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Review Article

The role of the renin-angiotensin system inhibitors in malignancy: a review

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Abstract: Hypertension is one of the most prevalent diseases in cardiology. The angiotensin receptor blockers (ARBs)/angiotensin converting enzyme inhibitors (ACEIs) are widely used drugs to stabilize the blood pressure via inhibition of the renin-angiotensin system (RAS). Studies have found that the exposure to RAS inhibitors (RASi) can suppress the development of cancers via multimodal mechanisms and has attracted increased attentions in the recent past. Owing the potential of RASi to inhibit tumor growth, proliferation and metastasis, they are considered as the potential and exciting candidates to enhance the effect of chemo-radiotherapy and targeted therapy efficacy. However, there are conflicting reports as to the use of ARB/ACEI in all facets of tumor growth. In this study, we comprehensively summarize and review the potential mechanisms of RASi in cancer treatment, like inhibition of tumor angiogenesis, reduction of cancer-associated fibroblasts (CAFs) and extracellular matrix (ECM), regulation of immune cells and improvement of hypoxia. Additionally, based on the basic and clinical experiments, we analyze the views and results regarding the role of RASi plays in tumor from genesis to recurrence, and certainly cancer treatment (chemo-radiotherapy and targeted therapy). In the last, not only do we discuss the prospects of using RASi to enhance cancer treatment efficacy but also point out the conflicting situation with the intention to give some directions and inspiration on this topic.

Keywords: RASi, ARB, AECI, cancer treatment

Introduction

Cancer has been one of the devastating human diseases that threatens human health and researchers across the globe are directing studies for the development of cancer treatment. According to cancer statistics, in the United States 1,806,590 new cancer cases and 606,520 cancer related deaths are estimated to occur in 2020 [1]. Chemo-radiotherapy and targeted therapy are part of the established standard treatment strategies employed for the management of human cancers. Chemotherapy is one major treatment for malignancy, but the actual effects and responses to it are confined to drug distributions and immune milieu in tumor [2]. Similarly, radiotherapy efficacy has also been confronted with the resistance caused by tumor hypoxia [3]. While as one common targeted drug-tyrosine kinase inhibitors have also raised people's concerns due to its cardiovascular toxicity, like hypertension, heart failure and arrhythmia [4, 5]. Besides, researchers have discovered that the abnormal fibroblasts, extracellular matrix (ECM), and immune cells associated with tumors are all adverse to tumor microenvironment (TME), which on one hand accelerates the tumor progression and also impacts the effects of all kinds of anticancer therapies [6]. In this case, it is of highly importance to develop a strategy to improve anticancer effects and mitigate cardiovascular toxicity [2, 7, 8].

The renin-angiotensin system (RAS) is well-known for its role in maintaining cardiovascular homeostasis and electrolyte balance [9]. There are two main RAS inhibitors (RASi), angiotensin receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEIs). Both of these

