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Can cardiovascular drugs support cancer treatment? The rationale for drug repurposing

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Research on the concept of biological overlap between cardiovascular and oncological diseases is gaining momentum. In fact, in both conditions, the malfunction of common regulatory mechanisms, such as the renin-angiotensin system (RAS), sympathetic nervous system (SNS), coagulation cascade, sodium-potassium ATP-ases, and mevalonate pathway, occurs. Thus, targeting these mechanisms with well-known cardiology drugs, including angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), β-adrenergic receptor blockers, statins, cardiac glycosides (CGs), and low-molecular-weight heparins (LMWHs), could be a novel, promising adjuvant strategy in cancer management. Thus, here we discuss the idea of repurposing cardiology drugs in oncology based on available preclinical and clinical data.

Introduction

According to the WHO, cancer and cardiovascular diseases are currently two main causes of mortality worldwide, with an explicit tendency towards increasing incidence and growing social burden over the next 30 years [1]. As per epidemiological estimates, most of this trend stems from the improvement of corresponding survival rates and prolonging human life-expectancy, consequently leading to the formation and continuous growth of the population affected by both diseases concomitantly. It is not only common epidemiological aspects that underlay the frequent co-existence of cancer and cardiovascular conditions. In fact, accumulating clinical and preclinical data also suggest their interdependence and biological overlap, based primarily on their aging-related nature and pathophysiological links [2]. Thus, cancer was recently recognized as an evolutionary adaptive form capable of exploiting host cardiovascular-regulating mechanisms, such as RAS, β-adrenergic system, coagulation system, and sodium/potassium (Na^+/K^+)-ATP-ase pump system, to promote its own survival. Consistently with these assumptions, various cardiovascular system-normalizing drugs have been found to exhibit documented anticancer activity, including angiotensin-modulating agents, β-antagonists, statins, CGs, and LMWHs, which has suggested their potential repurposing in oncological adjuvant contexts (Fig. 1) [3]. Interestingly, the concept of drug repositioning from noncancer indications to new uses in oncology is a well-established and cost-effective strategy that has already succeeded in introducing aspirin and celecoxib into the prophylaxis of colorectal cancer (CRC) as well as thalidomide into the treatment of multiple myeloma (MM) [4]. Thus, in a specific group of cardio-oncological patients, optimization of cardiological regimens could support the management of coexisting malignancies and improve their performance. Here, we discuss this issue in more detail.

Anti-RAS strategies

Extensive experimental evidence has uncovered the role of RAS in malignant transformation and progression, and this relationship

