ORIGINAL ARTICLE

Effectiveness of hyperbaric oxygen therapy for virus-associated hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation

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Abstract

Although some studies have suggested the effectiveness of hyperbaric oxygen (HBO) therapy for hemorrhagic cystitis (HC) after allogeneic hematopoietic stem cell transplantation (HSCT), the role of HBO has not been established. We compared the treatment outcomes of 8 patients with viral HC (adenovirus [ADV], $n = 2$; BK virus [BKV], $n = 6$) treated with HBO (HBO[+]) and 8 patients (ADV, $n = 2$; BKV, $n = 6$) treated with conventional therapy (HBO[−]), such as urinary catheterization and intravenous cidofovir. HBO therapy was performed at 2.1 atmospheres for 90 min/day until clinical improvement was achieved. The median number of HBO treatments was 10 (range 8–12). The median duration of HBO treatment was 19.5 days (range 10–23 days). All 8 HBO(+) patients achieved complete remission (CR) at a median of 14.5 days (range 5–25 days). Of the 8 HBO(−) patients, 5 (62.5%) obtained CR and 3 remained symptomatic for 2–6 months. The cumulative incidence of transplant-related mortality at day 100 after allogeneic HSCT was significantly higher in the HBO(−) patients than in the HBO(+) patients (14.2 vs. 0%, $P < 0.05$). No severe HBO-related adverse effects were observed. In conclusion, HBO is a feasible option for treating viral HC after allogeneic HSCT.

Keywords Hyperbaric oxygen therapy · Hemorrhagic cystitis

Introduction

Hemorrhagic cystitis (HC) is a common complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT). HC occurs in 8.6–24% of allo-HSCT recipients and severely impairs their quality of life [1–6]. Early-onset HC, which occurs within 1 week after HSCT, mostly develops due to the regimen-related toxicity, while late-onset HC after engraftment is usually caused by viruses, such as human polyomavirus BK (BKV), polyomavirus JC, adenovirus (ADV), and cytomegalovirus (CMV). A number of retrospective studies have identified various risk factors for HC after allo-HSCT. These included busulfan (BU)-containing conditioning regimens, unrelated donor, the occurrence of graft-versus-host disease (GVHD), and CMV reactivation [6–9].

Supportive therapies, including forced diuresis, hyperhydration, continuous bladder irrigation, and platelet transfusion, have been the standard of care for HC. Several retrospective studies have reported the efficacy of cidofovir

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(CDV) for BKV-associated HC (BKV-HC) and ADV-associated HC (ADV-HC) after allo-HSCT [10–16]. However, its therapeutic efficacy for CDV has not been comprehensively validated by prospective controlled studies, and the optimal dose remains unclear. In addition, the use of CDV may exacerbate the renal dysfunction that is often associated with HC. The successful intravesical instillation of CDV has been reported, but their clinical efficacy is limited [17].

Hyperbaric oxygen (HBO) therapy is commonly used for the treatment of arterial gas embolism, poorly healing diabetic wounds, osteomyelitis, radiation tissue injury, and carbon monoxide poisoning, and is known to be safe, non-invasive, and cost-effective. HBO has also been shown to ameliorate radiation-induced HC by promoting fibroblast proliferation and capillary angiogenesis, decreasing edema, and facilitating regeneration of the damaged hypoxic urothelium [18, 19]. Recent studies indicated the clinical effectiveness of HBO therapy for BKV-HC after allo-HSCT [20–23]. Savva-Bordalo et al. presented 16 patients with HC after allo-HSCT who underwent HBO therapy, and who showed a high response rate (94%). However, few studies have compared the clinical effectiveness of HBO therapy with that of conventional therapy in the treatment of HC after allo-HSCT. In the present study, we analyzed the efficacy and safety of HBO therapy in comparison to conventional therapy for patients with post-HSCT viral HC who were managed in our institution.

