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Arterial hypertension and cancer

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Arterial hypertension and cancer are two of the most important causes of mortality in the world; correlations between these two clinical entities are complex and various. Cancer therapy using old (*e.g.*, mitotic spindle poisons) as well as new (*e.g.*, monoclonal antibody) drugs may cause arterial hypertension through different mechanisms; sometimes the increase of blood pressure levels may be responsible for chemotherapy withdrawal. Among newer cancer therapies, drugs interacting with the VEGF (vascular endothelial growth factors) pathways are the most frequently involved in hypertension development. However, many retrospective studies have suggested a relationship between antihypertensive treatment and risk of cancer, raising vast public concern. The purposes of this brief review have then been to analyse the role of chemotherapy in the pathogenesis of hypertension, to summarize the general rules of arterial hypertension management in this field and finally to evaluate the effects of antihypertensive therapy on cancer disease.

Arterial Hypertension and Antivascular Endothelial Growth Factor (VEGF) Therapy

Many chemotherapies are potentially responsible for the onset of hypertension (Table 1), but the most frequently involved are the newer anti-VEGF drugs, with a reported incidence of hypertension as a side effect ranging from 11 to 43%.[1–4]

Several factors influence incidence and severity of anti-VEGF-induced hypertension such as the specific molecule used, dosage, therapeutic program, patient's age and the presence of cardiovascular risk factors.[5]

Usually, this iatrogenic hypertension resolves when chemotherapy is stopped[6]; however, as the use of this class of drugs is associated with a significant increase in patient's survival, hypertension management becomes pivotal to avoid interruption of active therapy due to cardiovascular side effects.

Key words: arterial hypertension, cancer therapies, antihypertensive therapies, anti VEGF drugs

Abbreviations: ACEi: angiotensin-converting enzyme inhibitors; ARB: Angiotensin II receptor's antagonist; CCBs: calcium channel blockers; VEGF: vascular endothelial growth factors

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Pathophysiology of Hypertension Induced by Anti-VEGF Treatment

Many studies have been conducted to explain the mechanisms involved in the pathogenesis of hypertension related to anti-VEGF treatment, but much remains to be clarified. VEGF inhibitors include monoclonal antibodies against VEGF (as bevacizumab) and VEGF receptor's inhibitors (sorafenib, sunitinib and pazopanib). Latters are partially selective and acts also against others tyrosine kinase receptors (*e.g.*, platelet derived growth factor receptor's).[7]

The VEGF family includes four proteins (VEGF: A, B, C and D). VEGF-A is the most clinically relevant protein of the VEGF family, promoting angiogenesis in tumors. Several kinds of cells express VEGF: endothelial cells, podocytes, fibroblasts, macrophages, neurons and some tumoral cells.[8–10]

There are three VEGF receptors, VEGFR-1, 2 and 3. Of these, VEGFR-2 is expressed on endothelial cell membranes and mediates the angiogenic effects. Activation of VEGFR-2 by VEGF induces expression of nitric oxide (NO) synthase and subsequent production of NO, which promotes vascular permeability, vasodilation[7,11] and participates in maintaining the homeostasis of sodium[10] in the kidney. VEGFR cascade inhibition with suppression of NO synthesis is then a crucial mechanism underlying hypertension related to anti VEGF drugs.

Several other mechanisms have been hypothesized,[12–16] such as capillaries rarefaction, increased arterial stiffness and endothelial dysfunction. Mourad *et al.*[12] measured dermal capillary densities in fingers of patients treated with bevacizumab, using intravital video microscopy: a significant lower dermal capillary density was demonstrated after 6 months of treatment; together with an increase in blood pressure levels: from 129 ± 13 to 145 ± 17 mmHg and 75 ± 7 to 82 ± 7 mmHg for systolic and diastolic blood pressure values,