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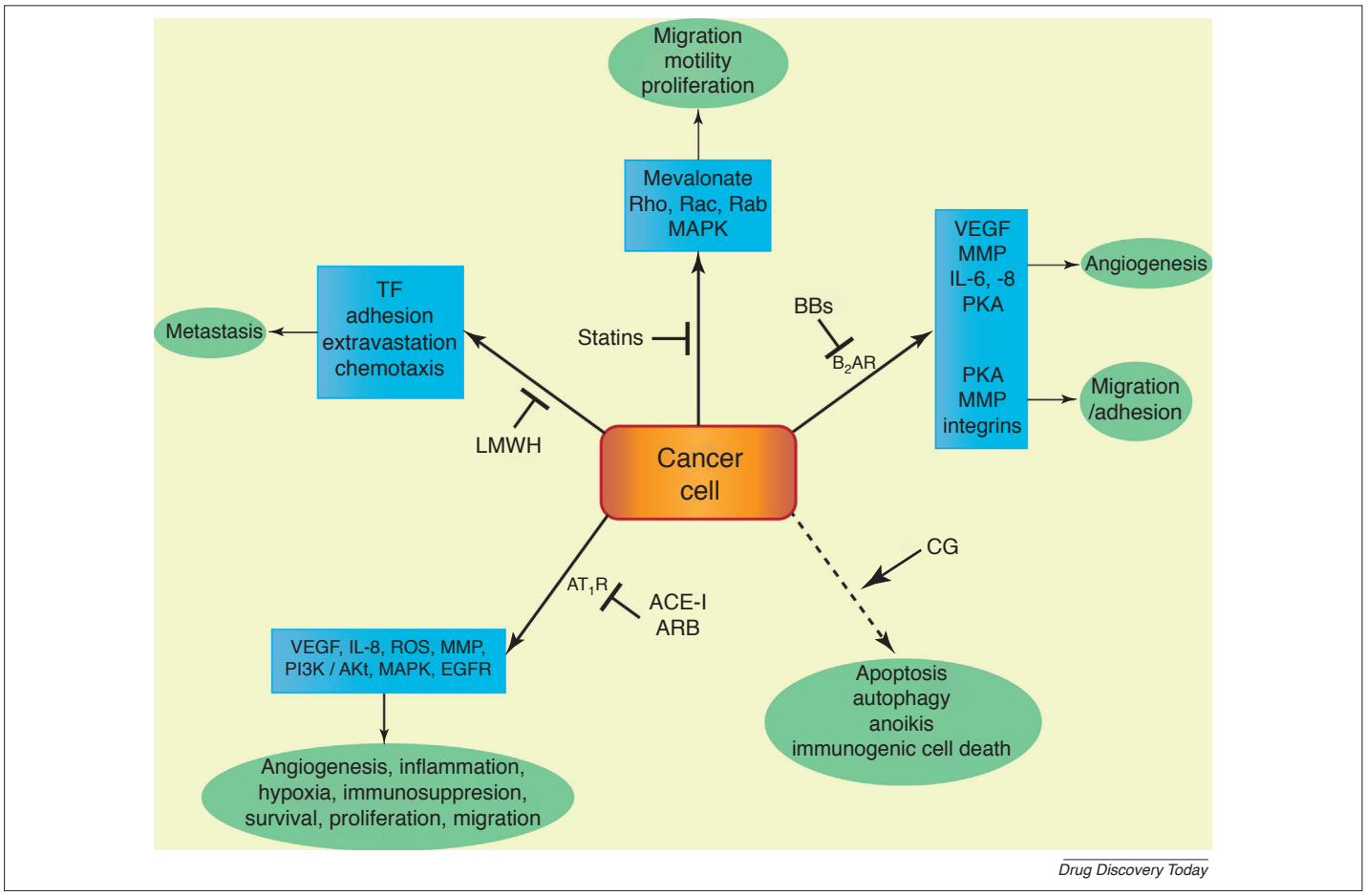

FIGURE 1

The mechanisms of the anticancer action of cardiovascular drugs. In malignant cells, the overexpression of angiotensin type I receptor (AT_1R) upregulates proproliferatory and antiapoptotic [epidermal growth factor receptor (EGFR); mitogen-activated protein kinases (MAPK); and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway] and proangiogenic, proinflammatory premetastatic [vascular endothelial growth factor (VEGF); matrix metalloproteases (MMPs); interleukin 8 (IL-8); and reactive oxygen species (ROS)] mediators. These effects can be antagonized by angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs). The overexpression of β-adrenergic receptor type 2 (B_2AR) contributes to proangiogenic cell responses via VEGF, MMPs, protein kinase A (PKA), and IL-8, 6. It also stimulates cell migration, effectively inhibited by β-blockers (BBs). The anticarcinogenic effect of statins involves the downregulation of Rac, Rho, and Rab (small G proteins), whereas statins are mainly antimetastatic. Cardiac glycosides (CGs) exert different modalities of cell death. Abbreviations: LMWH, low-molecular-weight heparin; TF, tissue factor.

