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FIELD OF VISION

Insights into cardio-oncology: Polypharmacology of quinazoline-based α1-adrenoceptor antagonists

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Abstract

New uses of cardiovascular drugs with proven experience are emerging, including for treating cancer. Quinazoline is a compound made up of two fused six member simple aromatic rings, benzene and pyrimidine rings, with several biological effects. Cardiologists first used quinazoline-based α1-adrenoceptor antagonists prazosin, doxazosin, and terazosin; currently available data support their use as safe, well tolerated, and effective add-on therapy in uncontrolled hypertension with additional favourable metabolic effects. Recent findings highlight the anticancer effects of quinazoline-based α1-adrenoceptor antagonists, indicating that they may have a significant role in uncontrolled hypertensive cancer patients without signs of ischemia.

Key words: Cardio-oncology; Multidrug resistance; Prazosin; Terazosin; Doxazosin

Core tip: New uses of cardiovascular drugs with proven experience and without high cost have been emerging, including to have anticancer abilities by targeting human ether-a-go-go-related gene K(+) channels, epidermal growth factor receptors, vascular endothelial growth factor receptors, as well as to overcome cancer multidrug resistance. Quinazoline-based α1-adrenoceptor antagonists (doxazosin, prazosin, and terazosin) exhibit anticancer abilities and emerging findings indicate that these drugs may have a significant role in uncontrolled hypertensive cancer patients without signs of ischemia.

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INTRODUCTION

Despite the tremendous efforts, the medicine field has not yet come to absolute conclusions in oncology and the emerging scenario of the onco-cardiovascular patients is emerging[1]. New targeted anticancer therapies have not proven to be free from cardiovascular side effects while old anticancer therapies have shown delayed serious consequences in long-term cancer survivors[1,2]. Moreover, the heavy burden of concomitant problems and diseases requires changes in setting to prevent serious diseases such as infective endocarditis or in

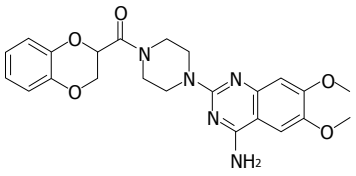	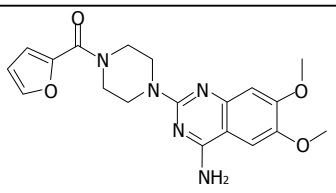	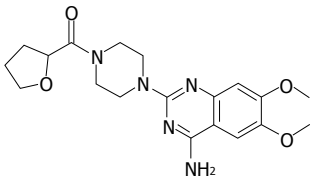
Doxazosin	Prazosin	Terazosin
Quinazoline-based	Quinazoline-based	Quinazoline-based
α_1-adrenoceptor antagonist	α_1-adrenoceptor antagonist	α_1-adrenoceptor antagonist
Antihypertensive effect	Antihypertensive effect	Antihypertensive effect
HERG ligand	HERG ligand	HERG ligand
EGFR inhibition	EGFR inhibition	
Anti-angiogenic activity	Anti-angiogenic activity	
Cancer cell growth inhibition		Cancer cell growth inhibition
Apoptosis induction	Apoptosis induction	Apoptosis induction
Anoikis induction		Anoikis induction
	Cell autophagy induction	Cell autophagy induction
Role in MDR	Role in MDR	Weaker or no effect in MDR
Akt inhibition	Cdk 1 inactivation	G_1 phase cell cycle arrest
Androgen receptor downregulation	DNA damage stress induction	p27KIP1 up-regulation
Bax expression upregulation	G_2 checkpoint arrest	Proteasome activity downregulation
Caspase-3 activity increase	Mitochondria-mediated apoptosis induction	Ubiquitinated protein accumulation
EphA2 agonism	p53-mediated mechanism	
FGFR-2 antagonism		
Focal adhesion kinase reduction		
HIF-1α inhibition		
MAPK activation decrease		
mTOR inhibition		
p27 downregulation prevention		
PDK1 inhibition		
PKB/Akt activation inhibition		
PI3K inhibition		
Rho kinase-Ⅱ activation decrease		
Soluble guanylate cyclaseα decrease		
TGF-β and IκB activation		
Tubulin-polymerization-enhancing activity		

Figure 1 Structure and polypharmacology of quinazoline-based α1-adrenoceptor antagonists doxazosin, prazosin and terazosin in cardio-oncology. MDR: Multidrug resistance; EGFR: Epidermal growth factor receptor; FGFR-2: Fibroblast growth factor receptor-2; HIF-1α: Hypoxia-inducible factor 1α; mTOR: Mammalian target of rapamycin; PDK1: 3-phosphoinositide-dependent protein kinase 1; TGF: Transforming growth factor.

perioperative oncosurgery[3-12]. The progress in cancer biology and treatment has led to a new frontier: the cardio-oncology[1-27]. New uses of cardiovascular drugs with proven experience have been emerging[1,4,5-9,27-32], including to have anticancer abilities by targeting human ether-a-go-go-related gene K(+) (HERG) channels[5], epidermal growth factor (EGF) receptors[9], vascular endothelial growth factor (VEGF) receptors, as well as to overcome cancer multidrug resistance (MDR)[4,26,29,33,34]. These old cardiovascular drugs do not have high cost, however, there was a lack of noninferiority randomized, controlled trials[33], comparing them with new anticancer therapies.

