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REVIEW ARTICLE

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Benefits of β-blockers in cancer treatment

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ABSTRACT

Cancer is one of the leading causes of death in the world. Researchers keep attempting to develop therapy modalities to decrease the mortality and morbidity of cancer patients by trying to comprehend the effect of sympathetic nerves (through catecholamine and adrenergic receptors) in cancer development. Catecholamine activation in β-adrenergic receptors (β1-AR, β2-AR, and β3-AR) may influence cytokine and cancer immunity system, initiate tumorigenesis, stimulate tumor-associated macrophage and angiogenesis, influence tumor microenvironment, and facilitate cancer cell metastasis, leading to increased progressivity of cancer cells. β-blockers may inhibit catecholamine on β-AR and various types of paths needed for cancer cells to develop. β-blockers also stimulate cancer cell apoptosis, decrease pro-inflammatory mediators and growth factors of cancer cells. In addition, β-blockers also have benefits as supplementary cancer therapy, increase chemoradiotherapy sensitivity, decrease cardiotoxicity, and improve cancer cachexia. The benefits of β-blockers are expected to reduce morbidity and increase the survival rates of cancer patients. This review comprehensively assesses the benefit of β-blockers as a part of the complete management of cancer patients.

Key words: catecholamine, β-blockers, cancer, therapy

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Introduction

Cancer is one of the leading causes of death in the world. Global Cancer Statistic estimated there were 19.3 million of new cases, and 10 million deaths of cancer found in 2020. Various therapy modalities have been developed to reduce cancer mortality and morbidity rates, however, the results are still not satisfactory [1]. Current research focuses on studying the role of sympathetic nerves (through catecholamine and adrenergic receptors) in cancer development [2].

The role of catecholamine and adrenaline in cancer progression is related to their receptors. Neurotransmitters of catecholamine epinephrine (EP) and norepinephrine (NE) are related to α-adrenergic receptor (α-AR) and β- adrenergic receptor (β-AR) [3]. β-AR consists of 3 types, β1-AR, β2-AR, and β3-AR. β-AR exists in almost all normal tissues of the human body. Interestingly, β-AR (especially β2-AR) expression increases significantly on the surface of some types of primary cancer cells (most strongly in melanoma, breast, esophagus, pancreas) and metastasis cancer cells. Activation of β-AR by catecholamine modulates the progression and proliferation of tumor cells [4]. In addition, activation of β-AR regulates the cellular metabolic process, which is related to initiation and progressivity of cancer cells, including cell inflammation, tissue angiogenesis, cell apoptosis, cell communication and movement, repair of damaged DNA, cancer-related cellular immune response, and cell epithelial-mesenchymal transition [5].

β-blockers are the adrenoceptor antagonist which inhibits the β-AR receptor. β-blockers are an inexpen-

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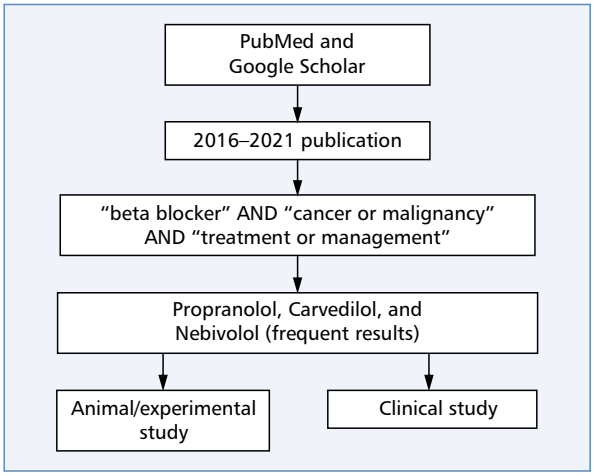

Figure 1. Flow chart illustrating article selection

sive drug, available throughout most of the world, with a relatively good drug safety profile [6]. β-blockers decrease the effect of catecholamine in human body cells [7]. Inhibition of beta-AR blockers slows down the progressivity of cancer progressivity of cancer and increases the survival rate of cancer patients [8]. The other beneficial effect of β-blockers is to prevent chemotherapy's side effects and increase the sensitivity of cancer cells to chemotherapy [9, 10]. The advantages of β-blockers as therapy in cancer management need to be studied further.

