8 Drug Repositioning of the Phenylpiperazine Derivative Naftopidil in Prostate Cancer Treatment

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Abstract

Naftopidil, a selective α_1-adrenoceptor antagonist, is commonly used for the treatment of benign prostatic hyperplasia, a prostatic disease occurring in elderly men. In drug repositioning studies conducted from our laboratory, we demonstrated that naftopidil has growth inhibitory effects by inducing G_1 cell cycle arrest in cancer cells, fibroblasts, and vascular endothelial cells. Moreover, naftopidil has been shown to bind directly to and inhibit the polymerization of tubulins; thus, naftopidil may exhibit general cytotoxicity in many types of cells. Recent evidence has supported that additive naftopidil treatment in combination with chemotherapy could be a new clinical application for the treatment of prostate cancer.

Keywords

Prostate cancer · Naftopidil · Drug repositioning · Cell cycle · Phenylpiperazine-based structure

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8.1 Introduction

In the clinical setting, benign prostatic hyperplasia (BPH), a common prostatic disease in elderly men (Kawabe 2006), is generally treated using α_1-adrenoceptor (AR) antagonists. Indeed, in patients with BPH, α_1-AR antagonists have been shown to decrease prostatic smooth muscle tone and rapidly affect urinary flow.

Based on the selectivity for α_1-AR, α_1-AR antagonists can be classified as subtype-nonselective α_1-AR antagonists or subtype-selective α_1-AR antagonists. Importantly, research has demonstrated that cardiovascular side effects are less frequent in patients administered with subtype-selective α_1-AR antagonists than in those patients administered with subtype-nonselective α_1-AR antagonists (Roehrborn and Schwinn 2004). In Japan, only subtype-selective α_1-AR antagonists, which were developed in Japan, are prescribed for patients with BPH because these drugs exhibit high tolerability with fewer side effects (Yokoyama et al. 2006; Tsuritani et al. 2010).

α_1-ARs are divided into α_{1A}, α_{1B}, and α_{1D} subtypes (Bylund et al. 1994). α_{1A}-AR is the most abundant subtype in the prostate gland, followed by α_{1D}-AR (Walden et al. 1999). Tamsulosin is an α_{1A}-AR- and α_{1D}-AR-selective antagonist, and silodosin is a highly selective α_{1A}-AR antagonist. Naftopidil is also an α_{1A}-AR- and α_{1D}-AR-selective antagonist but has a comparatively higher selectivity for α_{1D}-AR than tamsulosin. Notably, naftopidil has been shown to enhance bladder capacity, promote voiding by blocking the activity of afferent nerves (Yokoyama et al. 2006), and clinically alleviate obstructive voiding and storage symptoms associated with BPH (Nishino et al. 2006; Takahashi et al. 2006).

8.2 History of α_1-AR Antagonists

The global incidence of prostate cancer (PCa) in men is increasing continuously (Gronberg 2003). The majority of PCa cases arise in the prostate, concomitant with BPH (Bostwick et al. 1992). The incidence of BPH has been shown to increase with age, to a greater extent than that of PCa (Alcaraz et al. 2009). Thus, generally, α_1-AR antagonists are often administered for the treatment of BPH before the diagnosis of PCa.

In two observational cohort epidemiological studies, a low prevalence of PCa has been reported in patients with BPH administered with α_1-AR antagonists. Indeed, the quinazoline-based, subtype-nonselective α_1-AR antagonists doxazosin and terazosin were shown to decrease PCa incidence (Harris et al. 2007). Additionally, alfuzosin, a subtype-nonselective α_1-AR antagonist, and tamsulosin, a subtype-selective α_1-AR antagonist, reduce the incidence of high-grade PCa in a manner related to the cumulative duration of α_1-AR antagonist administration (Murtola et al. 2009). These data strongly suggested that α_1-AR antagonists may have anticancer effects.