was recently reviewed elsewhere [5]. Here, we present general aspects to provide a background for further discussion. In a typical cancer context, overactivation of RAS occurs in response to a neoplastic adaptive mechanism, leading to the amplification of proproliferatory, proangiogenic, promigratory, proinflammatory, and antiapoptotic responses in malignant cells and their milieu. Therefore, targeting RAS with ACE-Is and ARBs has received considerable attention as a promising strategy for anticancer intervention. Indeed, available *in vitro* and animal studies have shown that anti-RAS regimens affect various types of lesion (early-stage, advanced, and metastatic) primarily because of their combined and multidirectional antiangiogenic, anti-inflammatory, and immunomodulatory mechanisms. In this context, anti-RAS regimens have been reported to modulate nuclear factor (NF)-κB and hypoxia-inducible factor 1 (HIF-1), to inhibit matrix metalloproteinases (MMP-2 and MMP-9), which degrade extracellular matrix (ECM), suppress vascular endothelial growth factor (VEGF), stimulate angiostatin (only captopril), and reduce infiltration of tumor-associated macrophages by MCP-1 abolishment, eventually leading to decreased microvessel density, alleviation of the tumor inflammatory environment, and tumor growth regression [5]. In experimental studies, anti-RAS agents displayed antiapoptotic and antiproliferatory effects, which might have resulted from epidermal growth factor receptor (EGFR) trans-inactivation and subsequent suppression of the mitogen-activated protein kinase (MAPK) or phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathways [5]. Finally, anti-RAS regimens are also likely to reduce cancer fibrosis and solid stress, which is a physical barrier to the infiltration of immune cells and distribution of chemotherapeutic agents [6]. This activity is probably associated with their regulation of cancer-related fibroblasts and profibrogenic TGF-β, as evidenced for losartan [7].

Based on the above findings, the repurposing of ACE-Is or ARBs in oncology was examined in the context of both prophylactic and therapeutic indications. Although the former approach yielded conflicting results in the clinical setting, several studies provided interesting clues for further research. For example, an epidemiological retrospective study by Lever *et al.* confirmed the benefits of

chemopreventive strategies involving ACE-Is for female-specific and smoking-related cancers in patients with concomitant hypertension [8]. Moreover, in a retrospective case-control study by Lang *et al.*, it was revealed that ACE-Is reduced the incidence of esophageal, pancreatic, and colon cancer, secondary to their antiangiogenic actions [9]. Similar observations for ACE-Is and ARBs were made by Chiang *et al.* in their retrospective cohort study performed among the Taiwanese population [10]. By contrast, the prophylactic effect of ACE-Is and ARBs against hepatocellular carcinoma was not reported in high-risk patients with hepatitis B virus or hepatitis C virus infection [11]. In addition, Ronquist *et al.* and Sjoberg *et al.* failed to find any relationship between ACE-Is and prostate, esophageal, and gastric cancer occurrence [3]. Analogously, several studies dealing with the putative prophylactic properties of ARBs also provided negative conclusions. Pasternak *et al.* and The ARB Trialists Collaboration in 2011 found no association between ARB intake and cancer incidence, whereas Sipahi *et al.* postulated a significantly increased risk of new cancer diagnoses related to ARBs [5]. However, the latter study was questioned by a US Food and Drug Administration (FDA) report published in 2011 [12]. In another population-based cohort study, the use of ACE-Is over 5 years was associated with an increased risk of lung cancer [13]. Given these controversies, there is a clear need for further research in this area before the establishment of any chemopreventive application of ACE-Is and ARBs.

By contrast, the available clinical findings on the therapeutic utility of ACE-Is and/or ARBs are more convincing but still not conclusive. In this context, the potential introduction of these drugs into adjuvant regimens, either against cancers vulnerable to antiangiogenic therapies or against tumors resistant to platinum- or anti-EGFR-based chemotherapeutic schemes, represents an encouraging clinical approach, as explained by Pinter *et al.* in their excellent review [6]. In fact, the former application is mainly justified by the antiangiogenic activity of anti-RAS agents, resulting from VEGF attenuation, which was revealed in patients with the following malignancies: metastatic (but not non-metastatic) renal cell carcinoma (RCC) (when combined with sunitinib), advanced CRC, hepatocellular carcinoma (especially perindopril), and advanced gastric cancer. As for the latter indication, the ability of anti-RAS agents to downregulate VEGF was linked to overcoming cisplatin resistance in patients with advanced non-small-cell lung cancer (NSCLC), advanced gastric cancer, and metastatic CRC. Curiously, this effect translated clinically into prolonged patient survival for up to 11 months relative to controls. In addition, in several retrospective trials, ACE-Is exerted synergistic activity with various systemic antitumor regimens, such as EGFR-targeted drugs in NSCLC (based on their anti-EGFR activity), gemcitabine in pancreatic cancer, bevacizumab or temozolomide in glioblastoma, and hormonotherapy in prostate cancer [6]. Moreover, in a Phase II clinical trial, losartan combined with a neoadjuvant Folforinox scheme contributed to the improvement of the microscopically margin-negative resection rate in patients with locally advanced pancreatic cancer [14]. It also enhanced vessel perfusion and paclitaxel delivery to highly desmoplastic tumors on account of its antifibrotic activity, as shown most recently in an ovarian cancer model [7]. Finally, the advantage of ACE-Is (specifically imidapril) in preventing wasting syndrome in patients with NSCLC or CRC, but not in patients with pancreatic cancer, was documented in a Phase III clinical trial [5]. In contrast, several cancer types remain unresponsive to ACE-Is in the clinical setting, including: melanoma, MM, acute myeloid leukemia (AML), esophageal, breast, urinary tract cancers, and primary glioblastoma [6,15], indicting cancer-specific rather than the general efficiency of RAS-targeted drugs. However, this suggestion should be thoroughly considered against the existing data before launching further clinical trials.

