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Review

Reversing multidrug resistance by tyrosine kinase inhibitors

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Abstract

Recently, a large number of tyrosine kinase inhibitors (TKIs) have been developed as anticancer agents. These TKIs can specifically and selectively inhibit tumor cell growth and metastasis by targeting various tyrosine kinases and thereby interfering with cellular signaling pathways. The therapeutic potential of TKIs has been hindered by multidrug resistance (MDR), which is commonly caused by overexpression of ATP-binding cassette (ABC) membrane transporters. Interestingly, some TKIs have also been found to reverse MDR by directly inhibiting the function of ABC transporters and enhancing the efficacy of conventional chemotherapeutic drugs. In this review, we discuss ABC transporter-mediated MDR to TKIs and MDR reversal by TKIs.

Key words Tyrosine kinase inhibitors, multidrug resistance, reversal effects

Protein tyrosine kinases (PTKs), a large and diverse multigene family of enzymes, can catalyze the transfer of a phosphate group from ATP to target proteins and play critical roles in cell signal transduction pathways that regulate cell growth, differentiation, adhesion, motility, and death[1]. Approximately 90 PTKs have been identified, two-thirds of which are transmembrane receptors and one-third of which are cytoplasmic non-receptors[2]. Examples of receptor tyrosine kinases (RTKs) include vascular endothelial growth factor receptor (VEGFR), nerve growth factor (NGF)/neurotrophin receptor TrkA, Axl, Tie2, epidermal growth factor receptor (EGFR, ErbB), stem cell factor receptor KIT(c-KIT), and platelet-derived growth factor receptors (PDGFR) α and β. For RTKs, ligand binding induces receptor dimerization, resulting in autophosphorylation of their cytoplasmic domains and activation of tyrosine kinase activity. Then, multiple cytoplasmic signaling pathways, such as the Ras/Raf mitogen-activated protein kinase (MAPK) pathway, the phosphoinositol 3′-kinase/Akt (PI3K/Akt) pathway, and the JAK/STAT pathway[3], which induce important cell physiological responses, can be activated. Mutations in RTKs and aberrant activation of their intracellular signaling pathways can lead to numerous diseases, such as cancers, diabetes, inflammation, severe bone disorders, and arteriosclerosis[3,4].

Numerous protein tyrosine kinase inhibitors (TKIs) have been found to be effective as anticancer agents when given alone or in combination with conventional chemotherapeutics, and the involved molecular mechanisms have been reported[5]. These TKIs mainly block or interfere with protein phosphorylation-mediated cellular signaling pathways that control tumor cell growth by targeting various tyrosine kinases. However, multidrug resistance (MDR) that affects the therapeutic potential of conventional anticancer drugs also affects the effect of TKIs in cancer chemotherapy. Indeed, some MDR-related ATP-binding cassette (ABC) transporters are involved in resistance to TKIs[6]. Interestingly, some TKIs have also been shown to inhibit the drug efflux function of MDR-related ABC transporters and to overcome the resistance of cancer cells to traditional chemotherapeutic drugs[7]. In this review, we summarize TKIs as anticancer agents and the ABC transporter-mediated MDR to some TKIs, and provide detailed information on the reversal of MDR by various TKIs reported to date.

TKIs as Anticancer Agents

A number of TKIs have been generated and proven to be effective anticancer agents. Imatinib (Gleevec, STI571), the first TKI approved by the Food and Drug

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Administration (FDA) of the United States in 2001, was developed to treat chronic myelogenous leukemia (CML) by specifically targeting the breakpoint cluster region (BCR)–Abelson (ABL) fusion protein that results from the chromosomal abnormality known as the Philadelphia chromosome. In 2002, the FDA approved the use of imatinib for treating gastrointestinal stromal tumors (GISTs). Imatinib was also approved to treat other cancers, such as chronic eosinophilic leukemia and refractory Philadelphia chromosome-positive acute lymphocytic leukemia (Ph^+ ALL)[8]. Although imatinib achieved a successful use in clinic, long-term oral administration of imatinib may lead to the development of cellular resistance and subsequent treatment failure.