Drug repositioning (DR) is a strategy used to develop new applications for existing approved drugs by discovering novel therapeutic effects or drug targets

(Masuda et al. 2020). Based on epidemiological evidence, quinazoline-based, subtype-nonselective α_1-AR antagonists, such as doxazosin, prazosin, and terazosin, have been extensively investigated and have been shown to have growth inhibitory effects in PCa cells (Kyprianou 2000). In PCa cells, the growth inhibitory effects of quinazoline-based, subtype-nonselective α_1-AR antagonists have been shown to be involved with apoptosis induction (Kyprianou and Benning 2000; Lin et al. 2007). Kyprianou et al. evaluated the structures of quinazoline-based compounds and reported that quinazoline-based, subtype-nonselective α_1-AR antagonist-induced apoptosis may be independent of the α_1-AR signal and biological characteristics of PCa cells (Anglin et al. 2002; Benning and Kyprianou 2002). Additionally, Garrison et al. reported that doxazosin and the novel lead quinazoline-derived compound DZ-50 reduced the viability of vascular endothelial cells, leading to the suppression of tumor vascularity in PCa xenografts (Garrison et al. 2007). Although doxazosin and DZ-50 have quinazoline-based structures, these effects in vascular endothelial cells may not involve an apoptotic mechanism. Notably, several studies demonstrated that the subtype-selective α_1-AR antagonist tamsulosin has no growth inhibitory effects in PCa cells (Kyprianou and Benning 2000; Benning and Kyprianou 2002).

8.3 Important Observations

8.3.1 Anticancer Effects of Naftopidil in PCa Treatment

In DR studies from our laboratory, we demonstrated that naftopidil has growth inhibitory effects by inducing G_1 cell cycle arrest in PCa cells, renal cell carcinoma (RCC) cells, and colon adenocarcinoma cells, as well as in normal prostatic fibroblasts and vascular endothelial cells (Kanda et al. 2008; Hori et al. 2011; Iwamoto et al. 2013; Ishii and Sugimura 2015) (Fig. 8.1).

In PCa cells, naftopidil inhibits cell proliferation in human LNCaP cells, which are androgen sensitive and androgen receptor positive, as well as human PC-3 cells, which are androgen insensitive and androgen receptor negative, in a concentration-dependent manner (Kanda et al. 2008). The antiproliferative mechanisms of naftopidil involve the induction of G_1 cell cycle arrest linked to increased expression of p27 and p21 in LNCaP cells and p21 in PC-3 cells as well as the inhibition of AKT phosphorylation at Ser473, particularly in PC-3 cells. In vivo analyses have shown that oral administration of naftopidil suppresses PC-3 tumor growth by reducing microvessel density (MVD). Additionally, naftopidil-induced apoptosis was not detected by Hoechst 33258 staining, DNA ladder formation, or poly-(ADP ribose) polymerase cleavage.

Additionally, Hori et al. demonstrated that naftopidil exerts antiproliferative effects, which are independent of α_1-AR subtype (α_{1A}, α_{1B}, and α_{1D}) expression in PCa cells and normal prostatic fibroblasts; these findings supported that naftopidil is likely to promote G_1 cell cycle arrest in several types of cells (Hori et al. 2011). Accordingly, we hypothesized that the antiproliferative effects of naftopidil may be