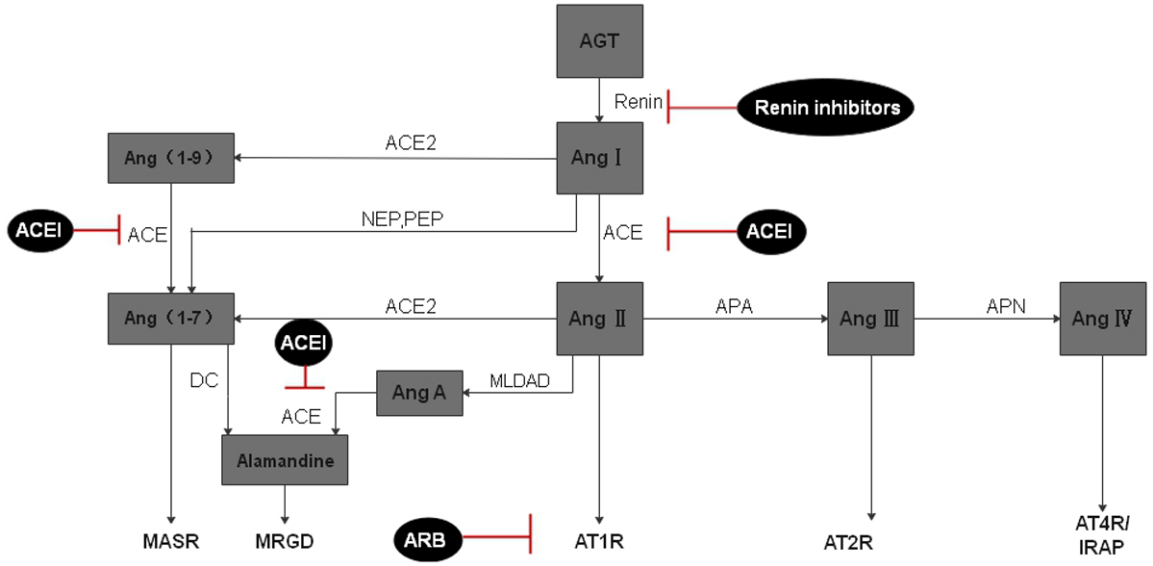

Figure 1. The conventional and identified pathways of RAS axis. Angiotensinogen (AGT) is produced by the liver, then hydrolyzed by renin. Renin, produced by the juxtaglomerular cells of the kidney and then form Angiotensin I (Ang I). Next, Ang I is hydrolyzed by angiotensin-converting enzyme (ACE), to produce the downstream receptor-angiotensin II (Ang II). Ang II usually responses to two receptors, angiotensin II type 1 receptor (AT1R) and angiotensin II type 2 receptor (AT2R). ACE2 catalyzes Ang II to Angiotensin (1-7) (Ang (1-7)), which are also the product of cleaving Angiotensin (1-9) (Ang (1-9)). Ang (1-7) commonly interact with mitochondrial assembly receptor (Mas receptor or MasR). Cleavaged by ACE and decarboxylase (DC) respectively, Ang A and Ang (1-7) was connected through Alamandine, which siganals through MbbAS-related G protein couple receptor D (MRGD). In addition to Ang II, there are Angiotensin III (Ang III) and Angiotensin IV (Ang IV) identified in this path. IRAP (insulin-regulated membrane aminopeptidase; also called AT4R) is a binding site for Ang IV (1-7). APA, aminopeptidase A; APN, aminopep-tidase N; DC, decarboxylase; MLDAD, mononuclear leukocyte-derived aspartate DC; NEP, neutral endopeptidase; PEP, prolyendopeptidase [9].

are widely used in the treatment of cardiovascular and renal disease [10-13]. ACEIs are known to inhibit synthesis of angiotensin II (Ang II), which exerts its cellular role predominantly by the angiotensin II receptor type 1 (AT1R). While ARBs selectively hinder its binding to downstream angiotensin receptors as shown in **Figure 1** [14]. Increased vascular wall thickness and vasoconstriction which are related to systematic or endocrine signaling of the RAS are both the critical factors for the distal metastasis of tumor cells [15]. Recently, attention has been shifted to its relationship with cancer. Many reports have suggested there exists an association between RASi and different aspects of tumor genesis, for instance, they may decrease the expression of the vascular endothelial growth factor (VEGF), enhance drug delivery, reduce the interstitial extracellular matrix (ECM) content so improve hypoxia and regulate TME [9, 16-18]. Thus, these multimodal mechanisms provide a basis for the potential applicability of the application of RASi in cancer treatment.

Indeed, more researchers and medical institutions have examined and confirmed the efficacy of implementing these strategies. Take losartan (one common drug of the ARBs) for example, researchers have found its role in reducing tumor growth rates in human pancreatic, breast and prostate cancer cell xenografts [2, 19, 20]. Similarly, captopril (one ACEI) not only inhibited tumor angiogenesis but also reduced the extent of liver metastases [21]. Given this background, the purpose of the present review was, therefore, to discuss the controversial effects of RAS blockade in experimental models and clinical practice. Nonetheless, whether RAS blockade has positive role in the incidence and intervention of cancer remains a topic of debate [22, 23]. Herein, we summarize such studies and their results in this essay. Although there have already been reviews that discussed this topic, but here we comprehensively and lately reviewed the potential mechanisms, which include but are not limited to drug distribution and TME, from the whole process of cancer (genesis, treatment

and recurrence) analyzed supportive and negative results or views so far about the role of RASi in cancers. Finally, we discuss the possible directions to current controversial points related to this subject.

