Hyperbaric oxygen treatment for haemorrhagic radiation cystitis

R F M Bevers, D J Bakker, K H Kurth

Summary

Radiation-induced severe haemorrhagic cystitis is difficult to treat. Conventional treatments may decrease haematuria but do not affect the radiocystitis itself. Hyperbaric oxygen treatment has been reported to do both.

We report the results of a prospective study of hyperbaric oxygen (20 sessions of 100% oxygen inhalation at 3 bar for 90 min in a multiplace hyperbaric chamber) to 40 patients with biopsy-proven radiation cystitis and severe haematuria. Haematuria disappeared completely or improved in 37 patients after treatment. Mean follow-up was 23·1 months (range 1–74); and the recurrence rate was 0·12/year. There were no adverse effects.

Hyperbaric oxygen treatment should be considered for patients with severe radiation-induced haematuria.

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Introduction

Radiation therapy is used as treatment for several pelvic cancers. Radiation-induced cystitis is a late adverse reaction that can develop after a delay of up to 21 years. Radiation causes a progressive obliterative endarteritis of the small blood vessels, resulting in cellular hypoxia.[1]

Patients with severe haemorrhagic radiation-induced cystitis may need regular blood transfusions. Different local treatments have been advocated, eg, aminocaproic acid; tranexamic acid; corticosteroids; oestrogens; antibiotics; prostaglandins; sodium pentosanpolysulphate; bladder distension; electrocoagulation; laser-coagulation; arterial ligation; embolisation; and intravesical instillation with alum, silver nitrate, phenol or formalin.[2,3] These treatments do not cure the radiation-induced cystitis itself, nor prevent recurrence of severe haematuria. The most successful (formalin and phenol) have serious side-effects and add to the bladder fibrosis brought on by radiation treatment.[2]

Hyperbaric oxygen (HBO) is a relatively new treatment for radiation-induced haemorrhagic cystitis; 56 cases have been reported,[4-9] apart from our experience.[10] It is the only treatment which is thought to reverse the vascular radiation-induced pathophysiology,[2,11] by causing neovascularisation of the bladder wall and so increasing tissue oxygen tension. HBO has potential side effects[12] caused by barometric pressure changes or oxygen toxicity. However, serious complications such as central nervous system toxicity and decompression sickness are rare in the low-pressure, short-duration oxygen inhalation treatments used clinically.[13]

We report results of treatment in 40 patients with radiation-induced severe haematuria.

Academic Medical Center (R F M Bevers MD, K H Kurth PhD), **University of Amsterdam, Departments of Urology and Surgery** (D J Bakker PhD), **Amsterdam, The Netherlands**

Correspondence to: Dr R F M Bevers, AMC University Hospital, Meibergdreef 9, 1105 AZ, Amsterdam ZO, The Netherlands

Materials and methods

From January, 1986, until January, 1994, 40 patients with severe haemorrhagic radiation-induced cystitis were treated with HBO. Inclusion criteria were severe haemorrhagic cystitis due to radiotherapy, not responding to other treatments. Exclusion criteria were tumour recurrence in the bladder at cystoscopy before treatment, concomitant bleeding disorders, and severe pulmonary disease with pulmonary bullae. End points of the study were recurrence of severe haematuria, cystectomy, or death. 33 patients were referred to our centre from other hospitals; 27 were male; mean age was 71·4 years (range 56–86). Patients had received radiotherapy for a pelvic cancer (table 1). Mean interval between radiation-therapy and the development of haematuria was 53·1 months (range 4–253).

