The Use of Antihypertensive Drugs as Coadjuvant Therapy in Cancer

José A. Carlos-Escalante†, Marcela de Jesús-Sánchez‡, Alejandro Rivas-Castro§, Pavel S. Pichardo-Rojas¶, Claudia Arce∥ and Talia Wegman-Ostrosky∗

† Plan de Estudios Combinados En Medicina (PECEM) (MD/PhD), Facultad de Medicina, Universidad Nacional Autónoma de México, Mexico City, Mexico, ‡ Facultad de Ciencias Biológicas y Agropecuarias, Universidad Veracruzana, Orizaba-Córdoba, Mexico, § Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Mexico City, Mexico, ¶ Faculty of Health Sciences, Universidad Autónoma de Baja California, Tijuana, México, ∥ Medical Oncology/Breast Tumors, Instituto Nacional de Cancerología, Mexico City, Mexico, ∗ Basic Research Subdirection, Instituto Nacional de Cancerología, Mexico City, Mexico

Cancer is a complex group of diseases that constitute the second largest cause of mortality worldwide. The development of new drugs for treating this disease is a long and costly process, from the discovery of the molecule through testing in phase III clinical trials, a process during which most candidate molecules fail. The use of drugs currently employed for the management of other diseases (drug repurposing) represents an alternative for developing new medical treatments. Repurposing existing drugs is, in principle, cheaper and faster than developing new drugs. Antihypertensive drugs, primarily belonging to the pharmacological categories of angiotensin-converting enzyme inhibitors, angiotensin II receptors, direct aldosterone antagonists, β-blockers and calcium channel blockers, are commonly prescribed and have well-known safety profiles. Additionally, some of these drugs have exhibited pharmacological properties useful for the treatment of cancer, rendering them candidates for drug repurposing. In this review, we examine the preclinical and clinical evidence for utilizing antihypertensive agents in the treatment of cancer.

Keywords: cancer, antihypertensive agents, repurposable drugs, Renin – Angiotensin – Aldosterone System, cancer therapy

INTRODUCTION

Cancer is the second leading cause of mortality in individuals younger than 70 years, just after cardiovascular diseases (1). Despite advances in the diagnostic, medical, and interventional fields, the number of new cancer cases increased by 33% from 2005-2015. Recent statistics show that in 2020 19,292,789 new cases were reported and 9,958,133 deaths were caused by cancer worldwide (2), being more relevant because cancer can be present at any age (3).

Cancer is a multifactorial and complex group of diseases that involves dynamic changes in the genome caused by an uncontrolled division of cells with the ability to spread to surrounding tissues (4). These changes are caused by endogenous factors, such as genes, hormones, age, and sex, as well as exogenous factors, such as solvents, ionizing radiation, or drug intake (5–7). In order to provide an organizing framework of cancer amidst all its diversity and complexity, Hanahan and Weinberg proposed the existence of eight principles or hallmark capabilities and two enabling characteristics
common to all cancers. These hallmarks of cancer are sustaining proliferative signaling, evading growth suppressors, resisting cell death, inducing angiogenesis, dysregulating energy metabolism, evasion of immune destruction, activating invasion and metastasis, enabling replicative immortality; and the enabling characteristics are genome instability and mutation, and tumor promoting inflammation (8).

Treatment for this complex illness involves radiotherapy, chemotherapy and surgery, which are the most common therapies (9). However, pharmacological treatment continues to develop and to search for more efficient treatments. During the process of drug development, drug repositioning appears to be an important source of possible pharmacological alternatives for cancer treatment.

Drug repurposing is a drug development strategy based on the idea of reusing existing drugs for new medical indications. This strategy has been considered an important alternative in many fields of medicine, especially in complex disorders (10, 11). Repurposing drugs represents an important advantage compared to developing new drugs, not only by economic standards but also by reducing the time to bring a new treatment to patients (12). Currently available drug products are considered a reservoir of agents with the potential to make important contributions in the oncology field (11).

Hypertension is the leading cause of cardiovascular disease and premature death worldwide. Consequently, there are a wide variety of drugs for treating this health issue (13, 14). Hence, repurposing of these drugs could be relevant as adjuvant treatment in cancer because antihypertensive drug targets can also affect the development of malignancy, either directly or indirectly, or both. In vitro evidence for the efficacy of antihypertensive drugs in different cell lines showed that they may have a coadjuvant effect against chemoresistant cell lines and may inhibit cell growth and increase chemosensitivity in different types of cancer (15–18). Additionally, these drugs are well tolerated, orally administered, and off-patent, making them cheaper than other cancer treatments (19).

This review aims to explore the repositioning of antihypertensive drugs as an adjuvant therapeutic option in cancer. Other aspects of antihypertensives in the context of cancer, such as the epidemiological association between these drugs and cancer, will not be discussed here. Although carcinogens and cancer chemotherapeutics are substances that share several biological effects, such as DNA damage induction, it should be noted that they are distinguished based on the cellular context: carcinogens select for apoptosis-resistant clones through oncogenic or non-oncogenic processes, whereas anticancer agents are aimed at suppressing cancer cells exploitation of different pathways than the carcinogen that originally selected for them (20).

ANTIHYPERTENSIVE DRUGS AND CANCER

Antihypertensive drugs can be classified into four main groups according to their mechanism of action: those that act in the renin angiotensin aldosterone system (RAAS), either by inhibiting converting enzyme (ACE), blocking the angiotensin type 1 receptor (AT1R), directly inhibiting renin action, or by antagonizing aldosterone binding to its receptor; those that act blocking the calcium channels, which can block either dihydropyridine or non-dihydropyridine calcium channels; beta blockers that block the β-adrenergic receptors; and diuretics, which decrease the volume in the circulatory system (21). These mechanisms are summarized in Figure 1.

The role antihypertensive drugs may play in cancer treatment remains unclear, considering that there are reports showing that some antihypertensives increase the risk of developing several neoplasms (22, 23). This does not automatically preclude antihypertensive drugs from being useful as adjuvants for cancer treatment. For instance, several known carcinogens, such as arsenic, tamoxifen or phorbol ester, are also effective treatments for other cancers (20). In the case of antihypertensive drugs, for instance, calcium channel blockers (CCBs) are associated with intracellular calcium accumulation, which promotes apoptosis and makes them potentially useful for the treatment of cancer, even if short-release CCBs have been associated with cancer (24–27).

Considering in vitro, in vivo and clinical evidence, four principal antihypertensive groups of drugs as cancer adjuvants will be discussed below. The cellular mechanisms in which antihypertensives exert their effects in cancer cells are described in Figure 2 and will be approached in the context of the hallmarks of cancer in Table 2. Additionally, we conducted a review at clinicaltrials.gov looking for studies from July 15th to March 8th of this year, that had the objective of repositioning antihypertensive drugs as adjuvant therapy in cancer were selected. The keywords used in the search were “cancer” as a condition, and the other terms were candesartan, captopril, diltiazem, enalapril, lisinopril, losartan, nicardipine, nifedipine, ramipril, telmisartan, valsartan, verapamil, delapril, fosinopril, cilazapril, spirapril, imidapril, quinapril, irbesartan, and felodipine. This search yielded 10 non duplicated trials, that are detailed in Table 2.