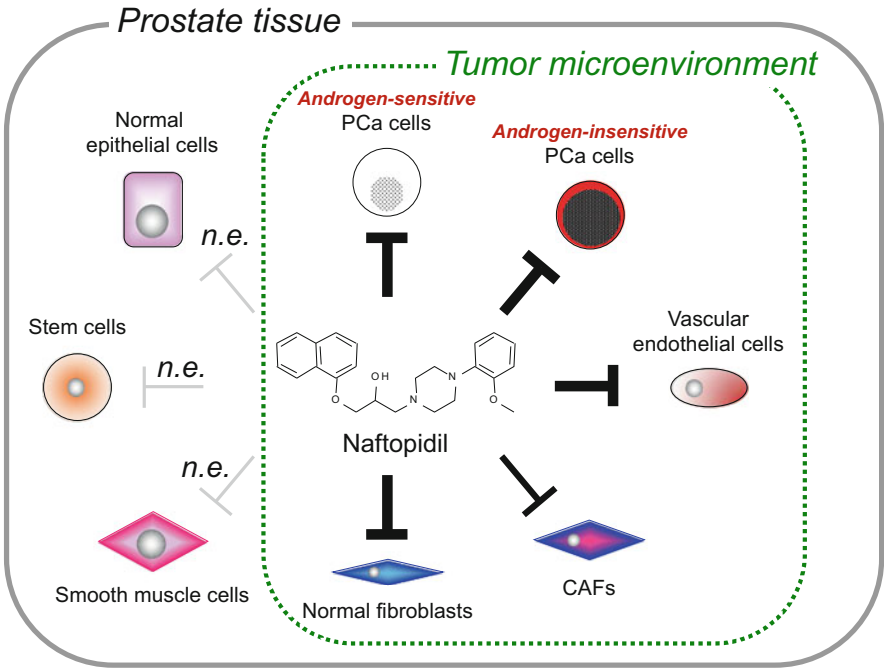

Fig. 8.1 Growth inhibitory effects of naftopidil in the tumor microenvironment. The tumor microenvironment in prostate cancer (PCa) includes a number of cells, such as androgen-sensitive PCa cells, androgen-insensitive PCa cells, normal fibroblasts, carcinoma-associated fibroblasts (CAFs), and vascular endothelial cells. Our studies of drug repositioning suggested that naftopidil may induce G_1 cell cycle arrest to block highly proliferative cell growth (Kanda et al. 2008; Hori et al. 2011; Iwamoto et al. 2013; unpublished data). n.e., not examined

related to its off-target effects. Interestingly, naftopidil strongly inhibits the proliferation of normal prostatic fibroblasts compared with that of PCa cells and decreases the secretion of the tumorigenic soluble factor interleukin-6 derived from normal prostatic fibroblasts, implying that stromal support of PCa cells may be suppressed by naftopidil in the tumor microenvironment. Importantly, no antiproliferative effects were observed following tamsulosin treatment in PCa cells or normal prostatic fibroblasts.

Similar to the results in PCa cells and normal prostatic fibroblasts, Iwamoto et al. demonstrated that naftopidil inhibits RCC cell and vascular endothelial cell proliferation via promotion of G_1 cell cycle arrest (Iwamoto et al. 2013). In an in vivo RCC xenograft model, oral administration of naftopidil was found to strongly decrease MVD in tissues, suggesting that naftopidil may have both direct effects in cancer cells and indirect effects in stromal cells, such as fibroblasts and vascular endothelial cells, in the tumor microenvironment. Additionally, tamsulosin did not show any antiproliferative effects in RCC cells or vascular endothelial cells. However, naftopidil has been shown to inhibit the proliferation of human lung fibroblasts

and bleomycin-induced lung fibrosis in mice (Urushiyama et al. 2019). Additionally, naftopidil also induces G_1 cell cycle arrest and decreases the mRNA expression of *COL4A1* (which encodes type IV collagen) and *ACTA2* (which encodes α smooth muscle actin) in human lung fibroblasts. These results suggested that naftopidil may have potent therapeutic effects on the tumor stroma of PCa, including fibroblasts and vascular endothelial cells.

Carcinoma-associated fibroblasts (CAFs) are present in the tumor microenvironment of PCa and are characterized as activated fibroblasts that promote PCa cell proliferation. In the PCa cell microenvironment, normal fibroblasts and CAFs secrete various growth factors, cytokines, extracellular matrix proteins, and microRNAs, which function to support PCa cell survival and proliferation in a paracrine manner (Ishii et al. 2018b). In our laboratory, we examined the effects of naftopidil on the proliferation of primary cultured CAFs derived from patients with PCa. Naftopidil weakly inhibited the proliferation of primary cultured CAFs compared with that of PCa cells, normal prostatic fibroblasts, and vascular endothelial cells (unpublished data; Fig. 8.1). This result may be explained by the slower proliferation of CAFs compared with that of other cells. Because naftopidil inhibits cell cycle progression, highly proliferative cells may be strongly affected by naftopidil in the tumor microenvironment of PCa. Additional work is needed to fully elucidate the roles of naftopidil in CAFs.