Table 1. Anti-cancer drugs and cardiovascular effects

Name	Indications	Heart effects	HTN	Kidney damage	Others Toxocity	Interactions with anti-HTN drugs	HF correction/ Renal correction
Alkylating agents: Nitrogen mustard							
Mechlorethamine	Lymphomas	No	No	No	Myelotoxicity, liver toxicity	No	ND/ND
Cyclophosphamide	Breast cancer; Leukemia, lymphomas, Multiple myeloma, ovarian cancer; retino/neurobalstoma, sarcomas	7–28%	No	Yes	Cardiac and liver toxicity, hemorrhagic cystitis	No	Caution/yes (↓dose)
Ifosfamide	Sarcomas testicles cancer	17%	No	Yes (tubular damage; Fanconi Syndrome like)	Cystitis neurotoxicity, nausea; alopecia	No	Caution/yes (↓dose)
Melphalan	Multiple myeloma, ovarian cancer	↓ Diastolic function	No	No	Gastrointestinal/liver/lung toxicity		Caution/yes (↓dose)
Chlorambucil	Chronic lymphocytic leukemia, Hodgkin lymphomas	No	No	No	Gastrointestinal/neural/liver toxicity/Myelotoxicity/liver toxicity	No	Yes (↓dose)/ND
Alkylating agents: Etilenimine							
Thiotepa	Breast, ovarian, bladder cancer	5%	No	No	Gastrointestinal/liver toxicity/ Myelotoxicity/ anaphylaxis	Diltiazem	Yes (↓dose)/yes (↓dose)
Alkylating agents: Alkyl sulfonates							
Busulfan	Myelofibrosis	Yes	No	No	Gastrointestinal/liver toxicity	No	ND/ND
Alkylating agents: Nitroso Ureas							
Carmustine	Brain tumors; multiple myeloma; Hodgkin/non Hodgkin lymphomas	No	No	Yes	Lung/liver toxicity/myelotoxicity	No	ND/Yes (↓dose)
Alkylating agents: Triazenes							
Dacarbazine	Melanoma; Hodgkin lymphomas	No	No	Yes	Leukopenia; liver/renal toxicity, allergic reactions	No	caution/ND
Antimetabolites: Folic Acids Analogs							
Methotrexate	Breast cancer, neck/head cancersosteosarcome, Chorioadenoma destruens; Hydatid Mole	Yes	No	Yes	Lung fibrosis, renal toxicity, medullary toxicity	No	Yes (↓dose)/yes (↓dose)
Antimetabolites: Pyrimidine Analogs							
5 Fluorouracil	Colorectal cancer; breast cancer	Coronaric vasospasm	No	No	Leukopenia; thrombocytopenia, allergic reactions, gastrointestinal/ stomatitis	No	Caution/caution
Cytarabine	Acute leukemias (myeloid and lymphatic)	Yes (if doxorub/ ciclofosf are added)	No	Yes	Arrhythmias, myelosuppression, thrombocytopenia, anemia, diarrhea, abdominal pain, mouth ulcers, liver failure	No	Yes (↓dose)/yes (↓dose)
Gemcitabine	Ovarian cancer; metastatic breast cancer; no small cell lung cancer n pancreatic cancer	Yes	No	Yes	Medullar toxicity, dyspnea; bleeding, heart failure	No	Yes (↓dose)/yes (↓dose)
Antimetabolites: Purine analogs							
6 Mercaptopurine	Lymphatic acute leukemia Chron disease; ulcerative colitis	Yes	No	No	Myelotoxicity, hepatotoxicit, pancreatitis	No	Yes (↓dose)/yes (↓dose)
Clofarabine	Lymphatic acute leukemia	27,00%	Yes	Yes	Myelotoxicity, hepatotoxicit, nephrotoxiciy	No	Yes (↓dose) yes(↓dose)
Thioguanine	Myeloid acute leukemia	No	No	No	myelotoxicity, hepatotoxicit, intestinal necrosis	No	ND/no
Pentostatin	Hair cell leukemia	No	No	Yes	Myelotoxicity, hepatotoxicit, nephrotoxiciy		ND/yes (if Creatinine clearance <60 ml/min avoid use)
Natural agents: Vinca Alkaloids							
Vinblastine	Hodgkin/no Hodgkin lymphomas; testicles cancer; Kaposi's Sarcoma, breast cancer, mycosis fungoides	Yes	Yes	No	Myelotoxicity, gastrointestinal toxicity, thrombocytopenia	Diltiazem; verapamil; felodipine; Nifedipine (increase of vinblastine)	Yes (↓dose)/no
Vincristine	Hodgkin/no Hodgkin lymphomas; rhabdomyosarcoma, leukemia	Yes	Yes	No	Myelotoxicity, neurotoxicity	diltiazem; verapamil; felodipine; Nifedipine	Yes (↓dose)/no

