Annals of Hematology & Oncology

Open Access

Austin Publishing Group

Case Report

Hyperbaric Oxygen Therapy for Refractory Hemorrhagic Cystitis after Allogeneic Hematopoietic Stem Cell Transplantation

Bento L[1,2*#], Ruiz S[1,2#], Gutiérrez A[1,2], Batle JM[3], Brugarolas X[4], Novo A[1,2], García L[1,2], Besalduch J[1,2] and Sampol A[1,2]

[1]Hematology Department, Son Espases University Hospital, Spain

[2]Instituto de Investigación Sanitaria de Baleares (IdISBa), Spain

[3]Institución MEDISUB, Institut de Recerca Hiperbárica, Clínica Juaneda, Spain

[4]Urology Department, Son Espases University Hospital, Spain

[#]These authors have collaborated equally

***Corresponding author:** Leyre Bento, Hematology Department, Son Espases University Hospital, Ctra. Valldemossa, 79 Planta +1, Módulo I, 07010 Palma, Illes Balears, Spain

Received: June 11, 2019; **Accepted:** July 18, 2019; **Published:** July 25, 2019

Abstract

Four cases of BK virus-associated Hemorrhagic Cystitis (HC) in an allogeneic Hematopoietic Stem Cell Transplant (allo-HSCT) setting are reported, including –for the first time– two patients who underwent haploidentical allo-HSCT. Outcome of conventional management was not satisfactory so a novel therapy with Hyperbaric Oxygen Therapy (HBOT) was used. Patients received a median of 35 sessions of HBOT at 2.2 Atmospheres Absolute (ATA) for 90 minutes, 5 days a week in a hyperbaric chamber. After treatment, hematuria was completely resolved without toxicity with a follow-up of between 7 and 36 months. HBOT should be considered as an option in refractory HC after allo-HSCT, including in haploidentical setting.

Keywords: Hyperbaric oxygen; Hemorrhagic cystitis; Allogeneic hematopoietic stem cell transplantation; BK virus

Introduction

Hemorrhagic Cystitis (HC) is a common cause of morbidity after Hematopoietic Stem Cell Transplant (allo-HSCT). Early bleeding is usually related to toxic effects of drugs, while late occurring cystitis is multifactorial. The main risk factors are: haploidentical or cord blood allo-HSCT, myeloablative conditioning [1,2], older age at transplantation, lymphopenia, acute Graft-Versus-Host Disease (GVHD), thrombocytopenia, the use of immunosuppression such as antithymocyte globulin with doses higher than 8 mg/kg, urinary excretion of Polyomavirus (PV), and a 3 log increase in BK viral load from urine baseline [3]. As the urinary tract is the main site of BK virus (BKV) latency, it is expected to be the first site of reactivation. Transient BKV viremia in urine occurs in all allo-HSCT patients, but only 4-25% of them develop sustained HC. A peak of BKV in urine ≥3 to 6 log correlates with the occurrence of HC [1].

Many treatment options have been proposed, while a standard therapy has yet to be defined. In our center, HBOT is initiated when conventional therapy options have been shown to be unsuccessful. HBOT is a non-invasive method involving the use of 100% oxygen under increased pressure, which penetrates to poorly perfused areas. HBOT reduces inflammation, stimulates neo-angiogenesis, maintains tissue oxygenation, and heals tissue hypoxia and radionecrosis. It also promotes capillary angiogenesis which increases the regeneration of damaged urothelium [4,8].

HBOT is useful in HC produced by pelvic radiotherapy [9] or chemotherapy. Radiotherapy is used for prostate, colon, and cervical cancer, and in other conditions like Wegener´s granulomatosis. The use of cyclophosphamide is harmful to bladder tissue and may also develop HC. Radiation or cyclophosphamide-induced HC is a severe and potentially life-threatening complication. HBOT has also been used to heal several sport trauma lesions involving tendons or joints [10] and for ischemic lesions [11]. With this in mind, we decided to test the use of HBOT in cases of refractory HC in the setting of allo-HSCT.

