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Repurposing itraconazole as an anticancer agent (Review)

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Abstract. Itraconazole, a common anti-fungal agent, has demonstrated potential anticancer activity, including reversing chemoresistance mediated by P-glycoprotein, modulating the signal transduction pathways of Hedgehog, mechanistic target of rapamycin and Wnt/β-catenin in cancer cells, inhibiting angiogenesis and lymphangiogenesis, and possibly interfering with cancer-stromal cell interactions. Clinical trials have suggested the clinical benefits of itraconazole monotherapy for prostate cancer and basal cell carcinoma, as well as the survival advantage of combination chemotherapy for relapsed non-small cell lung, ovarian, triple negative breast, pancreatic and biliary tract cancer. As drug repurposing is cost-effective and timesaving, a review was conducted of preclinical and clinical data focusing on the anticancer activity of itraconazole, and discusses the future directions for repurposing itraconazole as an anticancer agent.

Contents

1. Introduction

The development of anticancer drugs is a lengthy and expensive process (1). After a novel compound is identified or designed, preclinical and clinical data from phase I, II and III clinical trials are generated prior to approval. Drug repurposing represents the identification of the novel pharmacological effects of conventional drugs (2). As the pharmacokinetics, pharmacodynamics and safety in humans have already been established, expanding the application of a drug to additional diseases has advantages in terms of cost and time efficiency. Itraconazole is a common anti-fungal agent that was developed in the 1980s, which decreases ergosterol synthesis by inhibiting lanosterol 14α-demethylase (14DM), resulting in the destruction of the fungal membrane (3). However, the anti-fungal effect of itraconazole is unlikely to be associated with its anticancer activity. Preclinical and clinical data have proposed the use of itraconazole as a promising anticancer agent in monotherapy or in combination chemotherapy (3). This review focuses on the efficacy of itraconazole in cancer treatment and ongoing clinical trials.

2. Preclinical data

Certain chemotherapeutic drugs induce expression of the drug efflux protein P-glycoprotein (P-gp), also known as multi-drug resistance 1 or ATP-binding cassette (ABC) transporter B1 (ABCB1). In the 1990s, itraconazole was demonstrated to reverse chemoresistance in cancer cells overexpressing P-gp (Fig. 1; Table I) (4-6). In addition, the human breast cancer resistance protein is also inhibited by itraconazole (7).

A screen of US Food and Drug Administration (FDA)-approved drugs identified itraconazole as an anti-angiogenic agent in 2007 and as an inhibitor of Hedgehog signaling in 2010 (8,9). Itraconazole inhibits AKT (protein kinase B)/mechanistic target of rapamycin (mTOR) signaling in human umbilical vein endothelial cells (HUVECs), glioblastoma, endometrial carcinoma (EC) and melanoma cells (10-14). Inhibition of Hedgehog signaling was observed in basal cell carcinoma, medulloblastoma, pleural mesothelioma, breast cancer and melanoma cells (9,14-17), but not in EC cells (13). Inhibition of Wnt/β-catenin signaling was observed in basal cell and examined in melanoma cells (14). Itraconazole also induced autophagic cell death in medulloblastoma cells as well as in breast cancer cells (12,17), and suppressed lymphangiogenesis in lung carcinoma cells (18).

In HUVECs, itraconazole induced the accumulation of immature N-glycans on VEGFR2, which in turn inhibited autophosphorylation and downstream activation (19); itraconazole also exhibited synergistic effects with bevacizumab, a humanized monoclonal antibody against VEGF (20). Additionally, hypoglycosylation of the epidermal growth factor receptor was observed in renal cell carcinoma cells (19).

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Table I. Potential anticancer activities of itraconazole.

