Recent Studies & Advances in Breast Cancer

Chapter 5

Potential use of Antihistamines on Cancer treatment

A.I. Faustino-Rocha[1,2], M. Ginja[2,3], A. Gama[3,4], R. Ferreira[5], P.A. Oliveira[2,3]

[1] Faculty of Veterinary Medicine, Lusophone University of Humanities and Technologies, Lisbon, Portugal

[2] Center for the Research and Technology of Agro-Environmental and Biological Sciences (CITAB), University of Trás-os-Montes and Alto Douro, Vila Real, Portugal

[3] Department of Veterinary Sciences, School of Agrarian and Veterinary Sciences, University of Trás-os-Montes and Alto Douro, Vila Real, Portugal

[4] Animal and Veterinary Research Center (CECAV), University of Trás-os-Montes and Alto Douro, Vila Real, Portugal

[5] Organic Chemistry, Natural Products and Foodstuffs (QOPNA), Mass Spectrometry Center, University of Aveiro, Aveiro, Portugal

Correspondence to: A.I. Faustino-Rocha, *Center for the Research and Technology of Agro-Environmental and Biological Sciences (CITAB), University of Trás-os-Montes and Alto Douro, Vila Real, Portugal*

Phone: 00351 968914559; Email: anafaustino.faustino@sapo.pt

Abstract

Cancer is one of the most frightening diseases worldwide. Several medical options are available for breast cancer treatment, such as surgery, radiotherapy, chemotherapy, hormone therapy and immunotherapy. However, the possible ineffectiveness, the distinct response of cancer to the therapies and the devastating effects of some of these therapies for patients are the major concerns in cancer treatment. So, it is crucial to search for new or at least adjuvant therapies that may improve the lifespan and quality of life of oncologic patients. Antihistamines are one of the most frequently prescribed drugs worldwide. Since the histamine receptors are present in neoplastic cells of several tumors, and the antihistamines have low toxicity and are cheaper when compared with drugs used in chemotherapy, the antihistaminic drugs may be potentially used in the clinical management of oncologic patients.

Keywords: Antihistaminic drugs; Cancer; Histamine; Mast cells

1. Introduction

Cancer is one of the most frightening diseases worldwide, constituting a major public health concern [1]. Approximately 14 million of new cases and 8.2 million cancer deaths were recorded in 2012. Disappointing projections are being pointed for the next years, with an increase in the number of new cancer cases *per* year to 22 million over the next two decades [2].

Cancer may affect any part of the body, until now more than 100 types of cancer were described. Lung, prostate, colorectal, stomach and liver are the most common sites of cancer development in men, while breast, colorectal, lung, cervix and stomach are the organs mainly affected by cancer in women [1].

Cancer is a complex and multistage disease, progressing over several years. It may be divided into four different, but related stages: **initiation, promotion, progression** and **metastization** [3-5]. Cancer initiates with an irreversible deoxyribonucleic acid (DNA) - damage in a cell leading to the conversion of a normal cell into an initiated one. This DNA damage may occur spontaneously or may be induced by physical agents (gamma radiation, X-rays), chemical compounds (arsenic, asbestos, 7,12-Dimethylbenz (a) anthracene (DMBA), Diethylnitrosamine, N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN), N-methyl-N-nitrosourea (MNU), tobacco) or biological agents (papillomavirus, hepatitis virus, *Schistosoma haematobium, Helicobacter pylori, Clonorchis sinensis*). Once initiated, the cell grows and divide in an uncontrolled way as a consequence of cumulated abnormalities, originating a population of preneoplastic cells (promotion). The promotion is a relatively long process during which tumor growth may be modulated through different therapeutic strategies, like chemotherapy, immunotherapy, surgery or radiotherapy. A fast increase in tumor size and the conversion of preneoplastic cells into neoplastic ones occurs during progression, as a consequence of additional genetic changes. In the last step of carcinogenesis (metastization) is observed a migration of cancer cells from primary tumor to distant organs through blood or lymphatic system. The capacity to metastasize is exclusive of malignant tumors, despite this not all malignant tumors metastasize [6,7].

Since the success of cancer treatment and prognosis is intimately related to its early detection, screening programs are running in several countries worldwide in order to reduce cancer mortality [8,9]. Although several therapeutic approaches are available for cancer treatment, like surgery, radiotherapy, chemotherapy and immunotherapy, due to the distinct and unpredictable response of cancer to the therapies, the devastating effects of some of these therapies for patients and their ineffectiveness, arises the need to search for new or at least adjuvant therapeutic approaches that may improve the quality of life and lifespan of oncologic

patients [10].