Table 1. Anti-cancer drugs and cardiovascular effects (Continued)

Name	Indications	Heart effects	HTN	Kidney damage	Others Toxocity	Interactions with anti-HTN drugs	HF correction/ Renal correction
Natural agents: Taxanes							
Paclitaxel	Ovarian cancer; metastatic breast cancer; no small cell lung cancer, Kaposi's sarcoma	2.3–8%	Yes	No	Myelotoxicity, neurotoxicity; gastrointestinal/skin/liver toxicity	Diltiazem; verapamil; felodipine; Nifedipine	Yes (↓dose)/ND
Docetaxel	Metastatic breast cancer; no small cell lung cancer, prostatic cancer, gastric cancer, head and neck cancer	2.3–8%	Yes	No	Anemia, thrombocytopenia, neutropenia/leukopenia, hepatotoxicity arrhythmias	Diltiazem; verapamil; felodipine; Nifedipine	Yes(↓dose)/ND
Natural agents: inhibitors of the proteasome							
Bortezomib	Multiple myeloma	2–5%	No	Yes	Myelotoxicity, neurotoxicity, hypotension, nausea/vomiting, diarrhea, dyspnea, heart failure	No	Yes (↓dose)/no
Natural agents: epipodophyllotossine							
Etoposide	Small cell lung cancer, testicular cancer	No	No	No	Myelosuppression, nausea/vomiting, anaphylactic reactions, hypotension, mucositis, alopecia, hepatotoxicity	No	ND/yes (↓dose)
Natural agents: Camptothecins							
Topotecan	Metastatic ovarian cancer (II–III line); cervical uterine cancer; relapsing small cell lung cancer (II line)	No	No	No	Myelosuppression, mucositis, nausea/vomiting, diarrhea/constipation	No	No/yes (↓dose)
Natural agents: Antibiotics							
Actinomycin	Wilms's tumor; Soft tissues sarcomas; osteosarcomas; Edwing's Sarcoma; choriocarcinoma; testicular cancer; ovarian cancer	No	No	No	Anorexia, nausea, vomiting, stomatitis, bone marrow depression	No (digoxine)	ND/ND
Daunorubicin	Acute leukemia	Yes (cumulative dose 900 mg/m^2)	No	No	Myelotoxicity, stomatitis, nausea, vomit, cardiotoxicity	No (digoxine)	Yes (↓dose)/yes (↓dose)
Doxorubicin	Acute leukemia; Hodgkin/non Hodgkin limphoma small cell lung cancer Ovarian cancer, breast cancer,nasopharyngeal thyroid cancer Sarcomas, neuroblastoma retinoblastoma,	3–26%	No	No	Myelotoxicity, stomatitis, nausea, vomit, alopecia, cardiotoxicity (cumulative dose 450–550 mg/m^2)	No (digoxine)	Yes (↓dose)/no
Epirubicin	Breast cancer, limphoma, small cell lung cancer (↓dose)/yes(↓dose)	0.9–3.3%	No	No	Mielotoxicity; cardiotoxicity (cumulative dose 900/1000 mg/m^2), nausea/vomit; diarrhea; mucositis	No (digoxine)	Yes
Idarubicin	Hodgkin limphomaLH; Acute leukemia	5-18%	no	no	Mielotoxicity cardiotoxicity (cumulative dose 400 mg/m^2); arrhythmias	no (digoxine)	Yes (↓dose)/yes (↓dose)
Bleomycin	Squamous cell carcinoma (cervical uterine, facial, skin); germ cells tumor, lymphoma	Yes	No	No	Stomatitis; skin toxicity, lung toxicity, hypotension, allergic reactions	No	No/yes (↓dose)
Mitomycin	Bt̀reast cancer, lororectal cancer, cervical uterine cancer, bladder cancer	Yes	No	Yes	Mielotoxicity; interstitial pneumonie, renal toxicity, (hemolytic uremic syndrome); heart failure	No	ND/yes if Creatinine > 1,7 mg/dl
Natural agents: Enzymes							
L-Asparaginase	Acute lymphoblastic leukemia	Yes	No	No	Allergic reactions, nausea/vomit, liver toxicity, thrombophilia/coagulopathies; neurologic disorders(confusion); pancreatitis	No	No/no
Various: Platinum derivatives							
Cisplatin	Solid tumors and lymphomas, testicles, ovaries, bladder, cervical, head and neck cancer, stomach, esophagus, lung, osteosarcoma, pancreatic cancer	Yes	No	Yes (tubular damage-necrosis	Nausea/vomit, myelotoxicity, renal/neural/ toxicity	Thiazides diuretics, Class III antiarrhythmic agents, inhibitors of carbonic anhydrase, diuretics, aliskiren/ ARB/amlodipine/ beta-blockers in combination with thiazides	ND/ contraindicated