Suppression of sympathetic nervous system

Not only RAS overactivation, but also a well-established association between malignancy and inflammation is an aspect of cancer biology that provides the opportunity for cardiovascular drug repurposing. More specifically, the pathophysiological background behind this concept focuses on the correlation between chronic stress, inflammation, and the accumulation of catecholamines, which further translates into sustained overstimulation of the SNS, which promotes carcinogenesis. Indeed, many studies have confirmed that SNS is necessary for tumor development and, in this context, two strategies of adrenergic signal amplification in neoplasia have been described: (i) the increased density of β-adrenergic receptor type 2 (B_2AR) in tumor cells and their microenvironment (e.g., in brain, lung, liver, stomach, colon, etc.); and (ii) the release of neurotrophic factors (e.g., in pancreatic cancer) that contribute to the formation of a specific vascular-related innervation pattern to provide neuroeffector catecholamine molecules that act through overexpressed B_2AR [16,17]. These abnormalities typically lead to the induction of the coupled signaling pathways, with increased cAMP as a second messenger activating further transducers, such as protein kinase A (PKA), focal adhesion kinase (FAK), MAPKs, p43/p44 kinases, and EGFR [18]. As a result, potentiation of antiapoptotic, proproliferatory, promigratory, and proinflammatory cell responses occurs [19]. In addition, excessive SNS signaling contributes to the angiogenic switch in malignancy, which results from catecholamine-induced alternations of endothelial cell metabolism. Such a relationship was confirmed in a mouse model of prostate cancer, in which inhibition of B_2AR signaling potentiated oxidative phosphorylation in endothelial cells via increased expression of the mitochondrial cytochrome c oxidase assembly factor COA6, leading to impaired angiogenesis and inhibition of progression [20]. Aside from the procarcinogenic effects described earlier, the accumulation of catecholamines in malignancy also has other negative consequences, such as the desensitization of human breast cancer cells to trastuzumab, as demonstrated by Liu *et al.* Interestingly, this effect was explained by the formation of a positive feedback loop between HER2 and B_2AR as well as by the B_2AR-mediated activation of the trastuzumab resistance-dependent PI3K/Akt/mTOR pathway [21]. Thus, normalization of SNS by the well-known cardiology drugs, β-blockers (BBs), was recognized as an interesting adjuvant strategy for the management of neoplastic conditions, especially those whose etiology is closely related to stress or those resistant to HER2-targeted therapy.

