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Severe cyclophosphamide-induced haemorrhagic cystitis treated with hyperbaric oxygen

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Abstract

Aim Cyclophosphamide-induced haemorrhagic cystitis (CHC) is an uncommon but well-recognised condition caused by a metabolite, acrolein, which is toxic to the urothelium. Based on similarities in the histopathology of radiation- and chemotherapy-induced haemorrhagic cystitis, benefit from hyperbaric oxygen therapy (HBOT) has been proposed. HBOT produces an increased oxygen partial pressure diffusion gradient between the circulation and surrounding tissues, which enhances neutrophil function and fibroblast and macrophage migration into damaged hypoxic soft tissue, promoting collagen formation, fibroblast growth, angiogenesis and white-cell bacterial killing. There are only isolated case reports of HBOT for CHC, in the literature so we reviewed the New Zealand experience with HBOT in CHC.

Method The case records of all patients with CHC referred to the three hyperbaric medicine units in New Zealand between 2000 and 2007 were reviewed retrospectively.

Results Six patients, with life-threatening haemorrhage at the time of referral for HBOT weeks or months after initial presentation with CHC, were identified. Cessation of bleeding occurred in all six patients after 14 to 40 HBOT, without complications. All patients remained clear of haematuria at 11 to 36 months follow-up.

Conclusions We recommend the use of HBOT in the management of intractable cyclophosphamide-induced haemorrhagic cystitis as an effective and low-risk therapy.

Haemorrhagic cystitis is a recognised, common complication of cyclophosphamide chemotherapy that may occasionally be fatal.[1,2] Treatment is often unsatisfactory in severe cases, prompting a search for new therapies (Table 1).[1,2]

Hyperbaric oxygen therapy (HBOT) has been used successfully in the treatment of soft-tissue radiation-induced injuries.[3,4] Since the histological changes in radiation- and chemotherapy-induced cystitis are similar, with diffuse mucosal oedema, telangectasia and submucosal haemorrhage, HBOT has been used in a number of cases of cyclophosphamide-induced haemorrhagic cystitis (CHC) with apparent success.[5–14]

HBOT usually consists of breathing 100% oxygen for 1 to 2 hours at a pressure of 203–243 kPa (2.0–2.4 bar) in a pressure chamber, daily to a total of 20–40 treatments, depending on the nature and severity of the problem being treated and the response of the individual patient.

We reviewed the New Zealand experience with HBOT for CHC.

Table 1. Drugs used for the treatment of severe haemorrhagic cystitis (modified from reference 1)

Intravesical
Alum
Formalin
Carboprost (15-methyl-prostaglandin F2α)
Dinoprost (prostaglandin F2a)
Silver nitrate
Sorbitol
Intravenous
Conjugated oestrogens
Tranexamic acid
Recombined factor VIIa
Other
Neodynium: YAG laser therapy
Hyperbaric oxygen

Method

The case records of all patients with CHC referred to hyperbaric medicine units in New Zealand from January 2000 to December 2007 were reviewed retrospectively. Six patients, with various underlying, often complex pathologies, being treated with cyclophosphamide and presenting with life-threatening CHC, were identified and are reported here. Each patient or a parent provided written consent for data from their medical records to be used anonymously.

Case reports

Case 1—A 15-year-old female suffering from severe proteinuria secondary to grade 5 lupus nephritis (membranous), for which she had been receiving oral cyclophosphamide for 4 months, was admitted with grade 4 haematuria (Table 2) in haemodynamic compromise. Other pathologies included thrombocytopenia and haemolytic anaemia, and a past history of an upper GI bleed and reduced level of consciousness and convulsions, bilateral pulmonary emboli secondary to inadequate anticoagulation and spontaneous bilateral pneumothoracies.

MRI showed multiple brain infarcts and CT-scan of the abdomen revealed bilateral renal vein thrombosis. She was on anticoagulants despite the risk of bleeding with low platelets. She was treated with continuous bladder irrigation and cystoscopy and clot evacuation, but bleeding persisted. Bladder biopsy showed changes consistent with cyclophosphamide toxicity.

Two weeks after the onset of haematuria she was referred for HBOT. Because of her history of pneumothorax, she was considered high risk for pulmonary barotrauma with hyperbaric treatment. Despite this risk and given her life-threatening condition, HBOT was commenced and she received 30 90-minute sessions at 203 kPa in a monoplace chamber uneventfully. Macroscopic haematuria settled after 15 and microscopic after 22 HBOT. Follow-up at a year revealed no further haematuria.