RENIN-ANGIOTENSIN SYSTEM-BASED DRUGS

Renin-Angiotensin-Aldosterone System

The understanding of cancer development is related to a contemporary perspective of several systems, including the RAAS, a physiological regulator of systemic arterial pressure. However, the current perspective regarding this system is more complicated. It involves a balance between the processing pathways for angiotensin II (Ang II) peptide precursors and its interactions with several receptors that lead in several instances to opposite effects. In addition local activity of several RAAS components independent of systemic RAAS have been observed in different tissues and organs (18).

Intracellular effects of the RAAS system involve the

\[ \text{Ang I} \rightarrow \text{Ang II} \rightarrow \text{AT1R} \rightarrow \beta_{1,2} \text{-adrenergic receptors;} \]

- \[ \text{Ang II} \rightarrow \text{B2R} \text{-adrenergic receptors;} \]

- \[ \text{Ang II} \rightarrow \text{AT1R} \text{-mediated direct effects;} \]

- \[ \text{Ang II} \rightarrow \text{AT2R} \text{-mediated indirect effects;} \]

- \[ \text{Ang II} \rightarrow \text{Ang II} \text{-mediated feedback effects;} \]

- \[ \text{Ang II} \rightarrow \text{Ang II} \text{-mediated autocrine/paracrine effects;} \]

- \[ \text{Ang II} \rightarrow \text{Ang II} \text{-mediated systemic effects;} \]

- \[ \text{Ang II} \rightarrow \text{Ang II} \text{-mediated renin production;} \]

- \[ \text{Ang II} \rightarrow \text{Ang II} \text{-mediated aldosterone production;} \]

- \[ \text{Ang II} \rightarrow \text{Ang II} \text{-mediated angiotensinogen production;} \]

- \[ \text{Ang II} \rightarrow \text{Ang II} \text{-mediated renin release;} \]

- \[ \text{Ang II} \rightarrow \text{Ang II} \text{-mediated renin inhibition;} \]

- \[ \text{Ang II} \rightarrow \text{Ang II} \text{-mediated renin activation;} \]

- \[ \text{Ang II} \rightarrow \text{Ang II} \text{-mediated renin suppression;} \]

- \[ \text{Ang II} \rightarrow \text{Ang II} \text{-mediated renin stimulation;} \]

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other peptides), principally mediated by AT1R, angiotensin II receptor type 2, MAS receptor, insulin-regulated aminopeptidase receptor, and angiotensin II receptor type 4. Dysregulation of the components of this system has been described in several cancer (e.g., breast, ovary, prostate, pancreas, and gut) and, in some instances, has been correlated with prognosis (18). Signaling through AT1R increases cell proliferation in malignancy in two ways, by directly affecting tumor cells and by modulating vascular cell growth during angiogenesis (8, 18). Growing evidence suggests that Ang II, the main effector of the RAAS, contributes to each sequential step of cancer metastasis by promoting cancer cell adhesion to endothelial cells, transendothelial migration and tumor cell migration across the extracellular matrix (56).

Proposal of RAAS as an active element in cancer is associated with the development of hallmarks of cancer, such as constant angiogenesis, evasion of apoptosis, self-sufficiency in growth signals, tissue invasion and metastases, and limitless replicative potential. This system participates in regulating these capabilities, and many of the increased metastasis and invasion characteristics associated with RAAS expression are likely to be a direct consequence of angiogenesis (18, 56). RAAS affects multiple aspects of cancer, and blocking RAAS has been associated with an improved prognosis in some cancer types.
TABLE 1 | Hallmarks of cancer affected by antihypertensive drugs alone or in synergy with other drug in preclinical and clinical studies.

| Hallmark of cancer | Drug category | Antihypertensive Drugs | Mechanism | Sinergism | Source |
|--------------------|---------------|------------------------|-----------|-----------|--------|
| Resisting cell death | Aldosterone antagonist β-blocker | Spironolactone, Propranolol | -Reduces survivin mRNA expression -Increases protein degradation by proteasomes. -Downregulation of Bcl-2 -Upregulation of Bax and other pro-apoptotic molecules | NA | (29) |
| | CCB | Mibefradil* | -Inhibition of T-type VGCC results in cell death mediated by BAX and p27. | Temozolomide | (30, 31) |
| | | Verapamil | -Apoptosis in a myeloma cell line through unfolded protein response and Jun N-terminal kinase activation - Autophagy-like process in prostate cancer and colon adenocarcinoma cell lines. | Bortezomib | |
| Deregulating cellular energetics | CBB | Diltiazem, Amlodipine, Atenolol | -Reduced interaction between bax and Bcl-xL -Promotes Ca2+ entry, inhibiting YAP/TAZ signaling. -Inhibition of respiratory chain breast cancer cell lines, thus, reducing oxygen consumption. -Inhibition of hexokinase 2 and GLUT1 transporter. -Inhibition of hexokinase 2 and GLUT1 transporter. | Metformin | (32) |
| Sustaining proliferative signaling | ACEI | Captopril, trandolapril | -Increase apoptosis correlated with reduced expression of MYC. Active metabolites of candesartan inhibit EGF signaling. -Inhibition of the growth factors bFGF and PDGF. -Inhibits PI3K/AKT pathway | Vemurafenib | (34) |
| | ARB | Candesartan, Losartan | -Autophagy-like process in prostate cancer and colon adenocarcinoma cell lines. | | |
| | β-blocker | Non-selective (β-blockers (propranolol, carvedilol)) | -Co-inhibition of EGFR signaling and JNK/SAPK pathway | Afatinib | (40, 41) |
| | CCB | Amlodipine | -Reduces the phosphorylation of EGFR -Promotes Ca2+ entry, inhibiting YAP/TAZ signaling. -Reduced EGF mRNA expression, impairing EGF signaling. | | |
| Evading growth suppressors | ACEI | Captopril, perindopril, fosinopril | -Inhibition of cyclin D1, arresting cell cycle at G1. -Downregulation of cyclin D1, preventing progression across the G1 phase of the cell cycle. | | |
| | ARB | Losartan | | | |
| | β-blocker | Propranolol | -Increases the fraction of cells in G0/G1 -Reduced intracellular Ca2+ concentration inhibits several proteins necessary for cell cycle progression. | | |
| | CCB | Amlodipine, nicardipine | -Increases antitumor T cells and reduces immunosuppressive cells. | | |
| Avoiding immune destruction | ACEI | Captopril | -Hypersegmentation and induction of cytotoxic activity of tumor-associated neutrophils, mediated by mTOR. -Increases antitumor T cells and reduces immunosuppressive cells. | | |
| | ARB | Valsartan, Candesartan | -Upregulation of antitumoral T cells (CD3+ and CD8+) and reduction of immunosuppressive cells activity. -Decrease expression of VEGF transcription. Gemcitabine | Anti-PD-L1 and anti-CTLA4 antibodies. | (48) |
| | Aldosterone antagonist β-blocker | Spironolactone, Propranolol | -Increased surface expression of NKG2DL, recognized by NK cells. This is mediated by RXRγ rather than the MR. | | |
| | | Preproline | -Inhibition of adrenergic signaling upregulates tumor-infiltrating CD8+ T cells. | | |
| Activating invasion and metastasis | ACEI | Captopril, perindopril, fosinopril | -Direct inhibition of matrix metalloproteinase activity - Fosinopril decrease TFG-β activity. -Downregulation of TFG-β | | |
| | ARB | Losartan | | | |
| | Aldosterone antagonist β-blocker | Spironolactone, Propranolol | -Activation of RXRγ, which promotes the expression of antmetastatic genes TIMP2 and TIMP3. -Downregulation of TFG-β | FOLFIRINOX | (44, 45) |
| | | Preproline | -Inhibition of stress-induced metastasis, mediated by M2 macrophages. -Downregulation of MMP-2 and MMP9 | | |
| Inducing angiogenesis | ACEI | Perindopril, benazepril, captopril | -Downregulation of VEGF transcription. -Inhibition of IGF-1 | Interferon α, Cilomilene, meloxicam | (56, 57) |
| | ARB | Candesartan, losartan, Olmesartan | -Downregulation of VEGF transcription. -Inhibition of VEGF transcription. | Gemcitabine | (56) |
| | β-blocker | Propranolol | -Inhibition of tubulogenesis of endothelial cells and MMP-9 secretion. reduces the mRNA expression of VEGF. | Sorafenib | (58, 59) |
| | | | | Metformin | (49) |