2. Tumor Microenvironment

Cancers are complex organs composed not only of neoplastic cells, but also of other cells that are recruited to tumor microenvironment and may be changed by the transformed cells [11]. Among the non-malignant cells of tumor microenvironment are lymphatic and vascular endothelial cells, pericytes, adipocytes, mesenchymal stem cells, smooth muscle cells, fibroblasts, myofibroblasts, myeloid cells and inflammatory cells (B and T lymphocytes, neutrophils, dendritic cells, eosinophils, basophils, natural killer cells, macrophages and mast cells) [5,12]. These cells may be easily identified in the tumor microenvironment by their specific surface molecules [13]. They synthesize cytokines, reactive oxygen species (ROS), serine and cysteine proteases, metalloproteinases, growth and pro-angiogenic factors, inflammatory and matrix remodeling enzymes, chemokines, and adhesion molecules, acting as a tumor-promoting at all stages of carcinogenesis [14-17]. Taking this into account, targeting the non-malignant cells of tumor microenvironment or their mediators of communication may be used in cancer treatment.

3. Mast Cells

Mast cells are bone marrow derived leukocytes that were first described by Paul Ehrlich more than 130 years ago in his PhD thesis [18]. Since they were identified in all members of vertebrate family [19] and they may be found near common portals of infection, such as skin, gastrointestinal tract, urinary tract and respiratory tract, some authors consider them primitive cells, maybe the surviving remnant of an ancient model of the immune system [20]. Mast cells are not found in avascular tissues like cartilage, mineralized bone and cornea [21].

Inversely to other cells, leaving the bone marrow as fully matured cells, mast cells stem from non-granulated cells (immature precursors) that leave the bone marrow to circulate in the blood [22-24]. Then these precursors migrate into different tissues where they proliferate and differentiate into granulated cells (fully mature cells) through the linkage of microenvironment growth factors, like stem cell factor (SCF), to the c-kit receptor [25-27]. Previous studies observed a low number of mast cells in mice with a defective surface expression or catalytic activity of c-kit when compared with normal animals [28].

Mast cells have the ability to synthesize, store and release several molecules like histamine, serotonin, heparin, chondroitin sulphate peptidoglycans, tryptase, chymase, carboxypeptidase, tumor-necrosis factor (TNF), vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF2), leukotriene (LT) C4, LTB4, prostaglandin D2, prostaglandin E2, platelet-activating factor, interleukins (IL-1α, IL-1β, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12, IL-13, IL-15, IL-16, IL-18), interferon (IFN-α, IFN-β, IFN-γ), chemokins, nitric oxide, oxide

radicals and antimicrobial peptides [29,30].

Mast cells are activated via cross-linking of the cell surface receptor FcεRI and consequent activation of phosphorylation cascades, calcium influx and nuclear importation of transcriptase factors [31,32]. Upon mast cells activation, the granules content may be released from the cell to the exterior through two distinct processes: exocytosis also called anaphylactic degranulation (quick and massive release of granules' content occurring during type I allergic reactions) or piecemeal degranulation (selective release of granules' content occurring in chronic inflammatory processes like cancer) [20,33].

Depending on their location, rodent mast cells may be divided into two groups: connective mast cells (CTMCs) and mucosal mast cells (MMCs). CTMCs are mainly placed in connective tissue and only require SCF for their survival, while MMCs may be mainly found in mucosal tissues and require T-cell derived cytokines additionally to the SCF for their activation [28,34].

Mast cells are involved in several processes, like tissue remodeling, wound healing, fibrosis and angiogenesis. They have also an important role in the central nervous system where the histamine acts as a neurotransmitter [35,36]. Microscopically, they are seen as round to elongated cells with non-segmented monolobed nucleus with condensed chromatin in the periphery [20]. Mast cells may be easily identified in toluidine blue staining by their dark purple granules that fill the cytoplasm. Fully granulated mast cells may contain up to 1000 secretory granules occupying almost half of their cytoplasm [37].

3.1. Mast cells and cancer

Mast cells have been historically associated with response to parasites and bacteria, atopic diseases, allergic reactions and anaphylaxis [38,39]. Indeed, they are important sentinels of the immune system, interacting with invading pathogenic agents [38,40]. The knowledge of mast cells was increasing over the years and currently they are considered versatile tissue elements that play an important role in several biological processes, namely in angiogenesis, immune modulation, tissue repair and remodeling, and cancer [41,42].

