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INVITED RESEARCH HIGHLIGHT

Erectile Dysfunction

Does tadalafil prevent erectile dysfunction in patients undergoing radiation therapy for prostate cancer?

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A recently published paper addressed the interesting topic of prevention of erectile dysfunction (ED) with tadalafil, a phosphodiesterase-type 5 inhibitor (PDE5i) in patients undergoing radiation therapy for localized prostate cancer.[1] Tadalafil 5 mg or placebo was administered once-daily for 24 weeks in patients undergoing external-beam radiotherapy (EBRT) or brachytherapy (BT) for prostate cancer. This randomized trial did not show superior efficacy of the active drug compared with placebo 4–6 weeks after stopping the study drug. Furthermore, patients younger than 65 years did not respond significantly better than older patients.

Published rates of ED after radiotherapy for prostate cancer vary from 7% to 64%.[2] As on-demand PDE5-i have been found effective in the treatment of ED after radiotherapy of prostate cancer in about half of the patients in randomized, controlled trials,[3,4] one may hypothesize that these drugs might be useful in the rehabilitation process as well. Tadalafil once a day also showed similar efficacy but even better compliance than on-demand.[5] In patients treated by both radiotherapy and androgen deprivation therapy though sildenafil seems to be less effective.[6] Schiff *et al.*[7] have reported in a nonrandomized and nonblinded study that the early use of PDE5i after BT was associated with a significant improvement in and maintenance of erectile function compared with its late use.[7] An Australian trial randomized 27 men undergoing radiotherapy (mostly BT) for localized prostate cancer to receive daily sildenafil 50 mg (titrated to 100 mg) or placebo starting 1 month after completion of radiation therapy for 6 months.[8] Primary end-point was erectile function measured by the international index of erectile function (IIEF)[9] at 2 years of follow-up. The results showed no difference in erectile function between the two groups. The authors concluded that there is no evidence that sildenafil provides long-term erectile function for patients, while on medication, but also stated that larger trials are required to examine the effectiveness of sildenafil for the prevention of ED.[8]

Pisansky *et al.*[1] recently published a large placebo-controlled, multicenter, double-blinded, randomized trial (n = 242) to assess the efficacy of tadalafil once-daily in maintaining erectile function in patients undergoing radiation therapy for localized prostate cancer (clinicaltrials.gov, Identifier NCT 00931528). Almost two-thirds of the patients received EBRT; in almost all the patients intensity-modulated techniques (median total dose 78 Gy) were applied. One-third received low-dose rate BT (LDR-BT) with iodine 125 or palladium 103 (145 Gy or 125 Gy, respectively). Patients on hormonal treatment were excluded. Patients received tadalafil 5 mg or placebo starting within 1 week after initiation of EBRT or the same day as LDR-BT for 24 weeks. Two hundred and twenty-one patients were evaluable. The primary outcome was spontaneous erectile function at 28–30 weeks after radiotherapy was started (i.e. 4–6 weeks after tadalafil was stopped). The patient was considered to maintain erectile function without the study drug at week 28–30 if he answered "about half of the time" or more (score 3–5) to question 1 of the IIEF: how often were you able to get an erection during sexual activity?[9] 79% and 74% of the participants assigned to the tadalafil group or to placebo maintained spontaneous erections, respectively, showing a difference of 5% (P = 0.49), at primary end-point. Although patients younger than 65 years seemed to maintain erectile function more frequently than older patients, the difference did not reach a statistically significant difference. The same was found for EBRT versus LDR-BT. At 1 year similar results were found: 72% of the patients who received tadalafil versus 71% who received placebo maintained erectile function (P = 0.93). The authors are to be congratulated to help answer the important question whether a PDE5i, in this case daily tadalafil, can be advised for the prevention of ED in patients undergoing radiation therapy, after being confirmed effective in about half of the patients to treat ED following radiotherapy for prostate cancer.