Patients and methods

Patients

Among the patients who underwent allo-HSCT at our institution between May 2007 and August 2017, 22 patients developed virus-associated HC and 16 patients without grade II–IV acute GVHD (aGVHD) were included in the study. Their medical records were retrospectively analyzed. Eight of the 16 patients (50%) were treated with HBO therapy [HBO(+)], while 8 patients (50%) who received conventional therapies, such as intravenous hydration with forced diuresis, urinary catheter, and intravenous CDV [HBO(−)]. The selected treatments for viral HC were based on the judgment of each individual physician. The clinical characteristics of the patients, including the original diseases, clinical statuses, conditioning regimens, sources of allo-HSCT, and GVHD prophylaxis regimens are shown in Table 1. The median age of the HBO(+) patients was 51.5 years (range 32–64 years). Antithymocyte globulin (ATG) was administered to 2 (UPNs 3 and 15) of 16 cases as prophylaxis against GVHD. Four (UPNs 3–6) of 8 HBO(+) cases were grafted with peripheral blood stem cells (PBSCs) from an HLA-mismatched donor; three (UPNs 4–6) received PBSCs from

HLA-haploidentical donors using post-transplant high-dose cyclophosphamide. The 16 patients received 2–12 (median 12) Gy of total body irradiation. There was no significant difference in the age, original disease, performance status, hematopoietic cell transplant-comorbidity index (HCT-CI), conditioning regimen, or stem cell source between the HBO(+) patients and the HBO(−) patients.

All patients provided their informed consent in accordance with the Declaration of Helsinki. This retrospective analysis was approved by the ethics committee of the Kanazawa University Hospital (No. 2453).

Definitions

Engraftment was defined as a neutrophil count of $> 0.5 \times 10^9$/L for three consecutive days. HC was diagnosed when microscopic (blood in urine grade $\geq 1+$) or macroscopic hematuria accompanied by dysuria, pollakisuria, urinary urgency, and/or the sensation of residual urine, which developed without evidence of bacteriuria [24]. BKV- or ADV-HC was diagnosed when a qualitative PCR assay detected BKV or ADV in the urine of symptomatic patients. The date of onset of HC was defined as the first day on which the patient complained of urinary symptoms. The severity of hematuria was graded according to the criteria for adverse effects [25]. Transplant-related mortality (TRM) was defined as death due to any transplantation-related causes, other than disease relapse.

HBO therapy

HBO therapy was started at 2.1 atmospheres for 90 min per day from the day on which the patient showed grade II–III symptoms of HC, and therapy was continued until the patient achieved clinical improvement, which was defined as complete resolution (CR) or partial resolution (PR) of macroscopic hematuria and urinary symptoms, such as pain on urination. CR of HC was defined as undetectable blood in urine ([−] or [±] for hemoglobin) and the disappearance of dysuria, pollakisuria, urinary urgency, and the sensation of residual urine related to HC.

Statistical analysis

Fisher's exact test was used for the analysis of categorical variables and the Mann–Whitney's U test was used for the analysis of continuous variables. The Wilcoxon signed-rank test was used for paired samples. The probabilities of TRM were estimated based on the cumulative incidence method to compensate for any competing risks, and the groups were then compared using Gray's test. P values of < 0.05 were considered to indicate statistical significance. All statistical analyses were performed using the EZR software package

Table 1 Patient characteristics

UPN	HBO therapy	Age	Sex	Diagnosis	Clinical status	PS	HCT-CI	Conditioning regimen	Stem cell source	HLA disparity	GVHD prophylaxis
1	Yes	53	M	AML	CR1	1	0	CY+TBI 12 Gy	R-BM	Matched	CsA+sMTX
2	Yes	32	F	ALL	CR1	0	0	CY+ETP+TBI 12 Gy	CB	Two locus mismatched	CsA+sMTX
3	Yes	57	F	NHL	CR3	1	2	Flu+Bu+TBI 2 Gy	R-PBSC	One locus mismatched	TAC+sMTX+ATG
4	Yes	50	M	MDS	non CR	0	2	Flu+Bu+TBI 2 Gy	R-PBSC	Haplo	TAC+sMTX+PTCy
5	Yes	64	F	ATL	PR	1	3	Flu+Bu+TBI 2 Gy	R-PBSC	Haplo	TAC+sMTX+PTCy
6	Yes	57	M	ALL	CR1	1	0	Flu+Bu+TBI 2 Gy	R-PBSC	Haplo	TAC+sMTX+PTCy
7	Yes	45	F	ALL	CR2	1	3	CY+ETP+TBI 12 Gy	UR-BM	Matched	TAC+sMTX
8	Yes	33	M	AML	CR2	0	2	CA+CY+TBI 12 Gy	CB	Two locus mismatched	TAC+sMTX
9	No	47	M	NHL	CR1	1	2	Flu+Mel+TBI 4 Gy	UR-BM	Matched	CsA+sMTX
10	No	59	M	ATL	PR	1	2	Flu+Mel+TBI 4 Gy	UR-BM	Matched	CsA+sMTX
11	No	22	M	AML	REL1	1	4	Flu+Mel+TBI 4 Gy	CB	Two locus mismatched	CsA+sMTX
12	No	22	M	ALL	CR1	0	0	CY+ETP+TBI 12 Gy	R-BM	Matched	CsA+sMTX
13	No	44	M	CML	CCyR1	1	1	CA+CY+TBI 12 Gy	CB	Two locus mismatched	CsA+MMF
14	No	31	M	HL	CR1	1	0	CA+CY+TBI 12 Gy	UR-BM	Matched	CsA+sMTX
15	No	50	F	AML	CR2	1	1	CA+CY+TBI 12 Gy	UR-BM	Two locus mismatched	TAC+sMTX+ATG
16	No	31	F	AML	CR	0	0	CA+CY+TBI 12 Gy	CB	One locus mismatched	TAC+sMTX

