

Renin–Angiotensin System Inhibitors to Mitigate Cancer Treatment–Related Adverse Events

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Abstract

Treatment-related side effects are a major clinical problem in cancer treatment. They lead to reduced compliance to therapy as well as increased morbidity and mortality. Well-known are the sequelae of chemotherapy on the heart, especially in childhood cancer survivors. Therefore, measures to mitigate the adverse events of cancer therapy may improve health and quality of life in patients with cancer, both in the short and long term. The renin–angiotensin system (RAS) affects all hallmarks of cancer, and blockage of the RAS is

associated with an improved outcome in several cancer types. There is also increasing evidence that inhibition of the RAS might be able to alleviate or even prevent certain types of cancer treatment–related adverse effects. In this review, we summarize the potential of RAS inhibitors to mitigate cancer treatment–related adverse events, with a special emphasis on chemotherapy-induced cardiotoxicity, radiation injury, and arterial hypertension. *Clin Cancer Res*; 24(16): 3803–12. ©2018 AACR.

Introduction

Cancer is a major public health issue, with a projected number of 1,688,780 new cases and 600,920 cancer-related deaths in the United States in 2017 (1). The economic burden of cancer in the European Union rose continuously to €83.2 billion on health care expenditures and €19.1 billion on cancer drugs in 2014, not including production loss due to early death and lost working days (2).

Treatment-related side effects represent a major problem in oncology because they can severely interfere with the patient's quality of life and require dose reductions and treatment delays or even discontinuation of therapy. This reduces the effectiveness of anticancer treatment and ultimately increases morbidity and mortality (3). Side effects also increase the number of emergency room visits and hospitalizations, resulting in increased costs for health care systems and patients. Hence, smart prevention strategies might not only prolong patients' survival and improve their quality of life, but also help to reduce health care costs (4).

The circulating renin–angiotensin system (RAS) plays a pivotal role in maintaining cardiovascular homeostasis as well as fluid and electrolyte balance. Additionally, a local RAS is expressed in many tissues and regulates cellular functions, including growth and metabolism (5, 6). Dysregulation of the local RAS is involved in the pathophysiology of several diseases, such as inflammation

and fibrosis (7), and promotes cancer growth and dissemination (8, 9). A recent meta-analysis demonstrated that the intake of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) is significantly associated with improved cancer progression-free and overall survival (10).

Notably, angiotensin II (AngII) is also involved in the development of several cancer treatment–related side effects, such as cardiotoxicity (11), radiation-induced tissue injury (12), and muscle wasting (13–15). Hence, inhibition of AngII/angiotensin II receptor type 1 (AT1R) signaling by renin–angiotensin inhibitors (RASi; i.e., direct renin inhibitors, ACEi, and ARBs) may not only improve the outcome of cancer treatment but also help to treat or prevent certain adverse events. Notably, in addition to inhibiting AngII production, ACEi can also increase angiotensin (1–7) [Ang(1–7)] by blocking its breakdown through ACE. Ang(1–7) is known to counteract many effects of AngII/AT1R signaling (5, 16). ARBs increase AngII levels by blocking the AT1R and thereby also contribute to Ang(1–7) generation from AngII via ACE2 (17, 18). Thus, the beneficial effects of ACEi and ARBs may not only result from inhibiting AngII/AT1R signaling but also partly be mediated by Ang(1–7) (17).

We have recently proposed that RASi-mediated improvement of drug delivery may allow for dose reductions of anticancer drugs without decreasing the therapeutic benefit, which could eventually result in a decreased number of side effects (9). In this review, we discuss the potential of RASi to prevent or improve tumor cachexia as well as cancer treatment–induced adverse events, such as cardiotoxicity, radiation injury, and arterial hypertension.

Chemotherapy-induced Cardiotoxicity

Several anticancer agents, of which anthracyclines and trastuzumab are widely prescribed, can cause severe and even fatal cardiac side effects, with heart failure due to left ventricular dysfunction (LVD) being the most relevant (19). Of note, the presence of cardiotoxicity not only affects immediate and long-term cardiac outcomes but also limits the therapeutic options in case of disease recurrence. The term "cardiotoxicity"

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encompasses all side effects affecting the heart, which span the entire cardiac domain, including detectable biomarkers, arrhythmia, structural changes, or clinical symptomatic heart disease. Currently, a general standard definition of cardiotoxicity is lacking, and definitions apply to the specific domain affected [e.g., left ventricular ejection fraction (LVEF) in heart failure; ref. 11].

Cardiotoxicity following chemotherapy or targeted therapy can be divided into acute cardiotoxicity (immediately after administration), early-onset cardiotoxicity (within the first year of treatment), and late-onset cardiotoxicity (several years after chemotherapy; ref. 20). The distinction between early and late onset, however, is more or less artificial, as cardiotoxicity is rather a continuum where some injury occurs/manifests early and others not until later (19).