Table 2. Grading of haemorrhagic cystitis

0 = No symptoms of bladder irritability or haemorrhage **1** = microscopic haematuria, urine frequency and dysuria **2** = macroscopic haematuria **3** =macroscopic haematuria with small clots **4** =Massive macroscopic haematuria requiring instrumentation for clot evacuation and/or causing urinary obstruction

Case 2—An 82-year-old male with chronic myeloma had been receiving weekly oral cyclophosphamide 600 mg for 4 months when he developed grade 4 haematuria with clot retention and bladder spasms. Haemoglobin on presentation was 55 g L^{-1} and his coagulation profile was normal. Flexible cystoscopy showed diffuse bladder-wall oedema and haemorrhage consistent with CHC. Despite oral tranexamic acid and bladder irrigation with Alum 1% solution, bleeding continued and he was referred for HBOT several weeks after admission.

During 38 treatments, haematuria ceased 5 weeks after the start of therapy, by which time he had received a total of 35 units of resuspended red cells. Bilateral myringotomies were necessary as he was unable to effectively equalise pressure in the middle ear. The urinary catheter was removed prior to discharge with preservation of reasonable bladder function. He remained well until a short terminal illness 19 months later.

Case 3—A 65-year-old female with Churg-Strauss vasculitis and a worsening peripheral neuritis was on prednisone 40 mg and had been on cyclophosphamide 100 mg daily for about a year. She also had α-1 antitrypsin deficiency. The combined disease processes had resulted in severe emphysema and exercise limitation; she presented with grade 4 CHC requiring transfusion, continuous bladder irrigation and tranexamic acid. Bleeding continued, and she was referred for HBOT from another centre 2 weeks after admission.

She was considered at high risk for pulmonary barotrauma because of her emphysema. Breathing was occasionally laboured at pressure (203 kPa), and during two treatments she was switched to a 50/50 helium/oxygen mix (less dense and, therefore, easier to breathe at pressure) for short periods. Otherwise, treatment was uneventful. After 17 HBOT, her urethral catheter was removed. After 26 HBOT, haematuria was mild and she was discharged back to her referring hospital. She required a total of 18 units resuspended red cells, 12 prior to HBOT. At one-year follow-up she was free of bleeding apart from an episode at 3 months post HBOT associated with a urinary tract infection.

Case 4—A 64-year-old female suffering from systemic lupus erythematosis, cirrhosis and portal hypertension had been on cyclophosphamide for 10 years when haematuria started. She was also on prednisone 10 mg daily. Cyclophosphamide was ceased, but she continued to bleed and 4 months later she presented with grade 4 haematuria and in acute urinary retention, with haemoglobin 58 g L^{-1}. She was started on continuous bladder irrigation, tranexamic acid, transfusions and received two Alum bladder instillations.

Cystoscopy confirmed typical appearances of CHC. Haematuria continued and she was referred for HBOT from another centre. She required a total of 17 units resuspended red cells, 13 prior to HBOT. After 10 HBOT, she underwent laser diathermy, and she continued on HBOT as an outpatient to a total of 28 treatments. She also required drainage of 5 litres of ascites. She remained free of haematuria for 3 months, when it recurred. However, at one-year follow-up she was again free of bleeding and had required no further transfusions after the HBOT course.

Case 5—A 19-year-old male underwent a bone marrow transplant for acute myelocytic leukaemia. Cyclophosphamide was part of the pre-transplant regimen. He had been an inpatient for 4 months when referred to a free-standing hyperbaric facility for HBOT, in severe pain from bladder spasms, requiring morphine PCA via a PIC-line in very large doses per day (he needed 30 mg per 2-hour session at start of HBOT course); almost daily blood and platelet transfusions and had undergone multiple bladder evacuations for clot retention. He received four 2-hour HBOT at 243 kPa in the multiplace chamber but HBOT had to be suspended for 12 days because of a recurrent pneumonia. The remainder of his 30 treatments was at 203 kPa in a monoplace chamber.

He was discharged 1 week after completion of his hyperbaric treatment; urine macroscopically clear. He was placed on a morphine withdrawal programme which he completed successfully over one month. Six months later he was admitted to another hospital with haematuria, but this settled on antibiotics and a further platelet infusion. On follow-up at 11 months post-HBOT, he was fit and well, and in employment.