Methods

This literature review aimed to review recent developments and publications concerning the role of the *β-blocker* in cancer treatment. We reviewed all publications from the database of PubMed and Google Scholar published between 2016–2021 as illustrated in Figure 1. Older articles are included if they provide important information. First, we used the terms "catecholamine" AND "cancer or malignancy." Then, we continued using the terms "beta blocker" AND "cancer or malignancy" AND "treatment or management." We also searched for other specific keywords, such as "chemo-radiotherapy" OR "cardiotoxicity" OR "cancer cachexia" OR "survival."

Results

Catecholamine influences cytokine and cancer immune system

Catecholamine released during chronic stress influences immune response [11]. Stimulation of catecholamine on β-AR causes macrophage polarization (Fig 2.) and cytokine production and gives rise to the development and progressivity of breast cancer [12].

Chronic activation of β-AR signal on mice suppresses the activity and number of natural killer cells (NK cell), increasing the risk of cancer cell metastasis [13]. Activation of the β-AR signal also increases the expression of the anti-apoptotic protein molecule (BAD, BCL-2, and MCP-1) on tumor cells. Norepinephrine activates the path of transforming growth factor β (TGF-β) in cancer cells and increases the capability of distant metastasis [11, 14]. Norepinephrine also increases the chemotaxis ability of breast cancer cells for distant metastasis mediated by chemokine [15].

Catecholamine stimulates polarization of macrophage M2

The activation of β-AR by catecholamine strongly stimulates macrophage to polarize into macrophage M2 (Fig. 2). Stimulation of β-AR can reverse M1-like macrophages into M2. Decreasing the content of catecholamine in the body may reduce the polarization of macrophage into M2. M2 exists in a large number around tumor cells along with growing new tiny blood vessels that support the life of tumor cells [12, 16].

Catecholamine triggers tumorigenesis

DNA damage may trigger tumor formation [17]. The direct effect of catecholamine on cancer cells is to promote tumorigenesis, tumor cells proliferation, anti-apoptotic, and promote metastasis through the DNA damage pathway [18, 19]. The effect of catecholamine on β2-AR increases the degradation of p53 and causes DNA damage. This process occurs through arrestin beta 1 (ARRB1) pathways, protein kinase A (PKA), and activation of proto-oncogene Src and Her2 [20, 21].

Chronic activation of adrenoceptor by G-coupled protein may induce normal cells to have malignant transformation [22]. Prolonged exposure of norepinephrine and epinephrine to NIH3T3 cells (experiment mouse fibroblast cell) and murine 3T3 cells increases DNA damage, cell proliferation rate, and tumor formation. This shows that the normal cellular genes act as a proto-oncogene, which is the initial stage of tumor formation [20, 23]. Activation of PKA by β2-AR receptor will result in reactive oxygen species (ROS) which damages DNA. This study demonstrates that catecholamine induces DNA damage in normal cells and triggers cancer cell development [21].

Other evidence states that norepinephrine induces phosphorylation of voltage-dependent calcium channels (VDCC) L-type through the β-adrenergic receptor (β-AR) -PKA pathway. VDCC triggers calcium mobilization, inducing activation of IGF-1R through exocytosis of insulin-like growth factor (IGF2). Mice expressing