The mechanisms of RASi's potential therapeutic possibilities in tumor

Tumor angiogenesis and AT1R

Angiogenesis is one of the key hallmarks of cancer and is regulated by numerous growth factors, among which VEGF may be the most crucial one in tumor angiogenesis [24-26]. Consistently, a number of studies have found that ARB can inhibit the proliferation of pancreatic cancer cell lines by inhibiting VEGF-mediated angiogenesis in tumors [9, 27]. Besides, reduced vessel leakiness by inhibiting VEGF has shown to induce structurally leaky and hyper-permeability, which could also prevent tumor hypoxia and acidosis. One certain thing is that RASi can decompress tumor blood vessels to enhance drug and oxygen delivery. For example, results from the drug losartan showed a significant improvement in the perfused vessel fraction, both in breast and pancreatic tumors [2]. In addition, Zhao et al also found that losartan improved perfusion and attenuated tumor hypoxia. In this report, they measured the fraction of perfused vessels and the level of tumor hypoxia by immune histology [28]. The results showed that the percentage of perfused blood vessels in losartan group greatly surpassed the control group. It has suggested that Ang II/AT1R may promote VEGF secretion and expression in various cancers [29, 30]. Moreover, about the two prominent angiotensin receptors-AT1R and angiotensin II type 2 receptor (AT2R), so far there also have been conflicting reports on them. Some studies implied a negative growth regulatory function for AT1R, wherein it has been found that *Agtrα1* gene (encoded AT1R) is down-regulated in melanoma cell lines by methylating CpG island. Conversely *Agtr2* gene (encoded AT2R) was over-expressed in 75% melanoma brain metastatic cell lines. Other studies have suggested the expression of AGT1R is much higher than AGT2R in breast and pancreatic tumor cells. This implies that the role of AT1R and AT2R is possibly cell type specific and context dependent [31-33].

Cancer-associated fibroblasts (CAFs)

Fibroblasts are spindle-shaped cells that synthesize collagen in connective tissues [34]. In normal tissues, located in the ECM, fibroblasts are activated during the process of wound healing, tissue inflammation and organ fibrosis [35]. Such activated fibroblasts associated with cancer are called as CAFs or myofibroblasts [36]. Generally, CAFs are indispensable in shaping the TME to promote tumor growth through the production of multiple ECM proteins and diverse interactions with cancer and immune cells. Consequently, CAFs interfere with tumor immunity, metabolic reprogramming of the TME, ECM remodeling, and efficacy of therapies [34, 37]. Several studies have demonstrated that by blocking Ang II signaling and targeting AT1R, losartan reprogrammed the state of CAFs-from active to quiescent, and reduced the level of α-smooth-muscle actin (α-SMA, as the marker of activated CAF) [2, 38].

Solid stress and ECM content

Solid stress is a result of the physical forces generated by ECM and cancer cells in the TME [39, 40]. Therefore, lowering the levels of crucial components of the ECM-collagen and hyaluronic acid is a valid approach to anticancer treatments, which has been strongly confirmed by several reports. Zhao et al reported that the number of intra-tumoral α-SMA positive stromal cells decreased significantly thus also reduced ECM content after the use of losartan. When the solid stress levels were assessed, the losartan treatment group showed lower levels than the control group, regardless of compressive stress or tensile stress [28]. The same effect was suggested in a report that tested a therapy targeting both collagen and hyaluronan. Moreover, it turned out that losartan reduced collagen I production in CAFs. In two cell lines tested (pancreatic and breast tumors), the solid stress of control group was double that of the losartan group, which suggests that the treatment, via its anti-fibrotic effects, could possibly reduce the tumor solid stress [2].

Macrophage

Available studies have demonstrated that Ang II/AT1R axis is of great importance in the maturation and function of immune-stimulatory

myeloid cells [9]. Similarly, multiple studies have reported that the Ang II can stimulate the release and infiltration of macrophage/monocyte chemo-attractant protein. This has been shown to accelerate cancer progression and correlates significantly with high prostate-specific antigen (PSA) that is linked to recurrence rates in human prostate cancer [41-44]. Meanwhile, studies have pointed that the use of ARB could down-regulate monocyte chemoattractant protein (MCP)-1 expression and macrophage infiltration in prostate cancer. In contrast, the effects of ACE on macrophages seem to be independent of Ang II/AT1R axis [45]. One study suggested that *in vitro* overexpressed ACE resulted in the myeloid maturation reduction of myeloid-derived suppressor cells (MDSCs), which are believed to inhibit T-cell activity and immune response [46]. *In vivo*, they found that macrophages from overexpressing ACE mice are more pro-inflammatory and have more antitumor ability compared to those from wild-type mice [47]. These discrepant data emphasized different targets and receptors in RAS system may result in different immune effects of tumors. Thus we need more specific and definite experiments to verify the mechanisms.

