Review

Therapeutic Value of Quinazoline-based Compounds in Prostate Cancer

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Abstract. *Certain α1-adrenoreceptor antagonists induce significant apoptosis and impair tumor vascularity without affecting cellular proliferation, effects specific to the quinazoline structure. These anticancer effects have been attributed to both induction of classical apoptosis and reversal of anoikis resistance via disruption of integrin-mediated cell survival pathways. Recent drug optimization efforts have generated several novel compounds with quinazoline-derived chemical structure that exert potent anti-tumor activity via anoikis. Results from pre-clinical and clinical studies implicate a potential value of quinazoline-based analogues in prostate cancer prevention and therapy. A retrospective study of a large patient cohort at our center, revealed that treatment with α1-andrenoreceptor antagonists significantly reduced the risk of developing prostate cancer, indicating a potential chemopreventative mechanism for these FDA-approved agents. In the present review we discuss the current understanding of the signaling mechanisms reversing anoikis resistance by the quinazoline-based compounds in prostate tumors, towards enabling identification of novel therapeutic targets for the treatment of metastatic castration-resistant prostate cancer (CRPC).*

Abbreviations: CRPC, castration resistant prostate cancer; AR, androgen receptor; BPH, benign prostatic hyperplasia; FADD, Fas-associated death domain; VEGF, vascular endothelial growth factor; HUVEC, human umbilical vein endothelial cells; ECM, extracellular matrix; FAK, focal adhesion kinase; RCC, renal cell carcinoma; PFS, progression-free survival; OS, overall survival; Non-small cell lung cancer (NSCLC).

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Prostate cancer is the most prevalent form of cancer and the second leading cause of cancer-related death among men (1). Treatment modalities effective for localized disease include prostatectomy, radiotherapy, and medical or surgical androgen deprivation. While survival rates for localized disease approach 100%, the mortality associated with advanced metastatic prostate cancer results in 1 out of 6 men diagnosed with the disease losing their life. Thus, there is poor overall prognosis and no effective treatment currently available for advanced metastatic disease (1-4). Castration-induced (surgical or medical) androgen-ablation is the only therapeutic regime used for the treatment of prostate cancer metastasis *via* induction of apoptosis of androgen-dependent prostate tumor cells. Most tumors however eventually relapse after the initial response with the emergence of castration-resistant prostate cancer (CRPC), due to their ability to evade apoptosis despite significantly reduced circulating serum androgen levels. Such resistance develops through aberrations in androgen receptor (AR) signaling, such as significant overexpression of AR or promiscuous, constitutive activation of AR by non-specific ligand binding (5-7). CRPC can also develop through the activation of cellular survival pathways that completely bypass AR (6). Cell survival ultimately leads to tumor angiogenesis and metastasis. In prostate cancer, increased angiogenesis positively correlates with tumor stage and Gleason score (8, 9). A lack of effective treatment for CRPC results in a drastic increase in overall patient morbidity and mortality (10, 11). The dismal statistics for advanced prostate cancer necessitate the development of effective therapies targeted at the nuances of metastatic disease towards increasing patient survival, as well as enhancing quality of life after treatment.

Continuing molecular dissection into the mechanisms of prostate tumorigenesis has led to a greater understanding of the importance of anoikis resistance in cancer progression and has generated interest in the potential therapeutic value of targeting cell survival pathways (12). A class of FDA-approved α1-adrenoreceptor antagonists used clinically for

the treatment of hypertension, and more recently as first-line treatment for benign prostatic hyperplasia (BPH), has demonstrated potent activity against tumor vasculature (11-15) in addition to strong pro-apoptotic activity in both benign prostatic epithelial cells and malignantly-transformed cells (16-18). This discovery has inspired attempts towards optimizing the molecular structure of new, more potent compounds based on the quinazoline parent structure (11, 19-22). This review will discuss how the quinaozoline-derived compounds target tumor growth and neovascularization; the mechanistic evidence of such actions both *in vitro* and *in vivo*; the pharmacological exploitation of quinazoline-based compounds towards the development of higher-efficacy novel compounds; and the clinical implications and potential value of such compounds in the treatment of advanced CRPC.

