REVIEW PAPER

THE PHOSPHODIESTERASE-5 INHIBITORS AND PROSTATE CANCER - WHAT WE RELY KNOW ABOUT IT?

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ABSTRACT

Phosphodiesterase-5 inhibitors (PDE5Is) represent a group of drugs that are registered for the treatment of erectiledysfunctions predominantly, but recently also for treatment of pulmonary hypertension and benign prostatic hypertrophy. However, more and more research deals with possible antitumor potential of PDE5Is in different types of cancers, including prostate cancer. Prostate cancer represents theone of the most common carcinoma in the male population, whose incidence is continuously increasing. Early detection combined with radical prostatectomy increases the survival rate, but also it is necessary to keep in mind the quality of lifeof patients undergoing prostatectomy in light of bladder control and erectile function. Authors of various clinical studies presented the results that often lead to totally opposing conclusions. For example, Chavez and colleagues have shown that use of PDE5Is in men with erectile dysfunction decreases the risk of developing prostate cancer, while, on the other hand, Michl and colleagues pointed out the adversely effect of PDE5Is on biochemical recurrence after bilateral nerve sparing radical prostatectomy. In that sense, the aim of this review was to present as many as possible of existing results dealing with of action of PDE5Is in the field of prostatic carcinoma. Taking into account all presented data, it can be concluded that effect of PDE5Is on formation, development andoutcome of treatment in patients with prostate carcinoma isvery intriguing question, whose response requires additionalboth experimental and clinical research.

Keywords: *Phosphodiesterase-5 inhibitors, Prostate carcinoma, Sildenafil, Tadalafil.*

INTRODUCTION

Phosphodiesterase-5 inhibitors (PDE5Is) were originally synthesized for the treatment of hypertension and angina pectoris, but they did not show efficacy in this therapeutic field. Sildenafil was firstly synthesized compound that belongs to this class of drugs, and therefore was the most intensively investigated. Namely, during experimental investigations it was shown that sildenafil induces penileerection, which was completely unexpected (1, 2). Consequently, clinical trials were conducted to investigate clinical benefit and safety for the treatment of erectile dysfunction (ED) with sildenafil (3) and sildenafil was approved foruse in ED and became the first official oral drug for ED treatment (4). After sildenafil, vardenafil and tadalafil wereapproved for treatment of ED (5, 6), and recently some newPDE5Is have been investigated, such as avanafil, lodenafil, udenafil and mirodenafil (7-10).

Besides the well documented and well described effects of PDE5Is in therapy of ED, there are grooving interests regarding actions of PDE5Is in other pathological andpathophysiological entities. There are a lot of data regarding cardioprotective effects of PDE5Is in patients with different forms of heart failure and in patients with diabetes mellitus (11, 12). It is shown that PDE5Is have protective effects due to other complications associated with diabetes mellitus such as neuropathy and diabetic nephropathy (13-16). In rat and mouse experimental models of stroke both sildenafil and tadalafil improved neurogenesis and neurological outcome (17-19), but there are still limited information considering the neuroprotective and neuro- restorative effects of PDE5Is human stroke patients (20). PDE5Is are also used for treatment of pulmonary arterial hypertension, since it has been shown that sildenafil causesvasodilatation of pulmonary arteries and improves the ex- change of gases in the lungs in patients with pulmonary hypertension (21).

Most intriguing effects of PDE5Is are probably related to their antitumor effects, increase of tumor sensitivity to anticancer drugs and protective effects to other organs and tissues during chemotherapy and radiotherapy. It was shown that PDE5Is induce apoptosis and reduction of cellgrowth in different human tumors, such as bile duct carcinoma, colorectal carcinoma, cervical cancer, and breast carcinoma (22, 23).

The objective of this paper is to review and summarizethe experimental and clinical findings considering the effects of PDE5Is as antitumor agents.

