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Renin-angiotensin system inhibitors to mitigate cancer treatment-related adverse events

Matthias Pinter^{1,2}, Wilhelmus J. Kwanten^{1,3}, and Rakesh K. Jain¹

¹Edwin L. Steele Laboratories for Tumor Biology, Department of Radiation Oncology, Harvard Medical School & Massachusetts General Hospital, Boston, MA 02114, USA

²Division of Gastroenterology & Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, A-1090, Austria

³Laboratory of Experimental Medicine and Paediatrics (LEMP), University of Antwerp, Antwerp, B-2610, Belgium

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 cancer patients, both in 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.

Keywords

Angiotensin-converting enzyme inhibitors; Angiotensin receptor blockers; Chemotherapy; Radiation therapy; Cardiotoxicity

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 €3.2 billion on health care expenditures and €9.1 billion on cancer drugs in 2014, production loss due to early death and lost working days not included (2).

Correspondence. Rakesh K. Jain, 100 Blossom Street, Cox 7, Massachusetts General Hospital, Boston, MA 02114, USA, Tel: 617-726-8143, Fax: 617-724-5841, jain@steele.mgh.harvard.edu.

Treatment-related side effects represent a major problem in oncology since they can severely interfere with the patient's quality of life, require dose reductions and treatment delays, or even discontinuation of therapy. This reduces effectiveness of anti-cancer 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 healthcare systems and patients. Hence, smart prevention strategies might not only prolong patient survival, improve their quality of life, but also help to reduce healthcare 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 (ARBs) 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 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 may 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 may 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 anti-cancer 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 (HF) 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' 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 HF) (11).

Cardiotoxicity following chemo- or targeted therapy can be divided in acute cardiotoxicity (immediately after administration), early-onset cardiotoxicity (within the first year of treatment) and late-onset cardiotoxicity (several years after chemotherapy) (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 HF depends on, amongst others, the cumulative dose, concomitant anti-cancer therapy and pre-existing cardiovascular disease. (11,20). For example, the overall incidence of echocardiographic LVD was 9% after a median period of 5.2 years or 1–3% 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 follow-up (24).

The generation of reactive oxygen species (ROS)/oxidative stress represents a commonly recognized pathological mechanism and is a key player in anthracycline-mediated cardiotoxicity (Figure 1). On one hand, oxidative radicals are the consequence of the anthracyclines or its complexes with iron themselves. On the other hand, more recent evidence suggest 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, while 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 cardiotoxicity of concomitant treatment with anthracyclines and trastuzumab is increased, since 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). Beside the direct inhibition of the pro-survival 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 (30) (Figure 1).

Preclinical studies demonstrate that ACEi, ARBs as well as 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 preventive setting (Table 1) (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% CI, 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) (50).

Both ACEi and ARBs are corner stones 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 ACE 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, natriuretic peptides) and cardiac imaging (echocardiography, 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 to make 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 HF is similar to conventional HF therapy (52) and aims to reduce pathological left ventricle (LV) remodeling (57,58). ACEi and ARBs represent a mainstay since 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 anti-vascular 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 HF, 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 pathophysiological mechanisms have been proposed including capillary rarefaction, downregulation of vasodilators (*e.g.*, nitric oxide, prostacyclin), shift in pressure-natriuresis curve, and upregulation of vasoconstrictors (*e.g.*, endothelin-1, thromboxanes) (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 anti-hypertensive 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 ([ClinicalTrials.gov: NCT01705392](https://clinicaltrials.gov/ct2/show/study/NCT01705392)) designed to investigate the ability of enalapril to prevent bevacizumab-induced hypertension compared to 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 anti-hypertensive 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.*, transforming growth factor (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 (Figure 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) while 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 radiation treated lung cancer patients was halted due to insufficient accrual (89).