Late-onset cardiotoxicity, usually preceded by an early asymptomatic period, is of significant importance for pediatric cancer survivors (21). The incidence of anthracycline- and trastuzumab-induced overt heart failure depends on, among other factors, the cumulative dose, concomitant anticancer therapy, and preexisting cardiovascular disease (11, 20). For example, the overall incidence

of echocardiographic LVD was 9% after a median period of 5.2 years or 1% to 3% for anti-HER2-targeted therapy (22, 23). Though incidences were much higher when anthracyclines and trastuzumab were concomitantly given, reaching up to 20% after 5 years of follow-up (24).

The generation of reactive oxygen species (ROS)/oxidative stress represents a commonly recognized pathologic mechanism and is a key player in anthracycline-mediated cardiotoxicity (Fig. 1). On the one hand, oxidative radicals are the consequence of the anthracyclines or anthracycline-iron complexes. On the other hand, more recent evidence suggests that topoisomerase-2 β in cardiomyocytes leads to increased oxidative stress via its effects on oxidative metabolism and mitochondrial functioning (11, 19). Anthracyclines also appear to affect the neuregulin (NRG)-ErbB (better known as HER) receptor signaling, which is also targeted by trastuzumab. Acute exposure increases the expression of HER2, whereas chronic exposure inhibits HER4 expression, hence disrupting its normal signaling (11). The downstream cellular pathways of the HER2/HER4 heterodimer are responsible for cell performance and survival (25, 26). This also explains why the