UPN unique patient number, M male, AML acute myeloid leukemia, Cy cyclophosphamide, ATG antithymocyte globulin, TBI total body irradiation, UR unrelated, BM bone marrow, FK tacrolimus, sMTX short course of methotrexate, CB cord blood, MDS myelodysplastic syndrome, NHL Non-Hodgkin lymphoma, ATL adult T cell leukemia-lymphoma, PS performance status. HCT-CI hematopoietic cell transplant-comorbidity index, Flu fludarabine, ALL acute lymphoblastic leukemia, Mel melphalan, CML chronic myelogenous leukemia, CyCR cytological complete remission, F female, Haplo haploidentical transplant

(Saitama Medical Center, Jichi Medical University, Saitama, Japan). Graphs were generated using GraphPad PRISM 8.0 (GraphPad Software, Inc., La Jolla, CA, USA).

Results

Development of HC

The 16 patients were diagnosed with virus-associated HC at a median 31 days (range 7–764 days) after allo-HSCT (Table 2). The median time to the onset of HC after allo-HSCT in the HBO(+) patients (median 29 days, range 13–764 days) and HBO(−) patients (median 48 days, range 7–630 days) did not differ to a statistically significant extent. Among the 8 HBO(+) patients, 2 (25%, UPNs 1 and 6) had ADV-HC, while the other 6 (75%, UPNs 2, 3, 4, 5, 7 and 8) had BKV-HC. Among the 8 HBO(−) patients, 2 (25%, UPNs 9 and 10) and 6 (75%, UPNs 11–16) had ADV- and BKV-HC, respectively. The severity of HC was comparable between the HBO(+) (7 had grade II and 1 had grade III) and HBO(−) (7 had grade II and 1 had grade IV) patients.

Three (UPNs 4, 8, and 16) of the 16 patients (19%) had grade I acute aGVHD; one of these patients received corticosteroids for the treatment of aGVHD at the onset of virus-associated HC and the patients responded to corticosteroids well. Five of the 16 patients (31%) had been treated with ganciclovir (GCV) and/or foscarnet (PFA) for the treatment of CMV antigenemia at the time of the diagnosis of virus-associated HC.

HBO therapy for virus-associated HC

Table 3 summarizes HBO and conventional therapies, as well as their outcomes. The median number of HBO therapy sessions was 10 (range 8–12) times and the median

Table 2 Clinical characteristics of patients with virus-associated cystitis

UPN	Engraftment	Acute GVHD	Steroid use	Onset of HC (d from SCT)	Hematuria (Grade)	Viruria	Viral infections	Antiviral therapy at HC	CR (day from therapy)
1	d15	–	–	764	II	ADV	–	–	25
2	d20	–	–	24	II	BKV	–	PFA	21
3	d15	–	–	59	II	BKV	CMV antigenemia	PFA	13
4	d17	I	+	38	II	BKV	–	–	13
5	d22	–	–	34	II	BKV	–	–	5
6	d18	–	–	18	II	ADV	CMV antigenemia	GCV	11
7	d17	–	–	13	II	BKV	CMV antigenemia	PFA	22
8	d18	I	–	21	III	BKV	–	–	16
9	d17	–	–	630	II	ADV	–	–	24
10	d17	–	–	21	II	ADV	–	–	17
11	d16	–	–	22	II	BKV	HHV-6	PFA	25
12	d25	–	–	7	II	BKV	–	–	13
13	d19	–	–	68	II	BKV	CMV antigenemia	GCV, PFA	NE
14	d21	–	–	28	IV	BKV	–	Ara-A	NE
15	d17	–	–	96	II	BKV	CMV antigenemia	PFA, DLI, CDV	NE
16	d27	I	–	200	II	BKV	–	–	216

