

Evaluation of Hyperbaric Oxygen Therapy in the Treatment of Radiation-induced Hemorrhagic Cystitis



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OBJECTIVE	To evaluate the efficacy of hyperbaric oxygen therapy (HBO) in the treatment of postradiation hematuria (PRH) and to identify the predictive factors for a successful outcome.
MATERIALS AND METHODS	We conducted a retrospective study and included all patients with PRH treated with HBO in a university hospital center between January 2003 and December 2013. We studied the patients' clinical characteristics, radiotherapy indication, treatments preceding HBO, the grade of hematuria diagnosed based on the Common Terminology Criteria for Adverse Events classification v 4.03 and the efficacy of HBO. The success of HBO was defined as the total or partial resolution of hematuria.
RESULTS	We included 71 patients with a median age of 72 (39-87) years. PRHs were severe (grade ≥ 3) in 50 (70.4%) of the cases. Radiotherapy was indicated in the treatment of prostate cancer in 61 (85.9%) patients. The median length of time between hematuria and HBO was 8 (1-154) months. Prior to HBO, 46 (64.8%) patients underwent electrocoagulation of the bladder. HBO sessions were compounded by 9 cases of barotraumatic otitis, 5 cases of transient visual disturbance, and 1 case of finger paresthesia. On average, 29 (3-50) sessions were carried out. Treatment was effective in 46 (64.8%) patients, 37 (52.1%) of whom were completely cured. A hematuria grade of less than 3 was a predictive factor in the successful treatment ($P = .027$). Median follow-up was 15 (1-132) months.
CONCLUSION	HBO completely resolves PRH in 52.1% of cases. Prolonged patient follow-up is required to confirm the efficacy of this treatment. UROLOGY 94: 42-46, 2016. © 2016 Elsevier Inc.

Pelvic radiotherapy, either alone or combined with other treatments, is a frequent therapeutic option in the management of urological and gynecological pelvic cancers. There are, however, nonnegligible mid- and long-term complications, with 3% to 6.5% of chronic lesions of radiation-induced cystitis occurring 6 months to over 10 years after radiation therapy.¹

Radiation-induced cystitis occurs secondary to progressive obliterating endarteritis due to fibrosis of the vascular intima of the submucosal arterioles and capillaries, resulting in tissue hypoxia. Cystoscopy reveals anarchic neovascularization in the form of telangiectasia. This neovascularization may sometimes cause severe macroscopic hematuria that is difficult to treat and warrants pro-

longed hospital stays. Hyperbaric oxygen therapy (HBO) was initially described in the treatment of postradiation hemorrhagic cystitis by Weiss in 1985.^{2,3} The Weiss approach involves administering oxygen at a pressure greater than atmospheric pressure to increase plasma oxygenation. The anticipated effects include increased oxygenation of hypoxic tissues, stimulation of neoangiogenesis, reduced fibrosis, and an increase in anti-infective defense mechanisms.⁴ HBO is currently reserved for endoscopic coagulation-resistant hematuria prior to cystectomy. The aim of this study was to evaluate the efficacy of HBO in the treatment of radiation-induced cystitis and to identify the predictive factors for a successful outcome.

MATERIALS AND METHODS

In this retrospective study, we included all patients treated with HBO for hematuria linked to radiation-induced cystitis at the Angers University Hospital between January 2003 and December 2013. Cystitis was diagnosed on the basis of a history of pelvic radiotherapy combined with observation of hemorrhagic cystitis on cystourethroscopy. All patients underwent a computed tomography scan with intravenous contrast to eliminate differential

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diagnosis (upper urinary tract tumors and stones). In case of antiaggregant or anticoagulant therapies, treatments were stopped, when possible, according to criteria evaluated by a cardiologist and an anesthesiologist.

We studied the patients' clinical characteristics (age, general condition, smoking habits, antithrombotic treatment, hemostasis disorders); laboratory characteristics (hemoglobinemia, platelets, hemostasis evaluation); use of transfusions; treatments preceding HBO (antifibrinolytics, antifibrotics, bladder irrigations, endovesical instillations, electrocoagulation); the type, indication, and dose of irradiation; the length of time between the onset of hematuria and radiotherapy; and the period between the onset of hematuria and the introduction of HBO therapy.