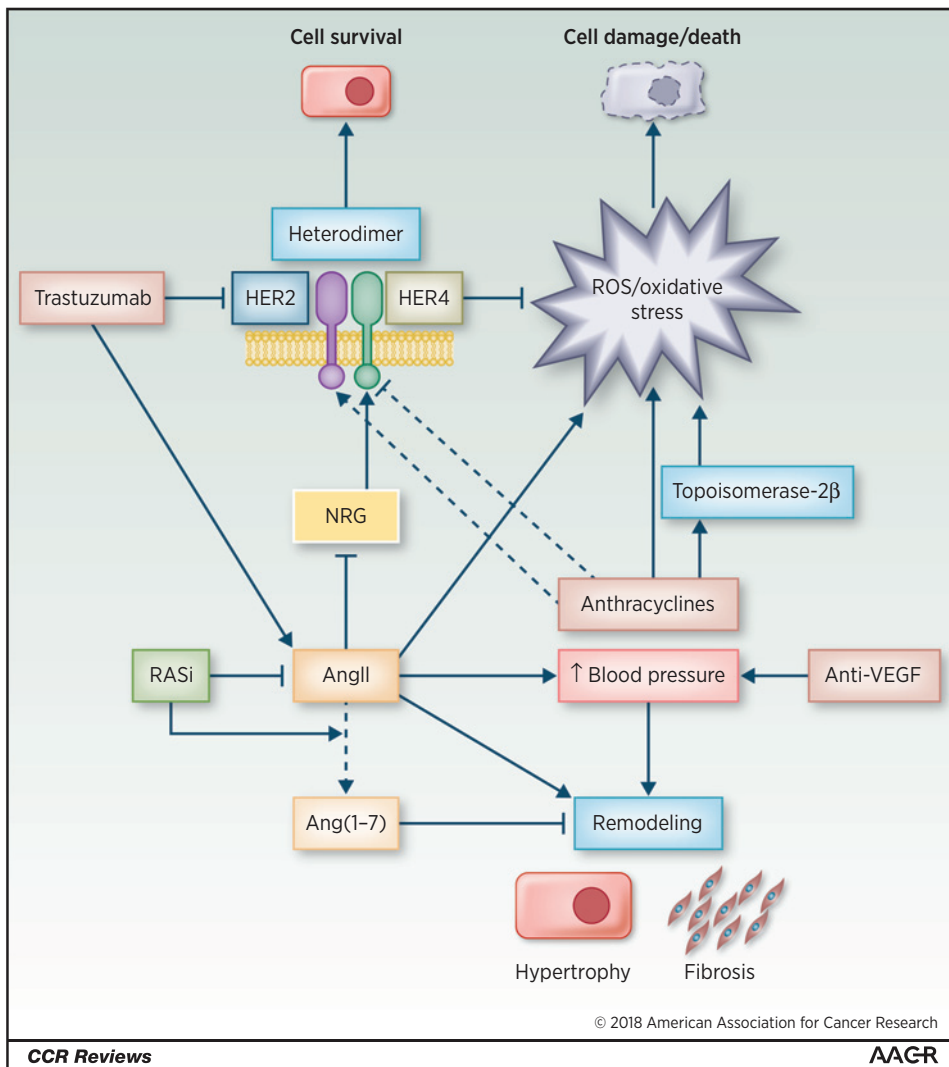


Figure 1. Mechanisms of chemotherapy-induced cardiotoxicity. Anthracyclines induce cellular damage via the formation of ROS and via topoisomerase-2 β . Anthracyclines may also affect HER2/HER4 signaling, where HER2 is induced after acute administration, but HER4 is reduced after chronic administration. Trastuzumab inhibits HER2 directly, preventing the formation of the cardioprotective HER2/HER4 heterodimer. AngII is stimulated by trastuzumab and contributes to the formation of ROS. It is also able to inhibit HER2/HER4 signaling via its inhibitory effects on the HER4 ligand neuregulin (NRG). The trophic effects of AngII lead to cardiac remodeling with cellular hypertrophy and fibrogenesis. This is also a consequence of increased arterial blood pressure, which is provoked by inhibition of vascular endothelial growth factor (VEGF). Inhibition of the RAS protects against the negative effects of AngII and stimulates the formation of cardioprotective Ang(1-7).

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cardiotoxicity of concomitant treatment with anthracyclines and trastuzumab is increased, because trastuzumab hampers the acute compensatory stress response (26).

When trastuzumab is given alone, it does not cause cell death but rather cardiomyocyte dysfunction by disrupting HER2-mediated signaling, resulting in myocyte stunning or cell-cycle hibernation (19, 27). Therefore, even though debated, trastuzumab-related cardiotoxicity is considered to be reversible (28, 29). Besides the direct inhibition of the prosurvival NRG-HER signaling, trastuzumab increases AngII, which is also a potent inhibitor of NRG. Additionally, AngII enhances ROS production via NADPH oxidase (25). In contrast, Ang(1-7) has cardioprotective effects in heart failure and counteracts the AngII/AT1R axis (ref. 30; Fig. 1).

Preclinical studies demonstrate that ACEi, ARBs, and direct renin inhibitors can protect against chemotherapy-induced cardiotoxicity (31-36) However, clinical data using ACEi or ARBs at standard doses for heart failure reported positive as well as negative/inconclusive results for both substance classes in the preventive setting (Table 1; refs. 37-49). A meta-analysis showed that the prophylactic use of ACEi/ARBs is not able to attenuate the short- to medium-term development of LVD (defined by LVEF) or heart failure [odds ratio 0.24 (95% confidence interval, 0.03-1.73; *P* = 0.16; 50)]. However, results tend to favor ACEi/ARBs, and the lack of statistical significance is likely due to small sample sizes with relative short follow-up and low rate of heart failure (3.6% of all patients; ref. 50).

Table 1. Randomized controlled trials of RASi to protect against chemotherapy-induced cardiotoxicity

