Hyperbaric Oxygen Therapy for Hemorrhagic Radiation Cystitis

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ABSTRACT: **Background:** Hemorrhagic radiation cystitis (HRC) is a significant clinical problem that occurs after pelvic radiation therapy and is often refractory.

Objectives: To evaluate the efficacy and safety of hyperbaric oxygen therapy (HBO) for HRC.

Methods: Daily 90 minute sessions of HBO at 2 ATM 100% oxygen were given to 32 HRC patients with ASTRO grades 3-4 hematuria.

Results: The median age was 72.5 (48–88 years). The median time interval between radiation therapy and HBO was 4 years (1–26 years). The patients received a median of 30 HBO sessions (3–53). Hematuria resolved in 27 patients (84%) and persisted in 5. Cystectomy was required in two, and ileal-conduit and bilateral percutaneous nephrostomies were performed in one and two patients, respectively. With a median follow-up of 12 months (5–74 months), the hematuria cleared completely in 16 patients (59%) and mild hematuria requiring no further treatment recurred in 10 others. Another patient with ASTRO grade 4 hematuria needed bladder irrigation and blood transfusions. Complications included eardrum perforation in four patients and transient vertigo and mild hemoptysis in one case each. None of them required HBO discontinuation.

Conclusions: HBO controlled bleeding in 84% of the patients. A durable freedom from significant hematuria was achieved in 96% of the patients. HBO seems to be an effective and safe modality in patients with HRC.

IMAJ 2013; 15: 75–78

KEY WORDS: radiation cystitis, hyperbaric oxygen (HBO), hematuria

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Radiation is often used in the treatment of pelvic malignancies such as prostate, rectal, endometrial and cervical cancers. Because of anatomic proximity and the radiation energy distribution around the area of interest, exposure of nearby pelvic organs is often inevitable. A possible result is typical radiation-associated injury to the neighboring organs, most commonly the urinary bladder and rectum, and consists of progressive endarteritis of small blood vessels and chronic fibrosis. This in turn leads to fragile vasculature and spontaneous bleeding that may be persistent and difficult to control. Hemorrhagic radiation cystitis manifests months to years after radiation therapy and presents with hematuria and associated voiding symptoms [1].

It has been reported that HRC may occur in up to 10% of patients after previous pelvic radiation [2]. Occasionally, hematuria may be clinically significant, necessitating hospital admission and further measures to control the bleeding. To date however, a definitive curative treatment for HRC is not available. Nonetheless, various interventions have been employed to control bleeding, including bladder irrigation and intravesical instillation of substances such as alum, silver nitrate, prostaglandins or formalin, and fulguration of intravesical bleeding sites [3]. When such measures have proven ineffective, selective hypogastric artery embolization, supraversical urinary diversions and cystectomy have been offered to control life-threatening hematuria [4,5].

Hyperbaric oxygen has emerged as a promising treatment modality for HRC since 1985, as reported in several short series [6-11]. We report here the efficacy and safety of HBO in a series of 32 patients with HRC treated in a single institution.

PATIENTS AND METHODS

Between 2000 and 2011 HBO was used to treat HRC in 32 patients (10 women and 22 men). These patients had been treated with radiation therapy for various pelvic malignancies in several medical centers in Israel, and they represent a nationwide cohort that was treated with HBO in the single center in Israel that has a hyperbaric chamber. Cystoscopy

ASTRO = American Society of Therapeutic Radiology and Oncology

HRC = hemorrhagic radiation cystitis
HBO = hyperbaric oxygen therapy

and upper tract pyelographic imaging were performed in all patients to rule out other etiologies for hematuria. According to the American Society of Therapeutic Radiology and Oncology (ASTRO) classification of HRC, grade 4 and grade 3 hematuria were found in 17 and 15 patients, respectively [12].

Prior to the HBO treatment the patients were examined by an otolaryngologist and underwent a chest X-ray in order to prevent hyperbaric injury. The treatment consisted of multiple sessions of 100% oxygen delivery in a hyperbaric chamber at 2 ATM pressure for 90 minutes. Treatment was given daily for 5 days a week aiming for a total of 30 sessions.

Patients` charts were reviewed and data were collected on demographics, previous pelvic cancer history, radiation therapy dosage and date, time to the first episode of hematuria, time to HBO treatment, and prior treatments. We also noted the number of blood transfusions given prior to the HBO treatment, the number of HBO treatments and the number of HBO treatments until the hematuria resolved. The time to the next episode of hematuria was measured and the rate of freedom from hematuria following HBO therapy was calculated using the Kaplan-Meyer plot.

Descriptive statistics were applied. The Institutional review board approved the study, and due to its retrospective nature a waiver was given for signed informed consents.