Many promising new TKIs have been developed and approved for treating imatinib-resistant CML and other malignant diseases. Nilotinib (Tasigna, AMN107), a second-generation inhibitor of BCR-ABL tyrosine kinase, was designed and approved for treating newly diagnosed CML, imatinib-resistant or -intolerant CML[9]. Dasatinib (BMS-354825), another second-generation inhibitor of BCR-ABL tyrosine kinase, was approved for treating Ph^+ ALL and Ph^+ CML[10]. Sunitinib (Sutent, SU11248), a small-molecule TKI with direct anticancer and antiangiogenic activity that acts by targeting VEGFR, PDGFR, c-KIT, FMS-like tyrosine kinase-3 (FLT3), glial cell-line derived neurotrophic factor receptor (RET), and the receptor of macrophage-colony stimulating factor (CSF1R), is used to treat renal cell carcinoma (RCC), imatinib-resistant GISTs, and pancreatic neuroendocrine tumors[11]. Erlotinib (Tarceva, OSI-774), a selective and reversible inhibitor of EGFR, has been approved for treating advanced non–small cell lung cancer (NSCLC) and pancreatic cancer[12]. Lapatinib (Tykerb, GW572016), a potent and selective dual inhibitor of HER1 (also called EGFR) and HER2 (also called ErbB2) tyrosine kinases, was approved to treat HER2-positive advanced or metastatic breast cancer (MBC)[13]. Gefitinib (Iressa, ZD1839) is the first TKI marketed for treating advanced NSCLC[14]. Vandetanib (ZD6474) is the first approved TKI for treating late-stage (metastatic) medullary thyroid cancer[15]. Sorafenib (Nexavar), another oral multikinase inhibitor targeting VEGFR, PDGFR, c-KIT, Flt-3, and RAF-1, has been approved for treating advanced RCC and advanced hepatocellular carcinoma (HCC)[16]. Pazopanib (Votrient) is the newest TKI approved for treating advanced RCC[17].

ABC Transporter-mediated MDR to TKIs

Effects of ABC transporters on MDR

MDR is a complicated multifactorial phenomenon whereby cancer cells become insensitive or unresponsive to a variety of chemotherapeutic agents, thereby hampering the effective treatment of cancer[18]. MDR is known to be caused by several cellular mechanisms, including reduced drug accumulation, altered drug targets, and altered drug-induced apoptosis. However, the most common mechanism in cancer cells is increased drug efflux or reduced intracellular effective drug concentration by overexpression of MDR-related ABC transporters[19]. ABC transporters are categorized into seven distinct subfamilies, ABCA-ABCG, based on sequence homology and domain organization. Among them, ABCB1 (also known as P-glycoprotein, P-gp, MDR1), ABCG2 (also known as breast cancer resistance protein, BCRP), and ABCC1 (also known as multidrug resistance protein 1, MRP1) appear to play important roles in the development of MDR in cancer cells. They use the energy of ATP hydrolysis to transport various substrates, including a wide variety of anticancer agents, across cellular membranes and reduce the efficacy of anticancer agents, thus resulting in chemotherapeutic failure[20].

ABC transporter-mediated MDR to TKIs

As discussed above, TKIs are highly promising agents for treating many cancers. However, their therapeutic potential is also limited by ABC transporter-mediated MDR. Many reports suggested that the ABCB1/P-gp/MDR1, ABCG2/BCRP, and ABCC1/MRP1 transporters, especially ABCG2/BCRP, are involved in the resistance to TKIs. Some TKIs, including imatinib[21,22], nilotinib[22,23], dasatinib[23,24], gefitinib[25-27], N-[4-[(3-bromophenyl)amino]-6-quinazolinyl]-2-butynamide (EKI-785, an irreversible specific inhibitor of ErbBs)[25,26], danusertib (PHA-739358, a potent pan-aurora and ABL kinase inhibitor)[28], and canertinib (CI1033, a HER family TKI)[29], have been reported to be competitive or high-affinity substrates of ABCG2/ BCRP and to interact with this transporter at its substrate-binding sites. ABCG2/BCRP increases the efflux of these TKIs from cancer cells, thus inducing resistance to these TKIs. Some studies demonstrated that ABCB1/P-gp/MDR1 also conferred resistance to imatinib[30,31], nibotinib[32], and dasatinib[23,24]. In addition, Czyzewski *et al.*[33] showed that imatinib was a substrate for ABCC1/MRP1 and that it could increase the expression of ABCC1/MRP1, which played a role in imatinib resistance in CML. Recently, Shibayama *et al.*[34] suggested that sorafenib was a substrate for ABCC2/MRP2, which might contribute to sorafenib resistance. These findings suggest that overexpression of MDR-related ABC transporters should be considered an important clinical mechanism in developing resistance to TKIs. This mechanism also provides a rationale for how TKI resistance can be overcome *in vivo*. ABC transporter-mediated TKI resistance is summarized in Table 1.