CYCLIC NUCLEOTIDE PHOSPHODIESTERASES - BASIC CHARCTERISTICS

Cyclic nucleotide phosphodiesterase enzymes (PDEs) represent a large family of enzymes that selectively catalyze the hydrolytic breakdown of the 3' cyclic phosphate bonds of adenosine and/or guanosine 3',5' cyclic mono- phosphate to produce 5'-AMP and 5'-GMP, respectively. (24). Cyclic adenosine 3',5' monophosphate (cAMP) and cyclic guanosine 3',5' monophosphate (cGMP) are second messengers that have crucial roles in regulation of numerous physiological processes and functions in biological systems, such as cell growth, proliferation and death, energy homeostasis, muscle contractility and relaxation, neuronalsignaling, immune and inflammatory responses, etc. The cAMP and cGMP concentrations in the cell, and thereforethe functions they regulate, are precisely determined by activity of adenylyl and guanylyl cyclases, which catalyze their synthesis, and PDEs, which catalyze their hydrolysis. Consequently, any disturbance in intracellular content of cAMP and cGMP and their signaling pathways lead to dis-ease or dysfunction, such as diabetes, pulmonary hyper- tension, heart failure, erectile dysfunction, etc. (25-29).

Incredible complexity of regulation of cAMP and cGMP in the cell, what more in different parts of the same cell, pointed out the possibility of expression of several different PDE classes, as well as the specificity of their localization and different modes of regulation (30). So far, eleven PDE isoenzyme families have been identified encoded by large and distinct gene superfamily, and it is estimated that there are more than a hundred different mRNA products from this gene superfamily due to alter- native sites for transcription initiation and various splicing mRNA precursor molecules. Most of PDE mRNA can be translated to proteins, but it cannot be said with certainty how many different PDE mRNAs are transcribed, whether they are all translated into proteins, and maybe most importantly does all of them have physiological role in the body and which it is. PDE isoenzyme families are classified according to their affinities to cAMP and cGMP, regulatory properties, sensitivity to specific inhibitors and activators, tissue localization (Table 1). Based on the substrate specificities PDEs can be sorted in three large groups: PDEs selective for cAMP hydrolysis (PDE4, PDE7, and PDE8), cGMP selective PDEs (PDE5, PDE6, and PDE9), and PDEs with dual specificity, which hydro- lyses both cAMP and cGMP (PDE1, PDE2, PDE3, PDE10 and PDE11) (31, 32).

Bearing in mind the fact that PDEs have crucial importance in regulation of cAMP and cGMP concentrations in the cells, and thus the downstream signaling pathways and biological responses, on one hand, and many specific isoforms of PDEs which are differently represented in cells,

tissues and organs, in which they have diverse physiological roles, on the other, PDE superfamily represents excellent therapeutic target (30, 33). Also, one of the main reasons that make PDEs a good therapeutic target refers to the pharmacological principle that change of degradation of any ligand (or second messenger) often has greater impact on change in concentration of that ligand than changes in rate of its synthesis (30).

Different isoforms of PDEs are located in specific part of the cell, thus enabling activation of individual signaling pathways due to cAMP or cGMP and propagation of specific, desirable signals. This compartmentalization of cAMP or cGMP signals is related to PDEs sequestrationin specific subcellular locations where they are embedded into different macromolecules and make connections withdifferent cellular structures (34).

Table 1. Overview of PDE isoforms

PDE isoform	Substrate	Tissue presence	Intracellular localization
PDE1A	cAMP/cGMP	Smooth muscles, heart, brain, lungs, sperm	Cytosolic (predominantly)
PDE1B	cAMP/cGMP	Smooth muscles, neurons, lymphocytes, macrophages	Cytosolic
PDE1C	cAMP/cGMP	Brain, smooth muscles, spermatids, olfactory epithelium	Cytosolic
PDE2A	cAMP/cGMP	Brain, adrenal medulla, heart, platelets, macrophages, endothelium	Membrane bound and cytosolic
PDE3A	cAMP	Heart, vascular smooth muscles, platelets, kidney	Membrane bound and cytosolic
PDE3B	cAMP	Vascular smooth muscles, liver, adipocytes, kidney, pancreatic β-cells, sperm, lymphocytes, macrophages	Membrane bound (predominantly)
PDE4A	cAMP	Brain, olfactory system, immune system, testis	Membrane bound (predominantly)
PDE4B	cAMP	Brain, immune system	Membrane bound (predominantly)
PDE4C	cAMP	Lungs, testis, some neurons	Cytosolic (predominantly)
PDE4D	cAMP	Brain, inflammatory cells	Cytosolic and particulate fractions
PDE5A	cGMP	Platelets, vascular smooth muscles, brain, lung, heart	Membrane bound/Cytosolic
PDE6A/ PDE6B	cGMP	Photoreceptors in retina (rods), pineal gland	Cytosolic
PDE6C	cGMP	Photoreceptors in retina (cones), pineal gland	Cytosolic
PDE7A	cAMP	Immune cells, heart, skeletal muscle, endothelium	Cytosolic
PDE7B	cAMP	Brain, heart, skeletal muscle, liver, pancreas, testis	Cytosolic
PDE8A	cAMP	Testis (predominantly), spleen, small intestine, ovary, colon, kidney	Cytosolic/ Particulate fractions
PDE8B	cAMP	Brain, thyroid gland	Cytosolic/ Particulate fractions
PDE9A	cGMP	Highly represented in the body	Cytosolic/Nucleus
PDE10A	cGMP	Brain, testis, heart, thyroid gland	Cytosolic/ Particulate fractions
PDE11A	cAMP/cGMP	Skeletal muscle, prostate, testis, thyroid gland, liver, salivary glands	Cytosolic