Quinazoline Anti-Tumor Action

The anti-tumor activity of quinazoline-derived compounds has recently elicited exciting controversies in the field of prostate cancer therapeutics. The drugs were originally established to be efficacious in the treatment of BPH due to their ability to block the α1-adrenoreceptors, thereby reducing prostatic smooth muscle tone and relieving overall obstruction (23). Growing evidence from retrospective studies of BPH patients demonstrated that treatment with doxazosin and terazosin increased epithelial cell apoptosis in prostate tissue with no overall effect on the rate of cell proliferation (17, 18). Subsequent *in vitro* research revealed that the quinazolines' efficacy in inducing apoptosis was not limited to benign prostate epithelial cells but was also applicable to both androgen-dependent and CRPC cells. This effect was specific to quinazolines, as the sulfonamide-based α1-blocker tamsulosin failed to exhibit apoptotic activity (16, 19, 24). The molecular mechanisms *via* which the quinazoline compounds exert their pro-apoptotic effects are currently under intense investigation. Pre-clinical evidence suggests doxazosin mediates apoptosis in prostate epithelial cancer cells through the TGF-β signaling pathway, which controls cellular proliferation, differentiation, and apoptosis in numerous cell types. Doxazosin-activated transcription of the NF-κB inhibitor IκBα is another potential mechanism for the drug's increased apoptotic effects in CRPC, which exhibits constitutively activated NF-κB signaling (25, 26). Furthermore, more recent studies indicate that doxazosin induces apoptosis *via* the FADD-mediated Fas death receptor signaling pathway (27, 28).

Initial evidence of the quinazoline compounds' anti-angiogenic activity arose in a retrospective study of prostate cancer specimens in which tumors from patients treated with terazosin showed significantly reduced microvessel density compared to untreated specimens (13). Additional evidence revealed that terazosin inhibited VEGF-induced angiogenesis in both cultured HUVEC cells and an *in vivo* nude mouse model (14). Furthermore, doxazosin significantly impairs human endothelial cells by blocking cell adhesion, migration, and invasion due to loss of appropriate interaction between epithelial and endothelial cells and the extracellular matrix (ECM) (15).

Cell-ECM Interactions in Cancer Progression

The ability of endothelial and tumor cells to survive in the absence of proper ECM interactions is one of the driving forces behind tumor angiogenesis and metastasis. Cell attachment to the ECM is primarily mediated by integrins, which interact with fibronectin, laminin and a variety of other ECM proteins. Ligated integrins promote the formation of focal adhesion complexes, cytoskeleton-anchored signaling complexes associated with a number of non-receptor tyrosine kinases, such as focal adhesion kinases (FAK) and Src; actin-binding proteins, including talin and paxillin; as well as several other intracellular signaling molecules (27, 29, 30). Normal epithelial and endothelial cells undergo anoikis upon loss of integrin-mediated adhesion to the ECM, but malignantly-transformed cells can survive in an unanchored state by deregulating integrin-mediated survival pathways (31).

De-regulation of integrin signaling has been implicated in several types of cancer, including prostate cancer. FAK is expressed at very low levels in normal prostate secretory epithelium, while significant expression is observed at the earliest stages of transformation and continues throughout cancer progression (32, 33). FAK interacts with Src, which is also highly expressed in prostate cancer specimens and influences a variety of signaling pathways that affect cell survival, angiogenesis, proliferation, and motility (34). Talin-1 is significantly up-regulated in prostate tumor cells, leading to downstream activation of FAK/AKT signaling and, ultimately, anoikis resistance (31, 35). In a recent study, knockdown of β1-integrins in PC3-mm^2 cells abrogated anoikis resistance, and treatment with the β1-integrin-neutralizing antibody mAB 33B6 reduced tumor metastases *in vivo*, further implicating deregulated integrin signaling in the anchorage-free survival of malignant cells (36).

Reversal of anoikis resistance *via* targeting of integrin-mediated survival pathways is one of the most promising strategies for combating tumor metastasis and angiogenesis, and quinazoline-based compounds have demonstrated such activity in multiple cancer cell lines (27, 37, 38). Doxazosin reduces FAK expression in PC-3 cells and also exerts a modest disruptive effect on ILK-1, FAK, and paxillin binding with integrin-β1 in the human renal cell carcinoma (RCC) line 786-0 (27, 37). The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor gefitinib reduces cell

adhesion ability to fibronectin; reduces expression of integrin-α3, αv, β1, β4, β5, β6; and suppresses FAK phosphorylation in the oral squamous cell carcinoma line GFP-SAS-L1 (38).

Pharmacological Exploitation

The anti-tumor activity of quinazoline-based compounds has generated interest in the development of more potent novel compounds that maintain the quinazoline functional group (16, 24). In 2009, Giardinà *et al*. demonstrated that a related novel compound, cyclodoxazosin, exhibited greater anti-proliferative activity and repression of tumor vascularity compared to other novel quinazoline-based compounds. Cyclodoxazosin induced greater expression of caspase-3/7 and demonstrated greater growth inhibition of PC-3 cell line tumors inoculated in mice than doxazosin (22). In another study, the VEGFR2 inhibitor SKLB1002 significantly suppressed VEGF-induced phosphorylation of VEGFR2, extracellular signal-regulated kinases (ERK), FAK, and Src in endothelial cells. It also antagonized tumor angiogenesis in murine and zebrafish models without exerting any of the adverse side-effects associated with other VEGF receptor inhibitors, implying a therapeutic promise for optimized treatment modalities (39).