*Mibefradil is no longer used as antihypertensive drug due to its conflicting drug interaction profile.

ACEI, Angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; bFGF, basic fibroblast growth factor; CCB, calcium channel blocker; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; FOLFIRINOX, folinic acid, 5-fluoracil, irinotecan, oxaliplatin; IGF-I, insulin-like growth factor I; MMP, matrix metalloproteinase; MR, mineralocorticoid receptor; mTOR, mechanistic target of rapavinc; NK, natural killer; NKG2DL, natural killer group 2D receptor ligand; PDGF, platelet-derived growth factor; RXRγ, retinoid X receptor gamma; TFG-β, transforming growth factor β; VEGF, vascular endothelial growth factor; VGCC, voltage-gated calcium channel.
Angiotensin-Converting Enzyme Inhibitors (ACEI)

Mechanism of Action

In 1981, captopril became the first ACEI drug available and has since been widely used for treating diverse cardiovascular diseases. ACEI drugs act on the RAAS system by inhibiting the formation of Ang II, preventing the downstream effects mediated by AT1R (60, 61). Furthermore, ACEIs do not interfere with the conversion of angiotensin-I to angiotensin-1-9 because they are converted by endopeptidases. After conversion to angiotensin-1-9, it is cleaved by ACE-2, which seems unaffected by classical ACEI, to become angiotensin-1-7, which binds to MAS receptors, causing the opposite effect of AT1R (vasodilatation, apoptosis, antiproliferation) (62–66). Currently, there are many ACEIs in existence in addition to captopril: enalapril, benazepril, and fosinopril and others.

Evidence From Studies In Vitro and In Vivo

There is in vitro and in vivo evidence for the efficacy of this kind of drugs in cancer treatment. An example of this evidence has been shown using azoxymethane in 45 male C57BL/KsJ-db/db mice to induce premalignant lesions with the aim of comparing the effects of two different drugs on these groups. The results showed that captopril reduced the number of malignant preneoplastic lesions and the amount of DNA damage in the colon, showing that there is an important relationship between ACE activity and cancer, considering that captopril is a RAAS inhibitor and may nullify some of the oncogenic effects of azomethane by attenuating chronic inflammation and reducing oxidative stress (67). Another example comes from a model of pancreatic cancer of transgenic mice randomly treated with placebo, aspirin or enalapril. In this study, enalapril significantly delayed the progression of pancreatic cancer precursor lesions by downregulating NF-kB in tumor cells (68).

Another ACEI perindopril significantly inhibits tumor development and angiogenesis, possibly independently of AT1R blockade, and this inhibitory effect was accompanied by suppression of the vascular endothelial growth factor (VEGF) (69). Other in vivo studies have shown that perindopril has a potential inhibitory effect on tumor growth due to suppression of VEGF-induced angiogenesis in head and neck squamous cell carcinoma and renal cell carcinoma (70). Furthermore, it has been shown that captopril can reduce metastatic potential to lungs (70). The efficacy of ACEIs has been attributed to diminished expression of VEGF through AT1R decreasing signaling, in which ERK1/2 and Akt pathways take part downstream (71). ACEIs have been mostly studied in the context of the inducing angiogenesis hallmark, however, they can impair other hallmarks as well, such as evading growth suppressors, avoiding immune destruction and activating invasion and metastasis. A more detailed description of the hallmarks affected can be seen in Table 1.

Evidence From Clinical Studies

A systematic review suggested that ACEI or ARB use may be associated with improved outcomes in patients with cancer, such as non-small cell lung cancer, pancreatic cancer, or breast cancer; however, a sub-analysis for specific drug classes was not performed (72). A posterior meta-analysis also observed a survival benefit for urinary tract, colorectal and prostate cancer, but it also lacked data for ACEIs alone (73). In patients with pancreatic ductal adenocarcinoma, lisinopril extends the overall survival time independently of chemotherapy. Furthermore, it has been
## Clinical trials found in clinicaltrials.gov studying antihypertensive drugs in cancer.