Table 1. Resistance to tyrosine kinase inhibitors (TKIs) mediated by ATP-binding cassette (ABC) transporters

TKI	Alternative name(s)	ABC transporters linked to TKI resistance	Reference(s)
Imatinib	Gleevec, STI571	ABCG2/BCRP, ABCB1/P-gp/MDR1, ABCC1/MRP1	[21, 22, 30, 31, 33]
Nilotinib	Tasigna, AMN107	ABCG2/BCRP, ABCB1/P-gp/MDR1	[22, 23, 32]
Dasatinib	BMS-354825	ABCG2/BCRP, ABCB1/P-gp/MDR1	[23, 24]
Gefitinib	Iressa, ZD1839	ABCG2/BCRP	[25–27]
EKI-785	EKI-785	ABCG2/BCRP	[25, 26]
Danusertib	PHA-739358	ABCG2/BCRP	[28]
Canertinib	CI1033	ABCG2/BCRP	[29]
Sorafenib	Nexavar	ABCC2/MRP2	[34]

EKI-785, N-[4-[(3-bromophenyl)amino]-6-quinazolinyl]-2-butynamide.

Impact of ABC transporters on the pharmacokinetics and toxicity of TKIs

Besides mediating MDR, ABC transporters also have a significant impact on the pharmacokinetics and toxicity of TKIs. ABCB1/P-gp/MDR1 and ABCG2/BCRP are expressed not only in tumor tissues but also in normal tissues, such as the liver, kidneys, gastrointestinal tract, and blood-brain barrier. Thus, these two transporters can affect the pharmacologic behaviors (absorption, distribution, metabolism, and excretion) and toxicity of various anticancer drugs, including TKIs, by inhibiting their intestinal uptake and brain penetration or by facilitating their elimination. Marchetti *et al.*[35] reported that erlotinib was transported efficiently by ABCB1/P-gp/MDR1 and ABCG2/BCRP *in vitro* and *in vivo*, showing that the bioavailability of erlotinib after oral administration (5 mg/kg) was significantly increased in *Bcrp1/Mdr1a/1b*$^{-/-}$ knockout mice compared to wild-type mice. The brain distribution of gefitinib and dasatinib was found to be limited by active efflux mediated by ABCB1/P-gp/MDR1 and ABCG2/BCRP *in vivo*[36,37]. Yang *et al.*[38] demonstrated that tandutinib (MLN518) was a substrate of ABCB1/P-gp/MDR1 and ABCG2/ BCRP, affecting its oral absorption, systemic clearance, and brain penetration in rodents. These findings imply that potent inhibitors of ABCB1/P-gp and ABCG2/BCRP may improve the bioavailability and efficacy of TKIs and thus may have direct clinical implications in cancer treatment with TKIs.