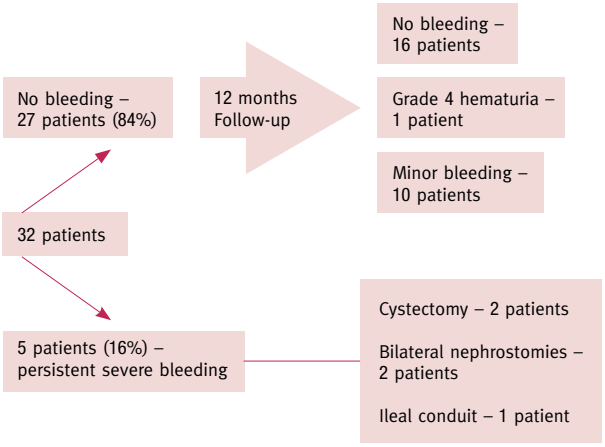
RESULTS

Patients' characteristics are summarized in Table 1. The radiation dose for prostate cancer was available in 17 of 21 patients and its median was 72 Gy (range 66–81 Gy). The median radiation dose in eight others with pelvic malignancies other than prostate cancer was 45 Gy; five women also underwent brachytherapy – two with cervical carcinoma, two with endometrial carcinoma and one with vaginal carcinoma.

Table 1. Patients' characteristics

Median age (yrs, range)	72 (48–88)
Gender Males Females	 22 10
Malignancy (n) Prostate carcinoma Rectal carcinoma Endometrial carcinoma Cervical carcinoma Vaginal carcinoma	 21 1 5 4 1
Median time interval between radiation therapy and HBO treatment (yrs)	4 (1–26)
Median number of HBO sessions (range)	30 (3–53)
Outcome at the end of treatment (n) Free of hematuria Refractory hematuria	 27 5
Late hematuria (n)	11
Median number of HBO treatments before hematuria resolved	14

Figure 1. Outcome following HBO treatment in the 32 patients



Hematuria resolved in 27 patients (84%) and persisted in 5 others [Figure 1]. Two of the latter had severe hematuria necessitating a prolonged hospital stay with multiple blood transfusions. These patients underwent cystectomy. Supravesical urinary diversion in the form of ileal conduit and percutaneous nephrostomies were necessary in one and two patients, respectively. In all five patients the hematuria resolved. Of the 32 patients 15 (47%) required multiple blood transfusions before or during HBO treatment.

With a median follow-up of 12 months (range 5–74 months), 16 patients (59%) remained free of further episodes of visible hematuria, while in 10 patients (37%) mild hematuria recurred requiring no further treatment. In one patient ASTRO grade 4 hematuria developed 5 months after HBO treatment, and blood transfusions and bladder irrigations were necessary. Thus, with a median follow-up of 12 months the likelihood of freedom from recurrent severe hematuria was 96%. Complications included spontaneous eardrum perforation in four patients and mild hemoptysis and vertigo in one patient each.

DISCUSSION

This is the third largest published series of patients undergoing HBO for HRC. We show that in these patients, who presented with significant hematuria (grade 3 or higher), HBO was effective in clearing the hematuria in 27 (84%). Although 11 of them experienced recurrent hematuria later on, this was mild in 10 of the 11 and required no further interventions. Treatment failure was noted in 5 patients (16%), none of whom required either cystectomy or urinary diversion to control life-threatening bleeding. The toxicity of HBO was mild and self-limited.

Although the natural course of HRC may be variable, allowing for spontaneous resolution of the hematuria in

some cases, ours was a challenging group of patients in whom blood transfusions were necessary, other modalities to stop bleeding had been attempted, and radical surgery or urine diversion was needed in some of the patients. Nonetheless, HBO proved effective in achieving durable bleeding control in this group. The importance of our study lies in confirming the high efficacy and low toxicity associated with HBO; in addition, we have provided data on the durability of the response to therapy and the median number of HBO sessions needed for hematuria clearance. Our data confirm previous reports of a 60–100% efficacy with durable response and low toxicity [6-11,13-15]. Despite the promising results of HBO, life-threatening hematuria may persist in some patients. Cystectomy or urinary diversion may be necessary to control the bleeding in such cases.

The pathophysiology of late radiation toxicity stems from the injury to the submucosal layer. Injury to blood vessels ends in progressive endarteritis. Such pathological blood vessels are associated with less effective oxygen delivery to the tissues, resulting in the development of hypoxic, hypocellular and hypovascular tissue [16]. Hyperbaric oxygen treatment is given for various indications such as carbon monoxide poisoning, decompression sickness, arterial gas embolism, necrotizing fasciitis, problematic wounds, chronic osteomyelitis and radiation-induced tissue injury [17-19]. The concept of hyperbaric treatment is to improve tissue oxygenation, thereby enhancing healing [3]. HBO treatment ameliorates hypoxia and tissue perfusion by enhancing neovascularization. This, in turn, may stimulate tissue repair and prevent infection.