Modulation by itraconazole	Cell types (Refs.)
Signaling pathways	
mTOR	HUVEC (10,11), glioblastoma (12), rat glioma (12), EC (13), melanoma (14)
Hedgehog	Mouse fibroblast (9), mouse medulloblastoma (9), mesothelioma (16), breast cancer (17), BCC (38), melanoma (14)
Wnt/β-catenin	Melanoma (14)
AMPK	HUVEC (11)
Autophagy	Glioblastoma (12), EC (13), breast cancer (17)
Microenvironment	
Angiogenesis	HUVEC (8,10,11,25)
Lymphangiogenesis	Mouse lung cancer (18)
Cancer associated fibroblasts	Colon cancer (20)
Drug resistance	
P-glycoprotein (MDR1, ABCB1)	Pig kidney epithelial cells (5,6)
BCRP/ABCG2	Breast cancer (7)
Transporter and pump of cholesterol	
SCP2	Glioblastoma (12), rat glioma (12)
ABCA1	EC (13)
NPC1	HUVEC (25)

mTOR, mechanistic target of rapamycin; AMPK, AMP-activated protein kinase; MDR1, multi-drug resistance 1; ABCB1, ATP-binding cassette transporter B1; BCRP, breast cancer resistance protein; ABCG2, ATP-binding cassette transporter G2; SCP2, sterol carrier protein 2; ABCA1, ATP-binding cassette protein A1; NPC1, Niemann-Pick C1 protein; P-gp, P-glycoprotein; HUVEC, human umbilical vein endothelial cell; EC, endometrial carcinoma; BCC, basal cell carcinoma.

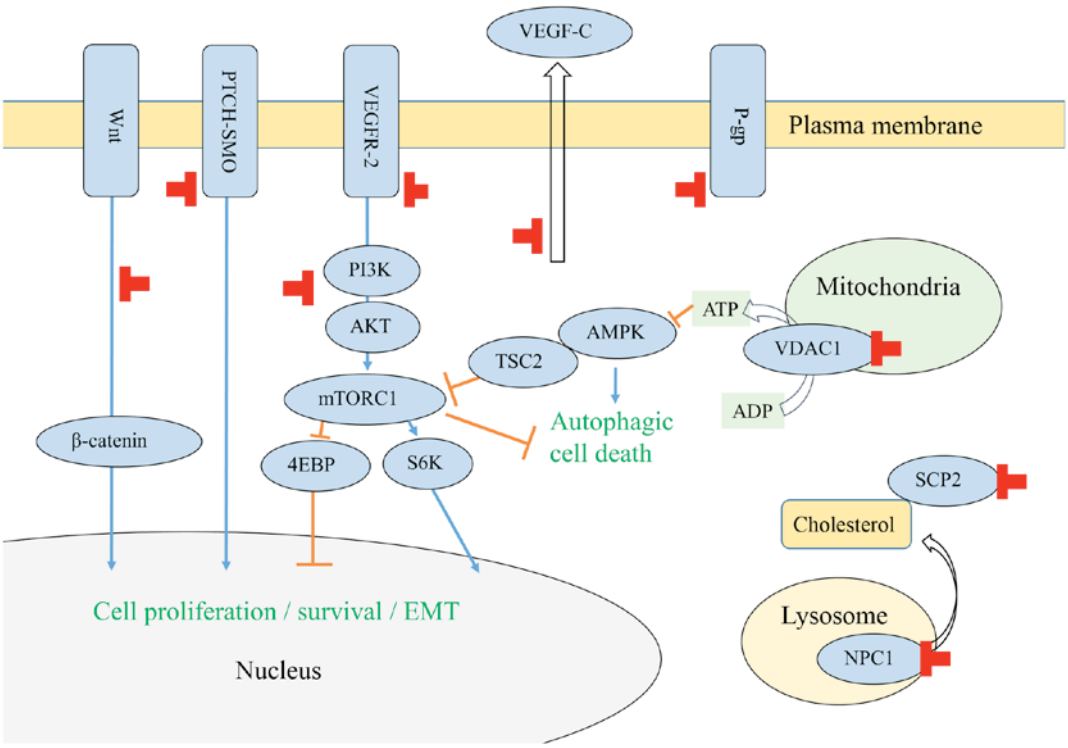

Figure 1. Schematic representation of the anticancer activity of itraconazole. AKT, protein kinase B; AMPK, AMP-activated protein kinase; 4EBP, eukaryotic translation initiation factor 4E binding protein; EMT, epithelial-mesenchymal transition; mTORC1, mechanistic target of rapamycin complex 1; NPC1, Niemann-Pick C1 protein; P-gp, P-glycoprotein; PI3K, phosphoinositide 3-kinase; PTCH-SMO, transmembrane receptor protein patched-transmembrane protein Smoothened (SMO); S6K, ribosomal protein S6 kinase; TSC2, tuberous sclerosis complex 2; VDAC1, voltage-dependent anion-selective channel 1; VEGF, vascular endothelial growth factor; VEGFR-2, VEGF receptor 2.