| Title                                                                 | Condition | Interventions                                                                 | Phase | Location | Status     | Purpose                                                                 |
|-----------------------------------------------------------------------|-----------|-------------------------------------------------------------------------------|-------|----------|------------|-------------------------------------------------------------------------|
| In Vivo Angiotensin Generation Using Tissue Plasminogen Activator and Captopril in Treating Patients with Progressive Metastatic Cancer | -Unspecified adult solid tumor | -Recombinant tissue plasminogen activator -Captopril -Temozolomide -Aprepitant -Minocycline -Disulfiram -Celecoxib -Sertaline -Captopril -Itraconazole -Ritonavir -Auranofin | Phase 1 | USA       | Completed   | This trial studied the side effects and best dose of tissue plasminogen activator and captopril and saw how well they treated patients with progressive metastatic cancer. |
| A Proof-of-concept Clinical Trial Assessing the Safety of the Coordinated Undermining of Survival Paths by 9 Repurposed Drugs Combined with Metronomic Temozolomide (CUSP9v3 Treatment Protocol) for Recurrent Glioblastomas | -Glioblastoma | | Phase 2 | Germany | Active, not recruiting | A proof-of-concept clinical trial assessing the safety of the coordinated undermining of survival paths by 9 repurposed drugs combined with metronomic temozolomide (CUSP9v3 treatment protocol) for recurrent Glioblastoma |
| Enalapril Maleate and Doxorubicin Hydrochloride in Treating Women with Breast Cancer | -Breast Cancer | -Doxorubicin hydrochloride -Enalapril maleate | Not applicable | USA       | Completed   | This randomized clinical trial studied enalapril maleate administration together with doxorubicin hydrochloride to see how well it works in treating women with breast cancer. |
| Losartan and Nivolumab in Combination With FOLFIRINOX and SBRT in Localized Pancreatic Cancer | -Pancreatic cancer | -FOLFIRINOX -Losartan -Nivolumab -Radiation SBRT -Surgery | Phase 2 | USA       | Recruiting  | This research study is studying a combination of interventions as a possible treatment for pancreatic tumors. |
| Proton w/FOLFIRINOX-Losartan for Pancreatic Cancer | -Pancreatic Cancer | -FOLFIRINOX -Losartan -Proton Beam Radiation | Phase 2 | USA       | Active, not recruiting | In this research study, they seek to determine whether combining FOLFIRINOX with Losartan before proton radiation therapy will be more efficient at controlling the growth or shrinking of tumors than just FOLFIRINOX alone. |
| Losartan and Hypofractionated Rx After Chemo for Tx of Borderline Resectable or Locally Advanced Unresectable Pancreatic Cancer (SHAPER) | -Pancreatic Cancer | -Losartan -Losartan -Potassium -Hypofractionated -Radiation Therapy | Phase 1 | USA       | Recruiting  | This clinical research studied whether gemcitabine can enter pancreatic cancer cells, measure its amount that may enter the cells, and biomarker testing. |
| Tissue Pharmacokinetics pf intraoperative Gemcitabine in Resectable Adenocarcinoma of the Pancreas Imaging Perfusion Restrictions From Extracellular Solid Stress – An Open-label Losartan Study Losartan + Sunitinib in Treatment of Osteosarcoma Serial Measurements of Molecular and Architectural Responses to Therapy (SMMART) PRIME Trial | Pancreatic Cancer | -Gemcitabine -Losartan | Early Phase 1 | USA       | Terminated   | To assess Losartan’s close-response relationship on imaging-based measures of tissue perfusion and mechanical forces in patients with brain tumors. |
| -Glioblastoma -Brain Metastases -Osteosarcoma | -Accelerated Phase Chronic Myelogenous Leukemia, BCR-ABL1 Positive -Anatomic Stage IV Breast Cancer AJCC v8 -Anemia -Ann Arbor Stage III Hodgkin Lymphoma -Ann Arbor Stage III Non-Hodgkin Lymphoma | Abiraterone | Phase 2 | Norway | Recruiting  | To determine the Maximally Tolerated Dose of Losartan and Sunitinib Combination Therapy. |
| | | -Afatinib -Beveracizumab | Phase 1 | USA       | Recruiting  | To determine if samples from a patient’s cancer can be tested to find combinations of drugs that provide clinical benefit for the kind of cancer the patient has. This study tries to understand why cancer drugs can stop working and how different cancers in different people respond to different therapy types. |
suggested that ACEIs may reduce the malignant potential of cancer cells and stimulate the immune microenvironment in patients with pancreatic ductal adenocarcinoma (74). Other retrospective reports analyzing long-term medication with ARBs and ACEIs in addition to platinum-based first-line chemotherapy suggest that when used in combination, they prolonged survival in patients with advanced lung cancer may result (75). Similar scenarios were found in a phase II trial reporting favorable overall survival outcomes when combining cimetidine, a cyclooxygenase-2 inhibitor and a renin-angiotensin-system inhibitor in metastatic renal cell carcinoma (57). ACEIs may be relevant in hepatocellular carcinoma as well. A systematic review including 3 interventional studies reported that ACEIs taken together with vitamin K or branched-chain amino acids reduced the risk of recurrence of this cancer (76). These data suggest that ACEIs may represent potential adjuvant therapies. Additionally, enalapril was observed to be well tolerated in women with female cancer and it did not alter doxorubicin pharmacokinetics, which open the door for further studies of this combination (77). There are two clinical trials undergoing or recently concluded involving captopril, and study of enalapril in combination with doxorubicin (Table 2).

ACEIs are generally regarded as safe and the adverse effects associated to its consumption are well tolerated by most patients. The most common adverse effect reported is dry cough, whereas hyperkalemia and hypotension are also reported. Angioedema is a far rarer event, however, in some cases it could lead to life-threatening scenarios (61). ACEIs may also exacerbate the nephrotoxic effects of certain antineoplastics agents (e.g., cisplatin) (78).

Direct Renin-Inhibitors
Although ACEIs and ARBs are the most common antihypertensive drugs, RAAS blockers do not guarantee total inhibition of the RAAS. Alsikiren was the first direct renin inhibitor suitable for oral administration.

Mechanism of Action
Aliskiren acts by blocking the interaction of circulating renin with angiotensinogen, which leads to angiotensin I (Ang I)
formation. As a result, the concentrations of Ang I and its derivative, Ang II, are decreased. In addition to the systemic reduction in blood pressure and vascular resistance, aliskiren also reduce plasma renin activity (79). They are one of the safest antihypertensive drugs because they are not metabolized by cytochrome p450. However, in contrast with the use of ACEIs and ARBs, Aliskiren have demonstrated a negative impact in patients with nephropathy or diabetes. The increase in plasmatic prorenin secondary to aliskiren intake is directly associated with the increase in microalbuminuria (79).

Evidence From Studies In Vitro and in Animal Models
Even though DRIs have not been investigated as antitumor drugs, their carcinogenic potential in rat studies has been described in a RAASH2 mouse study submitted to the FDA for product registration. Aliskiren may be an unlikely direct therapeutic candidate for cancer, and it may help with comorbidities associated with cancer, such as cachexia. Research suggests that aliskiren delays cachexia development by reducing tumor burden and prolonging survival in mouse models (80).

Evidence From Clinical Studies
No clinical studies evaluating the impact of renin-inhibitors on the prognosis of patients with cancer has been published as for 2021.

Angiotensin-Receptor Blockers (ARBs)
Mechanism of Action
ARBs function by blocking AT1R, preventing the binding of Ang II with this receptor (81). This specific blockade by ARBs reduces adverse effects secondary to kinins and substance P accumulation (degraded by ACE under physiological conditions) like cough and angioedema, more frequent in patients receiving ACEIs (82).

