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TREATMENT OF RADIATION INDUCED HEMORRHAGIC CYSTITIS WITH HYPERBARIC OXYGEN

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ABSTRACT

Purpose: Hemorrhagic cystitis can occur 6 months to 10 years after pelvic radiation therapy with moderate to severe persistent rates of hematuria as 3% to 5% after radiotherapy for pelvic malignancies. Current treatment modalities for hemorrhagic cystitis include oral and intravenous agents, intravesical therapy and selective embolization of the hypogastric arteries. Hyperbaric oxygen therapy is now a widely accepted treatment option for radiation induced hemorrhagic cystitis. We assess the efficacy of hyperbaric oxygen for treatment of hemorrhagic cystitis.

Material and Methods: From May 1988 through March 2001, 62 patients with radiation induced hemorrhagic cystitis were treated with hyperbaric oxygen at our institution. Followup ranged from 10 to 120 months. The primary pathological conditions were prostate cancer (81%) and bladder cancer (10%). Mean patient age was 70 years (range 15 to 88). Mean time between completion of radiation therapy and onset of hematuria was 48 months (range 0 to 355). Patients received an average of 33 hyperbaric oxygen treatments (range 9 to 68).

Results: Of the 62 patients treated information on 57 was available for analysis. Of the 57 patients (86%) 49 experienced complete resolution or marked improvement of hematuria following hyperbaric oxygen treatment. Of the 8 patients who did not improve 4 received fewer than 40 hyperbaric oxygen treatments and 7 prematurely terminated treatment (medical co-morbidities 4, claustrophobia 2, temporary resolution of symptoms 1).

Conclusions: Hyperbaric oxygen therapy for radiation induced hemorrhagic cystitis is an efficacious treatment modality for patients in whom other forms of management have failed.

KEY WORDS: cystitis, radiotherapy, hematuria, hyperbaric oxygenation

Hemorrhagic cystitis can occur 6 months to 10 years after pelvic irradiation. Levenback et al reported on 1,784 patients who received radiotherapy for stage Ib cervical cancer in a 29-year period and hemorrhagic cystitis developed in 6.5%.[1] Other studies have reported the incidence of moderate to severe hematuria in a range of 3% to 5% after radiotherapy for prostate cancer.

The primary treatment modality for hemorrhagic cystitis is bladder irrigation. Oral and intravenous agents such as aminocaproic acid, estrogens and sodium pentosanpolysulfate have been tried with limited success. Intravesical treatments with alum silver nitrate, prostaglandins or formalin are sometimes used if bleeding persists. Finally, selective embolization of the hypogastric arteries, urinary diversion and cystectomy may be performed as necessary in the most severe cases. Recently hyperbaric oxygen has emerged as a potential primary option for the management of this challenging condition. We review our experience treating refractory hemorrhagic cystitis with hyperbaric oxygen.

METHODS

From May 1988 through March 2001, 62 patients with radiation induced hemorrhagic cystitis confirmed by cystoscopy in whom all other attempts at management had failed and who had no evidence of infection or recurrent malignancy as an etiology for hemorrhage were treated with hyperbaric oxygen therapy at our medical center. There were 56 males and 6 females with a mean age of 70 years (range 15 to 88). The primary indications for radiation therapy were prostate cancer (82%) and bladder cancer (10%). Mean time between completion of radiation therapy and the onset of hematuria was 48 months (range 0 to 355). Mean interval between completion of radiation therapy and beginning hyperbaric oxygen treatment was 63 months (range 2 to 360). Followup ranged from 10 to 120 months. Patient characteristics are reported in table 1.

Patients received 100% oxygen in a multiplace hyperbaric chamber at a pressure of 2.4 atmospheres absolute for 90 minutes 5 to 7 days a week for an average of 33 treatments (range 9 to 68). Data were collected from retrospective review of medical records. The present series includes 14 cases previously reported from our institution.[2] The study was approved by the Institutional Review Board of Virginia Mason Medical Center.

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RESULTS

Of the 62 patients in this study outcome data with regard to hematuria were available for 57. Seven patients prema-

TABLE 1. *Patient characteristics*

	No. (range)
Sex:	
Male	56
Female	6
Pts. requiring pre-hyperbaric oxygen blood transfusions	8
Mean blood units/pt. requiring transfusion	4 (1–7)
Mean/median mos. between completion of radiotherapy and symptom onset	48/24 (0–355)
Mean mos. between completion of radiotherapy and beginning hyperbaric oxygen	63 (2–360)
Total mean hyperbaric oxygen treatments	33 (9–68)
Hyperbaric oxygen courses 1/2	50/12

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turely ended the hyperbaric oxygen treatment (medical comorbidities unrelated to hemorrhagic cystitis or hyperbaric oxygen 4, claustrophobia 2, temporary resolution of symptoms 1). In patients who did not complete the planned course of therapy outcome data were not always available. Of the 57 patients with evaluable data 49 (86%) experienced complete resolution or marked improvement of hematuria following hyperbaric oxygen treatment (table 2), which represents a response rate of 81% on an intent-to-treat basis. Of the 57 evaluable patients 8 did not improve, 3 of whom received fewer than 30 hyperbaric oxygen treatments.

All patients underwent cystoscopy before hyperbaric oxygen to exclude etiologies for bleeding other than hemorrhagic cystitis. Of the 62 patients in the series 22 also underwent post-hyperbaric oxygen cystoscopic evaluation to visually assess response to treatment, which revealed objective improvement in bladder mucosa appearance in 17 (77%).