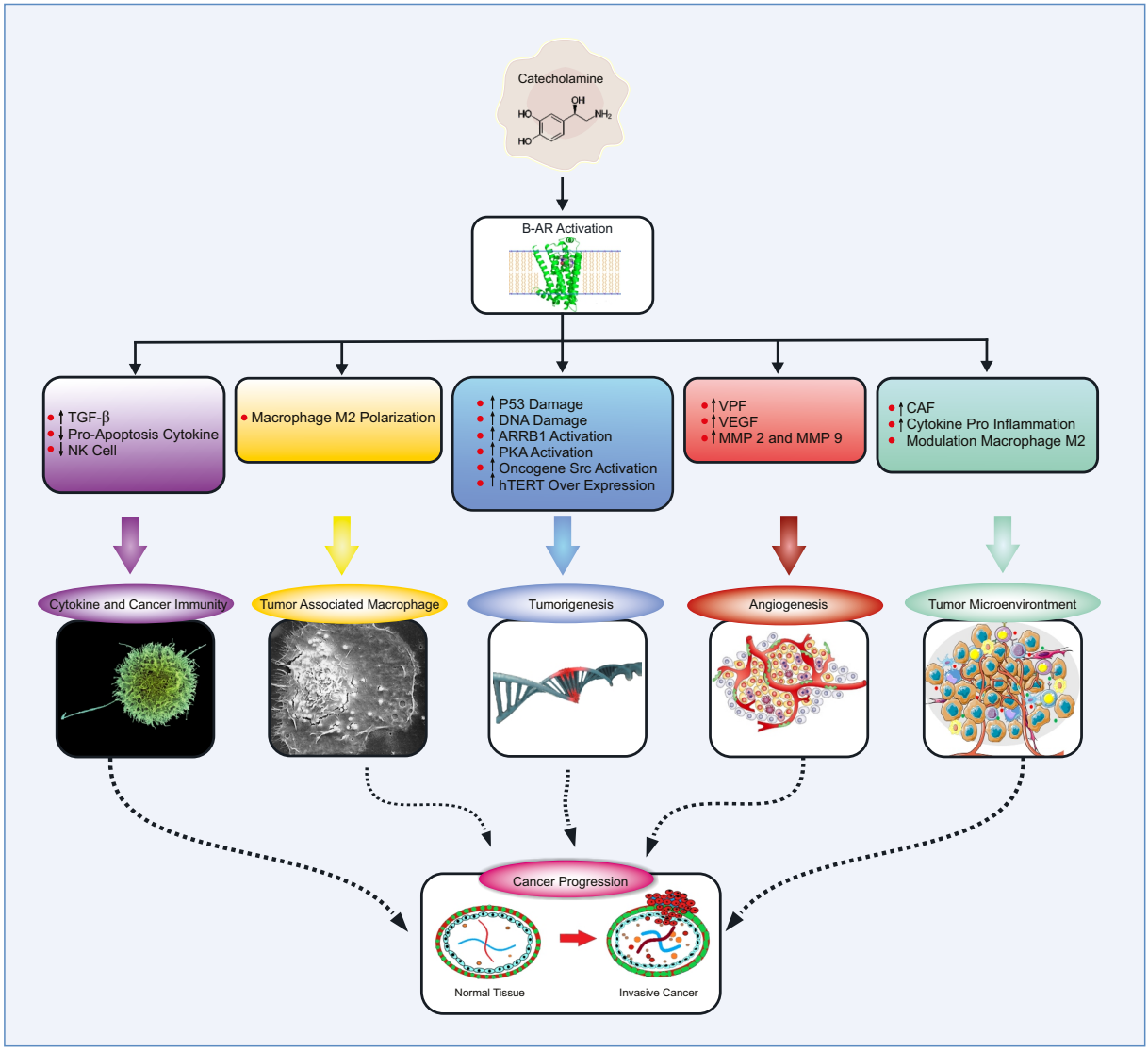

Figure 2. Catecholamine action towards cancer progressiveness; TGFb — tumor growth factor beta; NK cell — natural killer cell; ARRB — arrestin beta 1; PKA — protein kinase A; VPF — vascular permeability factor; VEGF — vascular endothelial growth factor; CAF — cancer-associated fibroblasts; hTERT — human telomerase reverse transcriptase; MMP — matrix metalloproteinase

lung-specific IGF-1R show faster development of lung tumors [24]. Norepinephrine also stimulates the expression of human telomerase reverse transcriptase (hTERT), which initiates cancer formation through epithelial-mesenchymal transition (EMT) [25].

Catecholamine influences angiogenesis

β-AR (β1-AR, β2-AR, and β3-AR) subtypes are expressed on the blood vessel of tumor tissue [26]. β2-AR activation by catecholamine on tumor cells increases the formation of proangiogenic factors [27]. Norepinephrine activates cAMP-protein kinase A (PKA), increases vascular permeability factor/vascular endothelial growth factor-A (VPF/VEGF) synthesis, and expression of matrix metalloprotease 2 (MMP 2) and MMP 9 are increased [28]. β2-AR also stimulates activation of Epac1 (exchange factor directly activated by cAMP1) and PKA that will increase vascular endothelial growth factor (VEGF) [29].