Case Report

Case 1

A 42-year-old woman received reduced intensity conditioning allo-HSCT from a sibling donor for relapsed Angio immunoblastic T-cell lymphoma. On day 30 of CD34+ boost due to graft failure, the patient developed HC with hematuria, clots, and thrombocytopenia associated with high levels of BKV in urine. The patient was treated with hydration, bladder irrigation, and packed cell transfusions but the hematuria did not subside although the BKV load was progressively lower. Finally, HBOT was initiated [2.2 ATA for 90 minutes, 5 days a week] for a total of 43 sessions. After treatment, clinical and microscopic hematuria was completely resolved. Currently, 3 years from the onset of HC, the patient has not developed any symptoms related to HC and leads a normal life.

Case 2

A 44-year-old man underwent haploidentical myeloablative allo-HSCT from a sibling donor for acute lymphoblastic leukemia. On day 50 the patient developed gross hematuria with a high BKV DNA load. Conservative modalities such as hydration, bladder irrigation, and immunosuppression tapering did not lead to any improvement or reduction in BKV viral load. Moreover, leflunomide, which has been described to have activity in this setting [12], was ineffective. Bladder

Citation: Bento L, Ruiz S, Gutiérrez A, Batle JM, Brugarolas X, Novo A, et al. Hyperbaric Oxygen Therapy for Refractory Hemorrhagic Cystitis after Allogeneic Hematopoietic Stem Cell Transplantation. Ann Hematol Oncol. 2019; 6(8): 1265.

Table 1: Clinical data and course of the patients analyzed treated with HBOT.

Patient number	Age	Sex	Diagnosis	Disease response	Donor	Conditioning	GVHD prophylaxis	HC symptoms	Day of onset after HSCT	Resolution of hematuria after HBOT	Time to resolution of symptoms
1	42	F	NHL	CR	MSD CD34+	CyTym	Tacrolimus	Macroscopic hematuria, clots	30 after CD34+ boost	Yes	40 days
2	44	M	ALL	CR	Haplo	BuFlu	Cy-post + MMF + CsA	Macroscopic hematuria, pain, clots	50	Yes	30 days
3	51	F	AA	Active disease	MSD	FluCyTym	MMF + CsA	Macroscopic hematuria, pain, clots	56	Yes	28 days
4	32	M	AML	CR	Haplo	BuFlu	Cy-post + MMF + CsA	Macroscopic hematuria, pain, clots	50	Yes	16 days

M: Male; F: Female; NHL: Non-Hodgkin Lymphoma; ALL: Lymphoblastic Acute Leukemia; AA: Aplastic Anemia; AML: Acute Myeloid Leukemia; CR: Complete Remission; MSD: Matched Sibling Donor; Haplo: Haploidentical. CyTym: Cyclophosphamide; Tymoglobuline; BuFlu: Busulfan, Fludarabine; FluCyTym: Fludarabine, Cyclophosphamide, Tymoglobuline; Cy-post: Post-transplantation Cyclophosphamide; MMF: Mycophenolate Mofetil; CsA: Cyclosporine.

artery embolization and endoscopic clot removal were carried out by the Urologist with no response. Finally, the patient was subjected to HBOT (a profile of 2.2 ATA for 90 minutes, 5 days a week) for a total of 41 sessions. After 20 sessions, clinical and microscopic hematuria was resolved. Unfortunately, one year after allo-HSCT, the patient developed severe liver and intestinal GVHD with multi-organ failure and died, albeit with no evidence of HC activity.

Case 3

A 51-year-old woman received allo-HSCT from a sibling donor for aplastic anemia. On day 56 the patient developed HC with hematuria and a high viral load of cytomegalovirus, so ganciclovir was started. The patient was treated with hydration, leflunomide, bladder irrigation, and packed cell transfusions but hematuria did not resolve and BKV was positive in urine samples. Finally, she received HBOT [2.2 ATA for 90 minutes, 5 days a week] for a total of 30 sessions. After treatment, clinical and microscopic hematuria was completely resolved. Eight months after the onset of HC, the patient is asymptomatic and is being monitored as an outpatient.

Case 4

A 32-year-old man underwent haploidentical myeloablative allo-HSCT from a sibling donor for acute myeloblastic leukemia. On day 50 the patient developed gross hematuria with a high BKV DNA load. Conservative modalities such as hydration, bladder irrigation, leflunomide, and immunosuppression tapering led to no improvement although the BKV load was progressively lower. Finally, he received HBOT [2.2 ATA for 90 minutes, 5 days a week] for a total of 25 sessions. After 12 sessions, clinical and microscopic hematuria was resolved. Seven months from the onset of HC, the patient is asymptomatic and is being monitored as an outpatient.