Evidence From Studies In Vitro and in Animal Models
In a study from 2017, human prostate cancer cell lines PC3, DU145, and LNCap-Ln3, growth, cell viability, proliferation and migration were evaluated under the effect of ARBs (fimasartan, losartan, eprosartan and valsartan) at concentrations of 100, 200 and 400 µM. The results showed that ARBs reduced cell viability compared to the control group, and at a concentration of 400 µM, all ARBs exerted antiproliferative effects on prostate cancer cells at each time point examined. Nevertheless, fimasartan exhibited the greatest cytotoxicity, while valsartan demonstrated the lowest antiproliferative activity compared to other ARBs in prostate cancer cells (83). In the same year, telmisartan was showed to inhibit cell proliferation and to induce G0/G1 arrest in two cholangiocarcinoma cell lines (84). In another study, telmisartan was reported to inhibit proliferation and tumor growth of esophageal squamous cell carcinoma cell lines, also by cell cycle arrest (85). Moreover, telmisartan appears to downregulate Bcl-2, an anti-apoptotic molecule, and to activate caspase-3, thus, inducing cell death, as observed in a cell line derived from human renal cell carcinoma (86). In general, in a similar manner to ACEIs, the main hallmark of cancer addressed by ARBs is angiogenesis, nonetheless, ARBs can interfere with several others (Table 1). Moreover, losartan is capable of suppressing YAP signaling, an effector of the Hippo pathway (37). Several hallmarks of cancers, such as resisting cell death, sustaining proliferative signaling, activating invasion and metastasis and avoiding immune destruction have been associated with dysregulating signaling at the Hippo pathway (87).

ARBs can modify tumor desmoplasia (fibrosis of the tumoral stroma) by regulating tumor-associated fibroblasts. Desmoplasia compresses vasculature and impedes infiltration of immune cells. Thereof, alleviation of tumor desmoplasia allows for T cell infiltration and improves perfusion, which in turn increases drug delivery to the site (56).

Evidence from Clinical Studies
The CHARM study, evaluating mortality in patients with chronic heart failure receiving candesartan in a double-blind, placebo-controlled manner published in 2004, showed significantly greater cancer mortality with the use of candesartan (88); however, this finding was considered coincidental by the authors after assessment of previous trials including candesartan. The results of this trial and another 12 clinical trials comparing telmisartan, irbesartan, valsartan, candesartan and losartan were condensed in a meta-analysis from 2020, revealing no difference in cancer mortality between patients taking ARBs and controls (89). In 2017, a meta-analysis evaluating 11 studies showed a significantly improved overall survival in patients taking any ARB (73). Concerning site-specific cancers, in an observational study including 878 patients, patients taking ARBs exhibited an improved progression-free survival (90). Improvement in overall survival was also observed for individuals with ovarian cancer taking losartan in a recent retrospective study (91). Clinical trials specifically evaluating the impact of ARBs in ovarian cancer are lacking.

For prostate cancer, a pilot study including 23 patients with hormone-refractory prostate cancer receiving candesartan dating from 2005 reported a decrease in serum levels of prostate-specific antigen in 8 patients and stable or improved performance status (92). However, no other clinical trial was completed thereafter. More data for the potential utility of ARBs came from a nationwide cohort study from Finland, in which ARBs significantly decreased the risk of death after radical prostatectomy, as well as the risk of starting anti-androgen deprivation therapy compared to no use of ARBs (93). The results of this study were confirmed in a larger cohort in Finland including patients in several stages of the disease (94). Even if there exists evidence from observational studies, clinical trials are still necessary to understand the benefits of ARBs in prostate cancer.

Since 2010, RAAS blockade was observed to favorably impact pancreatic cancer mortality, which prompted a phase I clinical assessment of the combination of candesartan and gemcitabine, which was deemed safe for a phase II clinical trial by the same group (95, 96). In a phase II trial including 35 patients with
advanced pancreatic cancer, patients receiving 16 mg of losartan had a modest but significant increase in progression-free survival compared to patients taking 8 mg (4.6 vs 3.5 months) (58). In another single-arm phase II clinical trial, in patients with locally advanced pancreatic ductal adenocarcinoma, losartan in combination with a cocktail of several adjuvant chemotherapeutics (FOLFIRINOX) and posterior chemoradiotherapy was useful in achieving complete surgical resection (52). Even if the study comprised a single arm, a parallel phase II trial evaluating FOLFIRINOX without losartan followed by chemoradiotherapy observed a similar rate of complete resection in patients with borderline resectable pancreatic adenocarcinoma, expected to higher by definition than the rate of complete resection of locally advanced tumors, a finding suggesting that losartan may increase their resectability (97). Double-blind, placebo-controlled trials are needed to adequately evaluate the role of losartan in these tumors. 3 other phase I/II trials involving losartan in patients with pancreatic cancer are active on recruiting phase (Table 2).

ARBs have been suggested to be useful for treating peritumoral edema, an important cause of impairment in patients with glioblastoma. A cohort study observed that individuals taking RAS blockers, primarily ARBs, required a significantly reduced dose of steroids, the drug of choice for treating peritumoral edema (98). A cross-sectional study in patients with glioblastoma added to the evidence, showing that intake of ARBs was significantly associated with reduced edema volume as measured by magnetic resonance (99). However, a multicenter, double-blind, placebo-controlled trial assessing the addition of losartan to standard treatment for glioblastoma (ASTER trial) in 75 patients (1:1 arms ratio) found no difference in the dosage of steroids prescribed between the groups (100). A losartan phase II trial in patients with glioblastoma is currently recruiting (Table 2).

A meta-analysis from 2017 studying the impact on the risk of cancer mortality and recurrence with RAAS blockers reported an improvement in disease-free survival for patients with urinary and colorectal cancer (in addition to pancreatic and prostate cancer) (73). A sub-analysis by specific drug class was not performed. No clinical trials involving patients with urinary tract or colorectal cancer and ARB intake have been completed; therefore, evidence is insufficient for the repurposing of ARBs as a treatment for these cancers. Concerning other cancers, two new clinical trials are recruiting for testing losartan among other drugs (Table 2).

Regarding adverse effects, the incidence of cough and angioedema is significantly lower than in patients treated with ARBs than in patients treated with ACEIs (61). However, the incidence of hypotension and hyperkalemia appears to be higher among individuals taking ARBs (101, 102). In a similar manner to ACEIs, ARBs are not recommended in the setting of nephrotoxicity, including drug-induced nephrotoxicity (78). The incidence of adverse effects of ARBs is unknown. In the trials with candesartan and losartan (in combination with gemcitabine and other chemotherapeutic drugs), the rate of hypotension varied from 6 to 40% (52, 58). In the gemcitabine-candesartan trial in patients with pancreatic cancer, hyperkalemia was reported in 6% of the patients, and reduced renal function (creatinine elevation) in 9% (58).

Aldosterone Antagonists

Aldosterone antagonists, such as spironolactone and eplerenone, are recommended in combination with other antihypertensive drugs for the treatment of resistant hypertension. These drugs also belong to the pharmacological category of potassium-sparing diuretics.