Reference	CHT type, FU time	Treatment (number of patients)	Main findings	Outcome
Primary prevention^a				
Nakamae, 2005 (37)	CHOP, 7 days	Valsartan 80 mg/d (20), control (20)	Control: increased LVEDD, BNP, ANP, QTc interval, QTc dispersion; valsartan: prevented changes except for ANP elevation	Positive
Georgakopoulos, 2010 (38)	Doxorubicin based, 36 months	Enalapril (mean, 11 mg/d) (43), metoprolol (mean, 89 mg/d) (42), control (40)	No significant difference between the groups in echocardiographic parameters, and development of early/late cardiotoxicity or HF	Negative
Cadeddu, 2010 (39)	Epirubicin based, 18 months	Telmisartan 40 mg/d (25), placebo (24)	Diastolic impairment, reduced strain rate, and increased IL6 and ROS in placebo group, but not in telmisartan group; echocardiographic findings persisted till 12 months FU	Positive
Dessi, 2011 (40)	Anthracycline based, 126 days	Candesartan 2.5 mg/d + carvedilol 10 mg/d (20), placebo (20)	Attenuated decrease of LVEF in intervention group; increased LVEDD and LVESD in controls, not in intervention group; attenuated ECG changes and arrhythmias in intervention group; reduced troponin in intervention group	Positive
Liu, 2013 (41)				
Bosch, 2013 (42)	Intensive CHT for hematologic malignancies, 6 months	Enalapril 20 mg/d + carvedilol 50 mg/d (45), control (45)	Decreased LVEF only in control group; reduced incidence of combined event (death, HF, or final LVEF<45%) in intervention group	Positive
Radulescu, 2013 (43)	Epirubicin based, until 12 months after end of CHT	Perindopril 10 mg/d (68), control (68)	Significantly decreased LVEF only in controls; deterioration of LV diastolic function and prolongation of QTc in both groups	Inconclusive
Janbabai, 2016 (44)	Anthracycline based, 6 months	Enalapril 20 mg/d (34), placebo (35)	Systolic (including LVEF) and diastolic function impaired only in placebo group; troponin I and CK-MB higher in placebo group	Positive
Gulati, 2016 (45)	Anthracycline based ± trastuzumab and radiation, 10-61 weeks	Candesartan 32 mg/d + metoprolol 100 mg/d (30), candesartan 32 mg/d (32), metoprolol 100 mg/d (32), placebo (32)	No interaction between candesartan and metoprolol; LVEF decline (primary outcome) was reduced by candesartan (but not by metoprolol) vs. placebo; no effect of candesartan on secondary outcomes (RVEF, LV global longitudinal strain, diastolic function, BNP, and troponin I)	Positive
Boekhout, 2016 (46)	Trastuzumab (after anthracycline-based CHT), 92 weeks	Candesartan 32 mg/d (103), placebo (103)	No difference in LVEF and cardiac events between groups; NT-proBNP and hs-TNT not affected by candesartan	Negative
Pituskin, 2017 (47)	Trastuzumab based, 52 weeks	Perindopril 8 mg/d (33), bisoprolol 10 mg/d (31), placebo (30)	Primary outcome LV remodeling (LVEDVi) was not prevented by bisoprolol or perindopril; bisoprolol prevented reduction in LVEF; less trastuzumab interruptions due to LVEF drop in perindopril and bisoprolol; multivariate: perindopril and bisoprolol were independent predictors of maintained LVEF	Inconclusive
Secondary prevention^b				
Silber, 2004 (48)	Anthracycline based, 34.6 months (mean)	Enalapril 0.15 mg/kg/d (69), placebo (66)	Enalapril had no effect on exercise performance (including MCI) but reduced LVESWS	Inconclusive
Cardinale, 2006 (49)	High-dose CHT, 12 months	Enalapril 20 mg/d (56), control (58)	Reduction in LVEF and increase in end-systolic and diastolic volumes only in controls; incidence of cardiac events higher in controls; troponin I normalized within 3 months in enalapril (↑ troponin I at month 3: 0% vs. 21%)	Positive

Abbreviations: ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisolone; CHT, chemotherapy; CK-MB, creatine kinase-muscle/brain; d, day; ECG, electrocardiogram; FU, follow-up; HF, heart failure; hs-TNT, high-sensitivity troponin T; LV, left ventricular; LVEDD, left-ventricular end-diastolic diameter; LVEDVi, indexed left-ventricular end-diastolic volume; LVESD, left-ventricular end-systolic diameter; LVESWS, left-ventricular end-systolic wall stress; MCI, maximal cardiac index; NT-proBNP, N-terminal of prohormone BNP; RVEF, right-ventricular ejection fraction.

^aProphylactic setting.

^bAfter detection of subclinical cardiotoxicity (e.g., ↑ troponin I, echocardiographic or ECG abnormalities).

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Both ACEi and ARBs are cornerstones in the treatment of heart failure due to their capability to prevent cardiac remodeling and to reduce fibrogenesis (51, 52). Hence, early treatment as soon as (subclinical) cardiotoxicity is detected (via echocardiography or biomarkers) is reasonable. Additionally, almost all cases of anthracycline-induced decline in LVEF are seen in the first 12 months following chemotherapy, implying that cardiotoxicity is a rather early phenomenon (22). Indeed, the sooner the ACEi enalapril alone or in combination with the β -blocker carvedilol was given after detection of LVEF decline following chemotherapy, the larger the potential of full recovery of cardiac function. When initiated after 6 months, recovery was incomplete (53). Real-life data in older patients with follow-up to 5 years confirm the beneficial effects of ACEi and β -blockers, where prompt start (i.e., within 6 months) was associated with lower cardiotoxicity risk and better cardiovascular outcomes (54).

The clinical guidelines of both the American Society of Clinical Oncology and the European Society of Cardiology recommend baseline and periodically surveillance of cardiac dysfunction. Screening includes cardiac biomarkers (troponins and natriuretic peptides) and cardiac imaging (echocardiography and cardiac magnetic resonance). It should be performed in case of clinical suspicion and in those patients at increased risk of developing cardiac dysfunction (20, 55). Both organizations acknowledge the potential of RASi as part of a preventive strategy but refrain from making a recommendation hereupon currently.

A proposed algorithm for anthracycline-related cardiotoxicity suggests enalapril in case of troponin I abnormalities and combined use of ACEi and β -blockers in case of LVD on echocardiography (19, 56). However, this algorithm has not been validated. In general, treatment of chemotherapy-induced LVD and heart failure is similar to conventional heart failure therapy (52) and aims to reduce pathologic left ventricular (LV) remodeling (57, 58). ACEi and ARBs represent a mainstay because they can improve remodeling by reducing LV afterload and by directly antagonizing AngII/angiotensin II receptor type 1 (AT1R)-mediated hypertrophy and fibrosis (58, 59).

