Success of sildenafil for erectile dysfunction in men treated with brachytherapy or external beam radiation for prostate cancer

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Purpose: *We undertook to determine if any significant differences in the efficacy of sildenafil citrate for erectile dysfunction (ED) exists between patients who have received external beam radiation or brachytherapy for prostate cancer.*
Materials and methods: *Thirty-one patients who had received external beam radiation and nineteen patients who had received brachytherapy for prostate cancer and were subsequently treated with sildenafil citrate for post-irradiation ED comprised the patient population. A chart analysis was performed to determine either the presence or absence of concomitant risk factors for ED (coronary artery disease, diabetes, hypertension and smoking history) as well as age at radiation and time lapse between radiation completion and sildenafil citrate administration. Patients were then contacted to ascertain sildenafil citrate efficacy (defined as the continued use of sildenafil citrate), dosage used and medication tolerance.*
Results: *Continued use of sildenafil citrate was reported by 12/19 (63%) of the brachytherapy patients and 7/31 (22%) of the external beam radiation patients, a significant difference (P<0.007). Of those with continued use of sildenafil citrate, the patients who had undergone external beam radiation had a longer mean period of use (33.7 months) than those who had been treated with brachytherapy (14.3 months) (P=0.006). The mean elapsed time between completion of radiation and administration of sildenafil citrate was 7.6 months and 21.6 months for the brachytherapy and external beam radiation patients respectively (P=0.002). A significant difference in mean age existed between the patient groups, with the external beam radiation group being significantly older (69.8 years and 65.1 years respectively, P=0.007) at the time of sildenafil citrate administration. Of the risk factors for ED examined in each patient group, none were found to predict treatment failure with sildenafil citrate. Of the patients who did not experience success with sildenafil citrate, both groups used the medication for comparable periods of time.*
Conclusions: *Sildenafil citrate improved ED in a significantly greater number of patients who had undergone brachytherapy over those who had received external beam radiation. However, the patients who had received external beam radiation were both older and experienced a longer lapse of time between completion of radiotherapy and administration of sildenafil citrate than the brachytherapy patient group. This may explain the poorer success in the external beam radiation patients. The success of sildenafil in both groups of patients was lower than has previously been reported.*

Key Words: impotence, prostatic neoplasms, radiotherapy, cyclic-GMP phosphodiesterase/ai

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Introduction

The development of erectile dysfunction (ED) is a relatively common complication of radiotherapy treatment of carcinoma of the prostate. The reported incidences of ED following administration of either of the two modes of radiotherapy currently used, prostate brachytherapy and three-dimensional conformal external beam radiotherapy (3D-CRT), are

highly variable. Brachytherapy has been reported to induce ED in between 15% to 51% of patients,[1-5] while between 15% and 62% of patients develop ED after undergoing 3D-CRT.[6,7] These rather large ranges of incidences is attributable to the interval of reporting of ED after radiotherapy completion, as the incidence increases with the reported interval after treatment completion.[8]

The prevalence of ED has spawned numerous treatment modalities. These include prostaglandin E1 intracavernosal injections, transurethral alprostadil, vacuum pump devices, penile implants and oral therapies, the most widely used being sildenafil citrate.[9] Sildenafil, a selective inhibitor of phosphodiesterase 5, has been shown to be highly efficacious in the treatment of ED after radiotherapy, as the etiology of ED in this patient group has been shown to be arteriogenic in nature.[10] Numerous studies have attempted to elucidate the efficacy of sildenafil in patients with ED after radiotherapy for prostate cancer. Sildenafil has been shown to be effective in between 62% and 80% of brachytherapy patients.[4,8,11] Likewise, sildenafil has been shown to be very effective in restoring erectile function in patients who have undergone 3D-CRT[12,13] with response rates of between 43% and 74% having been reported.[7,14.] There have been, however, no studies to date directly comparing the efficacy of sildenafil between patients who have undergone one of the two radiotherapy modalities for treatment of prostate cancer. In the present study, we report our findings concerning the efficacy rates of sildenafil for the treatment of ED experienced by these two subsets of patients.

Materials and methods

Fifty patients who had undergone radiotherapy for prostate cancer and were subsequently treated with sildenafil citrate for post-irradiation erectile dysfunction (ED) comprised the patient population. Of the 50 patients, 31 (62%) received external beam radiation while the remaining 19 (38%) underwent brachytherapy. All patients presented to either S.B.R. or J.C. with erectile difficulties at various periods of time after radiotherapy completion. None of the 50 patients reported erectile difficulties prior to receiving radiotherapy. None of the patients had received hormonal therapy at any time. After careful evaluation, a diagnosis of ED was made. All 50 patients included in this study requested and were prescribed sildenafil citrate as none of them had any contraindications for its usage (i.e. current use of nitrates or unstable angina). Each patient was instructed on how to use sildenafil to optimize effectiveness (i.e. empty stomach, timing and sexual stimulation). Each patient was also given an information/instruction form on how to use sildenafil. On subsequent follow-up visits each patient was once again instructed on how to use sildenafil. Furthermore, the dose was adjusted according to side effect profile and if successful intercourse was achieved or not. Patients were also instructed that at least six doses at the maximum dose, as tolerated by side effects, should be attempted to see if sildenafil was not successful. In this group of patients sildenafil was not routinely reintroduced at a later date if they were initial failures after six doses.