Vessel perfusion and hypoxia

The alleviation of solid stress could be associated with the decompression of collapsed vessels, which could improve tumor perfusion and decrease hypoxia. In human ovarian tumor and pancreatic tumor cells that were treated with losartan, an increase in the percentage of perfused vessels and a decrease in hypoxic levels has been reported [2, 28]. As a result of the lowered hypoxia conditions, the expression of VEGF was then reduced [48, 49]. However, there are conflicting reports on the levels of VEGF, which is inconsistent with the reports that AT1R expression correlates with VEGF and micro-vessel density (MVD) in different human tumors [29, 30, 50]. Further research is required to settle these discrepancies.

The role of RASi in tumor process

Except the above mentioned supportive mechanisms of RASi played in tumor, a comprehensive review about the relationship between ARB/ACEI and neoplasms on different angles of tumor process (including genesis, treatment and recurrence) was made. In brief, there are three different perspectives on this subject. A majority of the reports hold the view that ARB/ACEI may be a potential drug or therapy when combined with chemo-radiotherapy/targeted therapy to protect against tumor growth, promote the effectiveness of the different cancer therapies and even reduce the recurrence of carcinoma. On the other hand, there is an opposing view that the use of these RASi could actually increase the risk of cancer. A third perspective suggests that there is not an increased risk among those ARB/ACEI users, but in the meanwhile without definitive evidence to confirm the relationship between the two ARB/ACEI and tumors were positive.

The effect of RASi in tumor genesis

There are two conflicting opinions on the use of RASi in reducing cancer incidence. On one hand, some retrospective analyses demonstrated a reduction in colorectal cancer incidence, polyp formation, and distant metastasis in patients taking RASi [51-53]. Others showed that ARB/ACEI just does not have a risk of developing cancer but cannot imply conclusive findings on the positive effect that RASi may have. We can learn this view from a review conducted by The U.S. Food and Drug Administration (FDA) [54]. In this trial-level meta-analysis of clinical trials, researchers divided patients into two groups (ARB or non-ARB treatment) randomly. They included 31 trials and roughly 156,000 patients and did not find an elevated risk of cancer in the users taking any ARB drugs. In addition, a cohort research carried out among United States veterans also supported the conclusions of the FDA [55]. They identified a total of 543,824 unique veterans and classified them into either ARB treated or non-treated in a 1:15 ratio. A tiny but statistically significant reduction was observed in the incidence of clinically detected prostate cancer (PrCA) among patients receiving ARB treatment. On the other hand, a nationwide high-risk cohort study conducted in Taiwan was designed to analyze the comparative effectiveness of any RASi drugs in the chemoprevention of hepatocellular carcinoma (HCC) in high-risk cohorts [56]. It was revealed that compared with other high risk and protective factors for HCC, RASi use in the viral hepatitis type B (HBV) and viral hepatitis type C (HCV)-the two established risk factors for HCC cohorts did not

provide sufficient protection when used at standard dosages and also was not completely safe. What is more, a meta-analysis of randomized controlled trials found that the risk of cancer was higher in treatment groups than control group [22]. Last but not least, a population based cohort study included 992,061 patients who were prescribed with antihypertensive drugs from 1 January 1995 to 31 December 2015 and followed until 31 December 2016 and were classified into three mutually exclusive exposure categories: ACEI (335,135 patients), ARB (29,008 patients) and other antihypertensive drugs [24]. It was found that the use of ACEI was associated with an increased risk of lung cancer with 7952 lung cancer events occurring. Moreover, the association was more apparent among people using ACEI for more than five years [55].