The two lead doxazosin-derived compounds developed and characterized by our group exhibited higher anti-vascular and anti-tumor activity than their parent compound, both *in vitro* and *in vivo* (21). The novel agent DZ-3 induced classical apoptosis in prostatic cells, while the new compound DZ-50 induced cell death and targeted tumor vasculature *via* anoikis. DZ-50 significantly reduced the viability of multiple epithelial and endothelial cell lines, and PC-3 cells exposed to DZ-50 showed decreased cell adhesion to fibronectin and collagen. DZ-50 was effective in impairing prostate cancer cell invasion *in vivo* and more importantly, treatment with DZ-50 reduced primary tumor growth and formation of metastatic foci in an *in vivo* model system (21).

More recent studies from our laboratory established the anti-tumor effects of DZ-50 against human renal cancer. Using two human renal cancer cell (RCC) lines as experimental models, 786-0 and Caki, we documented that DZ-50 induced early apoptosis at lower doses compared to the parent compound doxazosin (27). Both drugs significantly decreased the adhesion potential of RCC to fibronectin and laminin in a time-dependent manner and suppressed the cells' migratory and invasive capabilities. Our results clearly demonstrated that in response to DZ-50, RCC metastasis was significantly impaired *in vivo via* anoikis induction. Mechanistically, reversal of anoikis resistance by DZ-50 proceeded *via* decreased phosphorylation of FAK, AKT, and GSK-β, thus inactivating critical cellular survival pathways. DZ-50 also exerted a more potent inhibitory effect than doxazosin on ILK-1, FAK, and paxilin binding to integrin-β1. Collectively these results support the concept that doxazosin induces apoptosis *via* caspase-8 cleavage and subsequent caspase-3 activation, while DZ-50 invokes anoikis susceptibility by disrupting integrin/FAK-mediated cell survival pathways (27).

Multiple pre-clinical studies have analyzed the anticancer effects of quinazoline-derived compounds in combination with cytotoxic agents and other treatment modalities (40, 41). In one such study, the anti-tumor effects of the VEGF receptor inhibitor cediranib alone and in combination with a number of other compounds, including gefitinib, bevacizumab, docetaxel, and cisplatin, were compared in various tumor xenograft models. In each case, combining cediranib with another anticancer agent led to greater activity than either agent alone, with some combinations producing near 100% growth inhibition or even tumor regression (40). Moreover, an independent group of investigators evaluated the effects of a combination of terazosin and the soy isoflavone genistein on the prostate cancer cell line DU-145 (41). Simultaneous treatment with the two compounds more effectively inhibited cell growth than either compound alone due to a significant increase in apoptosis. In comparison to mono-treatment, treatment with both compounds significantly decreased expression of *procaspase-3, Bcl-XL,* and *VEGF* mRNA, while markedly increased PARP cleavage (41).

Potential Clinical Value

The lack of effective clinical treatment for CRPC combined with the promising anti-tumor effects demonstrated by quinazoline compounds in pre-clinical studies has generated significant interest in the potential clinical value of these compounds. In 2003, following several positive clinical evaluations (42-44), gefitinib was FDA-approved as a monotherapy treatment for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of both platinum-based and docetaxel chemotherapies (45). Encouraging results from pre-clinical studies (46, 47) and a phase I trial of gefitinib in patients with advanced solid tumors, including prostate cancer (48), inspired a phase II study of two doses of gefitinib in patients with CRPC (49). However, this study failed to demonstrate any activity for either dosage of gefitinib as monotherapy in CRPC. In another phase II trial of prednisone with or without gefitinib in the treatment of CRPC, gefitinib demonstrated only very moderate activity (50).

The failure of gefitinib to elicit a survival benefit in CRPC patients is disappointing, but clinical trials of other quinazoline-derived compounds have produced more promising results (51, 52). For example, a recent phase II trial evaluated cediranib in patients with metastatic CRPC who had progressed after docetaxel therapy (52). Among patients with measurable disease, six had confirmed partial responses and one had an unconfirmed partial response. The probability of

progression-free survival (PFS) for all evaluable patients (n=58) was 43.9% at 6 months, median PFS was 3.7 months, and median overall survival (OS) was 10.1 months. Vascular permeability, which was assessed by dynamic contrast-enhanced magnetic resonance imaging, was reduced across large proportions of patients, as evidenced by statistically significant reductions in gadolinium uptake. The most common toxicities were hypertension, fatigue, anorexia, and weight loss, and these effects were reduced by concurrent treatment with prednisone (52).