PHYSIOLOGY OF PHOSPHODIESTERASE-5

Phosphodiesterase-5 (PDE5) was firstly identified and characterized from platelets and lungs (35, 36), but they came into focus after discovering the role in regulation of smooth muscle contractility, and even more after discovery of sildenafil, as specific inhibitor of PDE5. PDE5 now ismost famous as molecular target for treatment of erectile dysfunction (ED), and recently for treatment of pulmonary hypertension. However, investigations regarding the PDE5and different PDE5Is indicate other roles of interest such as:

1) regulation of function of Purkinje cells in cerebellum (37, 38);
2) regulation of platelet function (39);
3) regulation of sodium homeostasis via renal sodium excretion (40);
4) regulation of neurogenesis and cognition (41, 42);
5) regulation of function of intestine cells (43, 44).

Only one gene encoding PDE5 was found for now, but there are three different variants of mRNA for PDE5A in humans and consequently three different polypeptides (PDE5A1, PDE5A2 and PDE5A3), which vary in their amino-terminal parts, but their first exons followed by common sequence of 823 amino acids are identical (30).

As well as other PDEs, PDE5 is a dimer, and the monomers are made up of an amio-terminal part which contains

phosphorilation domain, two allosteric cGMP binding sites and dimerization domain (or part of it), and carboxyl-terminal part containing catalytic domain (45, 46).

As mentioned above, the precise regulation of PDEs enzymatic activity have pivotal role in maintaining thecAMP and cGMP in adequate ranges for physiologicalcellular function. Few different mechanisms are included in regulation of PDE5 activity, and one of them is phosphorylation by protein kinase A (PKA) or protein kinaseG (PKG). Phosphorilation changes conformation of PDE5 and thus increases affinity for cGMP and catalytic activity for cGMP hydrolysis up to 50-70% (47, 48). It has been shown that treatment of platelets, cardiomyocytes and smooth muscle cells with nitric oxide (NO) induces immense increase in cGMP concentration, followed by rapiddecrease, produced by NO-induced protein kinase activity (49-51). Another mechanism implies the presence of two allosteric cGMP binding sites (GAF), and binding of cGMP at these allosteric sites induce increase in catalytic activity of PDE5, which some authors see as a new therapeutic opportunity (52). Actually, it is postulated that after binding of cGMP to GAF and increased enzymatic activity of PDE5, PKG induces phosphorilation, thereby stabilizing and prolonging the increased catalytic activity of PDE5. Possible mechanism for PDE5 deactivation implies dephosphorylation by catalytic activity of protein phosphatases, mainly protein phosphatase 1 (PP1), while cleavage of PDE5 into inactive form is performed by the action caspase-3 (53-56).

Bearing in mind that PDE5 is mostly represented in smooth muscles, it is practically present in almost all tis- sues and organs in the body, with different distribution of PDE5 isoforms (PDE5A1, PDE5A2 and PDE5A3), whereby the PDE5A2 is the most widespread (57). Using appropriate methods such as RT-PCR, *in situ* hybridization (ISH), Northern blotting, Western blotting or immunohistochemistry methods, PDE5 mRNA or PDE5 protein arefound in vascular smooth muscle, heart, lungs, platelets, brain, liver, pancreas, skeletal muscle, placenta, gastrointestinal tissues and reproductive system, with different distribution of PDE5A isoforms between the species, tissues and organs (58-62).