This hypothesis has been validated preclinically in several cancer models in which BBs (mainly nonselective) showed antimigratory, antiangiogenic, and antimetastatic actions, secondary to VEGF and MMP attenuation. This in turn suggested their potential to suppress primary tumors, indicating the treatment of early-stage diseases as their most likely clinical application [18]. Furthermore, because of their synergistic effect with gemcitabine

associated with an increased concentration of Bax and reduced Bcl-2, as confirmed in pancreatic cancer cells, BBs could also be used as adjuvants in chemotherapy [22]. Interestingly, several clinical studies confirmed these assumptions, especially in melanoma, breast, ovarian, lung and prostate cancers (reviewed in. [3,23]). In addition, improvements in progression-free survival (PFS) and overall survival (OS) rates were reported in patients with breast cancer treated simultaneously with trastuzumab and propranolol compared with trastuzumab alone, suggesting a beneficial effect of BBs in overcoming resistance to anti-HER2 agents [21]. However, other available clinical trials have provided contradictory results, suggesting no influence of BBs on patient outcomes, specifically in breast, prostate, lung, stomach and renal cancers [3,23,24], questioned our understanding of the role of BBs in malignancy. In addition, the available meta-analyses also remain inconsistent. Three of these analyses ([25–27]) found that BBs prolonged the survival of patients with cancer, whereas more recent analyses reported the opposite. For example, in a meta-analysis covering 36 case-control and cohort studies, Na *et al.* reported that BB use had no impact on general cancer prognosis either in early (I/II) or in advanced (III/IV) stages of the disease. However, a subgroup analysis showed an association between BBs and improved survival among patients with melanoma, ovarian, or pancreatic cancer [28]. Analogously, in a meta-analysis of 27 studies, Yap *et al.* concluded that BBs had no impact on general cancer recurrence. In subgroups, disease-free survival (DFS) and OS were improved in melanoma and ovarian cancer, but reduced in endometrial, head and neck, prostate, and lung cancer [29].

These inconsistencies indicate that the anticancer effect of BBs is variable and tumor specific. It is probably also agent specific, as indicated by the dominant overexpression of B_2AR, rather than of B_1AR, in malignancy. In this context, nonselective BBs, such as propranolol, which exhibit high affinity to B_2AR, have superior antineoplastic effects compared with B_1AR-selective atenolol, confirmed experimentally and as described earlier. However, carvedilol (an α and β-antagonist with slightly higher affinity to B_1AR) in a retrospective cohort study was also associated with reduced risk of upper gastrointestinal tract and lung cancer [30]. This disparity substantiates the need for the differentiation of BB pharmacodynamic subclasses in further dedicated clinical trials.

Statins and mevalonate pathway

Another group of cardiovascular agents that could facilitate the pharmacotherapy of neoplastic conditions is statins. The molecular mechanism underlying their eventual role in this area is interference with the formation of mevalonic acid, which further interrupts the biosynthesis of isoprenoids [i.e., farnesyl pyrophosphate (FPP) and geranyl-geranyl phosphate (GGPP)]. Both of these are essential for the biological activation of small G proteins, including Ras, Rac, and Rho, whereas their deficiency significantly disturbs the conjugated transduction pathways regulating proliferation, migration, cytoskeleton function, and death. Consistently with these assumptions, in preclinical studies using diverse cancer models, it has been shown that statins at conventionally applied doses decreased the proliferation and migration, and increased apoptosis of cancer cells, secondary to the following mechanisms: upregulation of proapoptotic BAX and Bim and downregulation of antiapoptotic BCL-2, activation of caspases, G(1)/S cell cycle arrest associated with upregulation of p21 or p53, abolishment of MAPK, suppression of RhoC, and reduction of HIF-1 [31–33]. The relationship between these molecular effects and small G proteins can be justified by the fact that the immediate products of HMG-CoA reductase (mevalonate, GGPP, and FPP) reversed the proapoptotic activity of statins in a preclinical setting, as evidenced in AML and colon cancer [34,35]. Furthermore, as shown in highly invasive breast cancer cell lines, statin-induced suppression of Rho geranylgeranylation influenced cell migration through disturbance of actin fibers and disappearance of focal adhesion sites, correlated with a reduction in MMP-9 and urokinase, and, ultimately, loss of cell attachment [36].