Six patients who previously had noted improvement underwent re-treatment with hyperbaric oxygen for recurrent symptoms, all of whom had cystoscopically confirmed hemorrhagic cystitis a mean of 18 months (range 1 to 72) after completion of the first course of therapy. Of these 6 patients 4 (66%) had durable improvement in hemorrhagic cystitis symptoms. No major complications were observed in the patients undergoing re-treatment.

DISCUSSION

Radiation induced tissue injury is the result of progressive endarteritis leading to hypovascular, hypocellular and hypoxic tissue. The ability to replace normal collagen and cellular loss is compromised, resulting in tissue breakdown. Once irradiated tissue breaks down it is unlikely that healing will occur.[3]

Hyperbaric oxygen therapy has been found to enhance healing in a variety of radiation injured tissues.[4] In an animal model breathing 100% oxygen at normal atmospheric pressure produced no effect on angiogenesis in irradiated tissues.[4] However, hyperbaric oxygen produced an 8 to 9-fold increase in vascular density in irradiated tissues over normobaric oxygen and air-breathing controls. This stimulus for angiogenesis appears to be mediated at least in part through tissue macrophages responding to the steep oxygen gradient achieved in the hyperbaric environment.[5] Followup for as long as 4 years after hyperbaric oxygen therapy has revealed that transcutaneous oxygen measurements remain near normal levels, implying that the angiogenesis is essentially permanent.[6]

To date case series of radiation induced hemorrhagic cystitis treated with hyperbaric oxygen have been reported from a total of 14 institutions in 5 countries.[2,7–19] Except for the study by Bevers et al,[17] the reports are retrospective reviews. Despite the fact that the number of hyperbaric oxygen treatments administered and characteristics of hyperbaric exposure differed among the various reports, 13 of 14 authors concluded that hyperbaric oxygen is effective therapy for intractable radiation induced HC. If the case series reported before our study are combined, 145 of 177 patients (82%) treated with hyperbaric oxygen had improvement or resolution of hematuria, which is remarkably similar to the 81% response rate in the our series, which represents the largest group of patients reported on to date. Combining our patients with those previously reported, the response rate is 82% (184 of 225) from the total world literature.

TABLE 2. *Patient outcomes*

	No. (%)
Hematuria (57 pts.):	
Resolved	21 (34)
Improved	28 (45)
Unchanged	6 (10)
Worsened	2 (3)
Not available	5 (8)
Cystoscopy appearance (22 pts.):	
Improved	17 (77)
Unchanged	5 (23)

It should be noted that in all studies reported hyperbaric oxygen was used after hemorrhagic cystitis had failed to respond to other treatments, sometimes allowing deterioration to a severe state. In the prospective study by Bevers et al all 40 patients received 1 or more unsuccessful treatments before beginning hyperbaric oxygen.[17] The mean transfusion requirement per patient before hyperbaric oxygen was 8.2 units packed red blood cells. Patients were stratified into 3 groups according to the severity of hematuria. All 10 patients with slight hematuria improved with hyperbaric oxygen for a response rate of 100%, although 3 experienced a recurrence of hematuria at a mean of 13 months following hyperbaric oxygen treatment. In 2 of these 3 patients the hematuria was due to recurrence of cancer. All 12 patients with moderate hematuria improved with hyperbaric oxygen for a response rate of 100%, although in 4 bleeding recurred at a mean of 5 months due to recurrent cancers in all cases. Of 18 with severe hematuria 15 improved with hyperbaric oxygen for a response rate of 83%. Overall, 92% of patients responded to hyperbaric oxygen and bladder preservation was achieved in 36 of 40. The response to hyperbaric oxygen was dependent on the severity of the presenting hematuria and recurrent hemorrhage was often due to recurrent malignancy.

Although various authors have demonstrated a positive response of hyperbaric oxygen for the treatment of radiation induced hemorrhagic cystitis, duration of followup has varied. Del Pizzo et al reported on 11 patients treated with 28 to 64 hyperbaric treatments and followed for a mean of 5.1 years.[15] At a mean followup of 2.5 years 73% of patients (8 of 11) were asymptomatic while at 5.1 years 5 of the remaining 8 had recurrent hematuria requiring hospitalization, blood transfusion and ultimately supravesical urinary diversion. Of these 5 patients 2 eventually required embolization and cystectomy. Of the 11 patients 3 (27%) experienced a complete and durable resolution of symptoms at a mean of 5 years. This study highlights the progressive nature of radiation injury. The possibility that repeat hyperbaric treatment might provide additional benefit has not been explored in detail. Investigators at Duke University analyzed all published series and found that 40 hyperbaric treatments was the optimal number for acute resolution of symptoms and a long-term durable result.[20]

While most studies have used symptomatic hematuria as an outcome measure, at least 1 report described cystoscopic findings before and after hyperbaric oxygen treatment. In the study by Lee et al improvement in bleeding symptoms was reported to correlate with findings at cystoscopy.[10] In our study rates of improvement in hematuria and bladder appearance on cystoscopy were also similar at 81% and 77%, respectively.

At a cost of approximately $500 per hyperbaric treatment in the United States, a course of therapy can be expected to cost in the range of $20,000. This cost compares favorably to that of multiple conservative treatments, often including repeat hospitalizations, to control symptoms. Furthermore, these conservative treatments are aimed at controlling bleeding but may leave patients with a contracted bladder, urinary urgency, frequency and incontinence. Overall, hyperbaric oxygen appears to be an efficacious and economical approach to the treatment of radiation induced hemorrhagic cystitis, and it is the only therapy that has been demonstrated to promote healing in this condition. Early use of hyperbaric oxygen treatment should be considered before repeated instillations of chemicals that may leave the bladder fibrotic, contracted and noncompliant.

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