Activation of noradrenaline on β2-AR of endothelial cells is important to start the angiogenic process that triggers tumor cell growth. The removal of β2-AR on endothelial cells inhibits metabolic changes needed by the cancer cell angiogenesis process. Oxidative phosphorylation and formation of mitochondrial cytochrome C are also increased, and thus they inhibit angiogenesis and cancer cell growth [30].

Catecholamine influences tumor microenvironment

Neurotransmitter catecholamine of sympathetic nervous system modulates bone marrow cell microenvironment, thus increasing cancer cell progressivity [31]. Norepinephrine, through β3-AR, increases cancer-associated fibroblasts (CAF) activation, maintains pro-inflammatory cytokine secretion, which is important to maintain the tumor microenvironment. β3-AR also stimulates the mobilization of precursor cells (mesenchymal stem cells and endothelial precursor cells) of bone marrow into tumor cells. The precursor cells become adult CAF, which supports the inflammatory and angiogenesis processes of tumor cells [32]. β3-AR activation causes cancer cells to be more sensitive to environmental stimulation, namely hypoxia, nutritional availability, CAF count, and cancer-associated macrophages (CAM). The cascade described is like a vicious circle that will repair the microenvironment, inflammatory process, and cancer cell angiogenesis [33, 34].

Catecholamine also influences stromal cell-derived factor 1 (CXCL12) that serves to change the hematopoietic stem and progenitor cells (HSPCs) and bone marrow homing process. The microenvironment change is preferred as a place for cancer cell metastasis [35].

Catecholamine's role in cancer pathogenesis, as stated earlier, is that it influences cancer growth and development. Catecholamine action towards cancer progressiveness is presented in Figure 2. Inhibition of catecholamine receptors is also deemed to influence cancer progressivity. Thus, β-blockers, as the agonist of β-AR adrenoceptor, can be used to inhibit cancer development.

Effect of β-blockers on cancer

Denervation of tumor tissue stops catecholamine flow on β-AR in cancer cells, inhibiting the growth and spread of cancer cells. Administrating β-blockers also causes denervation of tumor tissue and inhibits the growth and spread of cancer cells [36, 37]. Catecholamines influence cancer development through their activity at β adrenergic receptors (β-AR 1, β-AR 2, and β-AR 3) [38]. In this article, we divide β-blockers (traditionally) into non-selective β-blockers and selective β-blockers. We used propranolol, carvedilol, and nebivolol as sample drugs in this study because they are representative of each type of β-blocker, and they are widely used in clinical practice and appear in our study search results. Propranolol represents an older non-selective β-blocker. Carvedilol represents a newer non-selective β-blocker. Nebivolol represents a selective β-blocker.

In this article, we divide the effect of β-blockers on cancer into experimental (*in vitro*) and clinical studies.

Effects of non-selective β-blockers in experimental cancer studies

Propranolol

The propranolol inhibition on β-AR is not selectively limited. This is beneficial since propranolol can inhibit catecholamine effects in every adrenergic receptor (β1-3AR) expressed by various cancer cells [4, 5].

Propranolol administration in an in-vitro study to some cancer types shows an inhibitory effect in various types of metabolic paths of cancer cells. Propranolol stimulates activation of poly (ADP-ribose) polymerase (enzyme serving to repair DNA, genome stability, and cell apoptosis) in liver cancer. Propranolol stimulates liver cancer cell apoptosis by influencing the expression of enzyme caspase-3 (the enzyme which disturbs the cell cycle until ceasing in phase S) [39]. Administration of propranolol to squamous cell carcinoma, induced by norepinephrine, decreases the cancer migration and invasion ability [40].

Melanoma patients present a good response to propranolol treatment [41, 42]. Propranolol decreases the level of VEGF, which plays a role in angiogenesis in melanoma cases. Propranolol also stimulates melanoma cell apoptosis by inducing phase G0/G1/S through the PKB/MAPK (protein kinase B/mitogen-activated protein kinase) pathway [43]. Ovary cancer cell apoptosis is stimulated by propranolol through inhibiting the cell life cycle at phase G2/M. The protein content of beclin-1 and p62 that stimulates the process of autophagy of ovary cancer cells is also increased by propranolol [44].