Reversing MDR by TKIs

The modulators of ABC transporters

Several studies have focused on modulating the structure and function of ABC transporters and developing ideal strategies and drugs with which to reverse MDR in patients. Three generations of compounds have been developed to modulate the activity of ABC transporters. For example, a typical example of the first-generation modulators of ABC transporters, verapamil (a calcium channel blocker), was indicated to inhibit the activity of ABCB1/P-gp, but its low binding affinity and high toxicity at doses required for MDR reversal limited its clinical benefits. And a example of the second-generation ABC modulators, valspodar (a derivative of cyclosporin D), has been found to reduce the effective doses of other concomitantly used anticancer agents due to complex pharmacokinetic interactions, so its clinical application is limited[7,20]. Elacridar, a dual ABCB1/P-gp and ABCG2/BCRP inhibitor and third-generation ABC modulator, was reported to exhibit significant MDR reversal effect with only minimal side effects[39]. Recently, much efforts have been undertaken to identify or synthesize selective modulators of ABC transporters with limited nonspecific toxicity.

The MDR reversed by TKIs

As summarized above, MDR-related ABC transporters mediate resistance to TKIs by increasing the efflux of substrate TKIs. Interestingly, numerous recent studies showed that, at clinically achievable concentrations, some TKIs could bind the substrate-binding site of MDR-related ABC transporters and inhibit their drug efflux function, thereby reversing the MDR to traditional chemotherapeutic drugs in cancer cells[26,40,41]. Because ABCB1/P-gp/MDR1, ABCG2/BCRP, and ABCC1/MRP1 are crucial for mediating MDR, most studies about MDR reversal by TKIs have been performed on these transporters (Table 2). However, other transporters, such as ABCC10/MRP7 or

Table 2. The reversal of ABC transporter-mediated multidrug resistance (MDR) by TKIs

TKIs that reverse MDR	Alternative name(s)	MDR-related ABC transporters involved	Clinical applications	Reference(s)
Imatinib	Gleevec, STI571	ABCB1/P-gp/MDR1, ABCG2/BCRP, ABCC1/MRP1, ABCC10/MRP7	CML, GISTs, Ph^+ ALL, and others	[8, 42–46, 48]
Nilotinib	Tasigna, AMN107	ABCB1/P-gp/MDR1, ABCG2/BCRP, ABCC10/MRP7	Newly diagnosed CML, imatinib-resistant or -intolerant CML	[9, 47, 48]
Sunitinib	Sutent, SU11248	ABCB1/P-gp/MDR1, ABCG2/BCRP	RCC, imatinib-resistant GISTs, pNET	[11, 49, 50]
Erlotinib	Tarceva, OSI-774	ABCB1/P-gp/MDR1, ABCG2/BCRP, ABCC10/MRP7	Advanced NSCLC and pancreatic cancer	[12, 51, 53, 66]
Lapatinib	Tykerb, GW572016	ABCB1/P-gp/MDR1, ABCG2/BCRP, ABCC10/MRP7	HER2-positive advanced or metastatic breast cancer	[13, 52, 53]
Gefitinib	Iressa, ZD1839	ABCB1/P-gp/MDR1, ABCG2/BCRP	Advanced NSCLC	[14, 54–57]
Vandetanib	ZD6474	ABCB1/P-gp/MDR1, ABCG2/BCRP, ABCC1/MRP1	Metastatic medullary thyroid cancer	[15, 58, 59]
Sorafenib	Nexavar	ABCB1/P-gp/MDR1	Advanced RCC, advanced HCC	[16, 60, 61]
Apatinib	YN968D1	ABCB1/P-gp/MDR1, ABCG2/BCRP	–	[62]
BIBF 1120	–	ABCB1/P-gp/MDR1	–	[64]
AG1478	–	ABCB1/P-gp/MDR1, ABCG2/BCRP	–	[65, 66]
Cediranib	Recentin, AZD2171	ABCB1/P-gp/MDR1, ABCC1/MRP1	–	[67]
Canertinib	CI1033	ABCG2/BCRP	–	[28]

CML, chronic myelogenous leukemia; GISTs, gastrointestinal stromal tumors; ALL, acute lymphocytic leukemia; RCC, renal cell carcinoma; PNET, primitive neuroectodemal tumor; NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma.

ABCC4/MRP4, may also play roles in MDR and MDR reversal by TKIs. A more detailed description of the reversal of ABC transporter–mediated MDR by individual TKIs is presented next.