These discrepant results may give us a hint that clinical trial designs, different tumor types, and follow up duration of patients all could be the impacting factors in delivering the effects of RASi against cancer. To obtain a definitive conclusion, large scale clinical trials with longer term follow up for each type of tumor are urgently required [57].

The therapeutic effect of ARB/ACEI

RASi use alone: Whether the sole use of any ARB/ACEI agents reduce cancer risk remains an issue to debate. Perhaps due to different limitations, such as healthy user bias (the inclusion of prevalent drug users), outcome detection bias or time-related bias, the clinical data is inconclusive [58-60]. Chen et al compared patients using ARB/ACEI drugs with the control group in esophageal squamous cell carcinoma. The median overall survival was 75.3 months for the ARB/ACEI group, and 58.3 months for the control (non-ARB/ACEI) group. In addition, the months of disease-free survival in the treatment group (50 months) was almost twice than that of the control group (28.6 months). The result may be attributed to the growth inhibition of the esophageal squamous cell carcinoma cell and VEGF secretion as reported previously [61]. Nonetheless, a population-based case control study reported a tiny increased risk with ARB/ACEI usage [62]. Meanwhile, one cohort study aiming at estimating the effects of RASi versus other antihypertensive agents on short term colorectal cancer (CRC) risk, concluded that there is no correlation between RASi administration and the short-term CRC risk [63]. But due to its short follow-up duration, the long-term effect needs to be investigated in the future. Apart from the clinical research, basic experimental studies have also provided differing opinions. In terms of tumor weight or growth, the use of losartan showed no significant positive effect and possibly even a worse outcome. Despite multiple reports have proved that losartan is a factor in promoting changes in the TME, the result related to sole use of losartan on ECM is still unclear. Some reports have indicated that the amount of α-SMA and collagen I (the crucial content in ECM) may have been sharply reduced after treatment with losartan [2, 28]. But the result in Chun-hua et al suggests that the effect of losartan on α-SMA and collagen I has almost no difference as compared to the control group [64].

RASi usage in conjunction with chemo-radiotherapy: For metastatic colorectal cancer (mCRC), enrolled patients firstly treated with first-line oxaliplatin-based chemotherapy in combination with bevacizumab, were divided into ARB and non-ARB groups. The ARB group showed longer progression-free survival (PFS) and overall survival (OS) [65]. These beneficial effects are not limited to mCRC, but also can been reported in other cancers, such as glioblastoma (GBM), HCC, advanced gastric cancer and advanced pancreatic cancer, to name a few [66-69]. A late and authoritative phase II clinical trial demonstrated that total neoadjuvant therapy and chemo-radiotherapy in combination with losartan was effective in downstaging locally advanced pancreatic cancer and helpful in improving R0 resection rate to 61% [70]. In another neoadjuvant treatment of rectal cancer, Zachary et al found the rate of pathologic complete response (pCR) to neoadjuvant radiation therapy among patients taking ARB/ACEI is two or three times the amount of those not taking an ARB/ACEI in two data sets [71]. Furthermore, compared with RASi, the results also were not found among other drugs, including statins, metformin, and aspirin. One newest completed clinical trial (NCT01821729) targeted pancreatic cancer by combining FOLFIRINOX (oxaliplatin+irinotecan+5fluorouracil), losartan and proton beam radiation treat-

ments. It was found that 73.5% of participants were given a lower score for Eastern Cooperative Oncology Group Performance Status (ECOG PS), which means better functioning of daily living abilities and activities of the patients. Among all these mentioned studies, they both generally attributed the improved outcomes to two different mechanisms: the role RASIs played in the inhibition of TME and/or down-regulation of VEGF expression [69, 70, 74]. However, these conclusions fail to explain several points, for instance, how the two combined therapies work synergistically or connect each other in different molecular pathways. To work out this could help us determine which kind of RASi drugs combined with different chemotherapies is the best for specific tumors.

Secondly, some preclinical studies have demonstrated that certain RASi might aid the alleviation of the radiation-induced injury of normal tissue without impairing the tumor response to radiation [72-77]. This effect, on one hand, could be due to the inhibition of ARB/AT1R signaling. Radiation has been shown to up-regulate the expression of Ang II, which contributes to the tissue damage and remodeling via the up-regulation of pro-fibrogenic (like the transforming growth factor β (TGF-β) pathway) and pro-inflammatory pathways [78, 79]. On the other hand, increased Ang (1-7) expression seems to be protective towards radiotherapy adverse effects [80, 81].