A chart analysis was subsequently performed to identify those patients with risk factors for the development of ED, including coronary artery disease, diabetes mellitus, hypertension and history of smoking. The elapsed time between radiotherapy completion and the administration of sildenafil was identified, as well as the age at radiation completion, length of time on sildenafil. The characteristics of all 50 patients can be found in Table 1.

All patients were contacted by telephone in order to ascertain treatment efficacy, dosages used and medication tolerance. Sildenafil success was defined as the continued use of the drug without any other treatment modalities. No SHIM or IIEF scores were used pre or post treatment. Patients who had experienced sildenafil failure were asked to identify reasons for discontinuation, as well as the amount of time the drug had been used. The characteristics of patients with sildenafil success and failure are outlined in Tables 2 and 3, respectively. All patients were asked about experiences with side effects while on sildenafil. These results are listed in Table 4.

Results

Of the 50 patients prescribed sildenafil for ED occurring after radiotherapy for prostate cancer, 12/19 (63%) patients who had received brachytherapy and 7/31 (22%) patients who had received external beam radiation experienced success with sildenafil, a significant difference ($P<0.007$). While the two patient groups did not differ significantly in their risk factors for the development of ED, two important differences were noted. The 31 patients who had received external beam radiation were both older at the time of radiation administration (mean age 69.8 years) and had elapsed a greater amount of time between completion of their treatment for prostate cancer and beginning sildenafil (mean 21.6 months). The brachytherapy group were

TABLE 1. **Characteristics of all patients**

	Brachytherapy	External beam radiation	P value
Number of patients	19	31	-
Age (mean, in years)	65.1	69.8	0.007
Coronary artery disease			
Present	3	8	0.498
Absent	16	23	
Diabetes			
Present	1	4	0.637
Absent	18	27	
Hypertension			
Present	4	6	1.000
Absent	15	25	
History of Smoking			
Present	13	19	0.764
Absent	6	12	
Mean time from radiation to sildenafil (months)	7.6	21.6	0.002
Sildenafil Outcome			
Success	12	7	0.007
Failure	7	24	

P values were calculated used Student's t-test for means and Fischer's test for 2x2 tables.

TABLE 2. **Characteristics of patients with sildenafil success**

	Brachytherapy	External beam radiation	P value
Number of patients	12	7	-
Age (mean, in years)	65.9	68.1	0.429
Coronary artery disease			
Present	3	2	1.000
Absent	9	5	
Diabetes			
Present	-	1	0.368
Absent	12	6	
Hypertension			
Present	2	1	1.000
Absent	10	6	
History of smoking			
Present	8	5	1.000
Absent	4	2	
Mean time from radiation to sildenafil (months)	7.9	15.0	0.029
Mean length of sildenafil use (months)	14.3	33.7	0.006

Values were calculated used Student's t-test for means and Fischer's exact test for 2x2 tables.

TABLE 3. **Characteristics of patients with sildenafil failure**

	Brachytherapy	External beam radiation	P value
Number of patients	7	24	-
Age (mean, in years)	63.7	70.1	0.013
Coronary artery disease			
Present	-	6	0.293
Absent	7	18	
Diabetes			
Present	1	3	1.000
Absent	6	21	
Hypertension			
Present	2	5	0.642
Absent	5	19	
History of smoking			
Present	5	14	0.676
Absent	2	10	
Mean time from radiation to sildenafil (months)	7.1	23.6	0.040
Mean length of sildenafil use (months)	1.6	2.0	0.640
Reasons for discontinuing sildenafil			
Didn't work	6 (86)	20 (83)	
Too expensive	2 (29)	9 (38)	
Side Effects	1 (14)	1 (4)	

Percentages in parentheses.
P values were calculated used Student's t-test for means and Fischer's exact test for 2x2 tables.

both younger (mean age 65.1 years) and received sildenafil sooner after completing their radiation treatments (mean 7.6 months). These differences were significant (P=0.007 and P=0.002 respectively).

The patients who had experienced success with sildenafil differed significantly in two areas. Firstly, in keeping with the above finding, the patients who had received external beam radiation had a longer

TABLE 4. **Side effects associated with sildenafil use**

	Brachytherapy	External beam radiation	P value
Number of patients	19	31	
Side effects			
Yes	3	8	0.498
No	16	23	
Side effects experienced			
Headache	3 (100)	5 (63)	
Dizziness	2 (67)	2 (25)	
Nasal congestion	1 (33)	1 (13)	
Facial flushing	0 (0)	2 (25)	

Percentages in parentheses.
P values were calculated used Student's t-test for means and Fischer's exact test for 2x2 tables.

mean time from radiation completion to starting sildenafil than those who had received brachytherapy (15.0 months and 7.9 months respectively, P=0.029). Secondly, it was found that the patients who had undergone external beam radiation had used sildenafil successfully for longer than the brachytherapy patients had (33.7 months and 14.3 months respectively, P=0.006). The majority of both groups of patients started with a 50 mg dose, with 2 (17%) of the brachytherapy group and 2 (33%) of the external beam radiation group having progressed to 100 mg to sustain efficacy.