Quinazoline is a compound made up of two fused six member simple aromatic rings, benzene and pyrimidine rings[35]. The search for quinazoline-based substances as cardiovascular agents begun after pharmacological identification of quinazoline compounds having a glycine amide or β-alanine amide residue in the 3rd position that display a hypotensive activity. Other quinazoline derivatives have also demonstrated significant anticancer activities[26,35-39] and new molecules have been synthesized as gefitinib, erlotinib, afatinib, and lapatinib[26,36]. Cardiologists first used quinazoline-based α_1-adrenoceptor antagonists, including prazosin, doxazosin, and terazosin[26] (Figure 1). Currently available data have supported the use of these antagonists as safe, well tolerated, and effective add-on therapy in uncontrolled hypertension with additional favorable metabolic effects[37] and without association with an increased risk of heart failure[26,37-39]. New data suggest that adverse cardiac outcome of doxazosin is only among patients with moderate-to-severe ischemia on myocardial perfusion imaging[26,40]. Furthermore, it has been reported that the β-plus α_1-blocker pretreatment (propranolol + prazosin) has led to better severity reduction of postresuscitation myocardial tissue injury and myocardial dysfunction with better neurologic function and prolonged duration of survival than propranolol treatment alone[41]. This latter finding will require certainly further evaluation.

Research has suggested several anticancer mechanisms of doxazosin, including upregulation of Bax expression, transforming growth factor (TGF)-β and IκB activation[42], focal adhesion kinase reduction[43],

inhibition of protein kinase B/Akt activation[44], and death receptor mediated apoptosis induction[45,46]. Doxazosin is known to be a HERG ligand, EGFR inhibitor[47], VEGF-mediated angiogenic response antagonist[48], and fibroblast growth factor receptor-2 antagonist[48,49]. Several signalling pathways are also inhibited from doxazosin VEGF antagonism including PI3K, Akt, 3-phosphoinositide-dependent protein kinase 1, mammalian target of rapamycin, and hypoxia-inducible factor 1α[49]. In addition, doxazosin is also an agonist of receptor tyrosine kinase triggering ephrin type-A receptor 2 internalization which, in turn, suppresses haptotactic and chemotactic migration of prostate cancer, breast cancer, and glioma cells[26,50]. Notably, a tubulin polymerization-enhancing activity of doxazosin has been found[51]. A doxazosin derivative, DZ-50, impairs tumour growth and metastasis *via* anoikis[52]; similarly, doxazosin induces changes in morphology consistent with anoikis in both benign and cancerous prostatic cells and increased caspase-3 activity[43]. Moreover, doxazosin significantly decreases benign prostatic hyperplasia-induced mitogen-activated protein kinase kinase and Rho kinase-Ⅱ activation and decreases expression of soluble guanylate cyclasea[53] also leading to prostate cancer cell growth inhibition[54] Doxazosin also downregulates expression of androgen receptor[54], prevents p27 downregulation[55] and may partly reverse P-glycoprotein/MDR1-mediated cancer multidrug resistance (CMDR) and the transport of anticancer drugs[56].

Terazosin, another quinazoline-based antihypertensive α_1-adrenoceptor antagonist[57], is also an HERG ligand[58], a cancer cell growth inhibitor[59], and an apoptosis and anoikis inductor[58,60]. Terazosin induces cell death which is associated with G_1 phase cell cycle arrest, upregulation of cyclin-dependent kinase inhibitor 1B (p27KIP1)[60], accumulation of ubiquitinated proteins and downregulation of proteasome activity[46]. Terazosin seems to have weaker or no effects regarding CMDR[55].

Prazosin, another quinazoline-based and anti-hypertensive α_1-adrenoceptor antagonist[60], is also an HERG ligand[58] and EGFR inhibitor[61]. Prazosin induces autophagic cell death *via* a p53-mediated mechanism[62] and cell apoptosis through the induction of DNA damage stress, leading to cyclin-dependent kinase 1 inactivation and G_2 checkpoint arrest triggering mitochondria-mediated apoptosis induction[62]. In addition, prazosin exhibits an anti-angiogenic activity[63] and its role in MDR modulation has also been suggested[55,64]. These emerging findings indicate that the quinazoline-based antihypertensive α_1-adrenoceptor antagonists may have a significant role in uncontrolled hypertensive cancer patients without signs of ischemia[26,29,38,40].

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