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INVITED RESEARCH HIGHLIGHT

Prostate Cancer

Prevention of erectile dysfunction after radiotherapy for prostate cancer

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With increasing scrutiny of prostate cancer (PCa) diagnosis and treatment, much attention has been given to the morbidity caused by radical prostatectomy (RP) and/or radiotherapy (RT). One of the most common side-effects of either treatment is erectile dysfunction (ED).[1] Approximately, 40% of patients will experience ED after RT for PCa. The post-RT ED causes significant patient dissatisfaction with cancer treatment as well as decrease in patient and partner psychosocial function.[2] To address this issue in patients undergoing RT, Pisansky *et al.*[3] conducted a prospective, randomized, double-blinded, placebo-controlled trial to assess the efficacy of a phosphodiesterase enzyme-5 inhibitor (PDE5i), tadalafil, as a preventive measure for patients undergoing RT for PCa and found no difference in erectile function between the control and treatment groups.

Earlier studies supported the use of on-demand tadalafil for treatment of ED after RT for PCa with good results. One prospective, placebo-controlled study compared tadalafil versus placebo taken on-demand in patients with PCa after RT treatment. They found significant improvement in the tadalafil group. They noted that 67% of the patients reported an improvement in erectile function with tadalafil compared with only 20% in the placebo group, and 48% reported successful intercourse with tadalafil compared with 9% in the placebo group ($P \leq 0.0001$).[4] Similarly, in another prospective trial, patients were randomized to receive on-demand tadalafil (20 mg) versus once-a-day dosing (5 mg). Results showed an overall improvement in all domains of the international index of erectile function (IIEF) questionnaire ($P = 0.0001$) in each group, while mean erectile function domain scores values were not different when comparing the two groups ($P = 0.19$). In addition, sexual encounter profile questions 2 and 3 in each group were also improved above baseline (0% to 81% and 70% in the 20-mg arm and 90% and 73% in the 5-mg arm, respectively), however, they were not different when comparing the two groups ($P = 0.27$).[5] This again highlights the efficacy of PDE5i in the treatment of ED in this setting. Until recently, tadalafil and other PDE5i had not been explored fully as prophylactic agents for patients undergoing RT as they had been predominately studied for patients undergoing cavernosal nerve-sparing RP.[6]

In the study by Pisansky *et al.*[3] 242 patients with organ-confined PCa (T1b-T2b) treated with either external-beam radiation (XRT) or low-dose brachytherapy (BT) were randomized to receive either tadalafil 5 mg daily or placebo for the duration of 168 days. Patients were substratified by radiation method (XRT *vs* BT) and age (<65 *vs* >65). The authors excluded patients with prior androgen deprivation therapy, lymph-node and distant metastasis, current use of erectile aids or penile prosthesis, and recent history of myocardial infarction, all of which could potentially interfere with sexual function or bias results. The primary endpoint was to determine whether tadalafil 5 mg daily maintained spontaneous erections 4–6 weeks after cessation of treatment. The patients were assessed using the IIEF, which assesses erectile function (score range 1–30), orgasmic function (range 1–10), intercourse satisfaction (0–15), and overall satisfaction (2–10) as well as assessment with the Sexual Adjustment Questionnaire and The Locke Marital Adjustment test.

The patients had similar baseline characteristics and erectile function. Although there were more patients who underwent XRT versus BT in each group, the percentage of patients who underwent XRT in each group was similar (64% *vs* 62% in the tadalafil *vs* placebo group). Results for the primary endpoint demonstrated retention of erectile function in 79% of patients in the tadalafil group versus 74% in the placebo group ($P = 0.49$), an absolute difference of 5% indicating a lack of efficacy of tadalafil in this study as a protective agent. Furthermore, when adjusting for covariates, there was no difference in the erectile function between RT groups. However, the median time to achieving a spontaneous erection post-XRT was 21 weeks (16–27 weeks), whereas in the BT group, median time was 30 weeks (26–36 weeks). Not surprisingly, younger men (<65) were more likely to retain erectile function than older men (>65) (score increase 0.89; 95% confidence interval, 0.01–1.78, $P = 0.05$) possibly reflecting better baseline sexual function rather than effects of tadalafil. The overall score results at 30 and 52 weeks for all three questionnaires (IIEF, Sexual Adjustment Questionnaire and The Locke Marital Adjustment test) were essentially equal between the groups. Importantly, there was a significant drop in response rate by week 30 (100% to approximately 57%–74%) and by week 52 (100% to 36%–57%) in all three questionnaires, which could potentially bias the data.

This study has some limitations that are noteworthy, as discussed by the authors. Alternative dosing schedules of tadalafil or other PDE5i were not explored. The authors justified the choice of tadalafil in their study as it is a once-a-day dosing with steady-state

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exposure to endothelial tissue. Furthermore, the exact etiology of ED after RT remains unclear.[7] It has been postulated that the post-RT ED could be of a vascular origin and thus the justification to use PDE5i.[8] However, it is unclear as to the tissue bioavailability of tadalafil at the site of interest, especially as RT treatment progresses. Next, as the authors indicate, the study was powered to detect a 20% difference between the groups, which was not observed. Coupled with a significant drop in response rate, the results may have masked a small difference between the groups. Finally, longer follow-up may have detected a late benefit of tadalafil.

In contrast to these findings, Zelefsky *et al*.[9] conducted a similar randomized, placebo-controlled, double-blinded study where patients received sildenafil or placebo. Interestingly, their results showed improvement in erectile function at 12 months and in overall satisfaction at 24 months. An important point to note is that the trial by Pisansky *et al*.[3] excluded patients with "ongoing erectile aid," yet approximately 20% of patients in each group had received prior PDE5i treatment, which could have masked a small benefit in the treatment group. Conversely, in the trial by Zelefsky *et al*.[9] patients who used "erectogenic agents" 4 or more times per month were excluded. However, it is not stated how many patients with even minimal prior PDE5i use were included. Furthermore, although there was a longer follow-up period of 24 months, there is no mention of the percentage of patients that were lost to follow-up. Given that both sildenafil and tadalafil have been shown to improve endothelial function,[10,11] these contrasting results are surprising. Perhaps, the etiology of ED is multifactorial, which may explain the disparate results from different trials using different agents.

The study by Pisansky *et al*.[3] provides valuable information regarding tadalafil as a prophylactic agent post-RT for PCa. Tadalafil may not be effective as once thought in this regard. However, given the attrition rate of patients responding, and the short follow-up, further investigation may need to be performed. In addition, given the contradictory results of other studies using different PDE5i, additional prospective studies of the different agents are warranted, as well as the elucidation of the exact pathophysiology of ED following RT.

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