The strengths of the trial are the multicenter distribution, covering different types of medical practices, the use of standardized, modern radiation techniques and doses, the use of validated questionnaires, and the assessment of other aspects of sexual functioning than erectile function only.[1]

I wonder whether question 1 of the IIEF is the right choice to evaluate erectile function. Getting an erection does not mean that this is rigid enough for penetration (question 2) and whether this is maintained during sexual performance (question 4). Another possible limitation might be the relatively short administration of the study drug; 24 weeks might be too short to prevent penile fibrosis as a consequence of radiation therapy. We can speculate that a PDE5i, by increasing nightly, spontaneous, and voluntary erections,

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might improve oxygenation of the corporal bodies and therefore preserve endothelial and cavernosal function. This could prevent fibrosis occurring in the first 6–12 months after radiotherapy by restoration and preservation of nitric oxide-mediated vasodilation in the irradiated corporal bodies and maintain erectile function of patients undergoing radiation therapy. Because of the extended period of effectiveness, tadalafil, which lasts up to 36 h after intake, might have advantages above other PDE5i because of its prolonged and continuous enhancement of vascular responsiveness.

It has been written (and discussed) a lot in the literature about the role of PDE5i in the penile rehabilitation process for patients after radical surgery for prostate cancer.[10] Trials assessing the efficacy of PDE5i to prevent ED in patients undergoing nerve-sparing prostatectomy have shown disappointing results. For example vardenafil taken one-nightly for 9 months improved erectile function during the active drug treatment when compared with placebo, but this effect was terminated when the drug was stopped.[11]

Unfortunately, the results of the tadalafil prevention trial,[1] similar to the one with sildenafil,[8] do not allow us to advice patients to take PDE5i to prevent ED when undergoing radiotherapy for localized prostate cancer. Nevertheless, it is important to inform patients that such drugs are effective in about half of the cases to treat ED, with limited side-effects.[3–6]

REFERENCES

1 Pisansky TM, Pugh SL, Greenberg RE, Pervez N, Reed DR, *et al*. Tadalafil for prevention of erectile dysfunction after radiotherapy for prostate cancer: the Radiation Therapy Oncology Group[0831] randomized clinical trial. *JAMA* 2014; 311: 1300–7.

2 Incrocci L, Slob AK. Incidence, etiology, and therapy for erectile dysfunction after external beam radiotherapy for prostate cancer. *Urology* 2002; 60: 1–7.

3 Incrocci L, Koper PC, Hop WC, Slob AK. Sildenafil citrate (Viagra) and erectile dysfunction following external beam radiotherapy for prostate cancer: a randomized, double-blind, placebo-controlled, cross-over study. *Int J Radiat Oncol Biol Phys* 2001; 51: 1190–5.

4 Incrocci L, Slagter C, Slob AK, Hop WC. A randomized, double-blind, placebo-controlled, cross-over study to assess the efficacy of tadalafil (Cialis) in the treatment of erectile dysfunction following three-dimensional conformal external-beam radiotherapy for prostatic carcinoma. *Int J Radiat Oncol Biol Phys* 2006; 66: 439–44.

5 Ricardi U, Gontero P, Ciammella P, Badellino S, Valentino F, *et al*. Efficacy and safety of tadalafil 20 mg on demand *vs* tadalafil 5 mg once-a-day in the treatment of post-radiotherapy erectile dysfunction in prostate cancer men: a randomized phase II trial. *J Sex Med* 2010; 7: 2851–9.

6 Watkins Bruner D, James JL, Bryan CJ, Pisansky TM, Rotman M, *et al*. Randomized, double-blinded, placebo-controlled crossover trial of treating erectile dysfunction with sildenafil after radiotherapy and short-term androgen deprivation therapy: results of RTOG 0215. *J Sex Med* 2011; 8: 1228–38.

7 Schiff JD, Bar-Chama N, Cesaretti J, Stock R. Early use of a phosphodiesterase inhibitor after brachytherapy restores and preserves erectile function. *BJU Int* 2006; 98: 1255–8.

8 Ilic D, Hindson B, Duchesne G, Millar JL. A randomised, double-blind, placebo-controlled trial of nightly sildenafil citrate to preserve erectile function after radiation treatment for prostate cancer. *J Med Imaging Radiat Oncol* 2013; 57: 81–8.

9 Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, *et al*. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997; 49: 822–30.

10 Mulhall JP, Morgentaler A. Penile rehabilitation should become the norm for radical prostatectomy patients. *J Sex Med* 2007; 4: 538–43.

11 Montorsi F, Brock G, Lee J, Shapiro J, Van Poppel H, *et al*. Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. *Eur Urol* 2008; 54: 924–31.

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