MDR reversal by imatinib Several studies have shown that imatinib can reverse MDR by suppressing the function of certain ABC transporters. Mukai *et al.*[42] found that 2.5 μmol/L imatinib could partially reverse resistance to vincristine, paclitaxel, etoposide, and actinomycin D in KB-G2 cells (an epidermal carcinoma cell line) that overexpress ABCB1/P-gp/MDR1 but could not reverse resistance to these agents in KB/MRP cells (human MRP1 gene-transfected KB cells) that overexpress ABCC1/MRP1. Imatinib was also reported to potently reverse ABCG2/BCRP-mediated resistance to topotecan and 7-ethyl-10-hydroxycamptothecin (SN-38), inhibit the substrate efflux function of ABCG2/BCRP, and increase the accumulation of topotecan in cells expressing functional ABCG2/BCRP [43]. Liu *et al.* [44] found that imatinib could increase the intracellular accumulation of photosensitizers in ABCG2/$BCRP^+$ cells but not in ABCG2/$BCRP^-$ cells and that imatinib could enhance photodynamic therapy efficacy both *in vitro* and *in vivo*. Hegedus *et al.*[45] found that imatinib could interact with ABCB1/P-gp/MDR1 and significantly inhibit the ATPase activity of ABCC1/MRP1. The combination of imatinib with 5-bromotetrandrine has been found to reverse MDR in K562/A02 cells (adriaraycin-resistant human myelogenous leukemia K562 cells), and the mechanism may be related to down-regulation of *MDR1* mRNA and ABCB1/P-gp/MDR1 expression along with increased apoptosis[46].

MDR reversal by nilotinib and sunitinib Similar to imatinib, nilotinib was shown to be a substrate for both ABCG2/BCRP and ABCB1/P-gp/MDR1[22,32]. On the other hand, nilotinib was also shown to be an inhibitor of these ABC transporters and to reverse MDR to their substrate drugs in cancer cells. Tiwari *et al.* [47] reported for the first time that nilotinib (2.5 and 5 μmol/L) significantly inhibited the efflux function of ABCB1/P-gp/MDR1 and ABCG2/BCRP without affecting their expression. They also reported that nilotinib enhanced the intracellular accumulation of paclitaxel (a substrate of ABCB1/P-gp/MDR1) in cell lines overexpressing ABCB1/P-gp/MDR1 and mitoxantrone (a substrate of ABCG2/BCRP) in cells transfected with ABCG2/BCRP, thus reversing ABCB1/P-gp/MDR1– and ABCG2/BCRP-mediated MDR [47]. Furthermore, Shen *et al.*[48] suggested that imatinib and nilotinib, at 5 μmol/L, significantly increased the accumulation and inhibited the efflux of

paclitaxel in HEK-MRP7-2 cells [human embryonic kidney (HEK) 293 cells transfected with MRP7/ABCC10] and, in a concentration-dependent manner, reversed ABCC10/MRP7-mediated paclitaxel resistance.

Shukla *et al.*[49] first reported that sunitinib could directly interact with two major ABC transporters, ABCB1/P-gp/MDR1 and ABCG2/BCRP. At a nontoxic concentration (2 μmol/L), sunitinib was able to partially reverse drug resistance mediated by ABCB1/P-gp/MDR1 and completely reverse resistance mediated by ABCG2/BCRP. Similarly, Dai *et al.*[50] showed that sunitinib significantly reversed ABCG2/BCRP-mediated MDR by inhibiting the drug efflux function of ABCG2/BCRP and increasing the intracellular accumulation of cytotoxic agents in ABCG2/BCRP-overexpressing cells, not by affecting the expression of ABCG2/BCRP at the mRNA or protein levels.