Although the mast cells infiltration in carcinomatous tumors was first described by Westphal in 1891, the role of these cells on cancer remains unclear [43,44]. Our research team also identified a mixed inflammatory infiltrate composed of numerous mast cells and less abundant lymphocytes in mammary tumors and urinary bladder tumors chemically-induced by the administration of the carcinogenic agents MNU and BBN in a rodent model, respectively [45,46]. The increase of the number of mast cells in the cancer microenvironment occurs not only due to the migration of mast cell precursors from the blood, but also due to the in situ division of the few mature mast cells [47]. Mast cells degranulation in tumor microenvironment

is activated by stimuli like alarmins, hypoxia, chemokins and cytokines [48].

Previous studies suggest that mast cells may exert a bivalent role on cancer, exerting both pro-tumor (extracellular matrix degradation, angiogenesis and immune suppression) and anti-tumor effects (immune cell recruitment and activation, and cytotoxic activity) [48]. In this way, the overall impact of mast cells infiltration in tumor microenvironment is unknown. The mast cells infiltration is linked with cancer mainly due to the release of potent angiogenic compounds, namely tryptase, chymase, FGF and VEGF [49]. According to Groot *et al.* [50], the mast cells density is an indicator of poor prognosis in different types of cancer, namely in melanoma, Hodgkin's lymphoma, esophageal, lung, prostate, cervical, endometrial, gastric and colorectal carcinomas. The mast cells into action on cancer may be controlled by the regulation of the number of mast cells or by the inhibition of their action (inhibition of mast cells' content release through the administration of a mast cell stabilizer drug or inhibition of the linkage of releasing substances, like histamine, to their receptors.)

4. Histamine

Histamine was discovered and classified as a biogenic amine in 1910 by Henry Dale and Patrick Laidlaw [51]. It is an endogenous physiological substance also called 2-(4-imidazolyl)ethylamine or 5b-amino-ethylimidazole. Histamine is synthetizedby the enzyme L-histidine decarboxylase from the amino acid histidine [52]. Although the mast cells are the main source of histamine, after synthetization it is stored within cytoplasmic granules or vesicles of other cells, namely platelets, enterochromaffin cells, lymphocytes and histaminergic neurons [53,54]. After release into the extracellular microenvironment, histamine has a half-life of approximately one minute, being then degraded by the enzymes *N*-methyltransferase and diamine oxidase [19]. The histamine may be found in all mammary tissues, ranging from less than 1 μg/g to higher than 100 μg/g. High histamine concentrations may be found in lung, gastrointestinal tract, connective tissue and skin [55]. The serum and tissue levels of histamine may be assessed by radio-enzymatic and fluorometric techniques [55].

Histamine is since early associated with allergic reactions. Indeed, high quantities of histamine are released by mast cells during the acute phase of allergic diseases, promoting vasodilation, endothelial permeability, stimulating sensory nerves and promoting smooth muscle contraction [57-60,63]. The histamine is responsible for the clinical manifestations of allergic disease, like edema, rhinitis, sneezing, itching, rhinorrhea, nose obstruction, skin erythema, pruritus and urticaria [57-60,64]. Histamine is also responsible for the activation of inflammatory cells, namely eosinophils and basophils, and release of proinflammatory mediators in chronic allergic inflammation [57]. Furthermore, histamine is involved in several physiological and pathophysiological processes, namely in conjunctivitis, atopic disorders, bronchoconstriction, urticaria, anaphylaxis, asthma, gastric acid secretion, mucus secretion, increase of

vasopermeabilization, stimulation of cardiac contraction, contraction of smooth muscle from the gut and respiratory tract [51,56-60]. It also induces shock-like syndrome when injected in animals and was recognized as a stimulator of the acid secretion in the stomach,and a mediator of anaphylactic and allergic reactions [51,52,56,61,62].

High levels of histamine and high activity of the enzyme L-histidine decarboxylase were observed in several tumors, namely in breast, endometrial, colon and small cell lung cancer, and melanoma [65-72]. Higher blood levels of histamine were found in human patients with breast, prostate and lung malignant tumor, when compared with healthy people. It was also observed a decrease in the histamine levels close to normal levels within three months after surgery [73].

According to some authors, the effects of histamine on carcinogenesis depends on its concentration. Studies on mammary carcinogenesis chemically-induced by the carcinogen MNU in female rats observed that histamine levels up to 50 nM promoted tumor cells proliferation, while higher concentrations inhibited tumor growth [74]. Similarly, the stimulation of human pancreatic carcinoma PANC-1 cells with low levels of histamine (0.01μM) increased tumor cells proliferation, while the stimulation with higher concentrations (10 μM) decreased cells proliferation [75].