Patients had received one or more unsuccessful treatments for haematuria: clot evacuation/electrocoagulation (40), tranexamic acid (12), alum (11), corticosteroids (3), neomycin (1), etoglucide (1), propantheline (1), silver nitrate (1), unspecified (17). Most patients required multiple blood transfusions (mean transfusion need 8·2 units [range 0–36]). A modified classification was used to categorise the severity of haematuria,[14] according to transfusion needs during the 3 months preceding and during hyperbaric oxygen treatment: slight haematuria required no transfusion, moderate haematuria required 1–6 units of blood; and severe haematuria required over 6 units (table 2). Severe haematuria was most often seen in patients who had had radiotherapy for bladder carcinoma. Pretreatment investigations were cystoscopy, intravenous urograms/or ultrasound of the upper urinary tract, chest radiograph, blood examination, exclusion of coagulation disorders, and urine culture.

HBO treatment was 20 sessions of 100% oxygen inhalation at 3-bar pressure for 90 minutes in a multiplace hyperbaric chamber. Treatment was given in daily sessions 5 or 6 times a week. In 4 patients, 40 sessions were given because of persistence of haematuria. Most patients required bladder washouts during the early phase of treatment. Before patients entered the chamber, eustachian-tube function was assessed, and a nasal decongestive spray was given if necessary. When this was insufficient, tympanostomy tubes or a myringotomy were considered. After HBO treatment, patients had a cystoscopy to evaluate the effects. Further follow up was carried out at our centre or by the referring urologist.

Results

Median follow up was 13 months. 11 patients died, after a mean of 23·8 months (range 1–61). Causes of death were: cancer metastasis (4), unrelated causes (3), unknown (4).

Four patients had a cystectomy for small bladder capacity (3) or recurrence of bladder cancer (1). Recurrence of severe macroscopic haematuria occurred in nine patients, leading to cystectomy in four. Figure 1 shows a Kaplan-Meier curve of cumulative freedom from recurrence of severe haematuria; cystectomy or death were censored observations.

Overall recurrence of severe haematuria was 0·12/year. Three groups of patients could be distinguished according to their reaction to HBO: group 1 had no haematuria after treatment for at least 3 months; group 2 had occasionally slight haematuria, and group 3 did not react to treatment.

Cancer type	Patients (no)	Mean radiation dose (Gy)
Bladder	20	63·1
Prostate	10	62·8
Uterus	5	52·3
Cervix	4	66·0*
Ovary	1	NK

*Radiation dose not known in one patient. NK=not known.

Table 1: **Cancer type and radiation dose in patients with haemorrhagic radiocystitis**

Cancer type	Severity of haematuria*			
	Slight	Moderate	Severe	
Bladder	2	7	11	20
Prostate	5	2	3	10
Uterus	1	1	3	5
Cervix	2	2	—	4
Ovary	—	—	1	1
T otal	10	12	18	n=40

*See text.

Table 2: **Cancer type, severity of haemorrhagic cystitis, and transfusion requirements (blood units)**

Group one (30 patients)

Mean follow up was 29·3 months (range 3–74). In this group, three patients had a recurrence of haematuria requiring treatment after a mean period of 13·3 months; haematuria was due to cancer recurrence in two. In three patients cystectomy was done because of small bladder capacity after a mean of 9·0 months. During follow up (mean 27·6 months) 9 patients died without cystectomy.

Group two (seven patients)

Mean follow up was 5·1 months (range 1–13). Severe recurrent haematuria was seen in 4 patients after a mean of 2·3. In one patient, cystectomy was done for cancer recurrence; one patient died from metastases. All patients in group two had recurrence of bladder (6) or prostate (1) cancer. In three patients, recurrence was seen 3 months after HBO. In these patients judgment of bladder pathology at pre-treatment cystoscopy was not possible because of bleeding, oedema, and inflammation. Random biopsy taken before treatment showed radiation-induced cystitis but no cancer. After HBO had cured the radiation cystitis, the previously hidden cancer became apparent (see Discussion).

Group three (three patients)

These patients did not benefit from HBO. They had a mean transfusion need of 25·7 units blood. HBO was stopped, and further treatment carried out in the referring urologists' hospitals: 1 patient had a cystectomy and 2 died due to heart disease.