Table 1. Anti-cancer drugs and cardiovascular effects (Continued)

Name	Indications	Heart effects	HTN	Kidney damage	Others Toxocity	Interactions with anti-HTN drugs	HF correction/ Renal correction
Carboplatin	Solid tumors and lymphomas testicles, ovaries, bladder, cervical, face, stomach, esophagus, lung, osteosarcoma)	No	No	Yes	Myelotoxicity; renal and neuro toxicity, nausea/vomit; allergic reactions	Thiazides diuretics, class III antiarrhythmic agents, inhibitors of carbonic anhydrase, diuretics, aliskiren/j-ARB/amlodipine/jbeta-blockers in combination with thiazide	ND/yes (↓dose)
Oxaliplatin	Colorecatal cancer, pancreatic cancer	No	No	Yes	Neurotoxicity, gastrointestinal toxicity, anaphilaxis, myelotoxicity, thromboembolism, acute renal failure	No	ND/caution
Varius: Antracenedione							
Mitoxantrone	Advanced prostatic cancer (hormone dependent; breast cancer, not lymphoblastic acute leukemia	Yes	No	Yes	Cardiotoxicity (heart failure; arrhythmias liver and renal toxicity, myelotoxicity; hypotension; nausea/vomit	No	Yes (↓dose)/no
Varius: Substituted urea							
Hydroxyurea	Chronic myeloid leukemia	No	No	Yes	Mielotoxicity; nausea/vomit; diarrhea; stomatitis; skin toxicity renal and liver toxicity	No	No/yes (↓dose)
Varius: Metildrazina derived							
Procarbazine	Hodgkin lymphoma	No	No	No	Myelotoxicity, neurotoxicity nausea/vomit	ACEi/aliskiren/ Amlodipine/thiazide/ alpha lithic/ARBs/beta blockers/diuretic/ calcium antagonists	Caution/caution
Varius: Adrenal suppressors							
Mitotane	Surrenalic cancer	No	No	No	Hypotension, depression, retinopathy	spironolactone; central agonists	Caution/ND
Varius: Anti Tyr Kinase Small Molecule							
Dasatinib	acute lymphocytic leukemia and chronic myeloid leukemia	2–4%	Yes	No	Nausea/vomit, myelotoxicity, heart failure	ACEi-aliskiren/Amlodipine/thiazides/alpha lithic/ ARBs/beta blocker/diuretics/calcium antagonists	Caution/ND
Imatinib	Acute lymphocytic leukemia and chronic myeloid leukemia, GIST	0.5N1.7%	Yes	No	Fluid retention, edema, myelotoxicity, gastrointestinal toxicity	ACEi-aliskiren/Amlodipine/thiazide/alpha lithic/ARBs/beta blocker/diuretics/calcium antagonists	Yes (↓dose)/yes (↓dose)
Lapatinib	Breast cancer	1.5–2.2%	Yes	No	Hand Foot Syndrome gastrointestinal toxicity, liver toxicity	Verapamil	Yes (↓dose)/ND
Sorafenib	Liver and renal cancer	Yes	Yes	Yes	Hand Foot Syndrome, gastrointestinal toxicity, hemorrhage, lymphopenia	No	Yes (↓dose)/ND
Sunitinib	GIST; renal cancer	2.7–11%	Yes	Yes	Heart failure, liver toxicity, hypertension, acute renal failure, hypothyroidism, hyperthyroidism, thromboembolism, myelotoxicity, mucositis	ACEi-aliskiren/thiazide-alpha lithic/ARBs/beta blockers/diuretics/calcium antagonists	ND/ND
Pazopanib	Renal cancer	Yes	Yes	Yes	Hepatotoxicity, stroke/tIA, QT prolungation, angina, hypertensive crisis, gastrointestinal toxicity, myelotoxicity	Diltiazem, verapamil, sotalol	Yes (↓dose)/no
Varius: Monoclonal Antiboby							
Bevacizumab	Metastatic breast cancer;metastatic colon cancer, glioblastoma, non small cell lung cancer, renal cancer	1.7–3%	Yes	Yes	Heart failure, liver toxicity, hypertension, gastro-intestinal perforation, hemorrhage, thromboembolism, angina, stroke	No	ND/ND
Trastuzumab	Metastatic breast cancer, metastatic gastric cancer	2–28%	No	Yes	Heart failure, cardiomyopathy, ventricular dysfunction, thromboembolism, anaphylaxis, angioedema, pulmunary fibrosis, glomerulonephritis, ARDS	No	ND/ND