4.1. Histamine receptors

Histamine acts by binding to and activating four specific receptors, known as histamine receptors: H1, H2, H3 and H4, which are expressed in several cells and tissues (**Table 1**) [57,64]. Biochemically, these receptors belong to the family of hepatahelical G protein-coupled receptors family [76,77]. These histamine receptors were also identified by genomics-based approaches in human tumors, namely in lymphoma, leukemia, melanoma, breast, cervical, ovarian, vaginal, uterine, vulvar and colorectal cancer [77].

The activation of different histamine receptors is responsible for different physiological reactions. The activation of H1 receptors lead to the activation of pathways that trigger several symptoms of allergy, like pruritus, bronchoconstriction, edema, rhinorrhea and smooth muscle contraction [55,78]. H2 receptors activation promotes gastric acid secretion, and in low grade vasodilation [77,79]. The activation of H3 receptors is responsible for the regulation of pruritus, inhibition of excessive bronchoconstriction and the control of release and synthesis of histamine and other neurotransmitters, such as dopamine, serotonin, noradrenaline, γ-aminobutyric acid and acetylcholine [55,80-83]. H4 receptors induce chemotaxis, regulate the differentiation of promyelocytes and myeloblasts, and have an important role in chronic inflammatory diseases of the skin [55,84-86].

4.2. Antihistaminic drugs

Antihistamines are inverse agonists that inhibit the linkage of histamine to its receptors [57,87]. They have a molecular structure similar to the histamine with which they compete [88]. The first antihistamine was synthetized by Staub and Bovet in 1937 [89]. Phenbenzamine was the first antihistamine applied in humans in 1942 for the treatment of allergies and skin conditions, like pruritus and irritation [55]. Since then, the antihistamines have been routinely used for the treatment of several clinical conditions, namely motion sickness, insomnia, vertigo, and allergic diseases (contact dermatitis, atopic dermatitis, dermatoses, rhinitis, allergic conjunctivitis, mild transfusion reactions, urticarial and hypersensitivity reactions to drugs) [53,57,90,91]. The effects of antihistamines vary among patients [57]. Despite their safety and appropriate use are not fully clarified, the antihistamines are frequently used in children and adults [57,92,93]. The knowledge of antihistamines pharmacokinetics and pharmacodynamics is essential to their correct use [57,92,93]. Their dose should be adjusted in patients with renal or hepatic diseases [92].

Antihistamines may be administered orally or topically applied [90,94]. Antihistamines have a good absorption and reach the plasma concentration within three hours after oral administration [85]. They are mainly biotransformed in the liver by the cytochrome enzyme system (CYP) [95-99]. The simultaneous administration of antihistamines and grapefruit juice change their plasmatic concentration due to the blockage of cytochrome P450 (CYP3A4) [85,95]. The metabolic products of antihistamines are excreted by the kidneys and eliminated in the urine [57,92]. Some antihistamines are eliminated in the feces after biliary excretion, without metabolic alterations [92].

Concerning to their pharmacodynamics, antihistamines may inhibit the action of histamine through the inhibition of the activity of enzyme L-histidine descarboxylase or by the blockage of histamine receptors (acting as inverse agonists) [100]. Some antihistamines, such as desloratadine and ketotiken, have also the ability to stabilize the mast cells' membrane, inhibiting their degranulation [57,101-104]. Antihistamines also inhibit the accumulation of inflammatory cells and their activation, exerting an anti-inflammatory activity [105].

4.3. Antihistamines classes

Considering their chemical structure, H1-antihistamines may be categorized into six groups: alkylamines, ethanolamines, ethylenediamines, phenotiazines, piperazines and piperidines [53,64,106–108] (**Table 2**). According to their toxic properties and side effects, H1-antihistamines may be subdivided into first-generation or second-generation antihistamines [57,92]. The first generation antihistamines affect the cognitive performance of people and prejudice daytime activities that require high concentration, because they cause sedation, incoordination, vertigo, agitation, excitability and lack of concentration. These effects occur due to

their low molecular weight, high liposolubility, their ability to easily cross the blood-brain barrier and high affinity to the H1-receptors of the brain [57,107]. Additionally to the inhibition of H1 receptors, H1-antihistamines also inhibit muscarinic and adrenergic receptors, causing urinary retention, blurred vision, hypotension, tachycardia, and drying of mouth and nasal secretions [57,85]. The first-generation antihistamines have a short half-life, being necessary the administration of multiple daily doses [107,108]. When compared with the second-generation antihistamines, the first-generation ones are less expensive [93].