Table II. Results of certain clinical trials.

Cancer type	Phase	Eligibility	No. of previous regimens	No. patients treated with itraconazole	Combination chemotherapy	Results	(Refs.)
Leukemia	P2 RCT sub-analysis	ALL AML	0	27	Including daunorubicin	Tendency for longer DFS in itraconazole-treated ALL patients (P<0.06)	(35)
Ovarian	Retrospective comparative	Progression during previous chemotherapy	≥1	19	Including docetaxel	PFS HR=0.24 (P=0.002) OS HR=0.27 (P=0.006) in favor of the itraconazole arm	(36)
Ovarian	Retrospective	Recurrent clear cell carcinoma	≥1	9	Including docetaxel in 8 patients	Median OS 34.9 m 95% CI, 15.4-44.4 m	(37)
Breast	Retrospective	Triple negative	≥2	13	Including docetaxel	Median OS 20.4 m 95% CI, 13.1-41.4 m	(38)
Pancreatic	Retrospective	Relapse	≥1	38	Including docetaxel	Median OS 11.4 m 95% CI, 8.5-21.2 m	(39)
Biliary tract	Retrospective	Relapse	≥1	28	Including docetaxel	Median OS 12.0 m 95% CI, 9.1-24.6 m	(40)
NSCLC	P2 RCT	2nd line	1	15	Pemetrexed	PFS HR=0.399 (P=0.089) OS HR=0.194 (P=0.012) in favor of itraconazole arm	(43)
Prostate	P2 RCT	Castration-resistant chemo-naïve	0	46	None	PSA-PFS at 24 weeks, 11.8% vs. 48.0% in favor of the high dose arm	(49)
Basal cell carcinoma	P2 single arm	≥1 tumor >4 mm in diameter	0	29	None	Decreased GLI1 and Ki67 among vismodegib-naïve 8 patients	(51)

No., number; m, months; P2, phase 2; RCT, randomized controlled clinical trial; DFS, disease-free survival; PFS, progression-free survival; OS, overall survival; CI, confidence interval; PSA, prostate-specific antigen; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; NSCLC, non-small cell lung cancer.

Itraconazole directly binds to the mitochondrial protein voltage-dependent anion channel 1 (VDAC1) and interferes with mitochondrial ATP production, leading to the activation of the AMP-activated protein kinase pathway and the subsequent inhibition of mTOR activity (11).

In 1909, White (21) observed that cholesterol accumulated in tumor cells. Since then, such changes in the lipid composition of cancer cells have been studied in association with drug resistance. In the 1970s, anti-fungal drugs were revealed to exert synergistic effects with certain chemotherapeutic drugs via altering the membrane lipid composition of cancer cells (22,23), and therapeutic strategies that target lipogenic enzymes have been investigated in preclinical and clinical studies (24). Aberrant activation of AKT is correlated with an increase in lipid raft formation, while the disruption of lipid rafts inhibits AKT activation (25). In HUVECs, itraconazole inhibited intracellular cholesterol trafficking to the plasma membrane by binding to Niemann-Pick C1 protein, resulting in cholesterol depletion (26). In glioblastoma cells, the redistribution of cholesterol was induced by the downregulation of sterol carrier protein (SCP2) (12), which is located in numerous organelles including mitochondria (27). In EC cells, the transcription of SCP2 was observed to be unaffected by itraconazole treatment. Among EC cells that were unaffected by itraconazole, the cholesterol efflux protein ABCA1 was downregulated (13).

The tumor microenvironment serves a key role in the cell proliferation, invasion and metastasis in cancer (28); however, the exact underlying mechanisms of cancer-stromal interactions are poorly understood. Cancer-associated fibroblasts

Table III. Ongoing clinical trials.