Table 1. Anti-cancer drugs and cardiovascular effects (Continued)

Name	Indications	Heart effects	HTN	Kidney damage	Others Toxocity	Interactions with anti-HTN drugs	HF correction/ Renal correction
Cetuximab	Metastatic colorectal cancer, Squamuous cell, Head and neck cancer	No	No	Yes	Skin toxicity, infusion reaction, diarreha, renal failure, fever, hypomagnesemia, hypocalcemia, hypokaliemia, arrhytmias, interstitial lung disease	No	ND/ND
Panitumumab	Metastatic colorectal cancer	No	No	Yes	Skin toxicity, diarrhea, hypomagnesemia, hypocalcemia, hypokaliemia, gastrointestinal toxicity, pulmonary fibrosis		ND/ND
Hormones: Corticosteroids							
Prednisone	Prostatic cancer	No	Yes	No	Adrenal insufficiency, Cushing syndrome, immunosuppression, diabetes mellitus, osteoporosis, gastrointestinal ulceration, steroid myopathy, sodium and fluid retention	Yes (increase risk of hypokaliemia)	ND/ND
Hormones: Antiestrogens							
Aromatase inhibitor	Breast cancer (adjuvant therapy and metastatic disease)	Yes (increase cardio/ cerebrovascular risk)	No	No	Artralgia/myalgia, osteoporosis, hot flashes, Hypercholesterolemia, stroke, angina, thromboembolism, endometrial cancer	No	ND/ND (letrozolo in Child C give q48h)
Tamoxifene	Breast cancer (adjuvant therapy and metastatic disease)	No	No	No	Thromboembolism, stroke, endometrial cancer, hot flashes, pancytopenia	Diltiazem, propafenone, verapamil	ND/ND
Hormones: Antiandrogens							
Flutamide	Prostatic cancer	No	No	No	Liver toxicity, thrombocytopenia, ginecomastia	No	Yes/ND
Abiraterone acetate	Prostatic cancer	Yes	Yes	No	Hypokaliemia, hepatotoxicity, arrhytmias, heart failure, fluid retention, hypertension	Flecainide, propafenone	Yes/No
Hormones: Gonadotropin-releasing hormone analogues							
Leuprolide	Prostatic cancer	Yes	No	No	QT prolungation, stroke, myocardial infarction, diabetes mellitus, pituitary apoplexy, depression	Class Ia and III antiarrythmics, flecainide, propafenone, ARB/ thiazide combos, beta blocker/thiazide combos, diuretics	ND/ND

Where not otherwise specified sources are Toxnet and Epocrates. Legend: Caution: if liver or renal function are altered, there are no standardized reductions of drug dosage, but in clinical practice usually dosage are reduced. HTN Hypertension; ND: not defined; ACEi: angiotensin converging enzyme inhibitor; ARB: angiotensin II receptor antagonists.

respectively ($p < 0.0001$). The authors concluded that regression and apoptosis of microvascular endothelial cells could be involved in the capillary rarefaction. This event could also be explained by a reduction in the NO availability.

Veronese *et al.*[14] reported that serum catecholamines, endothelin-1, renin and aldosterone levels were not modified in patients receiving anti VEGF drugs (sorafenib). This could mean that hypertension, during VEGF therapy, is not correlated to the renin-angiotensin system or sympathetic nervous system. In the same studied population, the vascular stiffness (measured by aortic pulse wave velocity and central aortic augmentation index) was meanwhile significantly increased.