The second-generation antihistamines, frequently named newer antihistamines, were developed in early 1980's to overlap the side effects of the first-generation antihistamines [107]. Conversely to the first-generation antihistamines, the second-generation antihistamines have a high specificity to H1-receptos and low affinity to non-histamine receptors, such as adrenergic and muscarinic receptors [57,95,107,109]. The second-generation antihistamines have a high molecular weight, they are low liposoluble and have a low affinity to the cerebral H1 receptors, being unprovided of effects on central nervous system when administered at therapeutic doses [57].When administered in high doses, these second-generation antihistamines may have sedative effects [57]. These antihistamines have a longer half-life when compared with first-generation antihistamines, allowing the administration of less doses (one or two doses daily) [95,107,109]. The third generation antihistamines were created as an attempt to improve clinical efficacy and minimize adverse effects of the first and second-generation antihistamines [106]. However, since they are active metabolites of first-generation antihistamines, their definition as a class is not consensual among the scientific community [57].

H2-antihistamines are frequently used in the prophylaxis of conditions where there is high gastric acidity and in the treatment of gastroesophageal reflux disease and duodenal ulcers [110]. Due to the interaction with H2-receptors, the H2-antihistamines may have a modulatory effect on immune system [110] (**Table 2**).

5. Potential use of Mast Cells and Antihistamines on Cancer Treatment

Mast cells, which are the main source of histamine, migrate into the tumor during the carcinogenesis, constituting one of the major non-neoplastic cell population of tumor microenvironment [111]. Despite this, the role of mast cells on cancer is not fully understood. If in one hand, some researchers suggest that the substances released by mast cells promote carcinogenesis by promoting tumor growth, angiogenesis, invasion and host immunosuppression, other researchers suggest that these substances have beneficial effects for the host by inhibiting tumor growth, inducing apoptosis, inhibiting tumor metastization and stimulating immune system [20]. The mast cells degranulation may be inhibited by antihistamine drugs, namely by the use of ketotifen that not only acts as antihistamine drug by inhibiting the linkage of histamine to its receptors, but also stabilizes mast cells' membranes inhibiting their degranulation. The

use of this antihistaminic drug may be a promisor therapeutic approach on cancer treatment.

The relation between the use of antihistaminic drugs and cancer risk development has intrigued the researchers. Indeed, it was observed in several studies that the aminoethyl ether group of antihistamines is structurally similar to N,N-diethyl-2-(4-(phenylmethyl) phenoxy) ethanamine HCl (DPPE) that is a tamoxifen derivative known to inhibit the *in vitro* growth of MCF-7 breast cancer cells [90,112,113].

In this way, investigators have studied this association with distinct results [114]. Nadalin and coworkers [90] enquired 3,133 women with breast cancer and 3,062 healthy women ranging from 25 to 74 years-old about the regular use of antihistamines, and they found no association between the antihistamines use and the risk of breast cancer development. Kelly and coworkers [115] also studied the association between antihistamines and breast cancer risk in 5,814 women with invasive breast cancer and in 5,095 healthy women between 18 and 69 years of age, finding no association between antihistamines use and cancer development [115].

The association of antihistamines exposition for a long period of time with the development of glioma is also contradictory. If according to some studies the antihistamines use promotes glioma development [116-120], Scheurer and colleagues [121] verified that the risk of glioma development is reduced with the exposition of antihistamines. Is was observed by several researchers that the use of antihistamines inhibit the growth of colorectal cancer [122], human melanoma [123], and leukemic [124] cell lines.

It was observed that C-3 fibrosarcoma and B16F10 melanoma cell lines injected in a syngeneic mice model grown quickly after the administration of human equivalent doses of the H1-antihistamines loratadine and astemizole (for both tumors) and hydroxyzine (for melanoma only), they also verified that doxylamine and cetirizine did not change the growth of any cell lines [113]. It was observed that hydroxyzine was cytotoxic against the MCF-7 and EVSA-T human breast cancer cell lines [112]. The H1 antihistamines terfenadine and loratidine inhibited the *in vitro* growth of HMC-1 human leukemia cell line, C2 and NI-1 canine mastocytoma cell lines [125].

The H2 antihistamine cimetidine is one of the most frequently prescribed medicine worldwide [126], being proposed as an anti-cancer drug in 1979 [127]. Indeed, it may inhibit tumor growth and metastasis by different ways: inhibits cell adhesion of tumor cells, exerts antiangiogenenic effects by the inhibition of VEGF that has been recognized as an important angiogenic factor, induces apoptosis, activates macrophages, activates the immune system through the increase of interleukin levels, increases infiltration of tumors by immune cells and inhibits immunosuppression [110]. Positive effects of cimetidine administration were observed in patients with malignant melanoma [128], renal cell carcinoma [129] and glioblastoma [130].

