Sexual Medicine

Early use of a phosphodiesterase inhibitor after brachytherapy restores and preserves erectile function

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OBJECTIVE

To investigate whether the early use of phosphodiesterase inhibitors (PDEIs) after brachytherapy (BT) is associated with better erectile function, as of men potent before BT 38–70% have erectile dysfunction afterward.

PATIENTS AND METHODS

We evaluated a prospectively created database of 2500 patients who had had BT at our institution since 1992. We measured baseline age, cancer stage, Gleason grade, prostate specific antigen (PSA) level at diagnosis, implant type, use of neoadjuvant and adjuvant hormonal suppression therapy, use of external beam radiotherapy in conjunction with interstitial therapy, and follow-up PSA levels. Men were stratified by their use of PDEIs at <1 year (early group) or >1 year after implantation (late group). We excluded all men who did not have baseline Sexual Health Inventory for Men (SHIM) scores and at least one follow-up SHIM score; the latter were obtained at 6-month intervals after BT. Data were analysed using the Mann-Whitney *U*-test.

RESULTS

In all, 210 men met the inclusion criteria; 85 began using PDEIs within a year of BT, and 125 started after a year. The mean time to PDEI use was 191 days in the early and 595 days in the late group. The median age was 62 years in the early and 63 years in the late group ($P = 0.02$). Baseline Gleason scores did not differ, nor did PSA levels between the groups. Of men in the early group, 48% received neoadjuvant and/or adjuvant hormonal suppression therapy, vs half of men in the late group. Baseline SHIM scores were not significantly different, nor were scores at the first two follow-up assessments, but the scores at 18–36 months after BT were significantly different.

CONCLUSION

The early use of PDEIs after BT is associated with a significant improvement in and maintenance of erectile function compared with late use. Men undergoing BT should be encouraged to use PDEIs early after implantation, to preserve erectile function.

KEYWORDS

erectile dysfunction, prostate cancer, sildenafil, outcome

INTRODUCTION

Erectile dysfunction (ED) is a well-known side-effect of treatment for localized prostate cancer, regardless of the treatment used. Brachytherapy (BT), using radioactive seed implantation into the prostate, is an

increasingly popular method for treating prostate cancer, because the biochemical control rates appear to be favourable in the long term [1–3]. A large meta-analysis of 172 patients treated with BT from five institutions estimated that the rate of ED after BT was 29% at 1 year, which compared favourably with other forms of localized therapy [4]. However, other studies found that 80% of men after BT have a decrement in erectile function, and that only 56% of men after BT alone return to the level of function before implantation [5,6]. Furthermore, most studies found that ED increases with time after BT [5,7–9].

The rates of ED after BT vary widely and several groups attempted to define factors that predict erectile function after BT. Several studies documented that erectile function before BT is strongly correlated with function afterward [9–12]. Other factors that are important in predicting erectile function after BT include radiation dose, use of adjuvant or neoadjuvant hormonal suppression therapy (HST), and patient age [3,6,9,13]. Of the studies thus far reported the function before BT is the most consistently documented predictor of function afterward.

Few studies have investigated the role of phosphodiesterase inhibitor (PDEI) therapy in modulating the impact of BT on erectile function. Initial data suggested that sildenafil improved erectile function after BT [14]. Ohebshalom *et al.* [15] reported that sildenafil use at any time after BT improved erectile function, but there was a decreased response to oral pharmacotherapy with time.

Currently, the time to initiation of oral PDEI therapy after BT has not been investigated as a factor in preserving erectile function. We hypothesised that earlier initiation of oral pharmacotherapy would result in a faster return of erectile function, and preserve erectile function better than starting oral therapy later.

PATIENTS AND METHODS

Patients treated with BT at the authors' institution were followed prospectively in a database since 1992. Patients were generally treated with one of three protocols, based on risk stratification. Patients with low-risk features were treated with an ^{125}I-implant alone; those at intermediate risk were treated with 3 months of androgen suppression before and for 3 months after the implant; and those with high-risk features were treated with 3 months of androgen suppression followed by a ^{103}Pd-implant and external beam radiotherapy to 45 Gy. The latter group were given 9 months of androgen suppression. The preferred androgen suppression regimen consisted of a short course of an antiandrogen followed by an LHRH agonist [10]. Since 2000, we included the Sexual Health Inventory for Men (SHIM) questionnaire to assess erectile function before and after BT.

The present study included men who had SHIM scores of ≥16 before the BT implant; men were also included in the study only if they used PDEIs and had a baseline and at least two follow-up SHIM scores. Variables assessed included age at the start of BT, Gleason grade and clinical tumour stage, PSA level at the time of diagnosis, implant type, use of neoadjuvant and adjuvant HST, use of external beam radiotherapy in conjunction with interstitial therapy, and follow-up PSA levels. Use of oral and other therapy to promote erectile function was also recorded.

Since 1998, we began prescribing sildenafil citrate at an initial dose of 50 mg as needed for up to three times per week for men with ED after BT. The dose was titrated to 100 mg/day as needed if there was no response at 50 mg. Vardenafil hydrochloride was approved in August 2003, and has been used by our patients at a starting dose of 10 mg up to three times/week. This dose was titrated to 20 mg three times weekly. Men were encouraged to take at least two doses/week, and up to 12 doses/month; the exact number of doses taken was not recorded. The patients were counselled about the proper use of medication; they were encouraged to continue taking the medication for at least six doses before considering the drug as a treatment failure. If one type of oral PDEI failed the patient was offered use of an alternative oral agent once it became available.

