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EARLY HYPERBARIC OXYGEN THERAPY IMPROVES OUTCOME FOR RADIATION-INDUCED HEMORRHAGIC CYSTITIS

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ABSTRACT

Objectives. To assess the clinical factors that affect the efficacy of hyperbaric oxygen (HBO_2) therapy in treating radiation-induced hemorrhagic cystitis. HBO_2 therapy is an effective treatment for radiation-induced hemorrhagic cystitis, with reported response rates ranging from 76% to 100%.

Methods. The data from patients with radiation-induced hemorrhagic cystitis treated at our institution between May 1988 and December 2001 were reviewed retrospectively. All patients received HBO_2 therapy at 2.36 atm absolute pressure, with 90 minutes of 100% oxygen breathing per treatment. The outcome was assessed after at least 12 months of follow-up. We evaluated patient demographics, types of pelvic malignancy and radiotherapy, total radiation dose, onset and severity of hematuria, and prior intravesical management. Clinical improvement was defined as the absence of, or reduction in, macroscopic hematuria.

Results. A total of 60 patients (55 men and 5 women), mean age 70 years, received an average of 33 HBO_2 treatments (range 9 to 63). Of the 60 patients, 48 (80%) had either total or partial resolution of hematuria. When treated within 6 months of hematuria onset, 96% (27 of 28) had complete or partial symptomatic resolution ($P = 0.003$). All 11 patients with previous clot retention had clinical improvement if treated within 6 months of hematuria onset ($P = 0.007$). Prior intravesical chemical instillation did not affect the clinical outcome. Patients who had undergone primary, adjuvant, or salvage external beam pelvic radiotherapy showed response rates of 81%, 83%, and 78%, respectively ($P = 0.950$).

Conclusions. Our results show that delivery of HBO_2 therapy within 6 months of hematuria onset is associated with a greater therapeutic response rate. Treatment efficacy was independent of prior intravesical therapy and the timing of radiotherapy. UROLOGY **65:** 649–653, 2005. © 2005 Elsevier Inc.

Pelvic radiotherapy causes chronic fibrosis and progressive endarteritis in poorly oxygenated bladder submucosal and muscular tissues, with eventual tissue scarring. This can potentially lead to bladder mucosal sloughing and symptomatic hemorrhagic cystitis. Delayed radiation-induced hemorrhagic cystitis (HC) may appear more than 10 years after pelvic radiotherapy.[1,2] The severity of hematuria has been classified,[2] and the Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) scoring criteria are commonly used in clinical trials to describe acute or late radiotherapy-related morbidities (Table I). Significant symptomatic grade 3 or 4 hematuria occurs in 2.1% to 8.2% of patients after external beam pelvic radiotherapy or brachytherapy.[3–7]

Hyperbaric oxygen (HBO_2) improves regional tissue oxygenation in previously irradiated tissue, resulting in neovascularization and capillary growth into hypoxic and scarred submucosal tissue. After HBO_2 therapy, 76% to 100% of reported patients with radiation-induced HC experienced a reduction or complete resolution of hematuria.[1,8–10] In this study, we assessed the clinical factors that may correlate with the effectiveness of HBO_2 in treating radiation-induced HC.

MATERIAL AND METHODS

The data of patients treated with HBO_2 for radiation-induced HC at our institution between May 1988 and December

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TABLE I. *Classification of hematuria events for both acute and late radiation morbidity scoring criteria for radiation-induced hemorrhagic cystitis*

Hematuria Morbidity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acute (RTOG)	NA	NA	Gross hematuria with or without clot passage	Hematuria requiring transfusion	Death from uncontrolled hematuria
Late (RTOG/EORTC)	Minor telangiectasia (microscopic hematuria)	Generalized telangiectasia (macroscopic hematuria)	Severe generalized telangiectasia (frequent macroscopic hematuria)	Severe hemorrhagic cystitis	Death from uncontrolled hematuria

KEY: RTOG = Radiation Therapy Oncology Group; EORTC = European Organization for Research and Treatment of Cancer.
Acute morbidity defined as treatment-related complications occurring within 90 days from first radiotherapy session.

2001 were retrospectively reviewed. All patients had negative urine cultures and underwent pretreatment cystoscopic evaluation to exclude bladder malignancy and to document the presence of radiation cystitis.

Patients received HBO_2 therapy in a multiplace hyperbaric chamber with 90 minutes of 100% oxygen breathing at 2.36 atm absolute pressure per session, including 5-minute air breaks after every 30 minutes of oxygen. An initial course of 40 treatments was planned, one session daily, five times per week. The number of sessions was reduced if a patient developed nonreversible side effects or unrelated medical problems or declined further therapy. After completing 40 sessions, another 15 to 20 sessions were sometimes administered if the hematuria persisted. The data were analyzed for patients with at least 12 months of follow-up.

We evaluated the patient characteristics, primary pelvic malignancy type, modality of radiotherapy, onset and severity of symptomatic hematuria using the RTOG/EORTC criteria, time from hematuria onset to the initiation of HBO_2 treatment, and prior intravesical management. The onset of hematuria was defined as the first episode of hematuria after the initiation of pelvic radiotherapy, independent of its RTOG/EORTC grade.

The clinical outcome measures after HBO_2 therapy included symptomatic assessment (either complete resolution, partial resolution, no change, or worsening hematuria) by physicians or as reported by the patients by way of returned postal survey forms.

Clinical improvement was defined as complete or partial resolution of macroscopic hematuria. Complete resolution referred to the absence of macroscopic hematuria. Partial resolution referred to a reduction in the severity or frequency of macroscopic hematuria that corresponded to a change to a lower RTOG/EORTC grade of radiotherapy-related hematuria.

The results of the post-treatment cystoscopic evaluation were not evaluated because most patients with symptomatic improvement did not undergo repeat cystoscopy to document the absence or reduction of bladder mucosal telangiectasia or petechiae. Microscopic examination of urine was not evaluated because some patients were followed up by postal outcomes surveys without returning to the clinician's office.

The total radiation dose delivered during pelvic radiotherapy was analyzed independent of the timing of therapy (primary, adjuvant, or salvage treatment).

The data were analyzed using Statistical Package for Social Sciences, version 11.0, with the one-sided Fisher's exact test in two by two tables and the two-sided Pearson chi-square test with two degrees of freedom in the three by two table. Statistical significance was reached at a P value of 0.05 or less.

RESULTS

A total of 60 patients (55 men and 5 women) with a mean age of 70 years (range 15 to 88) received an average of 33 HBO_2 treatments (range 9 to 63). Patients with complete resolution, partial resolution, no change, and worsened hematuria had an increasing mean age of 69, 70, 75, and 80 years, respectively. Of the 60 patients, 44 men and 4 women (80%) had either complete or partial resolution of macroscopic hematuria (Table II). In our series, the most common indication for pelvic radiotherapy was prostate cancer in 50 (83%) of the 60 patients. Of this subgroup, 76% improved with HBO_2 therapy.