Based on these data, the prophylactic activity of statins was postulated; however, as in the case of ACE-Is, the conducted studies are controversial. For example, no association between cancer risk and statins use was reported in bladder, endometrial, kidney, lung, pancreatic, skin, and mixed malignancies [37]. By contrast, a positive correlation between statins and reduced cancer incidence was found in melanoma, gastric, liver, esophageal, ovarian, uterine, and prostate cancers [31,37]. Furthermore, Poynter *et al.* reported a 47% reduction of CRC incidence in patients taking statins, including high-risk patients with a family history of colorectal malignancy, inflammatory bowel disease, or hypercholesterolemia [38]. Similarly, the reduction of breast cancer risk was established to be as high as 72% in statin users versus nonusers [39]. Graaf *et al.* in turn specified that the general chemopreventive potential of statins remained significant only after 4 years of treatment or after consumption of more than 1350 defined daily doses [32].

In addition to chemoprevention, the therapeutic utility of statins has also been investigated. Here, the available data are also conflicting. In particular, a recent secondary analysis of two large clinical trials showed no association between statins and outcomes of patients with newly diagnosed glioblastoma [15]. In addition, statins combined with chemotherapy had no effect on treatment results in a large study involving 846 patients with lung cancer [40]. By contrast, their beneficial effect was observed in breast cancer, which was particularly explained by the increase in intracellular HMG-CoA reductase, which contributed to the maintenance of a less aggressive tumour phenotype and improved DFS. This study also emphasized the utility of HMG-CoA reductase as a prognostic marker for statin efficiency in breast cancer [41]. In addition, three meta-analyses measured the protective efficiency of statins (especially lipophilic) against breast cancer reoccurrence, showing a reduced rate of disease relapse among users versus nonusers [42,43]. In breast cancer, statin users also had improved OS, cancer-specific survival [43,44], and reduced all-cause mortality rates (lipophilic and hydrophilic statins) [44,45]. Similar conclusions were drawn for CRC and prostate cancer based on the results of a systematic review and meta-analysis of observational studies by Zhong *et al.* [45]. Moreover, a potential radiosensitizing effect of statins was observed in prostate cancer [46]. Thus, given the evidence supporting the concept of statin repurposing to oncology, prospective clinical trials on their role as adjuvant treatments for breast, prostate, and colon cancers are now anticipated.

Another aspect of statins reprofiling is their probable synergistic activity with known chemotherapeutic agents, suggesting their potential role as adjuvants in chemotherapy. In fact, available preclinical experiments showed that lovastatin enhanced the cytotoxicity 5-fluoarouracil and cisplatin in CRC, cisplatin in melanoma, paclitaxel in human leukaemia, and doxorubicin in

melanoma, colon and lung carcinoma. Additionally, lovastatin in combination with anthracyclines showed cardioprotective actions in animal models of the above-mentioned cancer types, whereas simvastatin reduced resistance to liposomal doxorubicin secondary to increased low-density lipoprotein (LDL) receptor expression and attenuation of drug efflux via glycoprotein P (P-gp) in a colon cancer model [47].

Some recent studies have also suggested that modifying the pharmaceutical form of statins by incorporating them in nanoparticulate drug delivery systems could improve their anticancer performance. For example, pravastatin encapsulated in long circulating liposomes was able to reduce murine melanoma tumor growth by 70% more than free pravastatin [33], whereas pravastatin-loaded chitosan nanoparticles were more cytotoxic than single pravastatin in a hepatocellular carcinoma model [48]. Furthermore, an increased antitumor effect was reported for atorvastatin and simvastatin when incorporated into a nanoparticle carrier in studies using melanoma, breast, and colon cancer models. However, these novel pharmaceutical forms still await validation in clinical trials [33].

Beyond anticoagulant

Subsequent agents capable of supporting anticancer treatment are LMWHs; here, the idea of their reprofiling was developed on the grounds of the recognized relationship between malignancy and thrombosis. Currently, LMWHs are recommended for the supportive care of patients with cancer as a first-line prophylaxis and treatment of thromboembolic events. Although their survival benefit in this indication remains controversial, as well as tumour and agent specific, their potential appears to reach far beyond their anticoagulant action [49]. In fact, it has been implied that heparin and its derivatives could exert a direct anticancer effect, underpinned mainly by antimetastatic mechanisms. This indicates that early-stage neoplasms would be most vulnerable to such treatment. The molecular foundations for their coagulation-dependent anticancer efficiency have been experimentally shown to involve attenuation of tissue factor (TF) downstream signaling, with consequent suppression of thrombin and fibrin, which are part of the tumor stroma. The decreased thrombin level, in turn, inhibits the release of VEGF and platelet factor-4 from platelets, and impairs angiogenesis [50,51]. By contrast, it was suggested that the coagulation-independent mechanism of LMWH action was associated with the regulation of metastatic process via inhibition of cancer cell adhesion mediated by selectins; attenuation of their CXCL12–CXCR4-mediated chemotaxis; inhibition of heparinase; and suppression of endothelial membrane transmigration, confirmed in animal studies [51]. However, none of the above mechanisms has been sufficiently documented and confirmed as yet.