PHOSPHODIESTERASE-5 INHIBITORS

Phosphodestrase-5 AND mNO/cGMP signaling pathway in cancer

Results from a number of studies have pointed out the facts considering the presence of PDE5 in many types of carcinoma cells including colon adenocarcinoma, lung cancer, breast cancer, prostatic cancer and urinary bladder cancer,and also overexpression of PDE5 in breast malignant tumors, urinary bladder cancer, pancreas and prostatic cancer (63-70). Transformation of normal, healthy cell to malignantcell occurs as consequence of DNA damage and genetic alterations that appear due to procarcinogenic microenvironment. Chronic mild inflammation, for instance, increases NO production due to increased activity of inducible NO synthase (iNOS) which further enhances tumor growth, invasiveness and dissemination (71-73). Results from other investigations pointed out the other, anti-tumor nature of NOby inducing apoptosis and cytotoxicity (74, 75). This dual, paradoxical role of NO arises from the diversity of the signalpathways in which NO acts as a regulator, wherein the con-centration probably determines the promoting or inhibitoryeffects of NO in cancerogenesis (76, 77).

cGMP is synthesized by catalytic activity of solubleguanylyl cyclase (sGC) which is a receptor for NO. Namely,NO binds to ferrous heme of the β1 subunit of the sGC andcauses the rise in sGC activity and cGMP production (78).Consequently, cGMP level in the cells depends not onlyon enzymes involved in cGMP metabolism, but also on enzymes (endothelial, inducible and neuronal NOS) and pathways which regulate NO production and degradation (79). Similarly to NO, the roles of sGC and cGMP in tumor biology and cancerogenesis also remained paradoxical despite a large number of studies and investigations in re- cent decades, so the question considering the protective ordeleterious role of NO/sGS/cGMP signaling pathway still has no answer. Chang and coauthors recently indicated that activation of guanylyl cyclase and increased levels of cGMP have beneficial effects on inflammation-promoted colorectal neoplasia in mice (80). On the other hand Cesarini with colleagues highlighted the negative correlation between the increased expression of PDE5 and consequentdecreased levels of cGMP and tumor aggressiveness and clinical outcome in patients with glioblastoma multiforme (81). Scientific group gathered around Ferid Murad, No- bel Prize co-winner in Physiology or Medicine for NO signaling, assumed several possibilities for such effects:

1) beside role in physiological signaling, NO produced at high concentrations by iNOS, also exhibits cytotoxic and proapoptotic properties;
2) the components of NO/sGC/ cGMP (cGMP-dependent) pathway and NO oxidative pathway (cGMP-independent) vary between different cell types and tissues;
3) solid tumors are composed of parenchyma, which contains neoplastic cells, and stroma, whichincludes nonmalignant supporting tissues (connective tissue, blood vessels) with different behavior due to NO/ sGC/cGMP signaling (79, 82).

PHOSPHODIESTERASE-5 INHIBITORS AND PROSTATE CANCER

Prostate cancer is one of the most common solid malignant tumors in men population worldwide and thusrepresents a huge social and medical issue. In European Union prostate cancer is the most common malignancy in men with 365,000 new prostate cancer cases in 2015 (83). Early detection and radical surgical removal of the cancer (nerve-sparing radical prostatectomy) significantly increase the survival and quality of life due to recovery of bladder control and erectile function. Administration of daily doses of PDE5Is in patients after nerve-sparing radical prostatectomy (NSRP) due to localized prostate cancer showed increase in penile function

and positive effect on the recovery and maintenance of erectile function afterthe surgery (84). Despite routine use of PDE5Is in treatment of erectile dysfunction, as well as many researches dealing with problematics of different relations of PDE5Is and prostate cancer, many questions remained without answers and many results unclear.

Liu and coworkers dealt with role of PDE5/cGMP/PKG signal pathway in stemness and differentiation ofprostatic cancer stem cells (PCSC) (85). Namely, PCSC represent a small population of cancer cells with the ability for self-renewal, proliferation, invasive and meta- static growth. In their study these authors postulated that PDE5/cGMP/PKG signaling have crucial role in stemness remaining of PCSC. Furthermore, it is shown that activation of cGMP/PKG pathway by inhibition of PDE5 using vardenafil and tardalafil, results in activation of mammalian ste20-like protein kinase (MST – Hippo pathway) and consequent phosphorylation of transcriptional co- activator with PDZ-binding motif (TAZ), leading to its degradation and reduction of stemness in PCSC. Results from this investigation, conducted on *in vitro* on cell cultures and *in vivo* on xenografts, revealed interesting connection between PDE5/cGMP/PKG pathway and Hippo/ TAZ pathway in maintaining of PCSC stemness, as well as the possible reason for the usefulness of PDE5Is in prostate cancer therapy.