ACEi use was also associated with reduced risk of radiation-induced proctitis in a retrospective study (90). A prospective non-interventional 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 radiation for hematopoietic stem cell transplantation, captopril at a maximum dose of 25mg tid 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), while preclinical 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 cachexia (99) and should be considered as a partially preventable cancer comorbidity (100). Cachexia has a high prevalence in cancer patients (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 up-regulation of the ubiquitine-proteasome proteolytic pathway (13), inhibition of protein synthesis in myotubes (15), and induction of apoptosis in myocytes (14). While 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) (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), while 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 NSCLC and colorectal cancer, but not in pancreatic cancer; however, the trial missed its primary endpoint since the significance was gone in pooled analysis (http://www.apmhealthurope.com/print_story.php?numero=L1135).

Other cancer treatment induced side effects

Many cancer patients develop chemotherapy-induced peripheral neuropathy with long lasting and refractory pain in a substantial percentage of patients. In a retrospective study analyzing 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 angiotensin II receptor type 2 (AT2R)-mediated neuro-modulating 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 colorectal cancer patients 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 cancer patients. 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 analysis, or small prospective studies. Consequently, to date, definite recommendations cannot be made. Additionally, most studies evaluated the role of ACEi and ARBs in this context and only little data is 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 HF with RASi is more substantial. Therefore, prophylactic treatment with RASi should be limited to selected high-risk patients. Once (sub)clinical HF 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 HF (20).

Within the field of radiation-induced side effects, available data are scarce. Most studies currently investigating RASi in the setting of radiation are focusing 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 anti-cancer drugs, including immunotherapy, without 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 its effects on the glomerular filtration rate, RASi actually increase the risk on platinum-based nephrotoxicity (110).

Since 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 even further grow 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.

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Conflict of interest

M.P. served as advisory board member of Bayer, BMS, and Eisai, and received travel support from Bayer and speaking fees from Bayer and BMS. He is also an investigator for Bayer, BMS, and Lilly.

R.K.J. received honorarium from Amgen, consultant fees from Enlight, Merck, Ophthotech, Pfizer, SPARC, and SynDevRx, owns equity in Enlight, Ophthotech, SynDevRx, and XTuit, and serves on the Board of Directors of XTuit and the Boards of Trustees of Tekla Healthcare Investors, Tekla Life Sciences Investors, Tekla Healthcare Opportunities Fund and Tekla World Healthcare Fund.

Abbreviations

ACEi	angiotensin-converting enzyme inhibitors
AngII	angiotensin II
Ang(1–7)	angiotensin (1–7)
ARB	angiotensin receptor blockers
AT1R	angiotensin II receptor type 1
AT2R	angiotensin II receptor type 2
HF	heart failure
LV	left ventricle
LVD	left ventricular dysfunction
LVEF	left ventricular ejection fraction
NADPH	Nicotinamide adenine dinucleotide phosphate H
NRG	neuregulin
RAS	renin-angiotensin system
RASi	renin-angiotensin system inhibitors
ROS	reactive oxygen species
VEGF	vascular endothelial growth factor

