

# Let's rethinking about the safety of phosphodiesterase type 5 inhibitor in the patients with erectile dysfunction after radical prostatectomy

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As the radical prostatectomy (RP) for the patient diagnosed as localized prostate cancer has been increasing, erectile dysfunction (ED) associated with RP is increased and ED after RP is a significant risk factor to reduce the quality of life for the patient after RP. Therefore, the treatment concept called penile rehabilitation was introduced and phosphodiesterase type 5 inhibitor (PDE5I) is used widely for the prostate cancer patient after RP. Generally PDE5I is considered as safe and effective drug for the prostate cancer patient after RP. Recently, a report against the general opinion that PDE5I use is safe in the patient with prostate cancer was reported and the analysis of 5-yr biochemical recurrence-free survival after RP between the PDE5I users and non-PDE5I users after bilateral nerve sparing RP showed decreased 5-yr biochemical recurrence-free survival in the PDE5I users. In addition, a longitudinal cohort


study reported that sildenafil, a kind of PDE5I, use might be associated with the development of melanoma and this result suggested the possibility of adverse effect of PDE5I on some kinds of cancers as well as prostate cancer. Moreover, the studies to evaluate the influence of nitric oxide (NO) and guanosine monophosphate (cGMP) signaling pathway associated with PDE5 showed both cancer reduction and cancer development. Therefore, the role of NO and cGMP signaling pathway in cancer was reviewed based on the previous studies and suggested the necessity of further clinical studies concerning about the safety of PDE5I in prostate cancer.

**Keywords:** Phosphodiesterase type 5 inhibitor, Prostate cancer, Biochemical recurrence

## INTRODUCTION

Prostate cancer is the common malignancy in the male population and the effort to find prostate cancer by prostate cancer screening leads to the higher diagnostic rate (Siegel et al., 2014). Especially, the incidence of localized prostate cancer compared with the past has been increasing due to the prostate cancer screening. According to a data analyzed in the North America, 80% of the patients diagnosed as prostate cancer is the localized cancer which is confined to the prostate (SEER Stat Fact Sheets from Prostate Cancer, 2013). Therefore, most of the patients diagnosed as localized prostate cancer are treated by the radical prostatectomy (RP) and the 10-yr disease specific survival rate is about 90% (Talcott et al., 1997) Erectile dysfunction (ED) is a common

problem to increase distress and decrease quality of life after RP. Nerve-sparing RP is introduced to decrease the ED after RP, however about 25%–75% of patients still experienced ED (Baniel et al., 2001; Bates et al., 1998; Braslis et al., 1995; Cooperberg et al., 2003; Helgason et al., 1997; Hollenbeck et al., 2003; Lilleby et al., 1999; Litwin et al., 1999; Meyer et al., 2003; Roehl et al., 2004; Schover et al., 2002). As the ED patients after RP is increasing, Briganti and Montorsi (2006) introduced the term penile rehabilitation to help erectile function recovery using any of drug and device. The theory of penile rehabilitation is that early intervention using oral medication with phosphodiesterase type 5 inhibitor (PDE5I), intracavernous injection, or vacuum erection device maintains corporal oxygenation and it can prevent ED by reducing penile atrophy, veno-occlusive dysfunction, and smooth

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muscle apoptosis (Magheli and Burnett, 2009; Montorsi et al., 1997). Several clinical studies presented the effectiveness of the penile rehabilitation using daily PDE5Is based on this concept and penile rehabilitation using daily PDE5Is has been used to prevent ED after RP (Aydogdu et al., 2011; Bannowsky et al., 2008; Montorsi et al., 2008; Montorsi et al., 2014; Mulhall et al., 2013; Padma-Nathan et al., 2008). Recently, there was a study questioned about the safety of PDE5I use in the patients after RP. Michl et al. (2015) reported that use of the PDE5I after bilateral nerve sparing RP reduced 5-yr biochemical recurrence-free survival compared with the non-PDE5I users at a median follow-up of 60.3 months. To the contrary, Gallina et al. (2015) reported that PDE5I use did not associated with 5-yr biochemical recurrence-free survival at a median follow-up of 40 months. Therefore, the safety and role of PDE5I in the prostate cancer are necessary to be reviewed.

## NITRIC OXIDE AND GUANOSINE MONOPHOSPHATE SIGNALING PATHWAY; ANTICANCER OR CANCER?

PDE5I treats ED to block that destruction of cyclic guanosine monophosphate (cGMP) and activates cGMP-dependant protein kinase G, which decreases intracellular  $Ca^{2+}$  and induce smooth muscle relaxation. Moreover, recent several evidences about the effect of PDE5I have been introduced in the heart disease, diabetes and cancer associated with NO and cGMP signaling pathway (Das et al., 2015). In particular, the role of NO and cGMP signaling pathway on the cancer has been not yet determined. Bian et al. (2012) suggested the reasons that some investigators report the anticancer effect and others did not as follows; first, although NO participates in normal signaling (e.g., vasodilation and neurotransmission), NO is also a cytotoxic or apoptotic molecule when produced at high concentrations by inducible nitric-oxide synthase (iNOS or NOS-2). In addition, the cGMP-dependent (NO/nitric oxide-dependent soluble guanylate cyclase; sGC/cGMP pathway) and cGMP-independent (NO oxidative pathway) components may vary among different tissues and cell types. Furthermore, solid tumors contain two compartments: the parenchyma (neoplastic cells) and the stroma (nonmalignant supporting tissues including connective tissue, blood vessels, and inflammatory cells) with different NO biology.