MDR reversal by erlotinib and lapatinib Erlotinib and lapatinib can also modulate the function of certain ABC transporters and reverse the ABC transporter-mediated MDR in cancer cells. Shi *et al.*[51] reported that erlotinib reversed ABCB1/P-gp/MDR1– and ABCG2/BCRP-mediated MDR in cancer cells by directly inhibiting the drug efflux function of these transporters for paclitaxel or mitoxantrone in ABCB1/P-gp/MDR1– or ABCG2/BCRP-overexpressing cells. However, erlotinib was unable to reverse ABCC1/MRP1-mediated MDR and had no effect on the parental cells. Dai *et al.*[52] demonstrated that lapatinib could also reverse ABCB1/P-gp/MDR1– and ABCG2/BCRP-mediated MDR by directly inhibiting their transport function in cells overexpressing these transporters. In addition, Kuang *et al.*[53] found that erlotinib and lapatinib reversed ABCC10/MRP7-mediated MDR by inhibiting the drug efflux function for established ABCC10/MRP7 substrates, specifically docetaxel, paclitaxel, vinblastine and vinorelbine. In their study, Kuang *et al.*[53] found that lapatinib was a more potent inhibitor of ABCC10/MRP7 than erlotinib.

MDR reversal by gefitinib and vandetanib Gefitinib, an analogue of erlotinib, has been reported to reverse ABCG2/BCRP-mediated drug resistance to topotecan, SN-38, and mitoxantrone in resistant cells by inhibiting the function of ABCG2/BCRP [54,55]. Kitazaki *et al.*[56] observed that gefitinib reversed the resistance to ABCB1/P-gp/MDR1 substrates paclitaxel (PTX) and docetaxel in a dose-dependent manner (1–10 μmol/L) in a multidrug–resistant PC-6/PTX lung cancer and MCF-7/adriamycin (ADR) breast cancer cells that overexpress ABCB1/P-gp/MDR1 by directly interacting with ABCB1/P-gp/MDR1 and inhibiting its drug efflux function. Yang *et al.*[57] also reported that gefitinib could inhibit the cellular functions of ABCG2/BCRP and ABCB1/P-gp/MDR1 at clinically relevant concentrations and reverse chemoresistance in cells overexpressing ABCG2/BCRP or ABCB1/P-gp/MDR1.

Mi *et al.*[58] showed that clinically achievable levels of vandetanib reversed ABCB1/P-gp/MDR1–mediated MDR of ABCB1/P-gp/MDR1–overexpressing MCF-7/ADR cells and KBV200 human oral epidermoid carcinoma cells to anticancer agents ADR, docetaxel, and vinorelbine. Vandetanib achieved this effect by directly inhibiting the function of ABCB1/P-gp/MDR1 and not by inhibiting the expression of ABCB1/P-gp/MDR1. Notably, vandetanib was not a substrate of ABCB1/P-gp/MDR1. Futhermore, Zheng *et al.*[59] demonstrated that vandetanib could overcome ABCC1/MRP1- and ABCG2/BCRP-mediated drug resistance to doxorubicin (DOX) and rhodamine 123 by inhibiting transporter activity and increasing intracellular accumulation of DOX and rhodamine 123, substrates of ABCC1/MRP1 and ABCG2/BCRP, in drug-resistant cancer cells that overexpress these transporters. This effect was independent of the blockade of AKT and ERK1/2 signalling pathways. Moreover, vandetanib was found not to be a substrate of ABCC1/MRP1 or ABCG2/BCRP.

MDR reversal by sorafenib and apatinib Wei *et al.*[60] demonstrated that sorafenib, at 4 μmol/L, could partially reverse MDR in human hepatoma cells, probably in association with down-regulation of *MDR1* gene expression or ABCB1/P-gp/MDR1 protein expression, and increase the accumulation of chemotherapeutic agents adriamycine (ADM), 5-fluorouracil (5-FU), gemcitabine, and cisplatin (DDP) in the cells. Hoffmann *et al.*[61] also reported that addition of sorafenib to conventional chemotherapy, gemcitabine or DOX, restored the chemosensitivity of HCC cells by decreasing the ABC-protein mRNA levels by up to 74%–77% compared to conventional chemotherapy alone. These studies suggest that sorafenib modulated the MDR phenotype of HCC cells and consequently might lead to personalized therapies in patients with highly resistant tumors.

