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ABCG2 Inhibitors: Will They Find Clinical Relevance?

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Abstract

Multiple drug resistance (MDR) is a prominent way by which cancer develops resistance to various chemotherapeutic agents and continues to be a hurdle in treating cancer patients. A few ATP binding cassette (ABC) transporters have been described as comprising the main mechanism behind MDR: ABCB1, ABCC1, and ABCG2. Of these three, ABCG2 is unique in that it seems to be mainly expressed in solid tumors. Despite the recent discovery of many compounds that inhibit its activity, it remains one of the least well-studied transporters in both animal models and in humans with regard to its contribution to MDR. Though the blockade of the ABCG2 efflux protein has great potential in reversing MDR in cancer, will it be enough to overcome chemoresistance in the clinic?

Keywords: ABCG2; ABC transporters; Cancer; Inhibitors; Chemotherapy

Introduction

Resistance of cancer cells to chemotherapy has remained a major treatment difficulty for decades and results in approximately 90% of cancer treatment failures [1]. Intrinsic chemoresistance of cancer cells represents about 50% of all cancer cases [2]. The remainder of resistance in cancer is acquired and develops following treatment with chemotherapy or after a change in therapy. When simultaneous resistance of cancer cells to various agents occurs, it is referred to as multiple drug resistance (MDR). One prominent mechanism by which MDR develops in cancer is the overexpression of certain ATP Binding Cassette (ABC) transporter proteins. The ABC transporters are expressed within intra- and extracellular membranes and are involved in the transport of many substances across those membranes, including amino acids, peptides, vitamins, cholesterol, hydrophobic drugs, and chemotherapeutics [3]. Therefore, an aggressive development of therapeutics that target certain ABC transporters to help circumvent MDR was adopted at the time of their discovery in an effort to allow more patients achieve cancer remission.

The most well-studied ABC transporters contributing to MDR in cancer are ABCB1, ABCC1, and ABCG2, of 49 total ABC transporters reported to date [3]. Of these three, ABCG2 was the most recently discovered and is unique in that it is mainly overexpressed in drug-resistant solid tumors [4], although it has been found to be overexpressed in a number of hematopoietic tumors along with overexpression of ABCB1 and ABCC1 [5]. Another distinct feature of ABCG2 is its classification as a half transporter, since it has only one nucleotide binding domain (NBD) and one transmembrane domain (TMD), whereas most other ABC transporters have two NBDs and two TMDs [6]. Though ABCG2 normally serves a protective purpose in tissues that provide a barrier function or are involved in absorption, including the intestinal mucosa, placenta, liver, kidney, and the blood-brain-barrier (BBB), it may also serve to protect cancer cells from cytotoxic effects of certain chemotherapeutics [7,8]. ABCG2 has a large diversity of substrates, but the most well known in relation to MDR cancers are topotecan (TPT), mitoxantrone, SN-38 (the active metabolite of irinotecan), doxorubicin, and daunorubicin [9,10]. Of importance, clinical studies have shown that higher expression of ABCG2 may be associated with lower survival rates in small cell lung cancer, non-small cell lung cancer, pancreatic cancer, mantle cell lymphoma, acute myeloid leukemia, ovarian cancer, and breast cancer [11-19]. Additionally, ABCG2 expression may be associated with a worse prognosis and lesser response to treatment in patients with colorectal cancer and acute myeloid leukemia [20-22].

Considerable progress has been made since the discovery of ABCG2 in 1998 with multiple drugs having been identified that decrease its activity. However, only a handful of these drugs have been tested *in vivo* or in humans with limited success in reversing MDR. Therefore, translating additional compounds from the bench to the bedside may result in a solution for alternative therapies to help circumvent MDR, but remains a hurdle to be crossed in helping cancer patients achieve remission.