The two patient groups who experienced sildenafil failure both used the drug for comparable periods of time. The brachytherapy group used sildenafil for a mean period of 1.6 months, while the external beam radiation group used the drug for 2.0 months prior to discontinuation. It should be noted that these two groups differed significantly in their mean ages. The brachytherapy group who experienced failure were younger (mean 63.7 years) than the external beam radiation failure group (mean 70.1 years). In the 31 patients who experienced failure with sildenafil, the reasons cited for discontinuation of sildenafil included lack of efficacy in 26 (84%), prohibitively expensive in 11 (35%) and side effects in 2 (11%) (Patients may have reported more than one reason for discontinuation).

Comparison of the treatment success patients and treatment failure patients within each patient group (i.e. brachytherapy and external beam radiation) yielded no significant differences with respect to age, risk factors for ED, and mean time from radiation completion to sildenafil administration.

Sildenafil was generally well tolerated in most patients, with only 11 (22%) reporting side effects and 2 (4%) of the 50 patients reporting discontinuation of the drug due to its side effects. The side effects reported included headaches in 8 (16%), dizziness in 4 (8%), nasal congestion in 2 (4%) and facial flushing in 2 (4%) (Patients may have reported more than one side effect).

Discussion

This study was an attempt to assess the effectiveness of sildenafil in men who develop erectile dysfunction after either brachytherapy or external beam radiation for prostate cancer treatment.

We defined success as continued use of sildenafil for erectile dysfunction without any other treatment modalities. Hence, failure can be due to side effects and not being able to tolerate the medication or the medication not being satisfactory enough for sexual intercourse in the eyes of the patient. This is a clinical assessment. We found that those men with ED that had received brachytherapy 63% continued to use sildenafil as apposed to only 22% with men who received external beam radiation. This comparison was statistically significant. However, there were a number of important confounding factors that may have skewed the results in favor of brachytherapy. It is known that the incidence of ED increases with time after either brachytherapy or external beam radiation.[8] In the external beam group the interval from completion of radiotherapy to the administration of sildenafil was significantly longer than in the brachytherapy group (21.6 months vs. 7.6 months). Secondly, the external beam group who were successfully using sildenafil had used it for a significantly longer interval than those who had received brachytherapy (33.7 months vs. 14.3 months). With a longer time interval of use of sildenafil in those who received brachytherapy this may result in a deterioration of success as seen in the external beam group. Lastly, those men in the external radiation group were significantly older. It is know that the incidence of ED increases with age alone.[15] Hence, age itself may have also contributed to the poor success in the external beam group. Interestingly, in these patients who were successful with sildenafil the majority were on 50 mg. Failures were not due to not increasing the dosage. In both groups of patients sildenafil was well tolerated with the typical reported side effects. Furthermore, side effects were rarely a cause for discontinuation and hence failure of the medication (only two patients)Table 3. In these two patients the dose was adjusted in an attempt to reduce side effects.

Our patient population for this study had some selection bias. Some of the patients were treated with external beam therapy before the introduction of sildenafil, hence a larger interval from the completion of radiotherapy and starting sildenafil occurred. Since brachytherapy again became popular after the introduction of sildenafil and its availability, patients would have received sildenafil very early after completing brachytherapy. Furthermore, there has been a recent trend to treat ED early after radical prostatectomy or radiotherapy.[16,17] All of the above factors may have biased our patient population. Time interval difference between completing either form of radiation and starting sildenafil, the longer interval of use of sildenafil in the external beam group and a significant age difference between the groups makes it very difficult to compare the success of each of the

groups of patients directly. Clearly, a prospective trial comparing the use of sildenafil in those men who develop ED after brachytherapy or external radiotherapy in similar groups of men is needed to accurately assess the effectiveness of sildenafil. Although some controversy exists, most people believe that either mode of radiation therapy has a similar rate of ED.

However, what is clear is that the overall success rate of sildenafil in men with ED after either brachytherapy or external beam radiation for prostate cancer is only 38%. This is lower than what has been reported.[4,7,8,11,14,18] Incrocci et al had similar findings as our study with only 24% of patients still using sildenafil at least 2.5 years after having external beam radiotherapy for prostate cancer.[19] The reason we think this is so in our patients is due to the fact that the incidence of ED increases with time after completion of radiation, which was the case in many of our patients. Hence, the success of sildenafil will be less with time also.

Conclusions

Sildenafil citrate improved ED in a significantly greater number of patients who had undergone brachytherapy over those who had received external beam radiation. However, the patients who had received external beam radiation were both older and experienced a longer lapse of time between completion of radiotherapy and administration of sildenafil citrate than the brachytherapy patient group. This may explain the poorer success in the external beam radiation patients. Furthermore, the external beam radiation group that remained on sildenafil were much further out in time from the end of their radiation treatment. Hence, it is difficult to compare the two groups directly. The success of sildenafil in both groups of patients was lower than has previously been reported. □

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