Das and coauthors, on the other hand, pointed out the sensitizing activity of sildenafil to prostate cancer cellson doxorubicin induced apoptosis through CD95 (86). Only co-treatment of prostate cancer cells with doxorubicin and sildenafil induced decrease in expression of FLIP (FLICE-like inhibitory protein), which represents one of the major regulators of CD95-mediated apoptosis. Furthermore, combined application of doxorubicin and sildenafil increased CD95 cell surface localization and decreased expression of Fas associated phosphatase-1 (FAP-1). Fas (APO-1/CD95) is death receptor which mediates in apoptosis of various types of cells, but many neoplastic cells are resistant to apoptosis induced by Fas. Increased expression of FLIP is brought into connection with increased tumor growth and immunologic escapeof tumors. On the other hand increased surface localization and activation of CD95 leads to the formation ofdeath-inducing signaling complex (DISC) and inductionof apoptosis, while FAP-1 disables the moving the CD95 (human Fas protein) to the membrane. Doxorubicin and sildenafil co-treatment also reduced the nuclear translocation of p65 and p50 and activation of NF-κB, thereby reducing FLIP expression, because it is shown that NF-κB up-regulates the expression of FLIP. Based on these results it was identified a new mechanism of inducing cell death in prostate cancer cells which implies the increased surface localization of CD95, decreased expression of FLIP and FAP-1, as well as inactivation of NF-κB affected by concomitant action of sildenafil and doxorubicin. Similar, beneficial effects of combined application of PDEIs with standard chemotherapy were noticed also in bladder and pancreatic tumor cells (69). Despite the clinical efficacy in combat with different types of malignancies, doxorubicin, as well as other anticancer drugs, exhibit severe side effects such as cardiotoxicity. The same group of authors in their previous study showed that PDE5 inhibitor tadalafil can attenuate cardiac dysfunction induced by doxorubicin, without simultaneous reduction of doxorubicin antitumor effect (87). Tadalafil during combined use with doxorubicin induced significant increasein manganese superoxide dismutase (MnSOD), cGMP levels and PKG activity in the heart, with preservation of ejection fraction. Assessment of the effects on cell-killing potential of doxorubicin in human osteosarcoma cancer cell lines and xenografts showed that tadalafil did not impede the anticancer activity of doxorubicin neither *in vitro* nor in the *in vivo*.

Results of the Ammirante and coauthors indicated that PDE5Is prevent myofibroblast activation and CXCL13 induction in castration-resistant prostate cancer (88). Cancer-associated fibroblasts (CAF) represent a various cell population that has many promoting roles in cancer progression, and myofibroblasts are part of CAF family. Chemoattractant C-X-C motif chemokine 13 (CXCL13)is chemoattractant for B-cells and mediates movement of B-cells into prostate cancer. Those lymphocytes that infiltrate cancer tissue produce a number of cytokines, suchas lymphotoxin, which contribute to the survival, development and dissemination of prostate tumor cells. In this investigation sildenafil prevented myofibroblast activationand decreased quantity of CXCL13 in castrated Myc-CaP (allografts of androgen-dependent mouse prostare cancer) tumor-bearing mice.

In research by Chavez and colleagues it have been indicated that men with erectile dysfunction treated with PDE-5Is tended to have less of a chance of being diagnosedwith prostate cancer (89). Authors have conducted retrospective study using electronic medical records of men suffering of erectile dysfunction during a period of 7 years.Participants in the study were selected based on similar risk factors for the development of prostate cancer, andof total number of 4974 men included into investigation 47.5% of them used PDE5Is, while the others did not use any drugs from this group. Results led to conclusion that use of PDE5Is is associated with lower values of prostate- specific antigen (PSA), higher incidence of benign prostatic hyperplasia (BPH) and, most importantly, lover risk of developing prostate cancer.

Following this investigation Jamnagerwalla and co- authors conducted a 4-year multicenter study in North American men investigated the association between the PDE5Is use and prostate cancer risk (90). The research involved 6,501 men 50-75 years old, with PSA within the physiological values for age and a single negative prostate biopsy. TRUS (ten-core transrectal ultrasound) guided prostate biopsies were performed at 2nd and 4th year of trial,regardless of the PSA value. Results from these authors showed that PDE5Is use was not associated with prostate cancer diagnosis, but there was an inverse between PDE5Isand prostate cancer diagnosis, although this was not statistically significant. Limitations of this study that were mentioned by the authors include a small number of respondents who used PDE5Is (5.6%), as

well as unavailable data considering the use and dosage of PDE5Is.