These findings were partially in contrast with those obtained by Kappers et al.[17] who found an endothelin-1 increase after treatment with sunitinib, but this may be due to a specific molecule-effect (two different drugs were used in the two studies, sorafenib and sunitinib, respectively).

Finally, anti-VEGF therapy in general and Bevacizumab in particular, leads to an increased risk of developing proteinuria, with a dose-related relation. The incidence of proteinuria ranges between 21 and 41%: it is higher in treatments with high doses (22–66%), with a relative risk is of 1.4 (1.1–1.7; $p = 0.003$) for low dosage, and 2.2. (IC 1.6–2.9; $p < 0.0001$) for higher dosage, even after correcting for the underlying disease of the patients. However occurrence of proteinuria in nephrotic range (0.1%) is unusual.[18]

Management of Hypertension During Anti-VEGF Rherapy

Previous studies demonstrated that comorbidities affect cancer patient survival as much as the stage at diagnosis.[19,20] Hypertension is a significant determinant of cardiovascular comorbidities and has to be managed according to updated guidelines. Both, European Hypertension Management guidelines[20] and current recommendations[21] focused on oncological patients, underline the importance of evaluation of the different cardiovascular risk factors, to stratify the cardiovascular risk profile of each patient. Oncological patients should be stratified as low risk (no risk factors), high risk (one risk factor) and very high risk (two or more factors).[20] An adequate

blood pressure control should be obtained before the beginning of VEGF inhibitor therapy, and antihypertensive drugs should be titrated to obtain desired blood pressure levels as VEGF inhibitor therapy begins and proceeds. If this goal is not achieved, it may be reasonable to consult the hypertension specialist to reach optimal blood pressure control.[21]

Usually, blood pressure levels should be monitored weekly during the first cycle of antiVEGF therapy and then at least every 2–3 weeks during the following treatment. After the first cycle is completed and a stable blood pressure has been achieved, blood pressure control can be made with a routine clinical evaluation or home monitoring.[21]

Maitland *et al.*[21] set a goal of 140/90 mmHg for all patients with anti-VEGF induced hypertension; these values are in agreement with European and American recommendations for hypertension management in general population,[20,22] for patients without associated clinical conditions or diabetes. However, a blood pressure goal that is not achieved may not be necessarily considered as a mandatory reason for delaying VEGF inhibitor therapy.

Patients developing stage 1 hypertension (≥140/90 mmHg) or an increase in diastolic blood pressure of at least 20 mmHg compared with pretreatment values, should initiate or optimize antihypertensive therapy.

Temporary discontinuation of antiVEGF drugs must be considered when hypertension is difficult to control and when patients are highly symptomatic for high blood pressure.[23] Chemotherapy should be reinstituted at the same or lower dose once blood pressure control and titration of antihypertensive agents has been achieved.[21] Physicians should maximize support and specific antihypertensive therapy to avoid chemotherapy interruption and maintain the patient at the highest tolerable dose.

A recent study[7] recommends treating antiVEGF associated hypertension with angiotensin-converting enzyme inhibitors (ACEi) or calcium channel blockers (CCBs; specifically amlodipine or felodipine) as first-line agents. Nitrates or phosphodiesterase inhibitors can be used considering the hypothesized physiopathological mechanism underlying hypertension induced by anti-VEGF treatment. Clearly, lifestyle modification recommendations are mandatory for this kind of patients (reduction of salt intake, smoking suspension, alcohol intake reduction).

When sunitinib and sorafenib are used, nondihydropyridine CCBs (verapamil and diltiazem) should be avoided due to relevant pharmacokinetic interactions, since they are inhibitors of CYP3A4 system, which is involved in the metabolism of both sunitinib and sorafenib.