Clinical studies have shown that the incidence of PCa is reduced in patients with BPH administered with naftopidil for at least 3 months compared with that in patients administered with tamsulosin (Yamada et al. 2013). Moreover, our DR studies in patients with latent PCa concomitant with BPH also suggested that naftopidil may have applications in long-term prevention by blocking progression to clinical PCa. Thus, long-term naftopidil use for patients with BPH may have various clinical benefits, and naftopidil may have application in the chemoprevention of PCa in patients with BPH.

8.3.2 New Clinical Applications of Naftopidil in PCa Treatment

Recently, we proposed two possible clinical applications of naftopidil, i.e., in combination treatment with radiotherapy (RT) or as a chemotherapy for PCa treatment (Iwamoto et al. 2017; Ishii et al. 2018a).

Clinically, α_1-AR antagonists, including naftopidil, improve outcomes in patients with PCa and urinary morbidities related to brachytherapy (Merrick et al. 2005) and extra beam RT (Prosnitz et al. 1999) without impairing safety. Indeed, additive naftopidil treatment combined with RT has been shown to increase RT efficacy in PC-3 cells by directly suppressing growth and by blocking the RT-induced expression of the antioxidant enzyme manganese superoxide dismutase (Iwamoto et al. 2017). Conversely, additive tamsulosin treatment combined with RT did not exert these effects.

Additionally, additive naftopidil treatment combined with docetaxel (DTX) was shown to promote DTX efficacy in LNCaP cell-derived tumors (sub-renal capsule

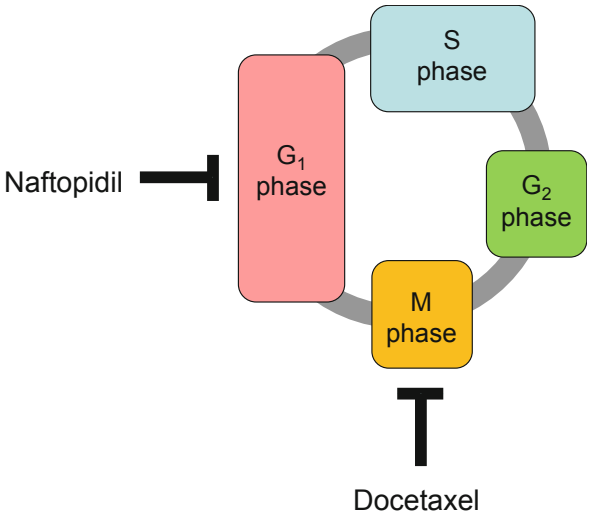

Fig. 8.2 The additive effects of naftopidil treatment combined with chemotherapy for prostate cancer. Naftopidil inhibits the proliferation of prostate cancer (PCa) cells by inducing G_1 cell cycle arrest. Docetaxel (DTX) induces G_2/M cell cycle arrest and apoptosis in PCa cells by inhibiting microtubule depolymerization. Our studies of drug repositioning strongly suggested that the combination of G_1 cell cycle arrest-inducing naftopidil and G_2/M cell cycle arrest-inducing DTX may inhibit cell cycle progression

grafting) and PC-3 cell-derived tumors (intratibial injection) in an in vivo analysis (Ishii et al. 2018a). Notably, additive naftopidil treatment showed synergistic effects on DTX-dependent apoptosis in PCa cells in both in vitro and in vivo analyses. Particularly in patients with castration-resistant PCa having bone metastases, this combined treatment strategy can result in enhanced clinical outcomes compared with DTX treatment alone. We suggest that a combination of G_1 cell cycle arrest-inducing naftopidil and G_2/M cell cycle arrest-inducing DTX may strongly inhibit cell cycle progression (Fig. 8.2).