The grade of hematuria was assessed prior to treatment, at the end of treatment, and on the latest findings according to the Common Terminology Criteria for Adverse Events v.4.03 (grade 1: microscopic hematuria; grade 2: moderate hematuria; grade 3: hematuria with clots or warranting hospital admission, or a transfusion or hemostasis; grade 4: hematuria warranting emergency hemostasis; grade 5: death).⁵

HBO was administered in 2 daily sessions of 90 minutes in a multiplace hyperbaric chamber at a pressure of 2.5 Atmosphere Technische Absolut. End-of-treatment success was defined by total or partial resolution of the hematuria. Improvement was defined to be partial in the case of grade 2 hematuria at the end of treatment. Twenty sessions were planned at baseline. There were 10 to 20 additional sessions proposed in case of persistent hematuria. The sessions were interrupted in the event of poor tolerance.

Statistical analyses were carried out with SPSS 15.0 software. Chi-square and Fisher's exact tests were carried out to assess the qualitative variables and Student *t* test for quantitative variables. *P* values of less than .05 were considered statistically significant, and all tests were two sided. Survival curves were analyzed according to the Kaplan-Meier method.

RESULTS

Population Characteristics

We included 71 patients. The median age was 72 (39-87) years and 63 (88.7%) patients were male. Thirty-six (50.7%) patients had a history of smoking. Radiotherapy was administered for prostate cancer in 61 (85.9%) cases, for cancer of the uterine cervix in 6 (8.5%) cases, and for other causes in 4 (5.6%) cases. External radiotherapy was administered in 65 (91.5%) cases, brachytherapy in 2 cases (3%), and a combination of both in 4 (5.5%) cases.

The median dose of irradiation delivered was 66 (45-138) Gy. The median length of time between radiotherapy and the onset of hematuria was 38 (1-384) months. Ten (14%) patients presented with recurrence of their tumor-related condition at the time of treatment for macroscopic hematuria. Nineteen (26.7%) patients had biopsies of bladder to exclude bladder cancer. Anticoagulant or anti-aggregation therapy was administered to 15 (21.1%) and 28 (39.4%) patients, respectively. Prior to HBO, 37 (52.1%) patients presented with severe anemia characterized by hemoglobin levels below 10 g/dL. Endoscopic electrocoagulation, antifibrinolytic therapy, or endovesical instillations were administered to 46 (64.8%), 15 (21.1%), and 6 (8.4%) patients, respectively. Transfusions were re-

Table 1. Population characteristics

	n = 71
Gender, male, n (%)	63 (88.7)
Median age (y)	72 (39-87)
Smoking habits (%)	36 (50.7)
Oral anticoagulation therapies (%)	
Antiplatelets agents	28 (39.4)
Anticoagulant	15 (21.1)
Anemia, Hb <10 (g/dL) (%)	37 (52.1)
Transfusions (%)	41 (57.7)
Grade of hematuria, n (%)	
I	3 (4.2)
II	18 (25.4)
III	47 (66.2)
IV	3 (4.2)
Indication of radiotherapy (%)	
Prostate cancer	61 (85.9)
Bladder cancer	2 (2.8)
Cervix cancer	6 (8.5)
Other cancers	2 (2.8)
Median radiotherapy exposure (Gy)	66 (45-138)
Pre-HBO endoscopic electrocoagulation (%)	46 (64.8%)

HBO, hyperbaric oxygen therapy.

Table 2. Adverse events

	n = 16 (22.5%)
Barotitis media	9 (12.7%)
Vision disorder	5 (7%)
Finger paresthesia	1 (1.4%)
Pain during mobilization	1 (1.4%)
Discontinuation for adverse events	2 (2.8%)

quired for 41 (57.7%) patients. Grades I, II, III, and IV hematuria were initially diagnosed in 3 (4.2%), 18 (25.4%), 47 (66.2%), and 3 (4.2%) cases, respectively. The population characteristics are presented in [Table 1](#).

HBO Treatments

The median number of HBO sessions was 29 (3-50). The median length of time between the onset of the first symptoms and the introduction of HBO was 8 (1-154) months. Adverse events occurred in 16 patients (22.5%). The adverse events occurring during treatment are listed in [Table 2](#). Treatment was discontinued in 4 patients (5.6%)—2 for adverse events, 1 for an intercurrent event (myocardial infarction), and 1 for emergency cystectomy.

Results of HBO

At the end of treatment, hematuria was completely resolved in 37 (52.1%) patients and partly resolved in 9 (12.7%) patients. No improvement in hematuria was recorded in 25 (35.2%) patients. After treatment and with a median follow-up of 15 months (1-132), 19 (26.8%) patients presented with a recurrence of hematuria. Among the patients who experienced a recurrence, 9 had a second course of HBO therapy, which proved effective in 8 cases.

After 1 year, the hematuria-free survival rate was 70%. Hematuria-free survival is shown in [Figure 1](#).

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