Antihypertensive Therapy as Cause of Cancer

The role of hypertension as a risk factor for tumors is known at least for some malignancies, such as kidney cancer: hypertension doubles renal cancer risk in Caucasic patients and triples in Afro-Americans.[24]

The biologic mechanisms underlying this association are unclear; hypothesis include formation of reactive oxygen species, and upregulation of hypoxia-inducible factors due to the chronic renal hypoxia that accompanies hypertension.[24]

However, many studies have been designed to investigate the relationship between antihypertensive drugs use and increased risk of cancer development, with highly discordant results. The largest and more recent meta-analysis has confuted this hypothetic link, reducing—but not concluding—an historic scientific debate.[25]

Calcium Channel Blockers and Cancer

The relationship between CCBs and cancer has been studied for a long time. CCBs could influence cellular replication and apoptosis interfering with calcium-mediated intracellular mechanisms[26]; this class of antihypertensive drugs seems to have a negative effect on carcinogenesis in most studies.[27] Moreover, CCBs have been used to increase the antitumor effects of some antineoplastic agents.[28–31] However, other studies[32,33] have shown an increased risk of cancer in patients treated with CCBs. One of the first studies that raised the suspicion of a possible association between CCBs and cancer was a retrospective study on hypertensive patients that showed a significant increase of tumor incidence in patients taking nifedipine (the relative risk of cancer for patients taking CCBs compared to that of beta-blockers-users was 2.02; 95% CI 1.16–3.54)[32]; this study was based on 61 cases of cancer among 750 patients after a follow-up of 6–10 years. However, Jick *et al.*[34] have shown that in hypertensive patients taking beta-blockers only (reference group), ACEi only or CCBs only, the relative risk estimated for development of all type of cancers combined were 1.27 (95% CI 0.98–1.63) and 0.79 (0.58–1.06) for users of CCBs and ACEi, respectively, relative to users of beta-blockers. Authors concluded that the slight positive association between CCBs and increased risk of cancer was unlikely to be causal since there was no greater risk with the increasing duration of CCBs use. After these trials many others were performed and most of them denied a role of CCBs on promoting cancer.[25,35–38]

In Nurses' Health Study during 6 years of follow-up, 18,635 female taking cardiovascular medications were analyzed as follows: 852 women were newly diagnosed with cancer and 335 women died of cancer. Women who reported the use of CCBs had no increased risk of newly diagnosed cancer compared with those taking other cardiovascular drugs (relative risk = 1.02; 95% CI 0.83–1.26).[37]

Similar results were obtained in the STEPHY study: in this cohort the combined incidence of fatal and nonfatal cancer (primary end point) was evaluated. The primary end point was reached in 10.9% of participants treated with calcium antagonists and 9.7% of patients not taking calcium antagonists (odds ratio 1.12, 95% confidence interval 0.7–1.8).[38]

Diuretics and Cancer

Diuretics have been implicated in increasing risk for cancer development,[39–42] especially in women: in previous studies

(case-control and cohort studies) this class was associated mostly with an increased risk of renal cancer.

Two large trials showed a 63% increase in the incidence of renal carcinoma in women who were receiving diuretics.[43,44] The underlying mechanism could be explained by experimental studies that highlighted histological alterations of kidney: rats that chronically received thiazides showed evidence of "subtle glomerular injury" characterized by periglomerular fibrosis and wrinkling and thickening of the glomerular basement membrane.[45]

Other studies also suggested an association between diuretics and increased risk of developing skin cell carcinomas.[46,47] However the most recent studies have rejected such a correlation.[25,48]

Beta Blockers and Cancer

Many studies have shown a role of beta-signalling antagonism in promoting carcinogenesis.[25,49–51] Beta-adrenergic antagonists could influence intracellular apoptosis signalling and various mechanisms of immune response.[52,53] Many studies[54–56] have been conducted to investigate an association between beta-blockers use and cancer incidence, yielding conflicting results. In a recent retrospective clinical trial[57] conducted on 1,762 patients affected by colorectal cancer and 1,708 control, long-term beta-blocker use (≥6 years) was associated with a significantly higher risk of stage IV colorectal cancer (OR, 2.02; 95% CI, 1.25–3.27). However, many studies are reinforcing the concept that some of these drugs may bear a protective effect against cancer progression.

In vitro studies[40,58–66] demonstrated the anticancer properties of propranolol, particularly against lung, colon, breast, nasopharyngeal, ovarian, pancreatic and gastric cancer cells. Pasquier *et al.*[67] found that propranolol showed modest effects on cell proliferation, and it was able to significantly inhibit angiogenesis *in vitro* at relatively low concentrations; the latter effect was mostly due to the inhibition of new capillary tube formation rather than the disruption of pre-existing vessels. Low concentrations of propranolol could modulate the antiproliferative effects of chemotherapeutic drugs *in vitro* in a cell type-specific and dose-dependent manner. In particular, human breast carcinoma and vascular endothelial cell lines were among the most responsive to the combination of propranolol and chemotherapy.