SCT stem cell transplantation, *EBV* Epstein–Barr virus, *CMV* Cytomegalovirus, *GCV* ganciclovir, *PFA* foscarnet, *CDV* cidofovir, *DLI* donor lymphocyte infusion, *CR* complete resolution, *GVHD* graft-versus-host disease, *NE* not evaluable

Table 3 Summary of the treatment of patients with virus-associated cystitis

		HBO+ group (n=8)	HBO− group (n=8)	
Onset of HC		29 (13–764)	48 (7–630)	n.s
Virus	BKV	6 (75%)	6 (75%)	n.s
	ADV	2 (25%)	2 (25%)	n.s
Number of HBO therapy	Median (range)	10 (8–12)	NA	
From therapy to CR	Median (range)	14.5 (5–25)	24 (13–216)	n.s
Response rate		8/8 (100%)	5/8 (62.5%)	n.s

HC hemorrhagic cystitis, *CR* complete resolution, *NA* not applicable, *n.s.* not significant

duration of HBO therapy was 19.5 days (range 10–23 days). The response rate was 100% (8/8) in HBO(+) patients and 62.5% (5/8) in HBO(−) patients. All eight HBO(+) patients achieved a PR in 2–17 (median 6.5) days and a CR in 5–25 (median 14.5) days after the start of HBO therapy. The time from therapy to CR in HBO(+) patients tended to be shorter than that in HBO(−) patients (median 14.5 vs. 24 days), but it was not statistically significant. The urine virus load decreased 2 weeks after the start of HBO therapy in one patient (UPN2), which we previously reported [22].

Of 8 HBO(−) patients, 3 (37.5%, UPNs 13–15) did not achieve a PR or CR and remained symptomatic for 2–6 months.

Safety and tolerability of treatment

There were no severe adverse effects due to HBO therapy in any of the 8 HBO(+) patients. One patient (UPN 4) had unilateral serous otitis media after HBO therapy, which was resolved with tympanostomy. Although an ear pain or discomfort and middle ear barotrauma (MEB) [26] are common adverse effects of HBO, none of the other 7 HBO(+) patients developed these complications.

One (UPN 14) of the HBO(−) patients with BKV-HC was complicated by renal dysfunction due to clot retention in the ureters and eventually died of uremia. None of the 8 HBO(+) patients and none of the other 7 HBO(−) patients developed renal functional impairment during the course of HC.

Transplant outcomes

All 8 HBO(+) patients survived more than 100 days after HSCT. Two HBO(+) patients (UPNs 1 and 5) died of relapse more than 1 years after HSCT, but there was no transplant-related mortality (TRM). Of 4 HBO(−) patients who died 2–17 months after allo-HSCT, 3 (UPNs 13–15) succumbed to TRM, which was associated with infection and organ failure. The other HBO(−) patient (UPN 11) died of relapse more than 1 years after HSCT. The cumulative incidence of TRM at day 100 after allo-HSCT was significantly higher in HBO(−) patients than in HBO(+) patients (14.2 vs. 0%, $P < 0.05$, Fig. 1).

Discussion

This retrospective study revealed several potential benefits of HBO therapy in the treatment of HC after allo-HSCT. HBO therapy produced a higher CR rate (100%) and shortened the time from therapy to CR in comparison to conventional therapies. In addition, the TRM rate at day 100 in HBO(+) patients was lower than that in HBO(−) patients, leading to a higher non-relapse survival rate in HBO(+) patients.