RASi usage in conjunction with targeted therapy: Increasing evidence indicates that it is worth exploring the combined use of ARB/ACEI with targeted therapy. Especially when combined with VEGF therapies in metastatic renal cell carcinoma (mRCC) agents. Recently, studies have shown that the concomitant use of RASi might significantly improve OS and PFS in mRCC patients receiving sunitinib [82, 83]. McKay et al conducted a retrospective analysis of people with mRCC who underwent targeted therapy [84]. It was found that RASi users had improved OS as compared with other antihypertensive drugs patients and individuals not receiving antihypertensive therapy. More interestingly, the benefit in OS was limited to RASi users receiving VEGF-targeted therapy rather than in patients taking other drugs (temsirolimus or interferon α). Similarly, another mRCC study sought to determine if there is an effective concomitant use of RASi on the outcome of sunitinib [85]. They showed an improved outcome of sunitinib after the use of RASi, providing evidence for the prospective future combinatorial therapy. The reason why the combinatorial use leads to greater effects is related to the independent role of RASi plays in the tumor cell proliferation, VEGF and angiogenesis. Similar to the effect in chemo-radiotherapy, it has been reported that in lung cancer patients receiving bevacizumab, the administration of RASi helps to reduce the risk of proteinuria, which may occur due to the higher dose of bevacizumab [86, 87]. However, the exact drug interactions between the RASIs and other targeted drugs still needs to be investigated to elucidate the precise underlying molecular mechanisms.

Taken together, RASi have a clear potential in combination with chemo-radiotherapy or targeted therapy (following **Table 1**). However, larger studies are needed to better understand the protective effects of long term RASi use after chemotherapy and the specific molecular mechanisms.

The effect of RASi in tumor recurrence

In this section, we discuss the beneficial effects that ARB/ACEI may have on the recurrence of tumors. One study has analyzed the medical records of patients diagnosed with stage II/III breast cancer from 1999 to 2005 [88]. A total of 168 patients who used ACEI or ARB for at least 6 months were included in the analysis. Moreover, the most frequent agents they used were lisinopril and valsartan. At the end of the study, 15% of the ARB or ACEI patients recurred, which is less than the rate of non-users (23%). Also, the disease-free survival of ARB/ACEI users, was significantly higher than non-drug users. These highlight that the use of ARB/ACEI was associated with a reduced risk of breast cancer recurrence. Another study also supported that RASi was associated with reduced risk of pathologic N3 (pN3) breast cancer recurrence [89]. A randomized controlled trial (in Japan) was designed to explore the collaborative effect of vitamin K_2 (VK) and ACEI (after curative treatment) on cumulative recurrence of HCC [90]. The results revealed that after administrating VK (menatetrenone; 45 mg/day) and/or ACEI (perindopril; 4 mg/day) for 48 months, the combination treatment markedly inhibited the cumulative recurrence

Table 1. Completed and available prospective/retrospective trials of RASi combine with other therapies to fight against cancer

NCT number	Classified & Design	Interventions	Conditions	Outcome
NCT01805453	CHT+RT+ARB; RCT	Losartan 50 mg*2/day Placebo	Newly-diagnosed glioblastoma	No results posted
NCT01434134	CHT+RT+ARB; RCT	Metoprolol 100 mg/d Placebo Candesartan 32 mg/d	Breast cancer Heart failure	No results posted
NCT00459771	Targeted therapy+ARB; RCT	Candesartan 32 mg/d Placebo	Breast cancer	No results posted
NCT00162955	RT+ARB, RCT	Valsartan 80 mg/d	Non-hodgkin's lymphoma	Positive
NCT01110824	CHT+ACEI; RCT	Enalapril 2.5 to 10 mg/d Carvedilol 6.25 to 25 mg	Acute myeloid leukemia Lymphoid neoplasm Multiple myeloma Lymphoma	Positive
NCT02651415	Targeted therapy+ACEI; Single arm	Regorafenibn 10 mg/d Perindopril 4 mg/d	Metastatic colorectal cancer	Positive
NCT00895414	CHT+ACEI; RCT	Doxorubicin hydrochloride Enalapril maleate	Breast cancer	Positive
NCT01754909	RT+ACEI; RCT	Enalapril 2.5, 5, or 10 mg escalating doses Placebo	Lung cancer Radiation pneumonitis	Positive