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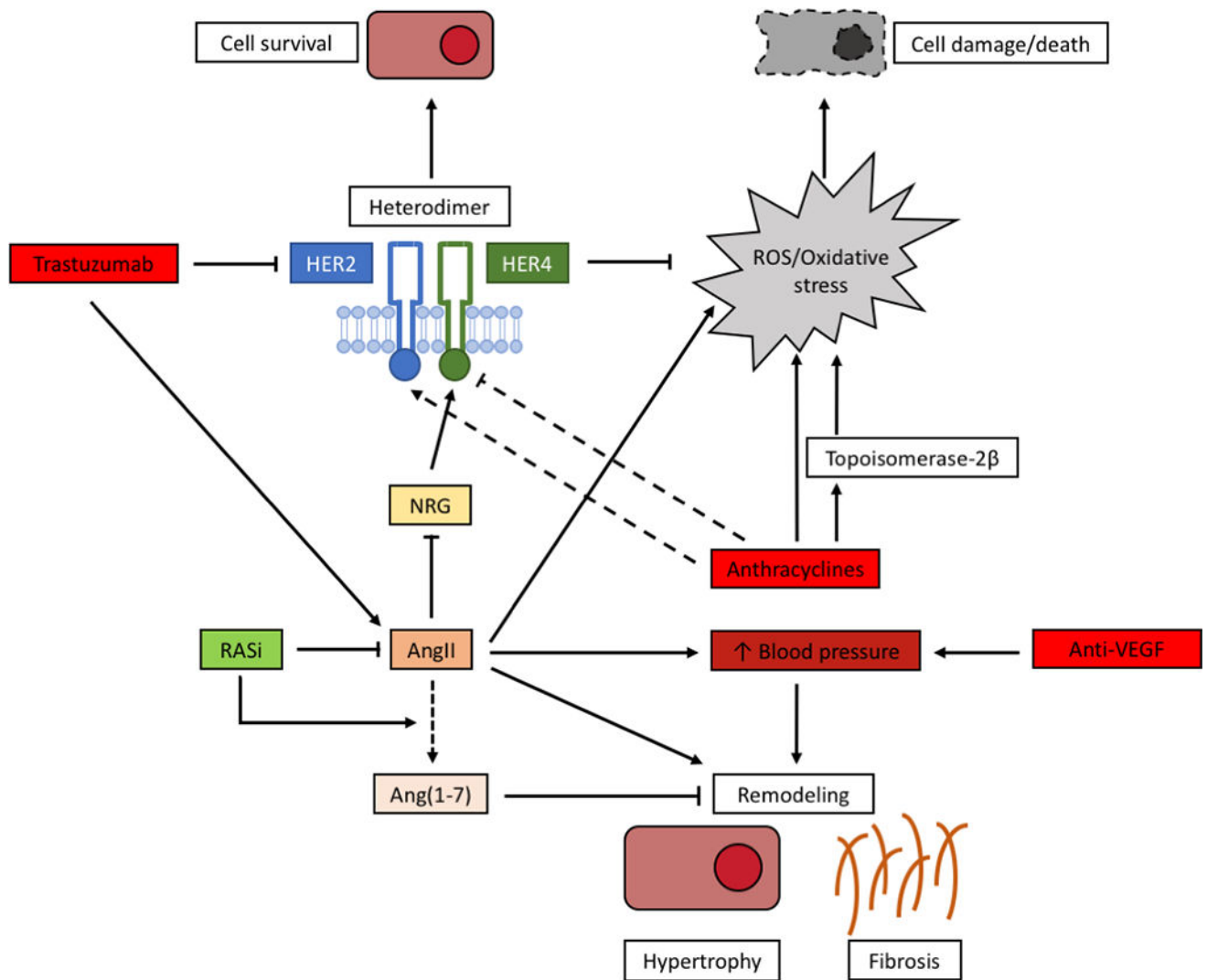


Figure 1. Mechanisms of chemotherapy-induced cardiotoxicity

Anthracyclines induce significant oxidative stress, leading to cellular damage, via the formation of reactive oxygen species (ROS) and via the suppression of 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. Angiotensin II (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 (BP), that is provoked by inhibition of vascular endothelial growth factor inhibition (VEGFi). Inhibition of the renin angiotensin system (RAS) protects against the negative effects of AngII and stimulates the formation of cardioprotective Angiotensin (1–7) (Ang (1–7)).