Historic Perspective

Prior to the discovery of the first ABC transporter gene, ABCB1/P-gp/MDR-1, involved in chemoresistance of cancer cells by Juliano and Ling in 1976 [23], it was well known that cancer cells could develop resistance to the administered chemotherapy in addition to structurally and mechanistically unrelated compounds [24]. In fact, the first report of cancer no longer responding to chemotherapy was in 1942 by Alfred Gilman and Louis Goodman treating an advanced lymphosarcoma, shortly after the advent of chemotherapy [25]. It wasn't until 1992 that a second ABC transporter contributing to MDR in a lung cancer cell line, ABCC1/MRP-1, was identified [26]. Shortly thereafter, in 1998, the third ABC transporter contributing to MDR in cancer, ABCG2/BCRP, was discovered in a mitoxantrone (MTX) resistant MCF-7 breast cancer cell line [27]. ABCG2 has also been shown to mediate resistance of cancer cells to camptothecin derivatives, such as TPT, irinotecan, and SN-38 [28]. Cross-resistance of ABCG2-overexpressing cell lines to doxorubicin and rhodamine-123 has been linked to a mutation in the amino acid sequence at position 428 from arginine to either glycine or threonine and decreases the efficacy of some ABCG2 inhibitors [28]. In addition, single nucleotide polymorphisms (SNPs) impact ABCG2 expression and function. Therefore, it may be important to identify patients with ABCG2 amino acid mutations and/or SNPs to help guide treatment strategies and determine candidacy for certain therapeutics. Despite many publications reporting the discovery of

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ABCG2 inhibitors since their discovery, only a few have reported successes in reversing MDR in animal models, and fewer still have been investigated in human trials with none moving past phase II trials and no observed clinical benefit. Thus, the future of ABCG2 inhibitors and their efficacy in humans remains in question.

ABCG2 Inhibitors Progress

The ability of ABCG2 inhibitors to reverse chemoresistance has been well-described *in vitro*. Fumitremorgin C was the first ABCG2 inhibitor to be described, in 1998, which reversed chemoresistance of colon carcinoma to MTX [29]. Since that time, over 60 agents have been described that inhibit *in vitro* the action of ABCG2 (Table 1). Of those completed studies, only 15 compounds inhibiting ABCG2 activity have been tested in animal models with human cancer xenografts and reported to have antitumor effects (Table 1 and 2). Moreover, only 6 of those compounds tested *in vivo* are direct antagonists specific for ABCG2: curcumin, FTC, Ko143, GF120918 (Elacridar), YHO-13177, YHO-13351, and our recently reported compounds 177, 724, and 505 [30-37]. Of the specific ABCG2 antagonists, only YHO-13177 and our recently reported compounds 177, 724, and 505 were reported to have an antitumor effect when combined with TPT. The other specific ABCG2 antagonists have only been described to increase the oral bioavailability of chemotherapy *in vivo*. In addition, some nonspecific ABC transporter antagonists have been demonstrated to decrease tumor burden in animal models when combined with chemotherapy. For instance, Dofequidar Fumarate, an ABCB1/ABCC1/ABCG2 inhibitor, was shown to reduce tumor burden in MDR cancer stem-like side population HeLa mouse xenografts when combined with CPT-11 [38].

A number of compounds have shown efficacy in animal models of cancer (Table 2). Some of these compounds have an indirect inhibitory effect on ABCG2, and include antimalarial agents, chemotherapeutic analogs of camptothecin, and an aurora kinase inhibitor (Table 2). Artesunate is an antimalarial agent, which down-regulates expression of ABCG2 and decreases tumor volume administered as a single dose without the presence of chemotherapy [39]. Camptothecin analogues ST1481 and CHO793076 are both able to overcome ABCG2-mediated MDR as single agents [40,41]. The aurora kinase inhibitor, CCT129202, was able to increase the accumulation of doxorubicin and rhodamine 123 in ABCB1 and ABCG2 overexpressing human colon cancer cells. Although the majority of success with CCT129202 has been seen in ABCB1-overexpressing human epidermoid carcinoma, both in a murine model and in humans [42].

Several tyrosine kinase inhibitors (TKIs) have also shown promise for reversal of ABCG2-mediated MDR in animal models (Table 2).

Table 1: ABCG2 inhibitors with in vitro efficacy.