RT: radiation therapy; RCT: randomized control therapy; CHT: chemotherapy.

of HCC in association with the suppression of VEGF. Nonetheless, when using VK or ACEI alone, these beneficial effects were not observed The idea that a single anti-angiogenic agent may not be sufficient to completely inhibit the tumor angiogenesis might explain this result [91]. The similar benefit is not only observed for breast cancer and HCC but also in the recurrence of the CRC, especially in left-sided CRC and early-stage CRC [92]. However, in one Danish nationwide prospective cohort study, which followed patients for 10 years, researchers found that there was an almost null association between the use of any RASi drugs and breast cancer recurrence, compared with non-users (ACEI: HR: 1.2, 95% CI, 0.97 to 1.4; ARBs: HR: 1.1, 95% CI, 0.85 to 1.3) [93]. In the Kaiser Permanente Northern California Cancer Registry, one study observed women with early stage breast cancer and examined the association between ACEI and breast cancer recurrence, breast cancer-specific mortality, and overall mortality [94]. In their Cox proportional hazards models, the exposure of ACEI was associated with breast cancer recurrence (HR 1.56, 95% CI 1.02, 2.39, P = 0.04), but did not cause specific or overall mortality.

Discussion and prospect

Substantial reviews and meta-analyses have reported this subject since many years ago [95]. For example, the previous reviews had elucidated the potential mechanisms of RASi in tumor angiogenesis, cell proliferation and metastasis. Also, they pointed towards the promising possibilities that ARB/ACEI may have in different types of human cancers [96-99]. Or with systematic literature research, some meta-analysis reached the conclusion whether the exposure of RASi increased the risk of cancer [22, 100, 101]. Different from these reviews, we focused more on the mechanisms of regulating TME and improving hypoxia by RASi, which are both the keen directions in nowadays cancer treatment. What's more, we have thoroughly analyzed its effects on chemo-radiotherapy and targeted therapy from cancer genesis to recurrence. Although it is not conclusive that RASi increases or decreases the incidence of cancer, most experiments so far suggest RAS blockade could slow down tumor process from various aspects. More specifically, compared with separate usage, lots of evidence are inclined to use RASi as an add-on to standard cancer treatment (just as the ongoing prospective trials showed in the **Table 2**). At the end, we put the existing controversial points together, suggesting that the current studies still cannot provide a consistent answer for cancer associated with RASi exposure.

The reason why there are still some inconsistent results is that different cancer types and

Table 2. Ongoing prospective trials of RASi combine with other therapies to fight against cancer

NCT number	Classified & Design	conditions	Interventions	Status
NCT03563248	RT+CHT+ARB+Targeted therapy; RCT	Pancreatic Cancer	FOLFIRINOX; Losartan Nivolumab; SBRT; Surgery	Recruiting
NCT03864042	ARB+RT; N-RCT (Sequential Assignment)	Advanced Solid Tumors Metastatic Melanoma	Losartan: 25 mg (day 1, 7, 14) Caffeine: 50 mg (day 1, 7, 14) Omeprazole: 20 mg (day 1, 7, 14) Midazolam: 2 mg (day 1, 7, 14) Encorafenib: 450 mg/d Binimetinib: 45 mg/d	Recruiting
NCT03951142	ARB+CHT+TT; RCT	Glioblastoma Brain Metastases	Losartan	Recruiting
NCT03900793	ARB+TT; N-RCT (Sequential Assignment)	Osteosarcoma	Losartan: 12.5~100 mg, escalating dose Sunitinib	Recruiting
NCT04092309	ACEI+ARNI; RCT	Hematopoietic Stem Cell Transplantation Cardiotoxicity	ACEI; Sacubitril-Valsartan	Recruiting
NCT03389724	ACEI+CHT; RCT	Cardiotoxicity Acute Myeloid Leukemia in Children Bone tumor	ACEI (Capoten): 0.5 mg/kg/day	Recruiting
NCT04288700	ACEI+β-receptor blocker; RCT	Infantile hemangioma	Oral propranolol: 2 mg/kg/d Oral Captopril: 0.1~0.3 mg/kg/d intralesional propranolol injection: 1 mg/mL	Recruiting
NCT02770378	ACEI+CHT; Single arm	Glioblastoma	Temozolomide: 20 mg/m^2 BSA *2/d Aprepitant: 80 mg/d Minocycline: 50 or 100 mg*2/d Captopril: 25 or 50 mg*2/d	Active, not recruiting
NCT02236806	ACEI+β-receptor blocker; RCT	Breast Cancer Cardiotoxicit	Bisoprolol: 5 mg/d Ramipril: 5 mg/d Placebo: 1 capsule/d	Recruiting
NCT03475186	ACEI+RRT; Single arm	Glioblastoma Radiotherapy; Complications Cognitive Decline Chemoradiation	Ramipril: 2.5~5/d	Recruiting
NCT01646437	ACEI+β-receptor blocker+thiazide; RCT	Cardiovascular Disease Fractures Cancers	Hydrochlorothiazide: 25 mg/d; Atenolol: 100 mg/d, Ramipril: 10 mg/d; Simvastatin: 40 mg/d; Placebo	Active, not recruiting
NCT02596126	ACEI+aspirin; RCT	Myocardial Infarction Cardiovascular Disease	Aspirin: 100 mg/d, Atorvastatin 40 mg/d; Ramipril: 2.5 mg, or 5 mg, or 10 mg/d	Recruiting
NCT01968200	ACEI; RCT	Cancer	Enalapril: 2.5~10 mg/12 h	Active, not recruiting