Jiang and collaborators [131] studied the effects of cimetidine administration on the growth of different cancer cell lines (SGC-7901 human gastric carcinoma metastatic lymph node cell line, MGC-803 human gastric mucinous adenocarcinoma cell line and GES-1 normal human gastric epithelial cell line) and they observed that cimetidine induced apoptosis in neoplastic cells and had almost no effect in the normal gastric cells. Jiang and collaborators [131] also observed that cimetidine injection two times a week, during four consecutive weeks in a xenograft model of BALB/c nude female mice subcutaneously injected with SGC-7901 cell line decreased tumor volume and weight in a dose-dependent manner.

Brandes and collaborators [113] did not observe any effect of the daily intraperitoneal injection of cimetidine for 18 days in B16F10 melanoma and C-3 fibrosarcoma cell lines subcutaneously injected in C57BL and C3H female mice.

Takahashi and colleagues [132] observed a reduction in volume and weight of colon adenocarcinoma in a sygeneic model of CT-26 mouse colon adenocarcinoma cell line intradermally injected in the lumbar region of BALB/c female mice.

Several researchers performed *in vitro* and *in vivo studies* with human cell lines of different types of cancer, namely leukemia, lymphoma, melanoma, breast, ovarian, vaginal, cervical, uterine, vulvar and colorectal cancer, demonstrating the positive involvement of histamine in cancer cell proliferation migration and invasion [77] (**Table 3**).

In a study performed by our research team, where the role of mast cells was evaluated in the initiation and progression of mammary tumors chemically-induced by the carcinogen agent MNU in Sprague-Dawley female rats, through the inhibition of mast cell degranulation by the administration of ketotifen, we observed that animals from ketotifen-treated groups developed less number of mammary tumors (palpable masses) but higher number of mammary lesions when compared with non-treated animals. A lower proliferation (Ki-67 immunoexpression) and apoptotic index (caspase-3 and -9 immunoexpression) was observed in mammary tumors from ketotifen-exposed animals. The main positive effect of mast cell inhibition seemed to be the reduction of tumor proliferation when the mast cell degranulation was inhibited before tumor development [133].

Table 1. Distribution of histamine receptors in cells and tissues [96,103,110,123,124,126–136].

Histamine receptors	Cells and tissues
H1	Adrenal medulla, Cardiovascular system, Chondrocytes, Dendritic cells, Endothelial cells, Eosinophils, Epithelial cells, Gastrointestinal tract, Genitourinary system, Hepatocytes, Monocytes, Nerve cells, Neutrophils, Smooth muscle, T and B cells
H2	Chondrocytes, Dendritic cells, Endothelial cells, Eosinophils, Epithelial cells, Gastric parietal cells, Heart, Hepatocytes, Monocytes, Nerve cells, Neutrophils, Smooth muscle, T and B cells
H3	Eosinophils, Histaminergic neurons, Monocytes
H4	Basophils, Bone marrow, Colon , Dendritic cells, Eosinophils, Heart, Hematopoietic cells, Hepatocytes, Lung, Mast cells, Monocytes, Nerve cells, Neutrophils, Small intestine, Spleen, Stomach, T cells, Thymus

Table 2. H1, H2, H3 and H4 antihistamines more frequently used [53,57,64,79,85,92,106–108,134].

<table>
<tr><th colspan="2">H1 antihistamines</th><th>H2 antihistamines</th><th>H3 antihistamines</th><th>H4 antihistamines</th></tr>
<tr><th>First generation</th><th>Second generation</th><td></td><td></td><td></td></tr>
<tr><td>Alkylamines: Brompheniramine; Chlorpheniramine; Dexbrompheniramine; Dexchlorpheniramine; Dimethindene; Pheniramine; Triprolidine</td><td>Alkylamines: Acrivastine</td><td rowspan="6">Burimamide; Cimetidine; Dimaprid; Famotidine; Lafutidine; Nizatidine; Pibutidine; Ranitidine; Zolantidine</td><td rowspan="6">Ciproxifan; Imoproxifan; Impromidine</td><td rowspan="6">Alobenpropit; Clobenpropit; Thioperamide</td></tr>
<tr><td>Ethanolamines: Bromazine; Carbinoxamine; Clemastine; Dimenhydrinate; Diphenhydramine; Doxylamine; Ophenadrine; Phenyltoloxamine</td><td>Piperazines: Cetirizine; Levocetirizine</td></tr>
<tr><td>Ethylenediamines: Antazoline; Mepyramine; Pyrilamine; Tripelennamine</td><td rowspan="4">Piperidines: Astemizole; Bilastine; Desloratadine; Ebastine; Fexofenadine; Ketotifen; Levocabastine; Loratadine; Mizolastine; Olopatadine; Terfenadine; Rupatadine</td></tr>
<tr><td>Phenothiazins: Methdilazine; Promethazine; Trimeprazine</td></tr>
<tr><td>Piperazines: Buclizine; Chlorcyclizine; Cyclizine; Hydroxyzine; Mebhydrolin; Meclizine; Oxatomide</td></tr>
<tr><td>Piperidines: Azatadine; Cyproheptadine; Diphenylpyraline</td></tr>
</table>