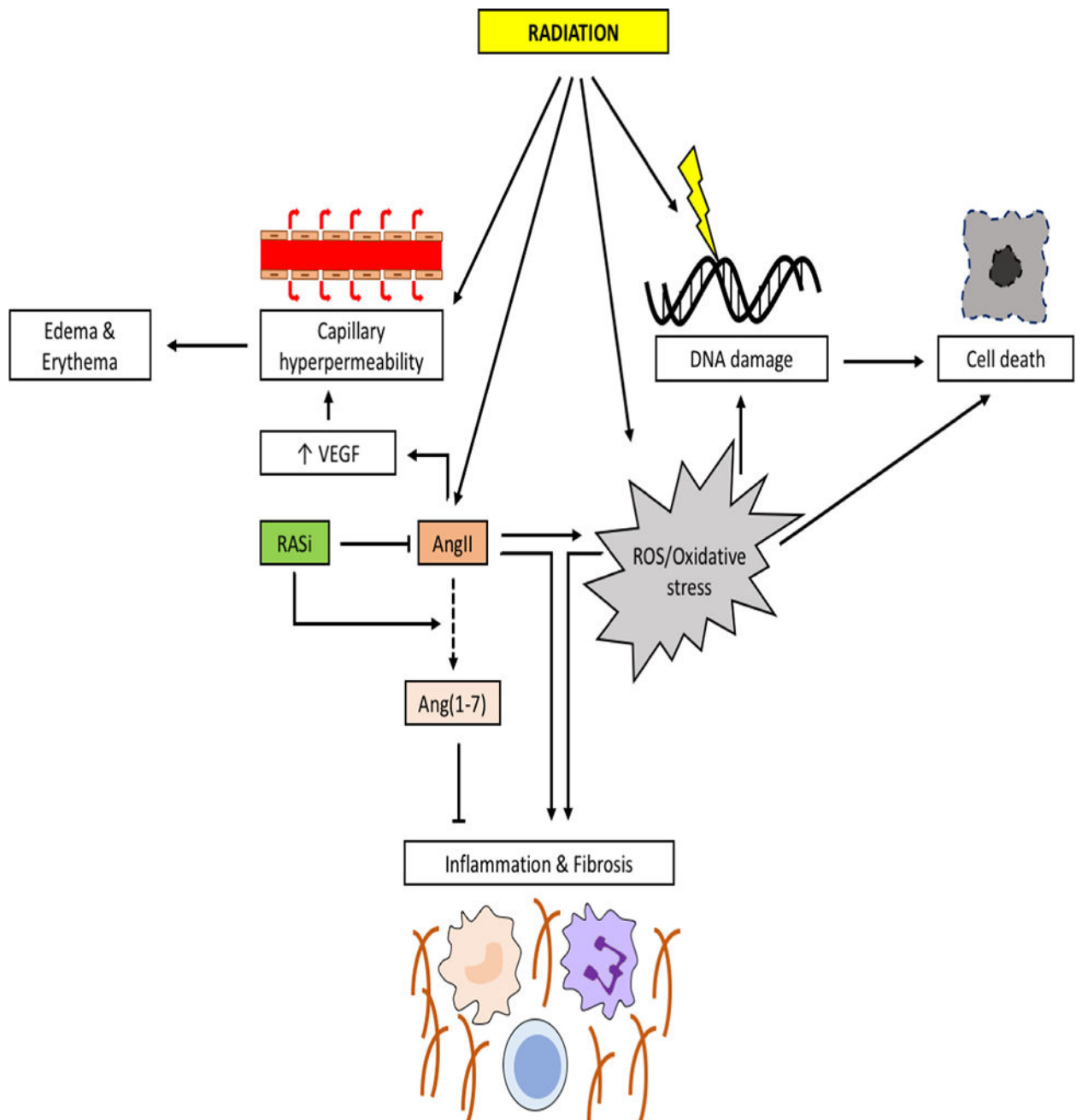


Figure 2. Mechanisms of radiation-induced tissue injury

Radiation damages cellular DNA, both directly as well as indirectly via the formation of reactive oxygen species (ROS), that eventually result in cell death. This is augmented by the capability of radiation to upregulate angiotensin II (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 vascular endothelial growth factor (VEGF). Increased AngII itself stimulates inflammation and fibrosis of tissues. Inhibition of the renin

angiotensin system (RAS) can reduce edema and lessens the effects on tissues. Moreover, induction of angiotensin (1-7) (Ang(1-7)) can counteract the effects of AngII.