There is a study to analyze the effect of sildenafil on the prostate cancer growth and metastasis. Sildenafil was orally administered from the 31 days after human prostate cancer cell line inoculation

into the prostate of nude mouse and 25 and 75 mg/kg body weight of sildenafil was given every other day 15 times (30 days). Intermittent oral administration with sildenafil showed no association with primary tumor growth and metastases (Qian et al., 2003). In addition, some of the investigators presented the tumor suppression effect of exisulind which is a selective PDE5I on the prostate cancer (Narayanan et al., 2007; Webster and Leibovich, 2005). However, Weight et al. (2012) reported the different result that neoadjuvant use of exisulind showed no significant difference of apoptotic biomarkers such as bcl-2, Bax, Par-4, caspase 3, phosphatase and tensin homolog between biopsy and post-RP specimens in the localized prostate cancer patient. There was a recent retrospective study to compare the incidence rate of the prostate cancer in the men with ED treated with PDE5I over 7 yr and men was not treated with PDE5I. The rate diagnosed as prostate cancer of men without PDE5I treatment was 9.9% (258 of 2,612) and this result was significantly higher compared with the men treated with PDE5I (4.1%, 97 of 2,362). Moreover, elevation of prostate-specific antigen was lower in the men treated with PDE5I compared with the men without treatment (Chavez et al., 2013).

However, there were opposite findings suggested the adverse effect of PDE5I on the prostate cancer. Tumor growth and metastases are associated with angiogenesis and neuronal development and there was a study to find the formation of autonomic nerve fibers in the prostate gland that regulates prostate cancer development and metastases from *in vivo* animal study (Magnon et al., 2013). And chemical or surgical sympathectomy and genetic deletion of stromal  $\beta$ 2- and  $\beta$ 3-adrenergic receptors prevented early phases of tumor development. Cholinergic-induced tumor invasion and metastasis were inhibited by pharmacological blockade or genetic disruption of the stromal type 1 muscarinic receptor, leading to improved survival of the mice. Moreover, the authors revealed that the densities of sympathetic and parasympathetic nerve fibers in tumor and surrounding normal tissue were associated with poor clinical outcome by the analysis of prostate cancer specimens. Previous other findings about the role of PDE5I such as sildenafil on the angiogenesis and decreased natural killer cell activity may be related with the development of prostate cancer and dissemination (Ding et al., 2011; Fokas et al., 2012; Jerzak et al., 2008).

## PHOSPHODIESTERASE TYPE 5 INHIBITOR AND MELANOMA

Melanoma is a common malignancy associated with sun expo-

sure and the incidence is reported as 15–25 per 100,000 persons (Schadendorf, 2015). Previously, possible relationship between PDE5 and melanoma was suggested. In particular, the concern about the influence of PDE5I on melanoma was brought because a recent prospective cohort study reported that the use of sildenafil is associated with the increased risk of incident melanoma (Li et al., 2014). The incidence of skin cancers, including melanoma, squamous cell carcinoma, and basal cell carcinoma was obtained in the self-reported questionnaires together with the question regarding sildenafil use for ED during follow-up (2000–2010). And the authors found that sildenafil use was associated with a higher risk of melanoma. The major pathogenesis of melanoma is mitogen activated protein kinase (MAPK)/extracellular signal-regulated kinase signaling pathway (Gray-Schopfer, 2007). This pathway regulates cell survival downstream of a cascade of cytokines, receptor tyrosine kinases, and G protein-coupled receptors. It begins with the G protein Ras, which activates Raf, a serine/threonine-specific protein kinase. Raf phosphorylates mitogen/extracellular signal-regulated kinase, another protein kinase, which then activates the third and final protein kinase, MAPK. With MAPK being hyperactivated in up to 90% of human melanomas, this pathway is a key regulator of melanoma cell proliferation. *NRAS*, one of the Ras genes in humans, is mutated in 15% to 30% of melanomas. However, the most commonly mutated component of this pathway is *BRAF*, one of the three human Raf genes. B-Raf (*BRAF*) is mutated in 50% to 70% of melanomas, specifically at the 600 position where glutamic acid is substituted for valine (V600E) (Dong et al., 2003). The *BRAF* mutation up-regulates a transcription factor, *BRN2*, which binds to the PDE5 promoter, inhibiting its transcription. This leads to increased cGMP levels, eventual increases in intracellular calcium, and actin-myosin contractions. These contractions lead to enhanced invasive potential of tumor cells. In addition, *PED5A* was found as one of the genes downregulated in response to *BRAF* activation of the MAPK signaling pathway (Arozarena et al., 2011). Likewise, decreased PDE5 by PDE5I may have a role to develop melanoma.

## CONCLUSION

PDE5I has been used widely to prevent and treat ED associated with RP and no doubt about the safety of PDE5I in prostate cancer. However, a recent retrospective analysis reported the possibility of adverse effect of PDE5I on the biochemical recurrence after RP and questioned about the safety of PDE5I in the prostate cancer. At present, the results of preclinical studies about the role of

NO and cGMP signaling pathway showed both suppression and development of prostate cancer. And these conflicting results about the influence of NO and CGMP signaling pathway might be the findings that introduced the necessity of questioning the safety of PDE5I in prostate cancer. And a longitudinal cohort study reported PDE5I increased the risk of the development of melanoma and this result also suggested the adverse effect of PDE5I on some kinds of cancers.

Majority of the clinical studies about the efficacy and safety of PDE5I after RP showed the effect of PDE5I on the recovery of ED and investigate the general adverse events of PDE5I such as hot flush, headache, dizziness, and dyspepsia. There was no study regarding the influence of PDE5I on the biochemical recurrence after RP. Therefore it needs to review the accumulating clinical data and prospective clinical studies about the association with PDE5I and the development of prostate cancer although PDE5I has helped many patients having ED associated with RP.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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