Taken together, ACEi/ARBs do have a clear potential to alleviate cardiotoxicity when given prophylactically or as soon as subclinical cardiotoxicity is detected. However, we are awaiting further larger studies. Little is known about the protective effects of long-term RASi use on cardiac outcome after chemotherapy (e.g., in childhood cancer survivors). Table 2 gives an overview of currently ongoing clinical trials.

Anti-VEGF Therapy-Induced Arterial Hypertension

Arterial hypertension represents a typical and mechanism-dependent "on-target" side effect of antivasculature endothelial growth factor (VEGF) therapy and has also been proposed as a biomarker for treatment response (60–62). The induced afterload following arterial hypertension is a risk factor for the development of congestive heart failure, with a 2.69-fold increased risk for patients receiving VEGF receptor tyrosine kinase inhibitors (63). Thus, treatment should start early and resolutely (20).

Several potential pathophysiologic mechanisms have been proposed, including capillary rarefaction, downregulation of vasodilators (e.g., nitric oxide, prostacyclin), shift in the pres-

sure-natriuresis curve, and upregulation of vasoconstrictors (e.g., endothelin-1, thromboxanes; refs. 62, 64). The renin-angiotensin-aldosterone system seems not to play a significant role in the pathophysiology of anti-VEGF-mediated hypertension (62), but renin concentration and activity might even be suppressed in patients with anti-VEGF-induced hypertension (65). However, if antihypertensive medication is required, ACEi represent a preferred first-line option, especially in case of concomitant anti-VEGF-induced proteinuria (20, 60, 64, 66). Moreover, treatment of VEGF-induced hypertension with RASi was associated with improved overall survival in metastatic renal cell carcinoma (67).

Notably, based on a small series, others hypothesized that ACEi might reduce the efficacy of bevacizumab by counteracting its antiangiogenic effect (68). This is not in line with other studies suggesting additive effects of RAS inhibition and anti-VEGF-based therapies (9, 69). Unfortunately, a phase II study (NCT01705392) designed to investigate the ability of enalapril to prevent bevacizumab-induced hypertension compared with propranolol was suspended due to insufficient financial support. Hence, even though ACEi represent a first-line option, prospective trials are needed to determine which class of antihypertensive agents is most effective in preventing and treating anti-VEGF-related hypertension.

Radiation Injury

Pathophysiologically, radiation can induce tissue injury through direct (radiation-DNA interaction) and indirect (production of ROS) DNA damage, and, if not repaired, eventually results in cell injury or death (70). There is some evidence that irradiation upregulates AngII expression in a dose-dependent manner (71, 72). The AngII/AT1R axis contributes to tissue damage and remodeling by upregulation of profibrogenic (e.g., TGF β) and proinflammatory pathways and by production of ROS via activation of NADPH oxidase (12). Hence, inhibition of AngII/AT1R signaling represents an attractive target to prevent or reduce radiation-induced injury (Fig. 2).

Indeed, treatment with ACEi or ARBs has demonstrated some efficacy in preventing radiation-induced damage of normal tissue in different organs in preclinical studies (73–76) without compromising tumor response to radiation (77).

ACEi and ARBs might inhibit radiation-induced toxicity not only by their effects on AngII and AT1R but also by increasing Ang(1–7) (16, 17), which indeed seems to have radioprotective effects (78, 79). Noteworthy, both AngII and Ang(1–7) improved hematopoietic recovery after total body irradiation in mice (80).

Data from clinical trials are scarce and inconsistent. Several retrospective studies reported a decreased risk of radiation pneumonitis in lung cancer patients using ACEi/ARBs (81–86), whereas others found no association (87, 88). Interestingly, in one study, a beneficial effect was only seen with ACEi and not with ARB (81).

As these retrospective studies only provide pooled analysis of different ACEi/ARB compounds, no conclusions on the effect of each drug within a RASi subclass can be drawn and no specifications on dosing can be made. However, one can assume that standard doses to treat cardiovascular diseases were used. Unfortunately, a large prospective study using captopril in patients with radiation-treated lung cancer was halted due to insufficient accrual (89).