The administration of propranolol in in-vitro research of colorectal cancer cells decreases the level of Hypoxia-Inducible Factor1 α (HIF1α) and carbonic anhydrase IX (CA-IX). CA-IX is a protein that repairs the microenvironment of cancer cells and improves cancer cells for distant metastasis. Propranolol reduces the amount of protein involved in oxidative phosphorylation, which may potentially reduce the risk of distant metastasis in colorectal cancer cells [45].

Propranolol can process immunomodulatory cellular immune responses related to cancer. Propranolol increases IL-2, IL-4, IL-12, IL-17, and IFN-γ cytokines that can suppress breast cancer in experimental studies on animals [46]. Propranolol increases the number of CD 8+ cells and the expression of GzmB/IFN-γ/T-bet on CD 8+ cells in colon cancer tissue of experimental mice [47].

Carvedilol

Research on carvedilol as cancer therapy until recently has remained in vitro. Skin cancer model cells, JB6P+, show high expression of β2-AR. The administration of carvedilol may inhibit epidermal growth factor (EGF) and activator protein (AP1) needed by JB6P+

Table 1. Summaries of β-blockers benefit in inhibiting cancer progression (*in vitro* study)

Ref.	Drugs	Type of cancer	Mechanism	Outcome
[39]	Propranolol	Liver Cancer	↑ ADP-ribose polymerase cleavage ↑ induced S-phase arrest ↓ the expression of caspase-3	↑ apoptosis in liver cancer cell
[40]	Propranolol	Squamous Cell Carcinoma	↓ norepinephrine effects	↓ cell migration and invasiveness
[44]	Propranolol	Ovarian Cancer	↑ cell cycle arrest ↑ phosphorylation of JNK	induced cell cancer apoptosis and protective autophagy
[45]	Propranolol	Colon Cancer	↓ levels of HIF1α and carbonic anhydrase IX ↓ proteins in oxidative phosphorylation	↓ metastatic potential ↓ cells viability and proliferation
[46]	Propranolol	Breast cancer	↑ immunomodulatory cellular immune responses related to cancer ↑ IL-2, IL-4, IL-12, IL-17, and IFN-γ	↑ cellular immunity against cancer
[47]	Propranolol	Colon cancer	↑ CD 8+ cells ↑ expression of GzmB /IFN-γ/ /T-bet on CD 8+ cells	↑ cellular immunity against cancer
[48]	Carvedilol	Skin Cancer	↓ EGF ↓ activator protein-1	↑ skin cancer chemoprevention
[50]	Carvedilol	Skin Cancer	↓ UV-induced AP-1 and NF-kB activity.	↓ inflammatory activity skin cancer ↓ malignant transformation of skin cells
[51]	Carvedilol	Mammary Epithelial Cells	↓ ROS-mediated phosphoinositide 3-kinase/protein kinase B signaling	↓ the malignant proliferation of mammary epithelial cells
[52]	Nebivolol	Unspecific Cancer Cell	↓ mitochondria respiration ↓ oxidative phosphorylation ↓ ATP synthase activities ↓ VEGF	↓ tumor growth and tumor angiogenesis
[53]	Nebivolol	Oral squamous cell carcinoma	↑ endoplasmic reticulum stress ↑ expression of inducible nitric oxide synthase	↑ mitochondrial dysfunction and cancer cell growth arrest

cells to transform into malignant cells [48]. Carvedilol reduces anti-inflammatory activity by attenuating UV-induced AP-1 and NF-kB activity. It may inhibit the malignant transformation of skin cells because of exposure to ultraviolet light [49, 50].

Ductal carcinoma by exposure to strong carcinogen benzo(a)pyrene can be prevented by carvedilol through inhibition of ROS production which stimulates activation of the PI3K/AKT signal pathway (important signal of excessive cell growth) [51].