Figure 1 Hosokawa, et al
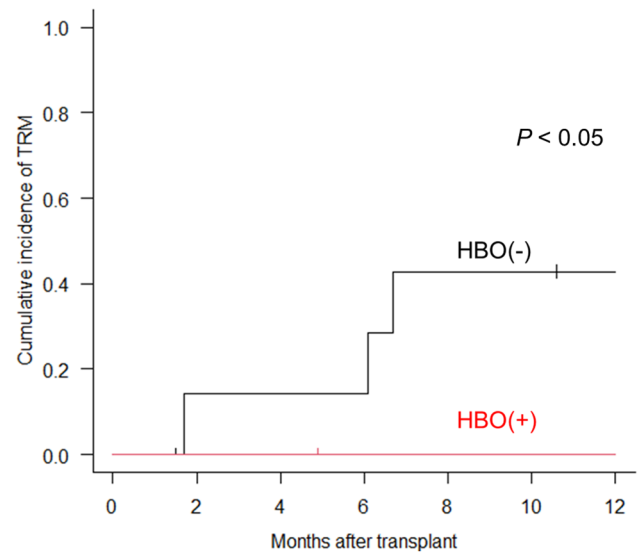
Fig. 1 The cumulative incidence of transplant related mortality in the patients with or without HBO therapy. The cumulative incidence of transplant-related mortality (TRM) in the patients with or without HBO therapy for virus-associated hemorrhagic cystitis after allogeneic HSCT. The cumulative incidence of TRM at day 100 was significantly higher in the HBO(−) patients than in the HBO(+) patients (14.2 vs. 0%, $P < 0.05$)

All eight patients completed HBO therapy without severe adverse effects, with success even in patients receiving corticosteroids for the treatment of aGVHD. HBO therapy is, therefore, thought to be feasible option for the treatment of virus-associated HC after allo-HSCT.

Several studies have demonstrated the effectiveness of HBO therapy for BKV-HC [20–23]. A retrospective study from Portugal showed that 15 (94%) of 16 BKV-HC patients treated with HBO therapy achieved a CR after a median of 17 days (range 4–116 days) [20]. In a pediatric cohort of 10 children with BKV-HC, HBO therapy produced a CR in 9 (90%) patients after a median of 15 days (range 10–37 days) [21]. Another retrospective study reported that all 5 adult patients transplanted from matched unrelated donors responded to HBO therapy and achieved a CR after the mean of 13 sessions (range 11–30 sessions). However, none of these studies directly compared the treatment outcomes between patients who received HBO and conventional therapy at a single institution. We showed that the time from therapy to CR in HBO(+) patients was significantly shorter than that in HBO(−) patients. Although the number of patients was limited, our comparative study provided further evidence that HBO therapy is a promising treatment option for patients with HC after allo-HSCT.

To our knowledge, there are no standard treatment guidelines for post-HSCT HC. Intravenous hydration with forced

diuresis is usually conducted; however, this is a supportive treatment that does not show reliable efficacy. The efficacy of CDV against ADV-HC has been demonstrated by a prospective clinical trial [12]; however, the role of CDV in the treatment of BKV-HC was only investigated in retrospective studies [14, 27, 28]. For example, in a report from the European Group for Blood and Marrow Transplantation (EBMT), intravenous or intravesical CDV was administered to 62 patients with BKV-HC [14], and 41 (66%) achieved CR and 8 (13%) achieved a PR. Notably, of the 57 patients who received intravenous CDV treatment, 17 (30%) experienced renal dysfunction. We did not use CDV for the treatment of our patients with HC, with the exception of one patient (UPN15) with severe acute respiratory distress syndrome caused by pneumonia, because CDV has not received approval in Japan. Given the nephrotoxicity of intravenous CDV and the safety profile of HBO therapy, it may be a reasonable approach to start treatment with HBO in the early course of HC, particularly for patients with renal dysfunction.

HBO has been utilized as primary or adjunctive therapy for several medical conditions where tissue damage is triggered by hypoxic injury, due to its stimulatory effects on fibroblast proliferation, angiogenesis, and wound healing [29]. Although the precise pathogenesis of virus-associated HC remains unclear, virus-infected urothelial cells may be associated with the denudation of the damaged mucosa in patients with HC [30]. HBO therapy may protect urothelial cells by stimulating fibroblast proliferation, angiogenesis, and wound healing.

The present study was associated with some limitations. The study population was relatively small and the patients were treated at a single center; thus, there may be some bias in relation to the treatment outcomes. Although the urine BKV load markedly decreased 2 weeks after the start of HBO therapy in UPN2, we could not monitor the change of the viral load in the other 15 patients. The impact of HBO therapy on HC needs to be determined in a prospective study where the viral load is sequentially followed in every sample.

In conclusion, our comparative study provided further evidence that HBO is a feasible option for the treatment of viral HC after allogeneic HSCT.

Declarations

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