RT: radiation therapy; RCT: randomized control therapy; CHT: chemotherapy.

the exact receptors of RASi are both the causes which affect the anti-cancer effects. Like AT1R has contradictory effects in different tumors. In breast and pancreatic cancers, AT1R positively regulates tumor growth but it negatively regulates growth in melanoma cancer [2, 31]. The different expression of Ang II receptors among the different types of cancer and patients may be another reason [95, 102]. It has demonstrated that peroxisome proliferator-activated receptor gamma (PPARγ) impacts tumor progression by affecting cell proliferation, apoptosis and angiogenesis in TME [103]. Losartan and telmisartan are demonstrated as partial PPARγ activators that impede cell proliferation through inducing cell cycle arrest [104, 105]. Whether different types of ARBs are the factors that could lead to different extent of PPARγ activation is yet largely unclear [57]. Though the multimodal effects of ACEIs/ARBs in cancer angiogenesis and TME provide us insights about cancer treatment and outcome, we are just at the beginning to elucidate the precise and sophisticated mechanism of RAS in various cancers.

Further research is required to explore dose and duration of RASi in different cancer types and identify the predictive or prognostic biomarkers as well. Generally speaking, firstly for patient diagnosed with hypertension and cancer, the use of RASi could be a promising strategy. But for a patient at normal tension, exploring an optimal dose and administration ways to avoid hypotension and other side effects is one problem that must be overcame during the use of RASi. Secondly perhaps biomaterials-assisted local treatment strategies are able to enhance anticancer outcomes and reduce systematic toxicity. For example, Chauhan et al has successfully designed a nano-conjugates to preferentially accumulate and act in tumors and consequently enhanced anti-tumor effects [38]. Thirdly studies have pointed out that normalized tumor vasculature in TME impacts both the tumor progression and the efficacy of all types of anti-tumor therapies [15]. Based on their advances, except the above combined therapies, RASis may be also combined with immune checkpoint blockers in immune-modulatory to achieve better anti-tumor effects. Lastly, other than just focusing on inhibiting tumors (such as pancreatic cancer, breast cancer, GBM), the role that RASi plays in mitigating cancer treatment-related adverse events (especially cardio toxicity) should also be priority. To decipher and make sense this point, larger and more credible verifications are required.

Conclusions

In general, there are lots of compelling clinical and basic reports that support the role of ARB/ACEI drugs in tumor treatment with its role in angiogenesis, ECM, TME and hypoxia. Of all the established therapies, using it as an enhancement to chemo-radiotherapy or targeted therapy is prospectively beneficial to fight against tumor. However, we still cannot ignore reports that show the opposite or conflicting views. Thus, larger and persuasive studies are indispensable to clarify this subject.

Disclosure of conflict of interest

None.

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