Comparison of the severity of initial haematuria and haematuria after HBO revealed that failure of treatment

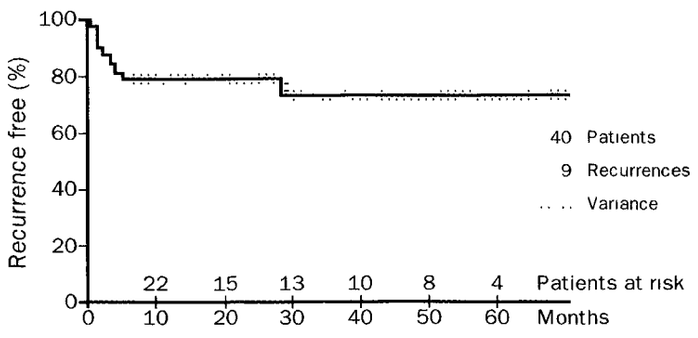

Figure: **Cumulative recurrence-free chance for radiation-induced haemorrhagic cystitis after HBO**

Haematuria* (Initial)	Result of HBO†			
	Good	Moderate	No effect	
Slight	9	1	—	10
Moderate	9	3	—	12
Severe	12	3	3	18
Total	30	7	3	n=40

*See text. †Good=no haematuria; moderate=occasional slight haematuria.

Table 3: **HBO and severity of haemorrhagic cystitis**

Cancer type	Result of HBO*			
	Good	Moderate	No effect	
Bladder	11	6	3	20
Prostate	9	1	—	10
Uterus	5	—	—	5
Cervix	4	—	—	4
Ovary	1	—	—	1
Total	30	7	3	n=40

*Good=no haematuria, moderate=occasional slight haematuria.

Table 4: **Cancer type and results of HBO**

was seen only in patients with a very severe haemorrhagic radiocystitis. However, the majority of patients with severe haematuria improved on HBO (table 3).

Discussion

These results confirm our initial findings[10] that HBO is useful in patients with severe radiation-induced cystitis causing haematuria.

Adverse effects of HBO have been reported[12,13] but were not observed in the present study. The effect of treatment was not influenced by sex, age, or radiation dose. Differences were seen according to the initial type of cancer for which patients were treated (table 4). In group two (7 patients) occasional slight haematuria after treatment was due to cancer recurrence. Cancer was only recognised after HBO when oedema disappeared and normal mucosa was restored in non-cancerous areas of the bladder—HBO may be even more effective if patients with cancer recurrence could be diagnosed with more accuracy before starting treatment.

HBO does not promote cancer growth. Feldmeier et al conclude in a review article that most published reports show no evidence for tumour growth-enhancement by HBO.[14] Until now, HBO has been used only for patients with severe end-stage haemorrhagic radiation cystitis. We treated patients who showed no reaction to conventional therapy. Because the only alternative treatment in such patients is cystectomy, a prospective randomised trial is not possible.

In this study, bladder preservation (in regard to cystectomy for recurrent severe haematuria) was achieved in 36 patients. HBO deserves a position in the treatment of radiation-induced haemorrhagic cystitis and should not be reserved only for severely affected and conventional therapy-resistant patients only.

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Response of steroid-resistant graft-versus-host disease to lymphoblast antibody CBL1

Helen E Heslop, Ely Benaim, Malcolm K Brenner, Robert A Krance, Lisa M Stricklin, Richard J Rochester, Ron Billing

Therapy of steroid-resistant graft-versus-host disease (GVHD) with antibodies to T cells or cytokines is of limited value because GVHD is mediated by a pleomorphic group of effective cells and cytokines. CBL-1, a murine monoclonal antibody, recognises an antigen on activated T cells, B cells, and natural killer cells. We administered CBL-1 to ten patients with grade III or IV steroid-resistant GVHD. Complete remissions occurred in five cases and partial remissions in four. The organ system(s) affected by GVHD was not a predictor of response. CBL-1 was well tolerated and did not exacerbate post-transplant immunodeficiency. Our findings support the use of CBL-1 in primary prophylaxis for GVHD.