In all cases, complete remission of hematuria and concomitant symptoms was obtained. The treatment was well tolerated with no complications, and there were no relapses reported during the follow-up periods.

Discussion

HC is a diffuse inflammation of the bladder related to an infectious or non-infectious complication causing bleeding of the bladder mucosa [5]. Early onset of HC occurs in the first week after transplantation, and is usually associated with the conditioning regimen. Late onset of HC is often the result of infection caused by a virus [5,8].

HC is a rare but severe complication of allo-HSCT and the optimal treatment has still not been established [4]. Normally, first-line treatment consists of hydrating the patient, alkalizing the urine, and the use of diuretics [13]. After that, especially in severe thrombocytopenia, intensive platelet support is a good choice to attempt to stop bleeding and heal damaged tissue in order to maintain patient platelet count between 30000 and 50000/μL. If there is no response, another alternative treatment could be bladder irrigation with isotonic saline fluid if there are clots.

There is no direct correlation between viral loads and development of HC, as HC is seen among patients with very low levels of viruria, and the proportion of patients with HC is similar among patients with both lower and higher levels of viral load. Among patients who were BKV positive prior to transplant, no significant difference was detected in the median pre-HSCT BKV load of patients who subsequently bled versus those who did not develop HC [2]. PV is not per se an independent risk factor for HC, however, PV viruria has been found to interact with conditioning intensity and donor type, leading to a high risk of hemorrhage after transplant [2].

For these patients, antiviral therapy such as Cidofovir (CDV) has been used: with a median time of 7 days to first dose delivery after the onset of bladder bleeding; an average dose of 1-5mg/kg; and a median treatment duration of 26 days [1]. 64% of cases presented a complete response and 7.7% a partial response [1,7]. Intravesical instillation of CDV is effective in some patients but has high nephrotoxicity rates despite being used with probenecid prophylaxis.

If HC is still active, third-line treatment with selective bladder artery embolization could be used. It is a very effective treatment with a success rate of over 90% in most cases. As another alternative, the use of mesenchymal cells is under investigation [14]. If the patient is still refractory, the last standard option could be cystectomy.

HBOT has been used as primary or adjuvant therapy for several medical conditions where tissue damage is triggered by hypoxic injury [13], owing to its stimulatory effects on fibroblast proliferation, angiogenesis, and wound healing [4]. HBOT improves local and

regional tissue oxygen supply [9] by increasing local oxygen saturation [5,6]. Moreover, HBOT stimulates phagocytosis, producing growth factors that enhance angiogenesis [6,8,9]; and promotes fibroblast proliferation, decreasing edema. Finally, healthy granulation tissue grows at the local sites [9].

HBOT has been used especially in chronic radiation cystitis but it could be an option for HC in the allo-HSCT setting. Some studies with isolated cases have reported encouraging results in allo-SCT recipients [4,5,8,13,15]. In the present study, HBOT therapy was found to be successful in 4 patients with clinical symptoms (Table 1).

Adverse effects such as visual disturbance, Eustachian tube dysfunction, ear barotrauma [13], and claustrophobia may occur, but are unusual. In our cases, the patients had none of them and HBOT was well tolerated, with no significant side-effects [4,5,9,6,13]. The time between the onset of hematuria and the beginning of HBOT is controversial, although in some studies, patients with a shorter pre-treatment interval between the onset of hematuria and the beginning of HBOT showed significantly better results [13], as was confirmed in our cases.

In conclusion, HBOT is an effective, safe treatment modality for patients with HC in whom conventional modalities of management have failed [9,15], with reported response rates ranging from 76% to 100% in cases related to BKV [7]. Although there are few reports concerning the use of HBOT in HC, we provide further evidence of its efficacy and the first report in the haploidentical HSCT setting. It is a safe, simple therapy with no adverse effects and as such should be considered as an option in refractory patients with HC after allo-HSCT, including in a haploidentical modality.

References

1. Gilis L, Morisset S, Billaud G, Ducastelle-Leprêtre S, Labussière-Wallet H, Nicolini FE, et al. “High burden of BK virus-associated hemorrhagic cystitis in patients undergoing allogeneic hematopoietic stem cell transplantation”. Bone Marrow Transplantation. 2014; 49: 664–670.