ABCG2 inhibitors with in vitro efficacy Drug	Animal Model	Clinical trials	Drug	Animal Model	Clinical trials
1,4-dihydropyridines [48]			Lapatinib [45-47,49]	X	X
Artesunate [39]	X		LY294002 [50]		
AST1306 [51]			MBLI-87 [52]	X	
Bifendate-chalcone hybrids [53]			Methoxy Stilbenes [54]		
Botryllamides [55]			Mithramycin A [56]		
Cadmium [57]			Quercetin derivatives [58]		
Calcium Channel Blockers (nicardipine, nitrendipine, nimodipine, dipyridamole) [59]			Naphthopyrones [60]		
Camptothecin analog (ST1481) [40]	X		Nilotinib [61]		
Camptothecin analog (CHO793076) [41]	X		Novobiocin [62]	X	
Cannabinoids [63]			NP-1250 [64]		
CCT129202 [42]	X		Olomoucine II and purvalanol A [65]		
Chalcone [66]			Organ chlorine and Pyrethroid [67]		
Curcumin [30]	X		OSI-930 [68]		
Cyclosporin A [69]			Phytoestrogens/Flavonoids [70]		
Dihydropyridines and Pyridines [71]	X		Piperazinobenzopyranones and Phenalkylaminobenzopyranones [72]		
Dimethoxyaurones [73]			Ponatinib [74]		
Dofequidar fumarate [38]	X		PZ-39 [75]		
Repurposed Drugs [76]			Quinazolines [77]		
EGFR Inhibitors [78]			Quizartinib [79]		
Flavones & Benzoflavones [80]			Sildenafil [81]		
Tropical Plant Flavonoids [82]			Sorafenib [83]		
Fruit Juices (quercetin, kaempferol, bergamotin, 6',7'-dihydroxybergamottin, tangeretin, nobiletin, hesperidin, hesperetin) [84]			Substituted Chromones [85]		
Fumitremorgin C [29,31]	X		Sunitinib [86]		
Fumitremorgin C analogue (ko143) [32]	X		Tandutinib [87]		
Gefitinib [44,88]	X		Tariquidar [89]		
GF120918, BNP1350 [32,33]	X	X	Terpenoids [90]		
GW583340 and GW2974 [91]			CI1033 [92]		
HM30181 Derivatives [93]			Toremifene [94]		
Human cathelicidin [95]			XR9577 [96],WK-X-34 [96,97],WK-X-50 [96], and WK-X-84 [96]	X	
Imatinib mesylate [43,98]	X	X	YHO-13177 [34] and YHO-13351 [34]	X	
177, 724, 505 [35-37]	X				

Imatinib mesylate was reported as a direct PDGFR and ABCG2 inhibitor, although other mechanisms of action could not be ruled out. Despite the lack of mechanistic clarity, Imatinib was able to successfully restore chemo sensitivity to TPT resistant Rhabdomyosarcoma *in vivo* [43]. Gefitinib, an ERBB1 inhibitor, was described to block ABCG2-mediated MDR in mice irrespective of the expression of ERBB1 and increase the bioavailability of the irinotecan administered [44]. Lapatinib, a HER2/neu and EGFR inhibitor, was reported to also directly inhibit ABCB1 and ABCG2, but this compound is unique in that at low concentrations it is also able to stimulate the ATPase activity of ABCG2. Additionally, lapatinib was shown to reverse MDR in both the wild-type and R482G/T variant of ABCG2, [45] which made it an ideal candidate to be tested in a phase I and later a phase II clinical trial. Since it is thought that inhibition of ABCG2 and other ABC transporters, such as ABCB1, may be a common mechanism for tyrosine kinase inhibitors, [44] they represent the most extensively investigated class of ABCG2 inhibitors.

To date, there have only been five clinical trials, four phase I and one phase II, investigating solely ABCG2 inhibitors and MDR reversal in advanced solid tumors (Table 3). Of these four trials, three include the use of TKIs as potential agents to reverse ABCG2-mediated MDR. Though completed trials were dose-finding studies with TPT/GF120918 and TPT/erlotinib. There is currently only one active trial investigating the combination of erlotinib and irinotecan in patients with advanced solid tumors and correlating EGFR phosphorylation and ABCG2 expression with treatment response. A phase I trial with lapatinib and TPT determined that this combination was a well-tolerated regimen up to 1800 mg/day, with diarrhea and rash as the dose limiting side effects [46]. From this investigation, it was suggested that this combination be evaluated in a phase II trial with a dosing regimen of 1,250 mg/d lapatinib for 28 days and 3.2 mg/m^2 TPT on days 1, 8, and 15 of a 28-day cycle. Subsequently, three years later in 2011, data from the phase II trial using lapatinib in combination with TPT for platinum-refractory/resistant ovarian and primary peritoneal carcinoma was published [47]. This combination did not show clinical benefit in patients and was canceled due to substantial hematologic side effects. Since lapatinib along with many other ABCG2 inhibitors studied in murine models were shown to effectively increase the bioavailability of the concomitant chemotherapy administered, it is possible that the substantial toxicity reported might have been due to inhibition of ABCG2 in normal tissues leading to increased levels of circulating TPT. Although, it was concluded that the inhibition of ABCG2, ABCB1, and erbB signaling was insufficient to reverse TPT resistance, indicating that additional mechanisms contributing to MDR may be involved.