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Graft-versus-host disease (GVHD) continues to be a major source of morbidity and mortality in patients undergoing allogeneic bone-marrow transplantation.[1] Whilst improved GVHD prophylaxis lowers the frequency and severity of this complication in recipients of MHC-matched sibling allografts,[1] the increased use of MHC-mismatched or unrelated-donor grafts has allowed GVHD to retain its status as the primary cause of death in allogeneic marrow-transplant recipients. Patients with severe (grade III or IV) GVHD who fail to respond to steroid therapy have an especially poor prognosis. Immunomodulation with antibodies or receptor antagonists intended to inactivate cellular or cytokine components of the immune system[2-5] are the most widely used second-line therapies, but none are satisfactory. Most antibody therapies are directed at T lymphocytes. Whereas these cells initiate GVHD, various additional cellular and cytokine mechanisms contribute to its persistence and progression. Although higher response rates may be seen with agents that interrupt the action of effector molecules, such as interleukin 1 or tumour necrosis factor, GVHD frequently recurs after the agents have been stopped.[4,6] Overall, fewer than 30% of patients with steroid-resistant GVHD have complete or partial responses to available therapy, and 1-year survival remains at 15% or less.[5] CBL-1 is a murine IgM monoclonal antibody directed against a 15 kDa glycolipid antigen of unknown function on activated T cells, natural killer cells, and a subpopulation of monocytes.[7] CBL-1 infusion can reverse rejection of human kidney allografts.[8] Because of the antibody's activity against a spectrum of cells implicated in established GVHD, we have assessed its effect in patients with the severe, steroid-resistant form of the disease.

The study was approved by our institutional review board and all patients gave informed consent. All ten patients (table) received targeted-dose cyclosporin for GVHD prophylaxis. As additional prophylaxis, all marrow from HLA-mismatched family members or from matched unrelated donors was first depleted of T cells.[9] Acute GVHD was graded[1] daily in these patients. Patients on study had grade II or greater GVHD that had persisted or progressed despite 8–42 days' treatment with steroids, including 5 mg/kg methylprednisolone for at least 5 days. CBL-1 was given as a test dose of 0·01 mL/kg (concentration varies with batch). 4 hours later, 0·1 mL/kg (up to a maximum of 1 mL) was infused in 100 mL 5% dextrose and saline intravenously over 1 hour. This dose was repeated for 3 days. CBL-1 was then given on alternate days in halving doses, until 0·025 mL/kg was reached. This lower dose was continued weekly for up to 6 weeks if mild to moderate GVHD persisted.

GVHD completely resolved in five patients and in four others the disease improved by at least two grades, which gives an overall response rate of 90% (table). In all responders, GVHD discernibly improved 2–14 days after the antibody infusion was begun. Remissions were generally well maintained in complete responders, even after the CBL-1 infusion had been discontinued. The only recurrence of acute GVHD in a complete responder developed 4 weeks after cessation of therapy and, unlike the primary condition, was steroid-responsive. One partial responder (case 138) had a recurrence in the gut 2 weeks after CBL-1 was discontinued, which was eventually fatal. The child (case 167) who failed to respond to CBL-1 subsequently responded to anti-thymocyte globulin and is alive with limited chronic skin GVHD at 1173+ days. Of six evaluable patients, four went on to develop chronic disease that was confined to the skin in three cases. The median survival of patients who received CBL-1 was 194 days (range 37–1000+ days), and four patients are still alive.

Whether or not a patient responded to CBL-1 did not appear to depend on the organ systems affected (table), so that even patients with severe involvement of skin, gut, and liver responded. CBL-1 administration was well tolerated. Two patients had fever, chills, muscle pain, and mild hypotension 1–2 hours after their initial dose, but these side-effects were controlled with diphenhydramine and hydrocortisone. No patient developed symptoms or