Table 2. Ongoing prospective trials of RASi to protect against cancer treatment-related side effects

ClinicalTrials.gov identifier					
(study acronym)	Condition, treatment	Design	Intervention	Primary endpoint	Status
Cardiotoxicity					
NCT03127631 (RADICALPC)	Prostate cancer, androgen deprivation therapy	RCT	SOC Behavioral interventions (nutrition, exercise, smoking cessation) + ASA + statin + ACEi	Composite of death, MI, stroke, HF, or arterial revascularization	Recruiting
NCT02907021 (SCHOLAR)	HER2-positive breast cancer (nonmetastatic) with moderate LV dysfunction, trastuzumab	Single arm, phase I	ACEi + BB	Development of cardiac dose-limiting toxicity	Not yet recruiting
NCT02236806 (SAFE)	Breast cancer (nonmetastatic), anthracyclines ± anti-HER2	RCT, phase III	Placebo Bisoprolol Ramipril Bisoprolol + ramipril	LVEF	Unknown
NCT01904903 (SAFE-HEaRT)	HER2-positive breast cancer with mild LV dysfunction, anti-HER2	Single arm, phase II	ACEi + BB	Completion of therapy without cardiac events or worsening of cardiac function	Recruiting
NCT03265574 (PROACT)	Breast cancer, adjuvant epirubicin	RCT, phase III	SOC Enalapril	Cardiac troponin T release, cardiac function	Recruiting
NCT01968200 (ICOS-ONE)	Cancer, treatment with anthracyclines	RCT, phase III	Enalapril (concomitant) Enalapril (after biochemical proven injury)	Occurrence of cTn elevation	Active, not recruiting
NCT01009918	HER2-positive breast cancer, trastuzumab	RCT, phase III	Placebo Carvedilol (extended release) Lisinopril	LVEF	Active, not recruiting
Radiotherapy-related toxicities					
NCT01805453 (ASTER)	Newly diagnosed glioblastoma, radiotherapy + temozolomide	RCT, phase II	Placebo Losartan	Steroid dose needed to control brain edema after radiotherapy	Active, not recruiting
NCT01754909	Lung cancer, radiotherapy	RCT, phase II	Placebo Enalapril	Radiation pneumonitis	Recruiting
NCT01880528	Lung cancer, radiotherapy	RCT	Placebo Lisinopril	Primary: adverse events of lisinopril Secondary: dyspnea, symptoms, QoL	Active, not recruiting
NCT00004230	Bone marrow or stem cell transplantation, following chemotherapy and radiotherapy	RCT, phase III	SOC Captopril	Lung injury	Completed
Others					
NCT02651415 (PARICCA)	Metastatic colorectal cancer, regorafenib	Single arm, phase II	Perindopril	HFSR, AHT	Active, not recruiting

Abbreviations: AHT, arterial hypertension; ASA, acetyl salicylic acid; BB, β-blocker; cTn, cardiac troponins; HF, heart failure; HFSR, hand-foot skin reaction; LV, left ventricular; MI, myocardial infarction; QoL, quality of life; RCT, randomized controlled trial; SOC, standard of care.

ACEi use was also associated with reduced risk of radiation-induced proctitis in a retrospective study (90). A prospective noninterventional study found that statins alone and ACEi in combination with statins (but not ACEi alone) reduced gastrointestinal toxicity after pelvic radiation (91). In a small randomized controlled trial of 55 subjects undergoing total body irradiation for hematopoietic stem cell transplantation, captopril at a maximum dose of 25 mg three times a day had no significant effect on the risk of chronic renal failure and on overall and pulmonary mortality (92).

Finally, radiation increases the permeability of the capillary wall and leads to endothelial dysfunction (93). The consequential edema is a frequent and threatening side effect when treating brain tumors. Two retrospective studies showed that the use of ACEi/ARBs was associated with reduced steroid doses for vasogenic edema in glioblastoma via blockage of VEGF production that is abundantly present in those tumors (94, 95). The

use of ACEi/ARBs is also protective for the adjacent normal brain tissue by preventing radiation necrosis (96), whereas pre-clinical evidence demonstrates the capability of an ARB to preserve cognition (97).

Taken together, ACEi/ARBs seem to be protective against the effects of radiation injury in several organ sites. However, prospective trials are needed for further validation. Trials currently testing RASi to prevent radiation injury are listed in Table 2.

Cachexia

Cachexia is a multifactorial catabolic condition characterized by substantial weight and muscle loss (with or without fat loss) due to an underlying disease that cannot be completely reversed by nutritional support (98, 99). Cancer cachexia can reach different stages ranging from pre-cachexia to cachexia and refractory

