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Research Article

Predictive Factors of Hemorrhagic Cystitis Severity Secondary to Prostate Radiotherapy Treatment

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Abstract

Introduction: Chronic and recurrent hemorrhagic cystitis often arises from pelvic radiotherapy. The treatment of radiation-induced hemorrhagic cystitis can be especially frustrating for the practicing urologist.

Materials and Methods: 39 patients with personal history of prostate cancer treated with radiotherapy who presented hematuria throughout the follow-up were retrospectively analyzed. Variables such as anticoagulant/antiaggregant therapy, mean radiation dose (Gy) and radiation field were analyzed.

Results: Any of the studied variables (anticoagulant and antiaggregant therapy, radiated field, radiotherapy mode and total radiation dose) presented a statistically significant association with the hematuria severity.

Conclusion: Treatment of chronic and recurrent hemorrhagic cystitis is challenging for the practicing urologist. In order to improve this condition's management we tried, unsuccessfully, to find some predictive factors of its severity.

Keywords: Hemorrhagic cystitis; Radiotherapy; Hematuria; Prostate cancer

Introduction

Hemorrhagic cystitis is defined as a diffuse inflammatory condition of the urinary bladder due to an infectious or noninfectious etiology resulting in bleeding from the bladder mucosa. The most common cause is bacterial infection. But chronic and recurrent hemorrhagic cystitis often arises from chemotherapy or pelvic radiotherapy. 6-12% of patients who receive pelvic radiotherapy develop hemorrhagic cystitis [1]. There are two forms of presentation of hemorrhagic cystitis: acute (3-6 weeks after treatment, with epithelium loss and telangiectasia predominance) and late (after years, with fibrosis predominance) [2]. However, the effects of radiation-induced cystitis can occur as early as 6 months to late as 20 years after radiation treatment [22]. Ionizing radiation limits cellular growth and is associated with progressive oblitering endarteritis and hypocelullar, hypovascular and hypoxic transformation of the vesical mucosa, with edema, ulceration, decreased regeneration and fibrosis, responsible for the cystitis symptoms [3-5].

The treatment of radiation-induced hemorrhagic cystitis can be especially frustrating for the practicing urologist [1,6]. This potentially severe condition can appear more than 10 years after pelvic radiotherapy. Hemorrhagic cystitis treatments have included bladder irrigation, fulguration with electro-cautery, oral and intravesical agents, hyperbaric oxygen therapy, and ultimately cystectomy [7].

In this article we analyze our experience in the management of hemorrhagic cystitis secondary to prostate cancer radiotherapy treatment. We aimed to prove if there are any predictive factors of hemorrhagic cystitis severity.

Materials and Methods

Clinical records from 39 patients with personal history of prostate cancer treated with radiotherapy at the Hospital General Universitario of Valencia, who presented hematuria throughout the follow-up were retrospectively analyzed. Patients with diagnosis of prostate cancer were treated with radiotherapy either primary, adjuvant or rescue therapy. At the end of the treatment, patients were evaluated at our center, where the further follow up was carried out. Analyzed variables included age, anticoagulant/antiaggregant therapy, Gleason, total radiation dose (Gy), radiation dose per session (Gy) and radiation field. Severity of hematuria was defined by the most invasive treatment necessary to manage it (hydration, urinary catheter and irrigation, intravesical agents, fulguration with electro-cautery, hyperbaric oxygen therapy and cystectomy).

Patients who presented hematuria throughout the follow-up underwent a diagnostic evaluation including ultrasound and cystoscopy. Diagnosis was focused on exclusion of other causes of hematuria, and it was performed during hospitalization or on an outpatient basis.Depending on the hematuria severity, the patients were evaluated in the Emergency department or in the Urology outpatient department. Treatment was carried out in a staggered way. If endovenous hydration was insufficient, a urinary catheter was placed and bladder irrigation and clot evacuation were made. Persistent hematuria despite this treatment required hospitalization. Continuous bladder irrigation, dymethilsulphoxide intravesical instillations, fulguration and hyperbaric oxygen therapy were applied in this order during hospitalization according to the severity of the hematuria. More aggressive approaches such as arterial embolization or ligation and cystectomy were only proposed for unresponsive patients Clinical data was analyzed using Statistical Package for Social Sciences (SPSS). Descriptive statistics and univariate analysis were used. Statistical significance was considered for P-values (0.05).

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Table 1: Sample characteristics.