The results from available clinical trials also remain inconclusive. In several trials, LMWHs (nadroparin and dalteparin) improved the survival of patients with nonmetastatic, early-stage malignancies at conventionally approved doses for thromboembolic prophylaxis (FAMOUS, MALT, CLOT, and PROTECHT studies) [50]. More recent analyses also demonstrated survival benefits in patients with small cell lung cancer using LMWHs [52]. In addition, the synergistic activity of dalteparin 5000 IU once daily with standard chemotherapy, including cyclophosphamide, epirubicin, and vincristine, in small cell lung cancer was reported [53]. Finally, in a comprehensive systemic review by Akl *et al.*, a small improvement in survival was noticed in patients with different cancer types using LMWH-based anticoagulant therapy, yet the routine application of these agents in patients with cancer for survival benefit without indications for thromboprophylaxis was questioned and depended on a risk-benefit evaluation [54]. By contrast, in many individual clinical trials, there was no correlation between LMWH and patient outcomes, especially in NSCLC, hormone-refractory prostate cancer, and locally advanced pancreatic cancer [52]. In addition, no improvement in OS was found in patients with small cell lung cancer using supraprophylactic doses of enoxaparin with standard chemotherapy, although the risk of venous thromboembolic events was significantly reduced [55]. Also, two recent meta-analyses demonstrated no survival gain in patients with solid tumors using LMWH [54,56].

Hence, four ongoing studies are now expected to clarify the role of LMWHs in the treatment of cancer in the following setting: enoxaparin with neoadjuvant chemoradiotherapy of nonmetastatic esophageal cancer (NCT03254511); long-term tinzaparin after surgical resection of CRC (NCT01455831); heparin, dexamethasone, floxuridine plus CapeOx or Folfox6 in an adjuvant setting after resection of liver metastases from CRC (NCT02529774); and desulfated heparin with standard induction and consolidation therapy for AML (NCT02873338).

Cardiac glycosides

Ultimately, CGs also exhibit pleiotropic anticancer activity, which makes them possible candidates for repurposing program in oncology. In fact, the primary rationale suggesting their potential link with neoplasia treatment has been identified as increased expression of their main pharmacodynamic target [sodium/potassium (Na^+/K^+)-ATPase] in several cancer models, such as NSCLC, gastric, bladder, and RCC [3,57]. In addition, further preclinical tests have shown that CGs exert reproducible, tumor-specific anticancer effects manifested in the activation of various modes of cell death, including apoptosis, autophagy, anoikis, and immunogenic cell death [57]. However, their exact mechanism of anticancer action remains unknown, given that the intermediate transducers integrating the final cell death response with (Na^+/K^+)-ATPase inhibition have not yet been elucidated [58]. Even so, their preclinically documented ability to eliminate malignant cells translated into the launch of trials assessing their chemo- and radiosensitizing potential. In this context, it was found that CGs increased the susceptibility of cancer cells to radiotherapy, especially in breast, lung, cervical, and prostate cancer cells [58,59]. However, for chemosensitization, the collected data were conflicting. Two reports confirmed their applicability in this area, showing a CG-dependent increase in cytotoxic activity of oxaliplatin in colon cancer cells [60] and sorafenib in hepatocellular carcinoma cells [61]. Digoxin also facilitated the antitumor effect of mitomycin C and cisplatin in immunocompetent mice, suggesting a local anticancer immune response based on the induction of immunogenic cell death [62]. By contrast, other studies suggested that digoxin counteracts cytotoxic activity, namely by reversing cell cycle arrest caused by paclitaxel, colchicine, vincristine, and vinblastine in human prostate cancer cells [63] as well as doxorubicin in colon cancer cells [64]. These observations were reliably explained by the CG-dependent upregulation of P-gp, which caused an efflux of chemotherapeutic agents. Furthermore, alter-