Table 3. *In vivo* and *in vitro* studies performed in order to evaluate the potential role of antihistamines on cancer treatment.

Model	Drug	Specie		Dose	Effects	Reference
In vivo studies	Chlorpheniramine	Mice	Syngeneic; Ehrlich carcinoma cells were inoculated	i.p.; 0.2mL/day of 6.4mM chlorpheniramine solution; for 7 or 11 days	Decreased tumor growth	[135]
	Cimetidine	C57BL mice	♀ LL57B004 (mice Lewis lung carcinoma); subcutaneous or intramuscular injection	p.o. in drinking water; 100mg/Kg/day; for 20 days	Decreased cell growth	[66]
		BALB/c nude mice	♀ Xenograft; SGC-7901 (human gastric carcinoma metastatic lymph node cells)	Intratumoral injection; 100mg/Kg for 2 days; 200mg/Kg for 2 days; for 4 weeks	Decreased tumors volume and weight	[131]
			♂ Xenograft; C170 and LIM2412 (human colon adenocarcinoma cell lines)	Subcutaneously implanted; 100mg/Kg/day; for 21 or 28 days	Inhibited tumor growth (lower number and volume of tumors)	[136]
			Xenograft; KK (ovarian carcinoma cell lines)	p.o. in drinking water; 25, 50 or 100mg/Kg/day; for 20 days	Decreased tumor growth	[137]
		♂ nude mice	Xenograft; MKN45G (gastric adenocarcinoma cell line); subcutaneous injection	p.o. in drinking water; 100mg/Kg/day; for 20 days	Inhibited proliferation of tumor cells	[138]
		50 Grey horses	Melanoma	p.o.; 3.5mg/Kg/2 times days or 7.5mg/Kg/day; for 60 days	It was not effective in the treatment of horses melanoma	[139]

		Human	Colorectal cancer	(1) p.o.; 400mg/Kg; for 2 years after surgery. (2) p.o.; 400mg/Kg; for 5 days before surgery. (3) p.o.; 800mg/Kg; for 5 years before surgery.	(1) Increased patients surveillance in 40 months (1) or 14 months (2 and 3)	[140,141]
	Cimetidine; Dipheny-dramine	Sprague-Dawley rats	Colonic tumors chemically-induced by 1,2-dimethylhydrazine	p.o. in drinking water; 100mg/Kg/day; for 26 weeks	Cimetidine did not reduce the incidence of colon tumors; both drugs did not affect the staging and degree of differentiation of tumor	[142]
	Clobenpropit	Immunodeficient nude mice	Xenograft; Mz-ChA-1 (human cholangiocarcinoma cell lines); subcutaneous injection	i.p.; 20mmol/Kg/day; for 39 days	Inhibited tumor progression and decreased tumor volume	[143]
	Cyproheptadine	DBA2 mice	Syngeneic; MDAY-D2 (mouse leukemic cells); subcutaneous injection	i.p.; 10mg/Kg/day; for 5 or 10 days	Abolished formation of malignant ascites; inhibited tumor growth; induced apoptosis of tumor cells	[144]
		Sublethally irradiated NOD/SCID mice	Xenograft; LP-1(human multiple myeloma line); subcutaneous injection		Delayed tumor growth; lower tumor volume; induced apoptosis of tumor cells	[144]
		Sprague-Dawley rats	Colonic tumors chemically-induced by 1,2-dimethylhydrazine	i.p.; 1mg/Kg; single doses	Reduced number of tumors; increased necrosis in neoplastic cells	[145]