Effects of selective β-blockers in experimental cancer studies

Nebivolol

Research on selective β-blockers in inhibiting cancer progression in vitro is still very limited. In our search, nebivolol was a selective β-blocker that was frequently used in studies (though it is still rare). Nebivolol is a selective inhibitor of β1-AR and has a good effect on certain types of cancer. Nebivolol inhibits the use of glucose and palmitate in mitochondrial respiration of colorectal cancer, breast cancer, lung cancer, and ovary cancer cells. The utilization of inhibited glucose causes cancer cells not to produce ATP needed for cancer cell development [52]. Nebivolol downregulates VEGF2 receptor expression, needed in endothelial cell proliferation, inhibiting the cancer cell angiogenesis process. The life cycle of cancer cells is stopped by nebivolol by preventing activation of extracellular signal-regulated kinase (ERK) participating in cell cycle phase S [52]. In oral squamous cell carcinoma, nebivolol activates the endoplasmic reticulum (ER) stress signaling pathway by increasing the expression of inducible nitric oxide synthase. ER stress triggers mitochondrial dysfunction and cell growth arrest [53]. Only a few research studies have been conducted related to selective β-blockers on cancer cases since the inhibition is specific only to β1-AR. Summaries of β-blockers' benefits in inhibiting cancer progression are presented in Table 1.

Effects of non-selective β-blockers in clinical cancer studies

Propranolol

Propranolol is useful and shows good results in patients with various types of breast cancer. Propranolol administered to early-stage breast cancer patients, downregulates the expression of protein pro-proliferative Ki-67. Phosphorylation of mediator regulating splitting of cancer cells (p44/42 MAPK, p38 MAPK, JNK, and CREB) lower, while phosphorylation of mediator stimulating cancer cell apoptosis (AKT, p53, and GSK3β) increases [54].

Propranolol administered as adjuvant therapy to late-stage breast cancer patients (stage 3 or higher) downregulates the expression of protein pro-proliferative Ki-67 and protein pro-survival Bcl-2 and increases the expression of protein pro-apoptotic p53. Propranolol is useful to deal with local and far-spread breast cancer cells [55].

The use of propranolol before diagnosis reduces the risk of cancer stage progression compared to patients without a propranolol use history. The breast cancer-specific mortality level also decreases significantly for patients who use propranolol [56]. Propranolol administration 7 days before breast cancer operation, reduces the biomarker of pro-metastatic inflammation (Activator protein-1, Snail/Slug, NF-KB/Rel) [57]. Meanwhile, propranolol administration to triple-negative breast cancer patients increases recurrence-free survival and reduces metastasis risk. Progression-free survival of HER2-negative breast cancer patients in the late stage is better with propranolol administration. Propranolol also improves the sensitivity to trastuzumab therapy for HER2-positive breast cancer patients [58].

Propranolol administration in combination with etodolac perioperative (20 days) improves colorectal cancer marking molecules, covering reduction of epithelial to mesenchymal transition, tumor-infiltrating CD14+ monocytes, and CD19+ B cells, and increases the number of tumor natural killer cells CD56+ [59]. Propranolol prolongs time-to-discontinuation of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) and improves the overall survival of lung adenocarcinoma patients receiving first-line EGFR-TKIs therapy [60]. Propranolol also improves the overall survival of unresectable hepatocellular carcinoma patients [61].

Carvedilol

In a population-based study, long-term use of carvedilol has been shown to reduce the risk of gastric and lung cancer [62]. Nonselective β-blockers (including carvedilol) reduce the incidence of hepatocellular carcinoma in patients with liver cirrhosis [63]. Carvedilol also blocks neural regulation to reduce cancer-specific mortality in breast cancer [64].

Effects of selective β-blockers in clinical cancer studies

Our search shows that clinical studies of nebivolol are still limited. The benefits of selective β-blockers remain in the area of cardiotoxicity induced by chemo-radiation therapy (as mentioned in Table 2).

β-blocker administration does not only affect cancer progressivity in clinical cancer studies but also serves as an adjunctive for conservative clinical cancer therapy.

β-blockers increase the sensitivity of cancer cells to chemo-radiotherapy

Chemo-radiotherapy is the modality commonly used in cancer patient treatment. Stimulation of catecholamine increases cancer cell progressivity and may reduce the effect of chemotherapy drugs, such as doxorubicin, on cancer cells. Inhibition of doxorubicin's efficacy occurs through increasing expression of silent information regulator1 (Sirt-1) by catecholamine stimulation [10].