Jo and colleagues focused their interest on effects of PDE5Is on oncologic outcomes in patients with prostate cancer after radical prostatectomy (91). A total numberof 1082 patients who underwent radical prostatectomybetween January 2005 and December 2014 were divided according postoperative use of PDE5Is into three groups: non-PDE5I group, on-demand group, and penile rehabilitation group. The patients within the last two groups used several types of PDE5Is: sildenafil, tadalafil, vardenafil, avanafil, udenafil, and mirodenafil. Using appropriate statistical tests biochemical recurrence were assessed between groups that used PDE5Is and that did not, as wellas between group that used PDE5Is on demand and penilerehabilitation group. Based on data analysis authors concluded that PDE5Is treatment following radical prostatectomy have no impact on biochemical oncologic outcome and that PDE5Is use in patients after radical prostatectomyis clinically safe.

On the other hand, Michl and coworkers presented results that were completely opposite to the previously mentioned clinical and experimental investigations (92). Authors analyzed data of 4752 patients with prostate cancer, in whom bilateral nerve sparing radical prostatectomy was applied between January 2000 and December 2010, and assessed the risk of biochemical recurrence between the patients who used PDE5Is (23.4%) after the surgical treatment and patients who did not (76.6%). Five-year survival without biochemical recurrence in patients receiving PDE5Is was 84.7%, compared to 89.2% in group without PDE5Is treatment, and biochemical recurrencewas estimated due to PSA level (0.2 ng/ml or greater and increasing after). Based on the results conclusion weremade that use of PDE5Is following radical prostatectomy may adversely impact biochemical recurrence. For the explanation of the obtained results authors relied on previous researches where it have been demonstrated that PDEIs have proangiogenic and proneurogenic properties (93, 94). Although increased density of autonomic nerve fibers in tumor and surrounding tissue were brought into connection with poor clinical outcome, and angiogenesis is well known required factor for tumor development, conclusion that PDEIs represent independent risk factor for biochemical recurrence of prostate cancer due to enhancing role of PDEIs in nerogenesis and angiogenesis, remain in domain speculation (95, 96). On the contrary, recent study by El-Naa and coauthors showed that sildenafil potentiated antitumor activity of cisplatin by induction of apoptosis and inhibition of proliferation and angiogenesis in in Ehrlich solid-tumor-bearing mice (97).Few other authors also pointed out the limitations of the investigation conducted by Michl and coauthors such as lack of data due to the duration, dose, type and period of starting use of PDE5Is (98).

Regarding the results of the Michl and coauthors it was conducted investigation by Gallina and colleagues with similar but extended aims (99). Namely authors examined linkbetween usage of PDE5Is, therapy scheme of PDE5Is, number of taken PDE5-I pills, and biochemical recurrence (PSA $\geq$ 0.2 ng/ml) in 2579 patients with prostate carcinoma curedby bilateral nerve-sparing radical prostatectomy. Patients were classified in three groups due to PDE5Is usage withintwo years after the surgical procedure: on demand, rehabilitation schedule (daily use of PDE5Is for at least 3 months),and no use of PDE5Is. Using the multivariable Cox regression models it was confirmed that use of PDE5Is, either ondemand or on a rehabilitation schedule, was not associatedwith biochemical recurrence in patients treated by nerve- sparing radical prostatectomy due to localized prostate carcinoma. Furthermore, there were not significant differencesbetween patients taking PDE5Is pills on demand and thosewho were treated with a rehabilitation scheme, as well as due the number of PDE5-I pills taken by each patient.

CONCLUSIONS

Within this review are presented results from various investigations in which different experimental models were used regarding clarification role of PDE5Is in prostate cancer therapy, but still we cannot say with certainty where is the place of PDE5Is in cancer treatment protocols. It could be concluded that more results indicate a favorable role of PDE5Is in treatment of cancer, but this fact also remains in the domain of speculation, bearing in mind that the exact mechanisms of positive action of PDE5Is, as adjuvant anticancer drugs, are not fully understood. Additional experimental research is needed to clarify all potential mechanisms of action of PDE5Is in the field of cancer treatment, but also of crucial importance is to collect as many clinical data as possible. All these information together can allow us do fully understand all mechanisms of action of PDE5Is in tumor tissues and see should they be included in therapy or not, as well as should they be included in cure protocols of specific types of cancers.

COMPETING INTERESTS

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