Mechanism of Action

Physiologically, aldosterone exerts its effects upon binding to the mineralocorticoid receptor, an intracellular receptor identified in cells from several organs. Spironolactone and eplerenone competitively antagonize aldosterone binding to the mineralocorticoid receptor, and in the distal tubule of the nephron, this action leads to diuresis (103). Spironolactone has also been shown to bind to the androgen receptor, providing it with apparent antiandrogenic activity. At the same time, spironolactone has the ability to bind the progesterone receptor as an agonist (104). The spironolactone affinity for both androgen receptor and progesterone receptor is secondary to its structure, as this molecule is a derivative of progesterone (100). Eplerenone, on the contrary, was designed with this consideration in mind and has structural features that confer specificity for mineralocorticoid receptor (105). As a consequence of the no specificity of spironolactone, side effects related to its androgen receptor and progesterone receptor interaction include gynecomastia, breast pain and sexual dysfunction in men and menstrual irregularities in women (106–108). However, this antiandrogenic activity of spironolactone was considered to be of potential clinical utility for the treatment of prostate cancer.

Evidence From Studies In Vitro and in Animal Models

The antiandrogenic effect of spironolactone was first experimentally confirmed through radioactivity assays in prostatic tissue obtained from rats (104). Additionally, it was observed that spironolactone causes prostate weight reduction in this model (109, 110). However, in a posterior study, spironolactone exerted stimulatory activity in androgen-sensitive cells from a mouse mammary carcinoma model (111). This finding of partial agonist activity was later confirmed in a cell line specifically designed for testing androgen receptor transactivation (112). Furthermore, in addition to activating wild type androgen receptor, spironolactone has been observed to activate cells with point-variant androgen receptor that are commonly encountered in individuals with resistant prostate cancer (113). Finally, spironolactone was capable of negating the cytotoxic effects of the drug abiraterone, an inhibitor of CYP17 (and thus, synthesis of androgens) used in resistant forms of prostate cancer (114). Based on these reports, it appears that spironolactone acts as a
partial AR agonist in androgen-depleted environments, such as that in patients treated for prostate cancer.

Other anticancer effects of spironolactone are described in Table 1. The hallmarks affected by spironolactone are avoiding immune destruction, activating invasion and metastasis and resisting cell death. Spironolactone also acts on an enabling characteristic of cancer that is genome instability through the inhibition of DNA damage repair (115). Spironolactone is capable of sensitizing cancer cells to platinum-base compounds (116).

Evidence From Clinical Studies
Initially, in the 1970s, spironolactone was reported to further reduce androgen levels in orchidectomy men with prostate cancer, suggesting that the drug could be useful as an adjuvant in these patients (117). This observation was reported in healthy men after the administration of the spironolactone derivative canrenone (118). More recently, a case report from France was published describing normalization of prostate-specific antigen in a patient with antecedent prostate cancer after treatment with spironolactone (119). In addition, epidemiological studies have correlated spironolactone intake with a reduced incidence of prostatic cancer.

Analyzing the effects of spironolactone in individuals with androgen-depleted environments, there are no observational or experimental studies showing prostate cancer progression or treatment resistance after spironolactone initiation and resolving after spironolactone withdrawal have also been published (123–125). These accounts are better explained by the observation that spironolactone is a partial agonist rather than a pure antagonist of androgen receptor in androgen-depleted environments. Unfortunately, in addition to case reports, there are no observational or experimental studies analyzing the effects of spironolactone in individuals with prostatic cancer.

β-Blockers
Expression of specific receptors able to bind ligands, transduce extracellular signals and activate intracellular signaling pathways is a key process in cells (119). β-blockers represent a heterogeneous pharmacological class with different pharmacodynamic properties and long-term effects on mortality and cardiovascular disease (126).

Mechanism of Action
The effect of these antihypertensive drugs occurs by blocking the action of endogenous catecholamines on the β-adrenergic receptor part of the autonomic nervous system, which is known to participate in blood pressure control (126). It has been suggested that β-blockers act on receptors associated with mechanisms that trigger tumorigenesis, angiogenesis and tumor metastasis (127). Some β-blockers such as propranolol, interfere with angiogenesis, including cell proliferation. β-AR antagonism also modulates the expression and activation of angiogenic signaling pathways, including angiotropoietin/TIE2, VEGF, and hypoxia inducible factor. Additionally, propranolol exhibits a biphasic effect on vascular resistance, with low and high doses inducing vasoconstriction and vasodilation, respectively (127, 128).

There is evidence showing that the use of β-blockers, widespread to nonselective (carvedilol, labetalol, propranolol) and selective (β1-selective atenolol, nebivolol, metoprolol) agents, may have an important role in cancer treatment. However, the majority of preclinical studies have focused on the propranolol effect (129, 130).

Evidence From Studies In Vitro and Animal Models
It has been reported that propranolol activity reduces cell viability and migration in breast cancer cell lines, and the effect is increased when the drug is combined with metformin, another repurposed drug candidate. Combination of these drugs reduced tumor growth in two models of triple-negative breast cancer, improving survival. Additionally, the metastatic rate from breast cancer to distant metastasis was also attenuated, and the evidence suggests that propranolol abrogates the prometastatic process in tumor-bearing mice in dose-dependent antiproliferative and antiangiogenic effects in vitro (130, 131).

The traditional mechanism of action of β-blocker activity has been previously described, but in relation to cancer, the nonselective β-AR agonist isoproterenol increased activation of the ERK/MAPK pathway in pancreatic cancer cells (132). Propranolol and other β-blockers reduced the activity of MAPK in pancreatic cancer (29, 130, 133). In breast cancer, several alterations in tumor proliferation were observed in biopsies obtained from patients treated with propranolol, which may be related to propranolol administration. These findings were corroborated using the MDA-MB-231 breast cancer cell line, which was originally isolated from metastatic pleural effusion. Cell cycle analysis by flow cytometry in control and propranolol-treated breast cancer cells after 24 hours of treatment revealed important changes in cell viability (128).

Taking into consideration previous evidence, propranolol may be considered a strategy given its inhibitory effects on the MAPK pathway to overcome resistance in melanoma treatment. Through inhibition of the MAPK pathway and other important pathways, β blockers act on several hallmarks of cancer (Table 1).

Evidence From Clinical Studies
In the assessment of the clinical usefulness of β-blockers in breast cancer, a meta-analysis from 2020 including 17 observational studies concluded that there was no association between these drugs and cancer recurrence, breast cancer-related deaths or all-cause deaths (134). However, in a phase II, placebo-controlled, randomized, triple-blind clinical trial, the authors observed that administration of propranolol prior to the resection of breast cancer was significantly associated with a decrease in expression of several metastasis markers (135). Thus, survival benefits...
derived from β-blockers should be evaluated in a phase III clinical trial.

In men with prostate cancer, a meta-analysis of 4 observational studies comprising 16,825 patients observed decreased prostate cancer-specific mortality associated with β-blockers (136). To date, no results from clinical trials assessing the effects of β-blockade in prostate cancer have been published.

Concerning pancreatic cancer, a population-based cohort study from Sweden observed that individuals with pancreatic ductal adenocarcinoma taking β-blockers exhibited a lower cancer-specific mortality after adjustment for other variables (137).