TABLE 1

Potential use of cardiology drugs in oncology based on available clinical and preclinical data

Drug type	Chemoprevention		Treatment		Refs
	Reduced risk	None or negative effect	Effective	None or negative effect	
ACE-Is	Female-specific, smoking-related, esophageal, pancreatic, colon cancer, mixed cancers	Hepatocellular carcinoma, prostate, esophageal, gastric cancer	Metastatic RCC with sunitinib, advanced and metastatic CRC, hepatocellular cancer, advanced gastric cancer advanced NSCL, pancreatic cancer with gemcitabine, glioblastoma with radiotherapy and temozolomide, prostate cancer with radio- and hormone therapy, prevention of wasting syndrome in patients with NSCLC or CRC patients, but not pancreatic cancer	Melanoma, MM, AML, esophageal, breast, lung and urinary tract cancers, glioblastoma	[3,5–11,15]
BBs (nonselective)	No data	No data	Early-stage melanoma, lung, breast, ovarian, pancreatic, and prostate cancer: potential of overcoming resistance to trastuzumab, potentiation of gemcitabine cytotoxicity	Stomach, renal, lung, colorectal, endometrial head and neck, prostate, and mixed cancer	[23–29]
Statins	Melanoma, CRC, gastric, liver esophageal, ovarian, uterine, and prostate cancer	Bladder, breast, endometrial, kidney, lung, pancreatic, skin, and mixed malignancies	Breast, CRC, and prostate cancer: potentiation of cytotoxic effect of standard chemotherapy, cardioprotective with anthracyclines	Glioblastoma, lung cancer	[15,37,40–46]
LMWHs	No data	No data	Early-stage mixed cancers, lung cancer	Advanced malignancies, NSCLC, hormone-refractory prostate cancer, and locally advanced pancreatic cancer	[50–55]
CGs	Hormone-dependent uterus and breast, and prostate cancer	Breast, prostate	No data	No data	[58–67]

nations of cationic balance secondary to (Na^+/K^+)-pump inhibition might have contributed to the observed abolition of cytotoxicity [58]. To conclude, these anomalies suggest that CGs should be used with extreme caution in patients undergoing chemotherapy, especially with agents that are known substrates of P-gp, until conclusive data on their utility in this area are obtained.

In addition, discrepancy in the available clinical results also exists. Early observational studies with digoxin provided promising suggestions that its use could reduce the recurrence rate, severity, and mortality of breast cancer. However, this was not reproduced in subsequent trials [58]. Furthermore, more recent meta-analyses and systemic reviews revealed a CG-associated increased risk of estrogen-sensitive malignancies, such as uterus and breast cancer, an effect attributed to their estrogenic activity [65]. By contrast, CGs did not affect the incidence of ovarian and cervical cancer [66]. In prostate cancer, results were contradictory, indicating both a decreased and increased risk of disease in digitoxin users [67]. Finally, a Phase I/II clinical trial in patients with advanced unresectable head and neck cancer is underway to investigate the potential synergistic activity of cisplatin and digoxin in inducing immunogenic cell death (NCT02906800). Thus, further trials are needed to verify the exact role of CGs in oncology, as well as to identify their most likely clinical indications.

Concluding remarks

The above discussion confirms that our understanding of the interactions between cancer and cardiovascular diseases is relatively limited and, hence, the potential of cardiology drugs in oncology remains clinically untapped. In fact, most available clinical data originate from retrospective and small prospective studies with a low level of evidence, which are potentially biased (summarized in Table 1). Therefore, no definitive recommendations can be made until directed, randomized, controlled trials are completed. However, given the unsatisfactory level of both the efficiency and safety of oncological treatments, no opportunity to acquire new therapeutic options should be missed, especially given the amount of positive preclinical and clinical observations in this field, which set the direction for further research.

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