Case 6—A 40-year-old male with Wegener's granulomatosis had been on pulsed and then oral cyclophosphamide therapy for 10 years. He presented with grade 4 haematuria and underwent cystoscopy for evacuation of clot and bladder irrigation; bladder biopsy showed changes consistent with cyclophosphamide toxicity. Gross haematuria settled; however, he continued to have macroscopic haematuria (grade 2). Three months later, the patient had a further episode of grade-4 CHC requiring hospitalisation.

Despite conservative management, haematuria continued and he was referred for HBOT 3 months after presentation. He underwent 10 60-minute sessions of 100% oxygen at 203 kPa. Gross haematuria settled, but grade 2 CHC persisted. A further 10 HBOT resulted in complete remission of haematuria. There was no recurrence of haematuria, and annual cystoscopy for 3 years has shown no recurrence of CHC.

Discussion

Cyclophosphamide is an oxazaphosphorine alkylate drug, widely used as an anticancer and immunosuppressive agent. Cyclophosphamide is metabolised in the liver and produces acrolein, which is excreted in urine, and is toxic to the urothelium.[15–16] A viral aetiology has also been postulated.[2] In a detailed review article, the reported incidence of CHC is quoted as 2–40% with oral therapy and up to 75% with intravenous use, but there does not appear to be a clear dose-related relationship.[2]

The incidence of life-threatening CHC is estimated to be low, but the associated mortality is high.[2] In one series of 440 patients given low-dose cyclophosphamide

quoted in this review, the incidence was 10%, of whom 10 patients died from CHC.[2,17]

The majority of cases can be managed by adequate hydration and stopping the drug. An antidote, 2-mercaptoethanesulfonate (Mesna), binds and detoxifies acrolein within the urinary collecting system resulting in an inert thioether which is passed innocuously in the urine.[18,19] Prior to HBOT referral, Mesna had not been used in any of these six patients.

Other available therapies in severe CHC (Table 1) are fraught with variable success and toxicity.[1,2] HBOT was used as a non-surgical treatment of last resort in these six patients.

HBOT is a relatively safe, non-invasive therapy. Its efficacy in the treatment of chronic, non-healing wounds has been reported in a large number of studies, but there are relatively few randomised controlled trials.[3,4] Experimental studies have shown hyperbaric oxygen to be effective in CHC.[20–23] The increased oxygen partial pressure diffusion gradient between the circulation and surrounding tissues enhances neutrophil function and macrophage migration into the damaged, hypoxic soft tissues promoting collagen formation, fibroblast growth, angiogenesis and neutrophil bacterial killing.[24–26]

The commonest clinical management problem of HBOT is middle ear and/or sinus barotrauma. This is usually minor and with good management rarely interferes with the HBOT course.[27] About 5% of patients may require myringotomies to facilitate pressurisation (Davis FM, unpublished observations, 2008). Myopia, usually reversible, is a dose-dependent side effect of HBOT.[28]

Oxygen-induced convulsions at pressures of 243 kPa or less are rare, with an incidence of approximately 1:6,000 treatments.[29] Two of our patients were at high risk of pulmonary barotrauma because of pre-existing lung pathology, but completed their HBOT without complications.

To date, there are only isolated case reports of CHC being successfully treated with HBOT.[5–14] All six of our patients received cyclophosphamide as part of a chemotherapy regimen or as conditioning prior to bone marrow transplantation. Conservative treatment had been unsuccessful and referral to a hyperbaric unit was made 2 to 12 weeks after the onset of severe (grade 4, Table 2) haematuria. Complete cessation of bleeding occurred in all six patients after 14 to 40 HBO treatments, without complications related to pressurisation. All the patients were free of haematuria at 11 to 36 months follow-up. Whether HBOT is indicated in less severe cases of CHC remains unknown.

Since severe CHC is a relatively rare presentation in any one centre's experience and responses to various therapies are uncertain, it would be useful to develop a prospective database for these patients. This would certainly be possible where HBOT in Australia and New Zealand is concerned, given the close links between hyperbaric units through the Australian and New Zealand Hyperbaric Medicine Group (a sub-committee of the South Pacific Underwater Medicine Society).

Conclusions

With their underlying pathologies, patients with CHC often present management challenges for HBOT. All six patients we report had failed to respond to conventional non-surgical therapy for grade 4 CHC over weeks or months. They were referred for HBOT as a treatment of last resort, to which they all responded with cessation of haematuria after 14 to 40 treatments. We recommend HBOT in the management of severe chemotherapy-induced haemorrhagic cystitis as an effective and low-risk therapy, even if it means transfer to another centre.

Competing interests: None.

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