Future Directions

Since its discovery, ABCG2 expression has been correlated with a worse clinical outcome in multiple cancers including breast cancer, non-small cell lung cancer, and ovarian cancer [13,28]. While many ABCG2 inhibitors have been identified since its discovery in 1998, few have progressed to trial in humans with no observed clinical successes. If additional compounds blocking the activity of ABCG2 are tested in human clinical trials without demonstrating clinical success in restoring chemosensitivity, the question remains: is blocking the ABC

Table 2: Compounds antagonizing ABCG2 in animal cancer models.

Compounds antagonizing ABCG2 in animal cancer models Drug	Mechanism of Action	Cancer
Artesunate [39]	Down-regulates expression of ABCG2	NNon-Small-Cell Lung Cancer
Camptothecin analog (ST1481) [40]	Chemotherapy	Colon Carcinoma
Camptothecin analog (CHO793076) [41]	Chemotherapy	Ovarian and Breast Cancer
CCT129202 [42]	Aurora Kinase inhibitor	Colon Carcinoma
Curcumin [30]	ABCG2 inhibitor	Breast Cancer
Dihydropyridines and Pyridines [71]	ABCB1 + ABCG2 inhibitor	Breast Cancer and Non-Small-Cell Lung Cancer
Dofequidar fumarate [38]	ABCB1, ABCC1, ABCG2 inhibitor	HeLa side population cancer stem-like cells
Fumitremorgin C [31]	ABCG2 inhibitor	Ovarian Cancer
Fumitremorgin C analogue (ko143) [32]	ABCG2 inhibitor	Ovarian Cancer
Gefitinib [44]	ERBB1 inhibitor, ABCG2 inhibitor	Neuroblastoma, Osteosarcoma, Rhabdomyosarcoma, Glioblastoma
GF120918 [33], BNP1350[33]	ABCG2 inhibitor	Mouse Leukemia and Ovarian Cancer
Imatinib mesylate [43]	PDGFR inhibitor, ABCG2 inhibitor	Rhabdomyosarcoma
Lapatinib [45]	Tyrosine kinase inhibitor, ABCB1, ABCG2 inhibitor	Vincristine resistant epidermoid carcinoma
WK-X-34 [97]	ABCB1 and ABCG2 inhibitor	Ovarian Cancer
YHO-13177 [34] and YHO-13351 [34]	ABCG2 inhibitor	Human colon cancer and mouse leukemia

Table 3: Clinical trials employing ABCG2 inhibitors.

Clinical trials employing ABCG2 inhibitors Clinical Trial Title	Status	Cancer	Chemotherapy	Conjunctive Therapy	Phase
Erlotinib Hydrochloride and Irinotecan Hydrochloride in Treating Patients With Advanced Solid Tumors	Active, not recruiting	Advanced Solid Tumors	Irinotecan	Eroltinib	Phase I
A Phase I Study Of Oral Topotecan And Lapatinib In Subjects With Advanced Solid Tumors [46]	Withdrawn	Advanced Solid Tumors	Topotecan	Lapatinib	Phase I
Phase I, Dosage-finding and PK Study of IV Topotecan and Erlotinib With Refractory Solid Tumors [99]	Completed	Metastatic, Refractory Solid Tumors	Topotecan	Eroltinib	Phase I (Dose-finding)
A phase I, randomized, open-label, parallel-cohort, dose-finding study of elacridar (GF120918) and oral topotecan in cancer patients [100]	Completed	Cancer	Topotecan	GF120918 (Elacridar)	Phase I (Dose-finding)
Phase II trial of lapatinib and topotecan (LapTop) in patients with platinum-refractory/resistant ovarian and primary peritoneal carcinoma [47,49]	Terminated	Platinum-refractory/resistant ovarian and primary peritoneal carcinoma	Topotecan	Lapatinib	Phase II

transporters sufficient to reverse chemoresistance? Or, should we turn our focus elsewhere to other molecular pathways or genes regulating those pathways to continue the pursuit of re-sensitizing MDR cancer cells to chemotherapy?

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