Type of cancer	Phase	Prior chemo	Primary endpoint	Treatment	Clinical trial identifier	Institution of principal investigator
Solid tumor	Window trial	-	Ki-67 index	Itra 400 mg BID	UMIN000018388	Hyogo College of Medicine
NSCLC	P0	Chemo-naïve	Tissue microvessel density	Itra 600 mg BID	NCT02357836	University of Texas Southwestern Medical Center
Basal cell carcinoma	P0	-	GLI1 mRNA expression	Itra ointment	NCT02735356	Stanford Cancer Institute
Esophageal cancer	P1	-	Hh mRNA expression	Itra 300 mg BID	NCT02749513	Dallas VA Medical Center
Glioblastoma	P1	-	Toxicity	Multi-agent cocktail including Itra	NCT02770378	University of Ulm School of Medicine
Prostate cancer	P2	Chemo-naïve	Decline of PSA	Itra 300 mg BID	NCT01787331	University of California
Gynecological cancer	P2	≥2nd line	PFS	DOC/Gem Itra 400 mg BID	UMIN000013951	Hyogo College of Medicine
NSCLC	P2	Chemo-naïve	Response rate	Nab-P/Carbo/Bev Itra 400 mg BID	UMIN000019049	Meiwa Hospital
Gastric cancer	P2	Chemo-naïve	Response rate operability	Nab-P/Ox/S-1 Itra 400 mg BID	UMIN000021340	Meiwa Hospital
Pancreatic cancer	P2	Chemo-naïve	Response rate operability	Nab-P/Ox/Gem Itra 400 mg BID	UMIN000029075	Meiwa Hospital

All trials are recruiting participants in March, 2017. NSCLC, non-small cell lung cancer; GLI1, Glioma-Associated Oncogene Homolog 1; Hh, hedgehog; PSA, prostate-specific antigen; PFS, progression-free survival; Itra, itraconazole; BID, twice a day; DOC, docetaxel; Gem, gemcitabine; nab-P, nanoparticle albumin-bound paclitaxel; Carbo, carboplatin; Bev, bevacizumab; Ox, oxaliplatin; S1, tegafur/gimeracil/oteracil; Tem, temozolomide.

(CAFs) are essential for tumor growth (29). Itraconazole inhibited the proliferation of CAFs established from human colon cancer cells, as well as the secretion of monocyte chemoattractant protein-1 (20). Monocyte/macrophage marker CD14 is a glycosylphosphatidylinositol-anchored glycoprotein present in cholesterol-rich lipid rafts, which contain a variety of signaling proteins and receptors (30,31). In mouse macrophages, itraconazole treatment altered the N-glycosylation of CD14, and increased CD14 transcription and protein expression (32).

3. Clinical data

In a randomized trial of leukemia, anti-fungal prophylactic treatment with itraconazole was proven to be effective and safe in patients receiving remission induction therapy, including daunorubicin (33). Based on preclinical data detailing the reversal of daunorubicin resistance by itraconazole (34), a sub-analysis of itraconazole anticancer activity was conducted in 27 patients with acute lymphoblastic leukemia (35), and itraconazole treatment was likely to be associated with improved disease-free survival (Table II). The results of the clinical trial (35), as well as preclinical data on itraconazole reversing the resistance of taxane-resistant cancer cells (5,6), supported the treatment of refractory solid tumors with taxane-based chemotherapy in combination with itraconazole. A prior retrospective study demonstrated that overall survival (OS) was prolonged in 19 patients with refractory ovarian cancer, who had been treated with taxane-based chemotherapy with itraconazole (36). Additional retrospective studies supported the survival advantage of itraconazole treatment in refractory malignancies including ovarian clear cell, triple-negative breast, pancreatic and biliary tract cancer, as compared with the previous reports (37-40). In pancreatic cancer, itraconazole treatment combined with chemotherapy was conducted in progressive disease during chemotherapy (39). A total of 38 patients received docetaxel (35 mg/m^2), gemcitabine (1,000 mg/m^2) and carboplatin (4 mg/min/ml) in combination with itraconazole (400 mg), following which a median OS of 11.4 months was observed. In addition, 28 patients with biliary tract cancer received itraconazole, and subsequently experienced a median OS of 12 months (40).

