None	ANED (3)
6	30	13	Yes	$7 \times 10\text{^}8$	$2 \times 10\text{^}4$	None	ANED (6)
7	6	10	Yes	$1 \times 10\text{^}9$	$3 \times 10\text{^}4$	None	ANED (21)
8	80	84	Yes	$7 \times 10\text{^}8$	$5 \times 10\text{^}4$	None	ANED (50)
9	11	5	Yes	$5 \times 10\text{^}6$	$1 \times 10\text{^}5$	Ear barotrauma	Died, fungal infection (9)
10	10	5	No	$1 \times 10\text{^}7$	$2 \times 10\text{^}3$	Pressure intolerance	Died, bacterial infection (1)
11	8	24	Yes	$3 \times 10\text{^}6$	$2 \times 10\text{^}5$	None	ANED (31)
12	12	10	Yes	$1 \times 10\text{^}9$	$4 \times 10\text{^}3$	None	ANED (24)
13	9	15	Yes	$5 \times 10\text{^}8$	$1 \times 10\text{^}9$	None	ANED (5)
14	68	28	Yes	$5 \times 10\text{^}8$	$3 \times 10\text{^}4$	None	ANED (50)
15	18	16	Yes	$8 \times 10\text{^}8$	$8 \times 10\text{^}2$	None	ANED (8)
16	7	19	Yes	$6 \times 10\text{^}5$	$7 \times 10\text{^}2$	Claustrophobia	Died, progression (7)

Abbreviation: ANED = alive with no evidence of disease.

after HBO therapy in each individual patient, with the 16 patients showing a mean decrease in log urinary BK load after HBO treatment of -2.1 ($P < 0.05$). Three patients discontinued HBO, one each because of ear barotrauma, pressure intolerance and claustrophobia. One patient interrupted HBO temporarily owing to abdominal pain. Nevertheless, gross hematuria was eliminated in all patients, except for one with Fanconi anemia, who died because of a medical condition unrelated to HBO therapy (Table 3).

DISCUSSION

Hematuria during HC is caused by the diffuse inflammation of the bladder mucosa and is a frequent complication of HSCT.[24] The clinical manifestations of HC range from microscopic hematuria to severe hemorrhage with clot formation and urinary tract obstruction, accompanied by hydronephrosis and acute renal failure.[25] Early-onset HC, which occurs during the first week after transplantation, is usually related to a uroepithelial injury caused by the conditioning regimen and is usually transient and self-limiting. In contrast, late-onset HC can be a dangerous and potentially life-threatening condition, and is frequently associated with reactivation of different viruses such as polyoma, BKV and adenovirus. Moreover, patients with a higher plasma viral load have a poorer clinical course and decreased overall survival.[26,27] Nevertheless, the mechanism underlying the development of HC remains largely unidentified,[28] and its optimal treatment has not yet been established.

HBO is utilized as primary or adjunctive therapy for many medical conditions in which tissue damage is triggered by hypoxic injury. HBO can stimulate fibroblast proliferation, angiogenesis, and wound healing.[20] As this treatment has been used successfully in patients with HC after pelvic radiotherapy,[17-19] it may benefit patients with HC after HSCT.[5,10,11] To date, there have been a few case reports of successful HBO therapy in pediatric[13,15] and adult[12,14,16] patients. HBO showed a cure rate of 78.5% in pediatric patients with BKV-associated HSCT.[10] Similarly, we found that HBO was largely successful in 16 patients, with 15 (94%) showing clinical resolution of hematuria. Moreover, in agreement with previous findings, we observed more rapid responses in patients who started HBO earlier after diagnosis of HC.[19] Furthermore, although we did not measure BK viremia, we found that BK viruria was generally lower after HBO treatment, which may be associated with better outcomes.

None of our patients experienced severe adverse events,[29,30] such as gas emboli, pulmonary edema and seizures. However, three discontinued HBO therapy, although they did not have an absolute contraindication to HBO.[20] One patient experienced ear barotrauma after five sessions of HBO, with discomfort and damage to the ear, probably due to pressure differences between the inside and outside of the eardrum. A second patient discontinued treatment after 19 sessions because of claustrophobia. Both of these patients, however, no longer showed evidence of gross hematuria. Fanconi anemia (FA) has been described as a relative contraindication for HBO therapy, because of a patient who developed a severe capillary leak syndrome.[31] Nonetheless, our FA patient underwent five treatments with HBO, with close monitoring during treatment, interrupting HBO after five sessions owing to pressure intolerance, without resolution of hematuria. After BMT, the patient developed bacteremia, refractory septic shock and multi-organic dysfunction syndrome and died 6 weeks after HSCT.

In summary, we have shown that HBO therapy was generally effective and well tolerated in our patients. Prospective, randomized and well-controlled trials, however, are needed to establish its definitive efficacy and safety.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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