Administration of β-blockers increases the sensitivity of lung cancer cells to radiotherapy and drug cisplatin. Propranolol in combination with radiotherapy or cisplatin reduces the expression of phosphoprotein kinase A(p-PKA) that inhibits the survival of the clonogenic cells of lung adenocarcinoma compared to radiotherapy or cisplatin only [65]. The administration of propranolol to sarcoma increases the sensitivity to doxorubicin by changing drug metabolism in intracellular lysosomes. Propranolol inhibits the pump that releases doxorubicin to extracellular, increasing the level of intracellular doxorubicin and the ability of doxorubicin to damage the DNA of cancer cells [66]. Propranolol also increases the sensitivity to doxorubicin in myeloid leukemia cells [67].

Propranolol administered to experimental mice, increases the sensitivity of stomach cancer cells to radiotherapy. Propranolol reduces the expression of NF-κB, EGFR, VEGF, COX-2 in stomach cancer cells, becoming more sensitive to radiotherapy [68]. Propranolol and carvedilol can significantly reduce the number of fractions of a dog's osteosarcoma cells after 3 Gy radiation [69].

β-blockers increase the effectiveness of immune checkpoint inhibitors

β-blockers also serve to increase the effectiveness of immunotherapy. CD8+ cytotoxic T lymphocytes (CTLs) are one target of treatment through immune checkpoint

Table 2. Summaries of β-blockers benefit in clinical cancer study (in vivo study)

Ref.	Drugs	Type of cancer	Mechanism	Outcome
[54]	Propranolol	Early-stage breast cancer	↓ protein pro-proliferative Ki-67 ↓ Phosphorylation of mediator regulating splitting of cancer cells (p44/42 MAPK, p38 MAPK, JNK, and CREB) ↑ phosphorylation of mediator stimulating cancer cell apoptosis (AKT, p53, and GSK3β)	Reduces tumor proliferative index
[55]	Propranolol	Late-stage breast cancer	↓ protein pro-proliferative Ki-67 ↓ protein pro-survival Bcl-2 ↑ expression of protein pro-apoptotic p53	↓ cancer cell cycle progression ↑ cell apoptotic
[56, 58]	Propranolol	Breast cancer	–	↓ metastasis development ↓ tumor recurrence ↑ disease-free interval
[59]	Propranolol with etodolac	Colorectal	↓ epithelial to mesenchymal transition ↓ tumor-infiltrating CD14+ and CD19+ B cells, ↑ tumor natural killer cells CD56+	Improve colorectal cancer marking molecules
[60]	Propranolol	Lung adenocarcinoma	–	↑ time-to-discontinuation (EGFR-TKIs) and ↑ overall survival of lung adenocarcinoma
[62]	Carvedilol	Gastric and lung cancer	–	↓ risk of gastric and lung cancer
[63]	Nonselective β-blockers (including carvedilol)	HCC	–	↓ incidence of HCC in liver cirrhosis
[64]	Carvedilol	Breast cancer	Blocks neural regulation	↓ cancer-specific mortality ↓ Tumor growth

HCC — hepatocellular carcinoma

inhibitors (ICI). The lymphocyte cells kill cancer cells that represent major histocompatibility complex molecules MHC class 1 [70]. On the other hand, activation of β-AR in CD8+ CTLs cells reduces cells' ability to kill cancer cells, reducing interferon proliferation and production ability. The administration of β-blockers increases CD8+ CTLs count [71]. Non-small cell lung cancer patients receiving ICI therapy in combination with β-blockers show improved progression-free survival [72].

β-blockers prevent cardiotoxic effects of chemo-radiotherapy

Anthracycline is a chemotherapy drug with a cardiotoxic effect. Anthracycline causes increased reactive oxygen species (ROS) accumulated in cardiac muscle mitochondria [73]. β-blockers (carvedilol and nebivolol) serve as an antioxidant that reduces oxidative stress in cardiac muscle, preventing damage to the heart because of anthracycline [74, 75].

Carvedilol prevents reduction of left ventricular ejection fraction (LVEF), prevents diastolic dysfunction, and cardiac remodeling. Carvedilol reduces markers of heart damage in patients receiving anthracycline or trastuzumab therapy [76–79].

Nebivolol prevents reduction of myocardial velocities and deformation of the ventricular muscle structure of breast cancer patients receiving doxorubicin therapy [80]. This protective effect is caused by its ability to modulate caspase-3, e/i NOS, and TNF alpha that prevents apoptosis in cardiac muscle [81]. Nebivolol also increases nitrite oxide content serving as an antioxidant [82].