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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 prevention¹				
Nakamae, 2005 (37)	CHOP, 7 days	Valsartan 80mg/d (20), Control (20)	Control: increased LVDD, BNP, ANP, QTc interval, QTc dispersion; Valsartan: prevented changes except of ANP elevation	Positive
Georgakopoulos, 2010 (38)	Doxorubicin-based, 36 months	Enalapril (mean, 11mg/d) (43), Metoprolol (mean, 89mg/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) Dessi, 2011 (40)	Epirubicin-based, 18 months	Telmisartan 40mg/d (25), Placebo (24)	Diastolic impairment, reduced strain rate, and increased IL-6 and ROS in placebo group, but not in telmisartan group. Echocardiographic findings persisted till 12 months FU	Positive
Liu, 2013 (41)	Anthracycline-based, 126 days	Candesartan 2.5mg/d + carvedilol 10mg/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
Bosch, 2013 (42)	Intensive CHT for hematological malignancies, 6 months	Enalapril 20mg/d + carvedilol 50mg/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 10mg/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 20mg/d (34), Placebo (35)	Systolic (including LVEF) and diastolic function only impaired 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 32mg/d + Metoprolol 100mg/d (30), Candesartan 32mg/d (32), Metoprolol 100mg/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, left ventricular global longitudinal strain, diastolic function, BNP, and troponin I)	Positive
Boekhout, 2016 (46)	Trastuzumab (after anthracycline-based CHT), 92 weeks	Candesartan 32mg/d (103), Placebo (103)	No difference in LVEF and cardiac events between groups; NT-proBNP and hs-TNT not affected by candesartan	Negative

Reference	CHT type, FU time	Treatment (number of patients)	Main findings	Outcome
Pituskin, 2017 (47)	Trastuzumab-based, 52 weeks	Perindopril 8mg/d (33), Bisoprolol 10mg/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 prevention²				
Silber, 2004 (48)	Anthracycline-based, 34.6 months (mean)	Enalapril 0.15mg/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 20mg/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; ECG, electrocardiogram; FU, follow-up; HF, heart failure; hs-TNT, high-sensitivity troponin T; LV, left ventricular; LVDD, LV end-diastolic diameter; LVEDVi, indexed LV end-diastolic volume; LVEF, LV ejection fraction; LVESWS, LV end-systolic wall stress; MCI, maximal cardiac index; NT-proBNP, N-terminal of prohormone BNP; RASi, renin-angiotensin system inhibitors; ROS, reactive oxygen species, RVEF, right ventricular ejection fraction.

¹ Prophylactic setting

² After detection of subclinical cardiotoxicity (e.g. ↑ troponin I, echocardiographic or ECG abnormalities)

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

ClinicalTrials.gov identifier (Acronym study)	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 Revascularisation	Recruiting
NCT02907021 (SCHOLAR)	HER-2 positive breast cancer (non-metastatic) with moderate LV dysfunction	Single arm, Phase I	ACEi + BB	Development of cardiac dose-limiting toxicity	Not yet recruiting
NCT02236806 (SAFE)	Breast cancer (non-metastatic), anthracyclines ± anti-HER2	RCT, Phase III	Placebo Bisoprolol Ramipril Bisoprolol + ramipril	LVEF	Unknown
NCT01904903 (SAFE-HEaRT)	HER-2 positive breast cancer with mild LV dysfunction, anti-HER-2	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	HER-2 positive breast cancer, trastuzumab	RCT, Phase III	Placebo Carvedilol (extended release) Lisinopril	LVEF	Active, not recruiting
Radiotherapy-related toxicities					

ClinicalTrials.gov identifier (Acronym study)	Condition, treatment	Design	Intervention	Primary endpoint	Status
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: ACEi, angiotensin-converting-enzyme inhibitor; AHT, arterial hypertension; ASA, acetyl salicylic acid; BB, beta blocker; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisolone; cTn, cardiac troponins; HF, heart failure; HFSR, hand-foot skin reaction; LV, left ventricular; LVEF, LV ejection fraction; MI, myocardial infarction; NSCLC, non-small cell lung cancer; QoL, quality of life; RASi, renin-angiotensin system inhibitors; RCT, randomized controlled trial; SOC, standard of care