With the aim of enhancing the therapeutic efficacy of anticancer drugs, P-gp inhibitors were investigated in a clinical trial (41) that reported unsatisfactory outcomes. The phase III study was conducted in the ovarian cancer patients, in whom the paclitaxel dose was reduced from 175 mg/m^2 in control patients to 80 mg/m^2 with valspodar (5 mg/kg every 6 h for 12 doses) for patients undergoing the combination therpay (42). The addition of valspodar to standard chemotherapy regimens did not significantly improve progression-free survival (PFS) or OS, but increased the frequency of adverse events experienced. Therefore, the

survival advantage conveyed by combination chemotherapy with itraconazole among patients with various types of cancer could not be explained by P-gp inhibition alone. Repurposing itraconazole for the targeting of angiogenesis has been examined since 2009. In a randomized phase II clinical trial of non-small cell lung cancer (43), 23 patients were enrolled in the second-line setting. Of these, 15 patients who were treated with pemetrexed (500 mg/m^2, repeated every 21 days) and oral itraconazole (200 mg, daily) exhibited a prolonged OS time, as compared with the 8 patients who were treated with pemetrexed alone. A meta-analysis of randomized trials demonstrated that the VEGF inhibitor bevacizumab prolonged OS in colorectal, non-small cell lung and cervical cancer, but not in breast or ovarian cancer (44). Phase III trials of the VEGFR inhibitor ramucirumab reported prolonged OS in non-small cell lung, gastric and colorectal cancer, (45-48). Considering the results of the clinical trials using P-gp inhibitor or antiangiogenic agents (41,43-47), the clinical efficacy of itracoanzole treatment in various types of cancer (Table II) implicated the additional anticancer activities, which was demonstrated in preclinical studies (Table I).

In a randomized phase II clinical trial of metastatic castration-resistant prostate cancer (49), 46 chemotherapy-naïve patients were enrolled, of whom 29 received high-dose (600 mg/day) and 17 received low-dose (200 mg/day) itraconazole treatment. Prostate-specific antigen PFS rates at 24 weeks were 48.0 and 11.8% with median PFS of 11.9 and 35.9 weeks in the high- and low-dose arm, respectively. Plasma VEGF levels remained unchanged following itraconazole treatment in both arms, whereas the down-modulation of GLI1 was significantly correlated with the decline of PSA.

Basal cell carcinoma, the most common type of skin cancer, is associated with upregulated Hedgehog signaling, and two Hedgehog inhibitors, vismodegib and sonidegib, which target Smoothened have been approved by the FDA for treatment of basal cell carcinoma (50). In a recent study conducted on 29 patients with basal cell carcinoma (19 treated with itraconazole) (51), it was observed that the tumor area decreased by an average of 24% in 8 of the itraconazole-treated patients with accessible lesions. Among the vismodegib-naïve patients (n=8), the transcription of GLI1 and Ki-67 activity was significantly decreased after itraconazole treatment (51).

4. Future perspectives

Following exposure to cytotoxic agents, the residual tumors typically harbor cancer stem cells (CSCs) or develop stemness (52). The concept of CSCs was hypothesized to explain metastasis and recurrence following exposure to chemotherapy (53); CSCs are characterized by self-renewal, multi-differentiation and chemoresistance. Additional potential mechanisms underlying chemotherapy resistance may include dormant cell cycles, multidrug resistance transporters and protection by niche cells. The current focus is on the development of CSC-targeted therapy for preventing cancer relapse and improving survival rates (54). Aberrant signaling pathways, including AKT/mTOR, Hedgehog, and Wnt, have been reported in CSCs and multi-targeting therapies have been proposed (54). The first-in-class cancer stemness inhibitor napabucasin (BBI 608), which targets signal transducer and activator of transcription 3 (Stat3), Nanog, and Wnt/β-catenin pathways, has been reported to improve OS in patients with positive phospho-STAT3 recurrent colorectal cancer (55,56). Itraconazole may be a promising agent for targeting CSCs in relapsed disease of multiple types of cancer; therefore, further preclinical studies on CSCs and the surrounding stroma cells are warranted.

Ongoing clinical trials with itraconazole (as an anticancer agent) were identified from ClincalTrials.gov (https://clinicaltrials.gov/ct2/home) and UMIN-CTR Search Clinical Trials (http://www.umin.ac.jp/ctr/index.htm), as well as Google search (Table III). No ongoing clinical trials were registered at the EU Clinical Trial Register (https://www.clinicaltrialsregister.eu/ctr-search/search). Obtaining cancer tissues and blood from patients prior to and following itraconazole treatment is essential for exploring and characterizing novel targets in the tumor and the microenvironment, as well as for identifying biomarkers predictive of patient response for future enrichment clinical trials.

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