Men were followed every 3 months for the first 2 years, every 6 months in the next 2 years and annually thereafter. Blood samples were collected for PSA assay at these visits, and every 6 months the follow-up SHIM score were assessed. The primary outcome measures were SHIM scores to assess sexual function, and PSA levels to determine the efficacy of BT for prostate cancer. We compared SHIM scores in men who began using PDEIs at <1 year after the implant (early group) or >1 year later (late group). Data within a group were analysed using the Wilcoxon matched-pairs test and those between groups using the Mann-Whitney *U*-test.

RESULTS

In all, 210 men met the inclusion criteria; 85 used PDEIs within a year of therapy and 125 started after a year. The baseline and demographic data of the groups are shown in Table 1. The mean time to PDEI use was 191 days in the early group and 595 days in the late group. The median age was 62 years in the early and 63 years in the late group ($P = 0.02$). Of the 85 (54%) men in the early group, 46 had baseline SHIM scores of >20, while 73 of 125 (58%) in the late group had SHIM scores of >20.

The groups were comparable in terms of median Gleason score and tumour stage. Baseline PSA level tended to be higher in the early group. Of men in the early group, 48% received neoadjuvant and/or adjuvant HST, compared to half the men in the late group. Given the dates included in the study, 207 of the men initially took sildenafil citrate at escalating doses, and only three initially used vardenafil hydrochloride.

Baseline SHIM scores were not significantly different, nor were scores within a year of follow-up. However, SHIM scores at 18–36 months after BT were significantly different (Fig. 1). The men in the early group had earlier and sustained improvements in erectile function that were not apparent in the late group; the former had a higher median PSA level at follow-up, and 34 in the early group, vs 26 in the late group, had PSA levels of >0.4 ng/mL.

DISCUSSION

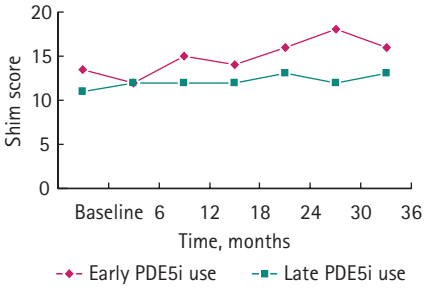
BT has become an increasingly used option to treat localized prostate cancer; one of the benefits of BT is preservation of erectile function [10,16,17], but more recent data suggest that there is a progressive deterioration in erectile function after BT [14]. Oral PDEIs are effective in ameliorating ED in

Variable	Early group	Late group	P
N	85	125	
Median age, years	62	63	0.020
Median stage (n at stage)	T1C (54)	T1C (79)	
Median Gleason score	6	6	
N with Gleason >7	23	31	
Median PSA level, ng/mL	6.5	5.6	0.053
D90	15800	17460	0.150
n with EBRT	35	40	
Median dose EBRT, Gy	45	45	
n (%) with HST	41 (48)	63 (50)	
PSA level at last follow-up	0.3	0.11	<0.001

TABLE 1 The baseline and demographic data

EBRT, external beam radiotherapy.

FIG. 1. Differences in SHIM scores at 18, 24, 30 and 36 months were significant, with P = 0.04, 0.03, 0.04 and 0.03, respectively.



most men after BT and external beam radiotherapy [10,14,15]. We assessed whether the time to starting oral pharmacotherapy after BT was related to SHIM scores during the follow-up. We postulated that the earlier use of PDEIs would better preserve erectile function; at all times beyond a year after BT the men in the early group had significantly higher SHIM scores than men in the late group.

While the result in the initial period might simply be explained by the observation that men in the early group were taking oral PDEIs and those in the late group were not, the periods beyond 18 months cannot explained by this difference. Men in the late group started oral PDEI therapy at a median of 595 days (≈ 18 months) after implantation, compared to 191 days (≈ 6 months) in the early group. Particularly at ≥2 years, when all men were on PDEIs, the difference in SHIM scores cannot be ascribed only to men being on treatment.

An emerging concept in radical prostatectomy is that of penile rehabilitation after surgery [18]. This theory suggests that early use of erectile aids, including PDEIs, helps to preserve healthy erectile tissue, and this leads to improved erectile function [19]. Similarly, while erectile function immediately after BT seems to be better preserved than after surgery, there is a progressive decline in erectile function after BT.

We think that using oral PDEIs early after BT helps to preserve the endothelium of the erectile tissue, and to preserve penile blood flow. These should decrease the corporal fibrosis that is often seen after radiotherapy. Preventing fibrosis should lead to better erectile function, as was apparently the case in the present patients.

Men treated at ≈6 months after BT had significantly higher SHIM scores than those treated at a median of 18 months after BT. This result agrees with the theory that earlier use of a PDEI prevents the degradation in penile function, probably by preventing fibrosis.

One of the major limitations of the present study is the retrospective analysis. We did not prospectively measure the response of men to PDEIs after BT, nor was there any randomization, but we think that these data are compelling. Given the minimal risks of their use, we recommend early use of PDEIs after BT. We are also in the process of enrolling men in a randomized prospective trial of the prophylactic use of PDEIs after initiating BT, to assess whether we can better preserve erectile function. Such a prospective trial should address more definitively the question of how best to preserve erectile function in the setting of BT for prostate cancer.

CONFLICT OF INTEREST

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Abbreviations: **BT**, brachytherapy; **ED**, erectile dysfunction; **SHIM**, Sexual Health Inventory for Men; **HST**, hormonal suppression therapy; **PDEI**, phosphodiesterase inhibitor.