For ovarian cancer, an observational study by Watkins et al. including more than 1400 patients evaluating the impact of β-blockers found that these drugs increased median overall survival compared to individuals not taking drugs. Further stratification revealed that patients taking selective β-blockers fared no better than control individuals, and the increase in overall survival was specifically associated with nonselective β-blockers (138). A meta-analysis from 2018 by Yap et al., including two other studies (with a combined sample size smaller than the Watkins study), nonetheless found no net benefit for any β-blockers in ovarian cancer (140). Therefore, more studies are needed to clarify the impact of β-blockers in women suffering ovarian cancer.

In metastatic melanoma, nonselective β-blockers (in addition to specific therapy) were correlated with improved overall survival compared to selective β-blockers, as observed in a cohort study comprising 195 patients (139). In the meta-analysis by Yap et al., nonselective β-blockers were related to improved disease-free survival in melanoma as well; however, only two observational studies were included for melanoma (140). More recently, a small cohort study directly addressing propranolol reported a significant increase in progression-free survival among individuals taking this β-blocker (141). The addition of β-blockers was noted to improve progression-free survival in patients with lung adenocarcinoma with EGFR mutations receiving afatinib compared to patients taking afatinib without any β-blockers, as observed in a reanalysis of a phase III clinical trial (40). Immune checkpoint inhibitors could also benefit from the inclusion of β-blockers in the treatment of non-small cell lung carcinoma, as reported by an observational study including 109 patients (142).

For metastatic colorectal cancer, an observational study with 514 reported that β-blockers in combination with bevacizumab, a monoclonal antibody directed against VEGF-A, increased median overall survival and progression-free survival compared to treatment only with bevacizumab (143).

Perhaps one of the most interesting cases of the utility of β-blockers is angiosarcoma. Propranolol has been successfully used for at least a decade for the treatment of infantile hemangioma, a benign vascular neoplasm (144). This precedent and two case reports from 2015 describing excellent responses for propranolol in patients with angiosarcoma prompted two small trials studying its incorporation into chemotherapy for the treatment of advanced or metastatic angiosarcoma, which showed benefit in patients with this disease (41, 144–146). Even if the trials were small, totaling only 16 patients, cases of complete remission were observed (144).

β-blockers have shown benefits for patients with several types of cancers; however, with few exceptions, evidence comes from observational studies. Therefore, clinical trials are required to further establish the utility of this drug class in the management of individuals with cancer.

Adverse effects due to consumption of β-blockers are mainly related to beta blockade. Bradycardia, one of the most common side-effects is a direct consequence of the negative chronotropic activity of beta blockers. Other side-effects significatively associated with beta blockers are claudication, dizziness, diarrhea and hyperglycemia (147). Relative to RAAS blockers, beta blockers significantly increase the risk of fatigue, and they are associated with increased risk of sexual dysfunction in comparison to CCBs (148). The particular side-effects profile of beta blockers in patients with cancer is unknown.

Calcium Channel Blockers (CCBs)

Calcium channel blockers are attractive targets for the potential treatment of diseases, such as inflammatory or neuropathic pain, Parkinson’s disease and cancer (149). Voltage-gated Ca 2+ channels are classified into at least five different subclasses (L-, N-, P, Q, and R type), and they have been targeted to treat hypertension, angina pectoris, and ventricular tachyarrhythmias (150).

Mechanism of Action

Calcium channel blockers inhibit the transmembrane flow of calcium by blocking L-type calcium ion channels, resulting in antagonism of vascular and myocardial smooth muscle, reduction of blood pressure, and coronary artery dilatation (150). Channel blocker drugs have been generally classified into two different groups according to their chemical structure: dihydropyridines, including amlodipine, bepridil, nifedipine, and nisoldipine; and nondihydropyridines, which include benzohtiazepines (diltiazem) and phenylalkylamines (verapamil) (150).

The effect of calcium channel blockers in hypertension treatment is well known; however, it is not the only therapeutic effect. There is evidence reporting the antiproliferative action of this group of drugs in different neoplastic cell lines (151).

Evidence From In Vitro and Animal Model Studies

Since 1992, there have been several in vivo studies using L-type voltage-gated calcium channel blockers, such as amlodipine, diltiazem, and verapamil, all of which inhibit the proliferation of HT-39 human breast cancer cells with inhibitory concentration values ranging from 1.5 µM (for dihydropyridine amlodipine) to 10 µM (for phenylalkylamine verapamil) (145). Amlodipine inhibits proliferation in human epidermoid carcinoma by reducing BrDU incorporation into nucleic acids in serum-starved A431 cells (144). Verapamil has been associated with anticancerogenic activity because it can inhibit P-glycoprotein, a protein associated with cancers with multidrug resistance.
phenotype when combined with chemotherapeutic agents due to its ability to promote intracellular drug accumulation (152).

Amlodipine is not the only CCB considered a possible alternative against cancer. Studies on verapamil showed that it has a direct effect on pancreatic cancer cells by inhibiting proliferation and inducing differentiation in human promyelocytic HL-60 cells. It has shown an inhibitory effect in human colonic tumor cells as well. Moreover, verapamil has shown antiproliferative effects in medulloblastoma, pineoblastoma, glioma, and neuroblastoma tumor cell lines (43, 153).

Diltiazem is another CCB normally used for treating hypertension; nevertheless, it is also considered an anticancer drug due to its effects on autophagy and apoptosis. In chemoresistant A549/D16 cells, diltiazem and verapamil have shown that both induce autophagy, and cotreatment with docetaxel or vincristine further enhances autophagy and apoptosis in typical and atypical chemoresistant lung cancer cells (16). The effects exerted by CCBs have been explained at the cellular level in several instances, and in a similar fashion to other antihypertensive drugs, they can be understood in the frame of the hallmarks of cancers, as shown in Table 1. Recently, amlodipine was reported to promote intracellular calcium entry through Orai1, a store-operated calcium entry channel in glioblastoma cells. This resulted in the suppression of YAP/TAZ signaling, effectors of the Hippo pathway (32) which is related to several hallmarks of cancer (87).

Some characteristics and mechanisms related to treatment of cancer are to be understood as directly related to hallmarks of cancer. An important example is verapamil, which has been observed to re-sensitize chemoresistant cells. Multidrug resistance phenotype is commonly associated with increased expression of P-glycoprotein, a membrane transporter protein that is capable of extruding cytotoxic substances (154). Verapamil has been observed to reverse multidrug resistance phenotype in cancer cell lines (152), probably by acting directly at P-glycoprotein active sites (155). Verapamil is capable of reducing MDR (the gene encoding for P-glycoprotein) transcription as well (156). The evidence indicates that verapamil reverses chemoresistance in leukemia, colon cancer, hepatocellular carcinoma, and breast cancer cell lines (152, 157–159).

Evidence from Clinical Studies
Several studies have explored the impact of CCBs on survival in cancer patients. For instance, a small study by Takada et al. from 2019 observed that CCBs did not alter prognosis in patients with breast cancer; however, the time of exposure to CCBs was not taken into account (160). Another study from the United Kingdom that included more than 20,000 women with breast cancer reported no change in mortality after adjustment for other covariates (161).