Despite the fact that the earliest reports on HBO therapy for HRC date back to the mid-1980s, HBO has mainly been reported in short case series. Our data parallel previous reports showing a 62–90% rate of efficacy in controlling hematuria and overall limited side effects [6-11,13-15]. While no direct head-to-head comparative studies were undertaken to demonstrate the superiority of HBO over other treatment options, it is important to consider the efficacy of HBO as compared to other treatment modalities. Previous studies on substance instillations for HRC have demonstrated a modest efficacy and possible toxicity. Arrizabalaga et al. [20] reported that 66% of the HRC patients treated with alum instillations achieved control of hematuria. Aluminum-induced toxicity has been observed, particularly in patients with renal failure [21]. Instillations of corticosteroid or prostaglandin solution resulted in a moderate response as well [22]. Intravesical administration of formalin solution has been shown to better control hematuria in 89% of the HRC cases. However, this option is far more toxic and usually requires general anesthesia [23]. Bilateral hypogastric artery embolization has also been attempted to control hematuria, but with limited efficacy [5]. Considering the high efficacy, durability and limited toxicity experienced with HBO, as reflected in the literature and in the current report, it seems reasonable that this should be the first line of therapy for HRC.

A possible concern related to HBO treatment is the fear that improved tissue oxygenation may boost residual malignant cells and rekindle cancer. Feldmeier et al. [24] reviewed this issue and concluded that there is no evidence for either malignant or metastatic cell enhancement under HBO treatment. In fact, malignant tumors that thrive under hypoxic conditions seem to be more aggressive and tend to metastasize [24]. Another study on that question investigated the effect of HBO on LNCaP cells and did not find any proliferative effect of HBO [25].

The limitations of our study are related to the retrospective nature of its design, preventing an accurate measurement of the effect of HBO on the rate of bleeding, and the relatively short follow-up period.

CONCLUSIONS

Hyperbaric oxygen therapy provides durable, effective and safe control for significant hematuria associated with HRC.

Acknowledgments

We thank Mr. Yair Bachor who assisted in the data collection.

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Capsule

Angiogenesis induced by CNS inflammation promotes neuronal remodeling through vessel-derived prostacyclin

Angiogenesis is a prominent feature of central nervous system (CNS) disease and has roles in both the continued promotion of inflammation and the subsequent repair processes. Muramatsu et al. report that prostacyclin (or prostaglandin I2) derived from new vessels promotes axonal remodeling of injured neuronal networks after CNS inflammation. In a localized model of experimental autoimmune encephalomyelitis (EAE), new vessels formed around the inflammatory lesion, followed by sprouting of adjacent corticospinal tract (CST) fibers. These sprouting fibers formed a compensatory motor circuit, leading to recovery of motor function. Capillary endothelial cell-derived prostacyclin bound to its receptor, the type I prostaglandin receptor (IP receptor), on CST neurons, promoting sprouting of CST fibers and contributing to the repair process. Inhibition of prostacyclin receptor signaling impaired motor recovery, whereas the IP receptor agonist iloprost promoted axonal remodeling and motor recovery after the induction of EAE. These findings reveal an important function of angiogenesis in neuronal rewiring and suggest that prostacyclin is a promising molecule for enhancing functional recovery from CNS disease.

Nature Med 2012; 18: 1658

Eitan Israeli

Capsule

Evolution of an HIV glycan-dependent broadly neutralizing antibody epitope through immune escape

Neutralizing antibodies are likely to play a crucial part in a preventive human immunodeficiency virus-1 (HIV-1) vaccine. Although efforts to elicit broadly cross-neutralizing (BCN) antibodies by vaccination have been unsuccessful, a minority of individuals naturally develop these antibodies after many years of infection. How such antibodies arise, and the role of viral evolution in shaping these responses, is unknown. Moore et al. show, in two HIV-1–infected individuals who developed BCN antibodies targeting the glycan at Asn332 on the gp120 envelope, that this glycan was absent on the initial infecting virus. However, this BCN epitope evolved within 6 months, through immune escape from earlier strain-specific antibodies that resulted in a shift of a glycan to position 332. Both viruses that lacked the glycan at amino acid 332 were resistant to the Asn332-dependent BCN monoclonal antibody PGT128, whereas escaped variants that acquired this glycan were sensitive. Analysis of large sequence and neutralization data sets showed the 332 glycan to be significantly under-represented in transmitted subtype C viruses compared to chronic viruses, with the absence of this glycan corresponding with resistance to PGT128. These findings highlight the dynamic interplay between early antibodies and viral escape in driving the evolution of conserved BCN antibody epitopes.

Nature Med 2012; 18: 1688

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