		Human	Mastocytosis	0.38mg/Kg/day; for 33 months	Reduced degree of blistering; child grown and developed normally without sign of disease	[146]
	Loratadine, astemizole, cetirizine, hydroxyzine	♀ C57BL mice/ ♀ C3H mice	Syngeneic; B16F10 melanoma cells and C-3 fibrosarcoma cells; subcutaneous injection	i.p. administration; human-equivalent dose; once a day; for 18-21 days	Loratadine and astemizolepromoted the growth of both tumors Hydroxyzine promoted the growth of melanoma. Cetirizine did not have any effects	[113]
	Mepyramine	♂ Syngeneic; McB6-1 (mice fibrosarcoma cell line); subcutaneous injection		i.p.; 0.2mg; 7days/ week; for 35 days	Induced a slight increase in tumor growth; decreases animals' survival	[147]
	Ranitidine	♂ nude mice	Xenograft; C170 and LIM2412 (human colonic adenocarcinoma cell lines)	p.o. in drinking water; 25, 50 or 100mg/ Kg/day (C170); 10, 25 or 50mg/Kg/day (LIM2412); for 28 days	Ranitidine had no effect in C170 cell line. Ranitidine stimulated tumor growth in LIM2412 cell line	[148]
		Human	Colorectal cancer	i.v.; 100mg intraoperatively followed by 150mg/Kg p.o. for 5 years	Increased patients surveillance in 80 months	[149]
	Ranitidine, cimetidine	Immunodeficient SCID mice	Xenograft; HT168 (human melanoma cell line); intradermal injection	p.o. in drinking water; 50mg/Kg/day	Both drugs inhibited tumor growth	[150]
	Ruptadine	Human	Mastocytosis	Concentration of 20mg/day; for 28 days	Controlled symptoms and improved quality of life	[151]

In vitro studies	Astemizole	SUM-229PE and T-47D (human invasive ductal carcinoma cell lines)		Concentration of 0.5-4.5 μM, for 6 days	Inhibited tumor cells proliferation	[152]
	Chlorpheniramine	MDA-MB231 and MCF-7 (human breast cancer cells)		Concentration of 250μM, for 48 hours	Induced a dose-dependent decrease in cell number	[153]
	Cimetidine, Terfenadine	A375 (human melanoma cell lines)		Concentration of 0-10μM; for 2-10 hours	Cimetidine did not show effects on cells; terfenadine induced a dose and time-dependent cytotoxicity	[154]
	Clobenpropit	Mz-ChA-1; SG-231; HuCCT-1; CCLP-1; HuH-28; TFK-1 (human cholangiocarcinoma cell lines)		Concentration from 1-50μM; for 48 hours	Inhibited cells proliferation in a dose-dependent manner	[143]
	Cyproheptadine	HBL-2, Granta-519 and Leko-1 (human lymphoma cell lines)		Concentration of 25μmol/L, 30 μmol/L and 40 μmol/L	Decreased mitochondrial membrane potential at high concentrations; induced apoptosis	[155]
	Loratadine followed by radiation treatment	HT29 (human colon carcinoma); DU145 (human prostate carcinoma); SF295 (human glioblastoma)		Concentration of 75μM	Pre-treatment with loratadine increased radiation induced citi-toxicity	[156]
	Meclizine	HT29 and COLO 205 (human colon adenocarcinoma cell lines)		Concentration of 10-100μM, for 24 hours	Induced a dose-dependent decrease in cell number	[157]

	Ranitidine	Tumors N-methyl-N-nitrosourea induced in ♀ Sprague-Dawley rats		Concentration of 10μM	Inhibited tumor cells proliferation	[158]
	Terfenadine	A375, HT144, Hs294T (human melanoma cell lines)		Concentration of 0-20μM; for 24 hours	Induced apoptosis	[159]
	Terfenadine, astemizole, diphenydramine, tripolidine	A375, HT144, HSs294T and MJOI (human melanoma cell lines)		Concentration of 0.1-1mM for diphenydramine and tripolidine; 1-10μM for terfenadine and astemizole, for 6 to 24 hours	All drugs induced apoptotic cell death in all cell lines	[123]
	Terfenadine, loratadine	HMC-1 (human mast cells leukemic cell line)		Concentration of 10μM, for 6, 12, 24, 48 or 72 hours	Both drugs induced apoptosis in neoplastic mast cells	[125]

Abbreviations: i.p: intraperitoneal injection; i.v: intravenous administration; p.o: oral administration

6. Conclusion

The existing therapies for cancer treatment have devastating effects for patients and are frequently insufficient to eradicate the disease. Since the histamine receptors are present in neoplastic cells of several tumors, and the antihistamines have low toxicity and are cheaper when compared with drugs used in chemotherapy, the antihistaminic drugs may be potentially used for the clinical management of oncologic patients.

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