Apatinib (YN968D1), a novel selective inhibitor of VEGFR-2, was demonstrated to reverse ABCB1/P-gp/MDR1– and ABCG2/BCRP-mediated MDR by inhibiting their transport function, but not by blocking the AKT or ERK1/2 pathway or by down-regulating the expression of ABCB1/P-gp/MDR1 or ABCG2/BCRP[62].

MDR reversal by BIBF 1120 and AG1478 BIBF 1120, a small-molecule triple kinase inhibitor that targets the VEGFR, PDGFR, and fibroblast growth factor receptor (FGFR) tyrosine kinases, is currently in phase III clinical trials for treating advanced NSCLC and ovarian cancer[63]. Xiang *et al.*[64] found that BIBF 1120 was able to reverse ABCB1/P-gp/MDR1–mediated MDR, but not

ABCC1/MRP1- or ABCG2/BCRP-mediated MDR, by inhibiting the function of ABCB1/P-gp/MDR1. This effect was not caused by altering the expression levels of *MDR1* mRNA or ABCB1/P-gp/MDR1 protein in ABCB1/P-gp/MDR1–overexpressing cancer cells. These findings suggest that BIBF 1120 might have clinical significance in combination therapies for certain resistant cancers.

AG1478 is a potent and specific inhibitor of EGFR. Shi *et al*.[65] first investigated the interaction of AG1478 with ABC transporters and found that AG1478, at non-toxic doses, partially inhibited resistance to ABCB1/P-gp/MDR1 substrate drugs and increased intracellular accumulation of [^{3}H]-paclitaxel in ABCB1/P-gp/MDR1–overexpressing cells, in addition to significantly reversing resistance to ABCG2/BCRP substrate drugs and increasing intracellular accumulation of [^{3}H]-mitoxantrone in ABCG2/BCRP-overexpressing cells. Shi *et al*.[65] also reported that AG1478 and erlotinib potently sensitized drug-resistant cells overexpressing either wild-type or mutated ABCG2/BCRP to the ABCG2/BCRP substrate drugs, flavopiridol and mitoxantrone, and enhanced the intracellular accumulation of mitoxantrone, suggesting that AG1478 and erlotinib could potently reverse ABCG2/BCRP-mediated MDR[66].

MDR reversal by other TKIs Other TKIs have been found to reverse ABC transporter-mediated resistance. Cediranib (recentin, AZD2171), an oral, small-molecule, multikinase inhibitor, was reported to reverse ABCB1/P-gp/MDR1– and ABCC1/MRP1- mediated MDR by directly inhibiting their drug efflux function [67]. Canertinib was first shown to increase the steady-state accumulation of SN-38 and topotecan and enhance their cytotoxic effect in cell lines overexpressing ABCG2/BCRP[29].

The above findings collectively suggest that the TKIs in study inhibit the function of MDR-related ABC transporters and reverse MDR to chemotherapeutic drugs at clinically achievable concentrations, and thus may be promising MDR inhibitors. This implies that simultaneous administration of TKIs with other anticancer agents, especially substrates of these transporters, may be beneficial for tumour patients that have transporter-mediated MDR. These findings provide a basis for the development of combination chemotherapeutic strategies with TKIs. However, whether these TKIs can be used with the established ABC transporter substrate anticancer agents to improve clinical outcome is worthy of further study in the clinic.

Conclusions

To date, numerous TKIs have been developed and approved for treating various human malignant diseases. However, MDR mediated by ABC transporters, especially ABCB1/P-gp/MDR1, ABCC1/MRP1, and ABCG2/BCRP, affects the therapeutic potential of TKIs in cancer chemotherapy. These TKIs are high-affinity substrates of MDR-related ABC transporters, which could result in TKI efflux and resistance in cancer cells. Interestingly, some TKIs are also inhibitors or modulators of MDR-related ABC transporters. These TKIs can inhibit or reverse MDR by directly blocking the efflux of ABC transporter substrates, and they play a crucial role in overcoming chemotherapy resistance. Therefore, simultaneous administration of TKIs with other anticancer agents, especially substrates of these transporters, may be applicable for chemotherapeutic practice clinically. However, further studies are still needed to identify safer and more effective combination chemotherapeutic strategies in the clinic.

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