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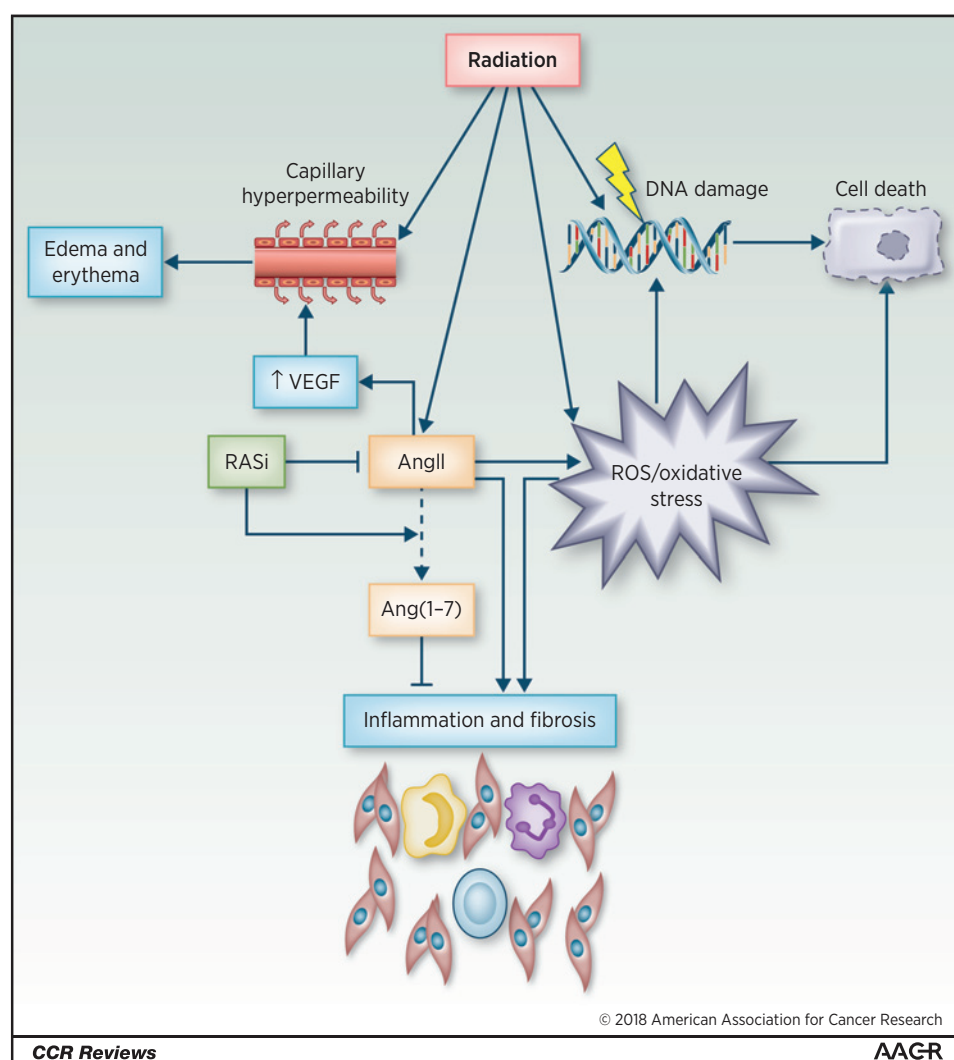


Figure 2.

Mechanisms of radiation-induced tissue injury. Radiation damages cellular DNA, both directly as well as indirectly via the formation of ROS, that eventually results in cell death. This is augmented by the capability of radiation to upregulate AngII that contributes to the formation of ROS. The direct effects of radiation lead to capillary hyperpermeability that can lead to edema/erythema. This can be further augmented by AngII, which increases vascular permeability via the stimulation of VEGF. Increased AngII itself stimulates inflammation and fibrosis of tissues. Inhibition of the RAS can reduce edema and lessens the effects on tissues. Moreover, induction of Ang(1-7) can counteract the effects of AngII.

cachexia (99) and should be considered as a partially preventable cancer comorbidity (100). Cachexia has a high prevalence in patients with cancer (30%–60%); accounts for up to 20% of deaths; and represents an independent predictor of mortality, treatment response, and quality of life (101, 102). AngII signaling contributes to muscle wasting by different mechanisms such as induction of muscle protein catabolism through upregulation of the ubiquitin–proteasome proteolytic pathway (13), inhibition of protein synthesis in myotubes (15), and induction of apoptosis in myocytes (14). Although the induction of skeletal myocyte apoptosis is mediated via AT1R (103), the effects of AngII on protein degradation in skeletal muscle are likely mediated via the angiotensin II receptor type 2 (AT2R; ref. 13), known to counteract the effects of AngII via AT1R (5). This suggests that ACEi—by inhibiting AngII formation—may have a more potent protective effect in preventing cancer cachexia than ARBs, which only block AT1R.

Interestingly, in an observational study of older hypertensive women, continuous ACEi use significantly slowed decline in muscle strength (104).