8.3.3 Structure of Subtype-Selective α_1-AR Antagonists With Anticancer Effects

Among approved drugs and unapproved compounds, the five subtype-selective α_1-AR antagonists can be divided into two groups: the α_{1A}-AR highly selective antagonists tamsulosin, silodosin, and RS100329 and the α_{1D}-AR highly selective antagonists naftopidil and BMY7378. Importantly, Hori et al. demonstrated that naftopidil and RS100329 show antiproliferative effects in PCa cells and normal prostatic fibroblasts (Hori et al. 2011). Moreover, both naftopidil and RS100329 have a phenylpiperazine-based structure and have been shown to promote G_1 cell cycle arrest. Similarly, in small-cell lung carcinoma cells, the Ca^{2+}/calmodulin-dependent protein kinase inhibitor KN-62, which exhibits a phenylpiperazine-based structure, also induces G_1 cell cycle arrest (Williams et al. 1995, 1996). Conversely, BMY7378, which also has a phenylpiperazine-based structure, does not induce G_1 cell cycle arrest at low concentrations (10 μM) but weakly promotes G_1 cell cycle arrest in PCa cells when used at a fivefold higher concentration (Hori et al. 2011). Tamsulosin and silodosin, which do not have a phenylpiperazine-based

structure, did not induce G_1 cell cycle arrest. These reports led us to hypothesize that α_1-AR antagonists with a phenylpiperazine-based structure may suppress the proliferation of cancer cells and stromal cells by inducing G_1 cell cycle arrest.

In studies evaluating the mechanisms of growth inhibition by phenylpiperazine derivatives, including naftopidil, Ishii and Sugimura demonstrated that naftopidil can bind directly to tubulins and that three phenylpiperazine derivatives, i.e., naftopidil, RS100329, and BMY7378, inhibit the polymerization of tubulin; indeed, the phenylpiperazine-based structure of these derivatives shows tubulin polymerization-inhibitory activity (Ishii and Sugimura 2015). These findings suggest that the chemical structures of α_1-AR antagonists contribute to differences in the growth inhibitory mechanisms of these compounds.

In a comparison of the growth inhibitory effects of the three phenylpiperazine derivatives, researchers have shown that the characteristics of the compound strongly depend on the substituent group. Our studies of DR suggest that the existing tubulin-binding drug naftopidil may exert a broad-spectrum cellular cytotoxicity in various cell types. For example, naftopidil inhibits the proliferation of cancer cells, such as PCa cells, RCC cells, and colon adenocarcinoma cells, as well as stromal cells, such as fibroblasts, CAFs, and vascular endothelial cells. Therefore, modification of the substituent group on naftopidil may facilitate the design and synthesis of novel tubulin-binding drugs.

After we reported that the phenylpiperazine derivative naftopidil could act as a tubulin-binding drug (Ishii and Sugimura 2015), several groups designed and synthesized new phenylpiperazine derivatives having antiproliferative effects (Guo et al. 2015; Prinz et al. 2017; Demirci et al. 2019). Particularly, Prinz et al. focused on the phenylpiperazine-based structure and developed a new tubulin polymerization inhibitor (Prinz et al. 2017). Thus, developing potent naftopidil-based anticancer drugs without compromising safety in patients with PCa is possible.

8.4 Concluding Remarks

Clinically, naftopidil has high tolerability with fewer side effects in patients with BPH. Our studies of DR imply that naftopidil-inhibited cell cycle progression may block the progression of latent PCa concomitant with BPH to clinical PCa. We believe that long-term orally active naftopidil may have clinical benefits in patients with BPH as a chemopreventive agent for PCa during BPH treatment.

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