In retrospective clinical studies, the use of beta blockers during chemotherapy was associated with increased survival and decreased metastatic spread and incidence of secondary cancer formation in breast cancer.[68–70] *In vivo* studies that used different animal models of human cancers (lung and pancreatic), propranolol produced protective effects against malignancy evolution.[52,71]

In humans trials nonselective beta blockers (*e.g.*, propranolol) have been associated to a lower risk of breast cancer progression compared with selective beta blockers (*e.g.*, atenolol or metoprolol).[69] These results support the conclusion that beta 2 receptors may be implicated in cancer metastasis spread.

Recent studies[72] demonstrated that use of beta-blockers for 1 year or more is associated with a reduced risk of progression of thick malignant melanoma, indicating the need for larger epidemiological studies and randomized clinical trials in this setting as well.

ACEi/angiotensin II Receptor's Antagonist (ARB) and Cancer

Regarding relationship between ACEi/aRB and cancer, many studies have been conducted with often-contradictory results, but mostly discouraging an association.[73–77] Yoon *et al.*[78] in a recent and carefully conducted meta-analysis showed an overall not significant association between the use of ACEi and ARB and risk of cancer. In a subgroup analysis considering cancer site, results demonstrated that the use of ACEi or ARBs was associated with an increase risk of melanoma (RR 1.09, 95% CI 1.00–1.19) and renal tumors (RR 1.50, 95% CI 1.01–2.23), but a decreased risk of oesophageal (RR 0.73, 95% CI 0.57–0.94) and prostatic (RR 0.88, 95% CI 0.80–0.97) tumor; moreover, long term use of ACEi or ARB was associated with a reduction of risk of smoking related cancer (RR 0.79, 95% CI 0.64–0.98). Explanation for such findings have been given by authors: ACEi-ARB have a protective effect against insulin resistance, a known risk factor for prostate cancer and counterbalance the increase in plasma renin activity and Angiotensin II caused by cigarette smoking, which represents a protective effect considering that Angiotensin II has been hypothesized to have a role in cancer development for its promoting effects on angiogenesis and subsequently on tumor progression. However, the increased risk of melanoma could be due to a photosensitizing effect of some ACEi and the increased risk of renal cancer development could be biased by hypertension itself, which has previously been associated to such a risk.

Studies on molecular mechanism gave some important insight: ARB/ACEi's use causes an increase in Ang-(1-7), an endogenous peptide of the renin-angiotensin system with vasodilator and antiproliferative properties, through a reduction of COX-2 and VEGF-A. These actions may be responsible for an inhibition of lung cancer cell growth and angiogenesis.[79,80]

The meta-analysis by Bangalore *et al.*[25] has refuted an association between ACEi/aRB and risk of cancer. However, the same meta-analysis underlined a possible consistent negative effect of the association of ACEi and ARB on cancer risk when compared with most of the classes of other antihypertensive agents. Use of ARB implies an increase of Angiotensin II and subsequent increased stimulation of Angiotensin II receptor type 2: this could lead to a stimulation of angiogenesis and tumor growth. However, this meta-analysis is biased

by a too short duration of considered trials, a limit that does not allow definitive conclusions.[77]

Finally, "The ARB trialists Collaboration,"[81,82] a solid meta analysis conducted on about 140,000 patients rejected any association between any renin-angiotensin system blockers, even when used together and cancer. Taken together these appear as conflicting results but incline more to the absence of a correlation between antihypertenisive drugs and cancer's risk. It's clear the need for long term follow up clinical trials to finally clarify the role of each antihypertensive drug on the risk of cancer development.

Conclusions

The association between cancer and hypertension is a growing problem considering the high prevalence of both conditions. Among chemotherapeutic drugs, anti VEGF are the most frequently involved in a rise of blood pressure levels, mainly through the decrease in NO synthesis. Regarding relationship between antihypertensive agents and risk of cancer development, many studies have been conducted, leading to conflicting results. However, the most recent studies have denied an increased risk cancer in patients receiving antihypertensive drugs.

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