Several preclinical studies have demonstrated that ACEi can control cancer cachexia in different rodent models (13, 105,

106), whereas imidapril had no beneficial effect on cardiac wasting in a rat hepatoma cancer cachexia model (107). In a subcutaneous murine colon cancer model, the direct renin inhibitor aliskiren had potent anti-cachexia effects. Aliskiren antagonized several mechanisms of cancer cachexia, namely, RAS activation, inflammation, oxidative stress, and stimulation of the autophagy–lysosome as well as the ubiquitin–proteasome pathway (108).

In a phase III trial conducted by Ark Therapeutics, the ACEi imidapril attenuated weight loss in non–small cell lung cancer (NSCLC) and colorectal cancer, but not in pancreatic cancer; however, the trial missed its primary endpoint because the significance was gone in pooled analysis (http://www.apmhealthurope.com/print_story.php?numero=L1135).

Other Cancer Treatment-Induced Side Effects

Many patients with cancer develop chemotherapy-induced peripheral neuropathy, with long-lasting and refractory pain in a substantial percentage of patients. In a retrospective study analyzing the results of a standardized panel testing sensory and

pain sensation of the small fibers of the peripheral nerves (i.e., of the hand), ACEi/ARBs were associated with attenuated sensory loss. The authors suggest an AT2R-mediated neuromodulating effect over the small myelinated fibers of the glabrous skin (109).

An ongoing trial (NCT02651415) is currently investigating the potential of the ACEi perindopril to mitigate the occurrence of hand-foot skin reactions—a well-known side effect of tyrosine kinase inhibitors—in patients with colorectal cancer treated with regorafenib (Table 2).

Conclusions

The renin-angiotensin system is, without doubt, closely intertwined with cancer. Available data suggest that concomitant use of RASi with standard cancer therapy may reduce morbidity and mortality of patients with cancer. Moreover, RASi might also alleviate treatment-related side effects of cancer therapies, such as cardiotoxicity and radiation-induced tissue injury. However, knowledge on the role of RASi herein is currently limited to experimental studies, retrospective analyses, or small prospective studies. Consequently, to date, definitive recommendations cannot be made. Additionally, most studies evaluated the role of ACEi and ARBs in this context, and only little data are available for direct renin inhibitors—the third class of RASi.

The main body of research is related to the potential effects of RASi to reduce cardiotoxicity in anthracycline- or trastuzumab-induced cardiotoxicity. There is a trend that RASi at standard doses could be useful in a prophylactic setting, but unequivocal evidence is lacking. The evidence for treating (sub)clinical heart failure with RASi is more substantial. Therefore, prophylactic treatment with RASi should be limited to selected high-risk patients. Once (sub)clinical heart failure is detected, treatment should be started promptly (20). Similarly, arterial hypertension should be treated aggressively and as early as possible in order to prevent the development of congestive heart failure (20).

Within the field of radiation-induced side effects, available data are scarce. Most studies currently investigating RASi in the setting of radiation are focused on the prevention of radiation pneumonitis, as this seems to be a promising approach.

Notably, by modulating the tumor microenvironment and improving drug delivery to tumors, RASi may also allow for dose reductions of anticancer drugs, including immunotherapy, with-

out decreasing their therapeutic benefit, and this could ultimately decrease toxicity (9).

Finally, even though RASi may help to attenuate various side effects of cancer treatment, decisions for using these drugs are to be made on a case-by-case basis. For example, due to their effects on the glomerular filtration rate, RASi actually increase the risk on platinum-based nephrotoxicity (110).

Because RASi are already FDA approved, have a well-known safety profile, and are relatively inexpensive, they are an appealing option to improve cancer-therapy substantially. Their future potential might grow even further in the quickly evolving landscape of cancer therapeutics. However, there is an obvious need for properly powered randomized controlled trials to evaluate the full potential of RASi in preventing or improving certain cancer treatment-related adverse events. Studies with extended follow-up have the potential to alleviate the long-term side effects.

Prospective studies should also investigate if standard doses of RASi are required in the prevention setting or if even reduced doses have the potential to mitigate cancer treatment-induced adverse events.

Disclosure of Potential Conflicts of Interest

M. Pinter reports receiving speakers bureau honoraria from Bayer and Bristol-Myers Squibb, and is a consultant/advisory board member for Bayer, Bristol-Myers Squibb, and Eisai. R.K. Jain reports receiving speakers bureau honoraria from Amgen, holds ownership interest (including patents) in Enlight, Ophthotech, SynDevRx, and Xtuit, and is a consultant/advisory board member for Enlight, Merck, Ophthotech, Pfizer, SPARC, SynDevRx, Tekla Healthcare Investors, Tekla Healthcare Opportunities Fund, Tekla Life Sciences Investors, Tekla World Healthcare Fund, and Xtuit. No potential conflicts of interest were disclosed by the other author.

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