Recently gathered pre-clinical evidence suggests cooperative anti-tumor effects of quinazoline-based compounds in combination with other treatment modalities (40, 41). Clinical trials of such combination therapies, however, have produced controversial results (53, 54, 55). For example, a phase II trial of docetaxel with erlotinib in elderly patients with CRPC failed to demonstrate a survival benefit by treatment with both compounds (54). On the other hand, a phase II trial evaluating carboplatin and paclitaxel in combination with either cediranib or placebo in patients with advanced NSCLC produced more encouraging results (55). There was a significantly higher response rate for cediranib than for placebo, with a hazard ratio of 0.77 for PFS, and a similar number of deaths in both arms. However, cediranib patients experienced more adverse effects, including hypertension, hypothyroidism, hand-foot syndrome, and GI toxicity. Concerns over tolerability precluded immediate advancement to phase III testing (55), but these results still support further exploration of quinazoline-derived compounds in combination therapies.

The anti-tumor effects of quinazoline-derived compounds observed at the cellular level may also translate to a chemopreventative action. In 2007, we first reported the results from a retrospective study in which the medical records of Lexington, KY, VA Medical Center patients treated with doxazosin or terazosin were reviewed and compared with the Markey Cancer Center's Kentucky Cancer Registry, a state-based portion of the NCI's Surveillance, Epidemiology, and End Results (SEER) program. Patients treated with the α1-adrenoreceptor antagonists showed an overall prostate cancer incidence of 1.65% compared to 2.41% in untreated patients, which is equal to a 1.46-times lower relative risk and 31.7% lower attributable risk of prostate cancer development in treated *vs.* untreated patients (56). These results yielded much promise and generated momentum towards conducting an expanded prospective, multi-center trial comparing prostate cancer incidence among BPH patients treated with α1-adrenoreceptor agonists *vs.* those treated with placebo. Such a study could include an evaluation of the results of monotreatment with various quinazoline-based compounds, which could ultimately lead to the identification of a parent compound to be utilized in the optimization of new chemical structures with greater preventative capabilities.

Conclusion and Future Directions

Resistance to anoikis plays an important role in prostate cancer progression to advanced metastatic disease. Doxazosin, terazosin, and other quinazoline-derived compounds have demonstrated pro-apoptotic activity in cancer epithelial cells as well as significant anti-angiogenic activity in endothelial cells. This apoptosis-driven anti-tumor action combined with functional reversal of anoikis resistance *via* targeting integrin-navigated survival signaling and focal adhesion, provide a rigorous interrogation platform for identification and optimization of therapeutic strategies to impair metastatic CRPC. Elucidation of the mechanisms of quinazoline action has allowed for development of novel quinazoline-derived compounds, such as DZ-50, with significantly greater anti-tumor activity compared to their parent drugs. Mechanistic dissection of the anti-tumor action of the novel quinazoline agents is being pursued in mouse models of prostate tumorigenesis. The focus is understandably the integrin and focal adhesion complex signaling pathways that contribute to anoikis resistance in the human prostate, several of which have not yet been analyzed in the context of treatment with the quinazoline parent compounds. For example, the mitochondrial protein Bit1, which is released into the cytoplasm upon detachment from the ECM, initiates a caspase-independent form of apoptosis. Although upstream integrin-ECM attachment prevents Bit1 release (57, 58), and quinazoline-compounds are known to disrupt the formation of focal adhesion complexes (27), the effects of doxazosin and related compounds on Bit1 activity have not been investigated. Further insight into the effects of quinazoline compounds on this and other integrin-mediated pathways can hopefully serve as a platform for the development of more potent drugs in the treatment of CRPC.

The development of CRPC cannot be attributed to a single molecular pathway; therefore, doxazosin and related compounds should be evaluated in combination with the full spectrum of CRPC treatment modalities, including anti-androgen compounds such as the recently developed selective AR modulators (SARMs); gene-based therapeutic agents such as siRNA and MDM2; AR-specific chemotherapeutic agents such as estramustine and perifosine; and AR-independent signaling pathway agonists such as ZD4054 and nordihydroguareacetic acid (NDGA) (59). Such therapeutic targeting at the cellular level begs for clinical evaluation to identify promising strategies to address the current lack of effective treatment for CRPC. The 5α-reductase inhibitor finasteride reduces the risk of prostate cancer development; however, it also increases the risk of developing high-grade tumors (60, 61). A 2003 study on the long-term effects of doxazosin, finasteride, and combination therapy on BPH progression revealed that combination therapy more effectively reduced the risk of overall clinical progression

than either compound alone (62). An expanded randomized, placebo-controlled study of the effects of doxazosin and finasteride combination treatment on the incidence of prostate cancer may provide a new strategy for decreasing the elevated risk of high-grade tumor development associated with finasteride. Such an effort, alongside the on-going characterization of cell survival pathways and further optimization of quinazoline-based anti-tumor compounds, will hopefully contribute to the improvement of the dismal statistics associated with advanced CRPC.

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