2. Silva L, Patah PA, Saliba RM, Szewczyk NA, Gilman L, Neumann J, et al. “Hemorrhagic cystitis after allogeneic hematopoietic stem cell transplants is the complex result of BK virus infection, preparative regimen intensity and donor type”. Haematologica. 2010; 95: 1183–1190, 2010.

3. Leung AYH, Yuen KY, Kwong YL, “Polyoma BK virus and haemorrhagic cystitis in haematopoietic stem cell transplantation: a changing paradigm”. Bone marrow transplantation, 2005; 36: 929–937.

4. Hosokawa K, Yamazaki H, Nakamura T, Yoroidaka T, Imi T, Shima T, Ohata K, et al. “Successful hyperbaric oxygen therapy for refractory BK virus-associated hemorrhagic cystitis after cord blood transplantation”. Transplant Infectious Disease. 2014; 16: 843–846.

5. Urbaniak-Kujda D, Kapelko-Słowik K, Biernat M, Dybko J, Laszkowska M, Kuliczkowski K, “The use of hyperbaric oxygen therapy in the treatment of hemorrhagic cystitis after allogeneic stem cell transplantation from an unrelated donor”. International Journal of Hematology. 2015; 102: 364–367.

6. Tanaka T, Kawashima H, Makino T, Kamikawa S, Kato N, Nakatani T, et al. “Hyperbaric oxygen therapy for interstitial cystitis resistant to conventional treatments”. International Journal of Urology, 2007; 14: 563–565.

7. Focosi D, Maggi F, Pistolesi D, Benedetti E, Papineschi F, Galimberti S, et al. “Hyperbaric oxygen therapy in BKV-associated hemorrhagic cystitis refractory to intravenous and intravesical cidofovir: Case report and review of literature”. Leukemia Research. 2009; 33: 556–560.

8. Zama D, Masetti R, Vendemini F, Di Donato F, Morelli A, Prete A, et al. “Clinical effectiveness of early treatment with hyperbaric oxygen therapy for severe late-onset hemorrhagic cystitis after hematopoietic stem cell transplantation in pediatric patients”. Pediatric Transplantation, 2013; 17: 86–91.

9. Degener S, Pohle A, Strelow H, Mathers MJ, Zumbé J, Roth S, et al. “Long-term experience of hyperbaric oxygen therapy for refractory radio- or chemotherapy-induced haemorrhagic cystitis”. BMC Urology. 2015; 15: 38.

10. Koren L, Ginesin E, Melamed Y, Norman D, Levin D, Peled E, et al, “Hyperbaric oxygen for stage I and II femoral head osteonecrosis”. Orthopedics. 2015; 38: 3.

11. Santema KTB, Stoekenbroek RM, Koelemay MJW, Reekers JA, van Dortmont LMC, Oomen A, et al. “Hyperbaric Oxygen Therapy in the Treatment of Ischemic Lower- Extremity Ulcers in Patients with Diabetes: Results of the DAMO2CLES Multicenter Randomized Clinical Trial”. Diabetes Care. 2018; 41: 112–119.

12. Chen XC, Liu T, Li JJ, He C, Meng WT, Huang R, et al. “Efficacy and safety of leflunomide for the treatment of BK virus-associated hemorrhagic cystitis in allogeneic hematopoietic stem cell transplantation recipients”. Acta haematologica, 2013; 130: 52–56.

13. Savva-Bordalo J, Pinho Vaz C, Sousa M, Branca R, Campilho F, Resende R, et al. “Clinical effectiveness of hyperbaric oxygen therapy for BK-virus-associated hemorrhagic cystitis after allogeneic bone marrow transplantation”. Bone Marrow Transplantation. 2012; 47: 1095–1098.

14. Wang Y, Chen F, Gu B, Chen G, Chang H, Wu D. “Mesenchymal stromal cells as an adjuvant treatment for severe late-onset hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation”. Acta haematologica, 2015; 133: 72–77.

15. Qian L, Shen J, Zhao D, Pan S. “Successful treatment of hemorrhagic cystitis after HLA-mismatched allogeneic hematopoietic stem cell transplantation by hyperbaric oxygen”. Transplantation. 2014; 97: 7.