Radiotherapy in the breast area can also cause cardiotoxicity. This damage includes cardiomyopathy, acceleration of formation of atherosclerosis, fibrosis pericardial valve and tissue, and cardiac conduction disorder [83]. These damages can generally be treated using β-blockers [84, 85].

Table 3. Summaries of β-blockers improve cancer survival

Ref.	Drugs	Type of cancer	Type of study	Outcome
[93]	β-blocker	–	Systematic review and meta-analysis	↓ all-cause mortality
[94]	β-blocker	–	Meta-analysis	↑ overall survival ↑ disease-free survival
[95]	β-blocker	Ovary cancer, pancreas cancer, breast cancer, and melanoma	Meta-analysis	↑ cancer-specific survival
[96]	β-blocker	Breast cancer	Retrospective	↑ disease-free interval
[61]	Propranolol	Unresectable HCC	Population-based study	↓ mortality risk

HCC — hepatocellular carcinoma

β-blockers prevent cancer cachexia

There is currently no specific therapy for cancer cachexia. One modality proposed as cancer cachexia therapy is to administer β-blockers [86, 87]. Cancer cachexia, besides extremely reducing muscle mass, also causes a reduction of cardiac muscle mass (cardiac cachexia). Cardiac cachexia makes it more difficult to treat the effect of chemotherapy-induced cardiotoxicity [88, 89]. β-blockers (particularly selective β1-blockers) prevent worsening cardiac cachexia [90, 91]. Espindolol increases body weight and body fat proportion in colorectal and lung cancer patients. The effect of Espindolol is related to its ability to reduce metabolism (nonselective inhibition on β-AR), reduce fatigue and thermogenesis (as an agonist of central 5-HT1α receptors), and pro-anabolic effect (as a partial agonist of β-2 receptors) [92].

β-blockers and cancer survival

Our review shows that β-blockers, especially nonselective β-blockers, are beneficial in improving overall survival by preventing cancer progression and as adjunctive therapy to conventional cancer therapy (as listed in Table 3). However, studies are not consistent in showing that β-blockers have improved overall survival (OS).

Meta-analysis research shows that β-blockers reduce the hazard ratio of all-cause mortality of cancer patients [93] and increase the overall survival and disease-free survival of cancer patients (particularly ovary cancer, pancreas cancer, breast cancer, and melanoma) [94, 95]. Administration of β-blockers to breast cancer patients significantly reduces metastasis occurrence, cancer recurrence, and longer disease-free intervals [96].

The research conducted by Na et al. states, conversely, that there is no evidence showing the correlation between the use of β-blocker and overall survival, all-cause mortality, disease-free survival, progression-free survival, and recurrence-free survival for cancer patients. The varied results are caused by different study designs, different drug working methods, type and stages of cancer, too heterogeneous sample population, and time of β-blocker administration [93, 97]. The other reasons are due to the progression of cancer through various molecular pathways, not only through the catecholamine pathway [98, 99]. In addition, many exogen factors affect cancer mortality/overall survival (i.e depression, economy, delayed treatment, surgery, nutrition) [100]. Another confounder that may influence the difference in the result of research on β-blockers in the survival of cancer patients is immortal time bias (ITB). ITB may cause the result of survival-related research to seem better. Meta-analysis and systematic review researches excluding ITB influence in their studies on the influence of β-blockers on cancer survival show insignificant results [101, 102].

Conclusion

Administrating β-blockers inhibits catecholamine activation through β adrenoceptors (β1-AR, β2-AR, and β3-AR), so that cancer cell formation, progression, and metastasis are inhibited. β-blockers are also useful as adjunctive therapy to prevent cancer cachexia, chemoradiotherapy-related cardiotoxicity, and can increase the sensitivity to immune checkpoint inhibitors and chemoradiotherapy. The benefits of β-blockers will be stronger when they are applied to cancers that strongly express β adrenergic receptors (e.g. melanoma, breast cancer). Non-selective β-blockers are superior to selective β-blockers since they block all three types of β adrenergic receptors.

Conflict of interest

Authors declare no conflict of interest.

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