Mean age (years)	75.9
Anticoagulant therapy (%)	10.3
Antiaggregant therapy (%)	15.4
Radiotherapy (%)	84.6 Primary
	10.3 Adjuvant
	5.1 Rescue
Mean total radiation (Gy)	74.90 Prostate
	58.93 Seminal vesicles
	48.20 Lymph nodes
Radiotherapy mode (%)	15.4 IMRT
	84.6 IG-IMRT

Results

Table 1 describes the characteristics of our sample, which included a total of 39 patients with personal history of prostate cancer. Mean age was 75.6 years (SD 8.88, 57-88 years). 9.1% of the patients received anticoagulant therapy and 20.5% antiaggregant treatment. 84.6% of patients were treated with primary radiotherapy, 10.3% adjuvant and 5.1% rescue. Mean total radiation on prostate was 74,90Gy (SD 3.6, 70.0-84.4Gy) on seminal vesicles was 58,93Gy (SD 6.97, 44.8-76.4Gy) and on lymph nodes was 48,20Gy (SD 2.28, 46.0-50.4Gy). Two different radiotherapy modes were used for the prostate cancer treatment, Intensity-Modulated Radiotherapy (IMRT) and Image Guided Intensity-Modulated Radiotherapy (IG-IMRT), being used in 15.4% of the patients the first mode and in 84.6% the second. Mean time to appearance of hematuria was 50.62 months (9.76-146 months). Hematuria was solved by using fluid therapy in 12.8% of patients, with urinary catheter and irrigation in 30.7%, with intravesical agents in 12.8%, with fulguration in 35.8%, with hyperbaric oxygen therapy in 5.1% and with cystectomy in 2.5%.

On the univariate analysis any of the studied variables presented a statistically significant association with the hematuria severity, showing a P-value > 0.474 for the antiaggregant therapy, P-value > 0.631 for anticoagulant therapy, P-value > 0.881 for radiated field, P-Value > 0.523 for radiotherapy dose and P-value > 0.501 for radiotherapy mode.

Discussion

Hemorrhagic cystitis is defined as a diffuse inflammatory condition of the urinary bladder due to an infectious or noninfectious etiology resulting in bleeding from the bladder mucosa. The urinary bladder is particularly sensitive to low radiation doses and is often more affected than other pelvic tissues [8], especially due to low urothelium cell turnover [9]. 6-12% of patients who receive pelvic radiotherapy develop hemorrhagic cystitis and this potentially severe condition can appear more than 10 years after the treatment. According to Borwne et al. [10] refractory hemorrhagic cystitis accounts for 23% to 80% of all complications related to pelvic radiation. Smith et al. study claim the effects of radiation-induced cystitis can occur as early as 6 months to late as 20 years after radiation treatment [20]. In our study mean time to appearance of hematuria was 50.62 months, which agrees to other studies experiences.

Management of radiation-induced hemorrhagic cystitis can be especially challenging. Bladder irrigation, fulguration with electro-cautery, oral and intravesical agents, hyperbaric oxygen therapy, embolization or ligation of the internal vesical and iliac arteries and cystectomy have been considered as different options for the treatment of this condition [15].

In our study we analyzed 39 patients with personal history of prostate cancer treated with radiotherapy who presented hematuria throughout the follow-up. They underwent a diagnostic evaluation including ultrasound and cystoscopy. Hemorrhagic cystitis not only can be caused by radiation but also by drugs, autoimmune diseases, viral and bacterial infections, chemotherapy, etc. [21]. Diagnosis was focused on exclusion of other causes of hematuria, and it was performed during hospitalization or on an outpatient basis. Depending on the hematuria severity, the patients were evaluated in the Emergency department or in the Urology outpatient department.

Hydration, bladder irrigation and clot evacuation, if necessary, were carried out in the Emergency room and persistent hematuria required hospitalization. Continuous bladder irrigation, intravesical instillations, fulguration, hyperbaric oxygen therapy and blood transfusion were considered during hospitalization according to the severity of the hematuria. (nosotros hicimos un trtatamiento secuencial According to Zwaans et al. [9] the most commonly used intravesical agents are alum and formalin, however, in our study patients were treated with dymethilsulphoxide in order to avoid the many adverse effects secondary to alum and formalin instillation [11,12]. The effectiveness of formalin treatment is not in doubt, with a high success rate of 80-92% [14]. However, the risks of treatment are significant. Thus, it has been suggested that it should be used as a treatment when others have failed, and individuals where life-long symptoms will not be a significant issue [15]. More aggressive approaches such as arterial embolization or ligation [13] and cystectomy were only proposed for unresponsive patients. Embolization of the internal iliac arteries was first reported in 1974 by Hald and Mygiand [16] and a subsequent review of reports showed successful control of severe hematuria in 32 of 35 patients (92%) [17]. More recently, superselective embolization has been used to treat severe hematuria. This technique is associated with a lower recurrence rate of hematuria [20]. However, the efficacy of embolization is variable [19]. Several urinary diversion methods have been used. Complications related to the defunctionalized bladder, including hemorrhage, pain and neoplastic transformation, occur in over 50% of patients who have undergone urinary diversion [22,23]; therefore, cystectomy is recommended at the time of urinary diversion. Because of high morbidity and mortality risk, surgery should be considered as the last option for refractory hematuria [24]. In our sample, only one patient required a cystectomy with a Bricker ureteroileostomy because of persistent hematuria after a superselective embolization.

Conclusion

Radiation-induced chronic hematuria appears in 6-12% of the patients receiving this therapy. Hemorrhagic cystitis treatment can be challenging. There are several available treatments, each one has benefits and disadvantages and there is no ideal management option. In our study we have not found any variables that could predict the severity of the hematuria after prostate radiotherapy treatment.

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