The effects of CCBs in several other cancers have been studied. In patients with head and neck cancer, the use of CCBs was associated with a significantly higher risk of recurrence in a retrospective study (162). CCBs have also been associated with higher mortality in respiratory cancers in addition to higher all-cancer mortality in a Chinese study (163). CCB intake has been observed to be related to a worse outcome in individuals with acute myeloid leukemia (164). A phase I/II trial was completed evaluating the effect of verapamil in combination with hydroxyurea in patients with refractory meningioma. This trial included 7 patients, and no radiological response was observed after introduction of the treatment (165).

To date, pancreatic cancer is the disease with the most studies concerning the prognostic impact of CCBs. A retrospective study from the United Kingdom reported a survival benefit associated with CCBs and aspirin in combination in patients with pancreatic ductal adenocarcinoma after undergoing resection; neither CCBs nor aspirin alone were associated with improved overall survival in multivariate analysis (166). A subsequent study reported a longer overall survival in patients with unresectable pancreatic ductal adenocarcinoma taking CCBs alone in multivariate analysis (167). However, a previous work from a different group described a positive effect of CCBs on survival only in univariate analysis (168). These results suggest that CCBs could be repurposed for pancreatic cancer treatment; nonetheless, prospective studies are necessary to further understand the effect of CCBs in this disease.

After the discovery of the ability of verapamil to inhibit P-glycoprotein function in vitro, several trials in patients with chemoresistant cancers were started. Results on efficacy were not satisfactory, and reports of significant toxicity arose, thus, verapamil would not be tested in a phase III trial (169, 170).

As the other antihypertensive drug classes, CCBs are well tolerated by most patients. However, several adverse effects have been described after its consumption. For dihydropyridine CCBs, these side effects include headache, tachycardia, gastroesophageal reflux, peripheral edema and gingival hyperplasia. Non dihydropyridine CCBs common adverse effects are related to their higher activity in cardiac muscle, and those include bradycardia and atioventricular block (171). Diltiazem and verapamil are known CYP3A4 inhibitors, henceforth, their administration is contraindicated in conjunction with drugs metabolized by this enzyme (e.g., sorafenib, sunitinib) (172).

DIURETICS
Diuretics work by increasing urinary output by decreasing net electrolyte and water reabsorption in different segments of the nephron, decreasing intravascular volume, and by decreasing vascular peripheral resistance (173). Although mechanisms regarding their role in oncology remain an area of active research, and limited studies are available, case-control studies and some reviews have associated some photosensitizing diuretics, such as thiazide and thiazide-like diuretics, besides their common adverse events such as orthostatic hypotension, hypokalemia, hyperglycemia and increase in uric acid concentration (173), with an increased risk for skin cancer.
(174). Other prospective studies have proposed that diuretics, such as furosemide plus spironolactone, may improve musculoskeletal symptoms induced by aromatase inhibitors in women with nonmetastatic breast cancer (175). Further studies are needed to provide more evidence to debate this matter.

**DISCUSSION**

In the present work, we summarized the preclinical and clinical evidence for the use of antihypertensive drugs belonging to 4 pharmacological categories in the management of several types of cancer. In several instances, potential anticancer activity is the result of the same mechanism of action that renders them useful for hypertension (shared biological pathways), such as in ARBs and ACEIs. For other drugs, such as propranolol or CCBs, this is the result of a different interaction not related to its hypotensive effect (drug pleiotropy). For practically all the drugs described here, their clinical usefulness in oncology is in combination with known chemotherapeutics, as they lack single-agent activity.

To date, the most frequently evaluated antihypertensive agents in the context of cancer belong to the β-blocker, ACEI and ARB pharmacological groups, whereas drugs from thiazide and thiazide-like diuretics remain less studied. This is likely a consequence of increasing understanding of the role of adrenergic receptors in cancer, as well as the role of the RAAS, especially the activity of the AT1R (18, 176). Nonetheless, the possibility of identifying new targets for pleiotropic drugs is present.

Drug repurposing has been regarded as a reasonable strategy for the development of new anticancer therapies, considering that the traditional development of oncology drugs has a phase I-to-FDA approval rate of 3.4%, one of the lowest compared to other therapeutic groups in recent years (177). Antihypertensive drugs are among the most prescribed drugs worldwide, most of them at an accessible price and with a well-known safety profile, making them of particular interest for drug repurposing. However, caution is advised. The majority of studies reporting a positive outcome related to the use of antihypertensive drugs in cancer patients are observational, which are more prone to bias that can lead to overestimation of their true effect. For instance, in a meta-analysis from 2016, Weberpals et al. found no evidence for an association between β-blockers and overall survival in patients with cancer after the exclusion of studies that may be affected by a specific bias known as immortal time bias. Other biases that need to be considered when assessing pharmacoepidemiologic studies (including studies of cancer outcomes and antihypertensive drugs) are confounding, selection and measurement biases (178). Therefore, randomized, blinded, placebo-controlled clinical trials are indispensable to evaluate a candidate drug for repurposing.

Only a few antihypertensive drugs have been evaluated with favorable results in clinical trials, as noted in this review, and just one of them in phase III, which was the combination of a β-blocker with afatinib in patients with lung adenocarcinoma and EGFR mutations. Currently, there are other 10 trials registered at clinicaltrials.gov in phase I/II on progress or completed but without published results, and 1 more trial with published results. These trials are mainly focused on pancreatic cancer, however, other tumors such as glioblastoma, breast cancer or osteosarcoma are also assessed in the remaining trials. One of the largest and most ambitious is the SMMART PRIME trial, in which information from multi-omics analysis of patients with different tumors will be used to test one or several among 55 drugs (including losartan). The results of these trials will be published in the coming years, thus informing what of those could progress to a phase III trial.

More rigorous phase III studies are necessary, the lack of financial incentives for pharmaceutical companies in the case of off-patent drugs imposes constraints on their design and funding. In light of these challenges, several approaches can be explored to refine drug candidates for repurposing. Computational approaches, such as pathway mapping, molecular docking and signature matching, can assist in the systematic (rather than serendipitous) prediction of new cancer targets for antihypertensive drugs (12). Better animal models (e.g., genetically engineered murine models) and patient-derived organoids can be used to more accurately predict the efficacy of a drug candidate at the preclinical stage (179, 180). Carefully designed observational studies considering selection bias and other biases are also necessary to more precisely identify the actual effects of these drugs. Finally, funding for all these efforts as well as phase II and phase III clinical trials could be primarily provided by public agencies and philanthropic organizations or via the creation of new financial incentives for industry, such as subsidies or tax credits (181).

In conclusion, a variety of antihypertensive drugs exhibit potential utility for repurposing as adjuvants in oncology, as observed in preclinical and clinical studies. However, higher quality evidence, particularly from randomized phase III clinical trials, is necessary to determine their impact in patients with cancer.

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