Antihistamines for cancer treatment: More than just allergy relief

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Abstract

Cancer is the primary cause of death worldwide, accounting for almost 10 million deaths. The most prevalent are lung, breast, colorectal, and skin cancer. Cancer does not obey the cell cycle which can lead to the formation of tumors. The biogenic amine histamine is synthesized by histidine. Increased amounts of histamine have been linked to the regulation of several tumors. The histamine receptors (H1, H2, H3, and H4) are distributed throughout the skin, where H1 and H2 are the primary targets for drug therapy. Repurposing of the current antihistamine drugs can be cost-effective, safe medications and allied with lesser adverse effects. Researchers examined Six H1-antihistamines (Cetirizine, clemastine, desloratadine, loratadine, ebastine, and fexofenadine) in a nationwide wide cohort study of all Swedish patients with ten types of immunogenic (melanoma, bladder cancer, kidney, prostate, lung, pancreatic, colorectal, breast cancer, and Hodgkin lymphoma) and six non-immunogenic (thyroid cancer, liver, ovarian, brain cancer and lymphoma) tumors. The study shows that Desloratadine and loratadine upsurge the survival rate for many tumors by inhibiting the growth of tumors and promoting apoptotic cell death. The other H1 receptor antagonist Cloperastine knockdown FGF13 expression which is responsible for anticancer agent cisplatin-resistance and selectively kills HeLa cisR cells. Some findings believe H1 receptor antagonists should be investigated in randomized clinical trials for immunogenic tumors. These drugs can be a curative therapy for several tumors including that prognosis with limited treatment options.

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ABSTRACT

Cancer is the primary cause of death worldwide, accounting for almost 10 million deaths. The most prevalent are lung, breast, colorectal and skin cancer. Cancer does not obey the cell cycle which can lead to formation of tumors. The biogenic amine histamine synthesized by histidine. Increased amounts of histamine have been linked in regulation of several tumors. The receptors of histamine (H1, H2, H3, and H4) are distributed throughout the skin, where H1 and H2 are the main targets for drug therapy. Repurposing of the current antihistamine drugs can be cost effective, safe medications and allied with lesser adverse effects. Researchers examined Six H1-antihistamines (Cetirizine, clemastine, desloratadine, loratadine, ebastine and fexofenadine) in a nationwide wide cohort study of all Swedish patients with ten types of immunogenic (melanoma, bladder cancer, kidney, prostate, lung, pancreatic, colorectal, breast cancer and Hodgkin lymphoma) and six non-immunogenic (thyroid cancer, liver, ovarian, brain cancer and lymphoma) tumors. The study shows that Desloratadine and loratadine upsurge the survival rate for many tumors by inhibiting the growth tumors and promoting apoptotic cell death. The other H1 receptor antagonist Cloperastine knockdown FGF13 expression which is responsible for anticancer agent cisplatin-resistance and selectively kill HeLa cisR cells. Some findings believe that H1 receptor antagonist should be investigated in randomized clinical trials for

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ABSTRACT

Cancer is the primary cause of death worldwide, accounting for almost 10 million deaths. The most prevalent are lung, breast, colorectal and skin cancer. Cancer does not obey the cell cycle which can lead to formation of tumors. The biogenic amine histamine synthesized by histidine. Increased amounts of histamine have been linked in regulation of several tumors. The receptors of histamine (H1, H2, H3, and H4) are distributed throughout the skin, where H1 and H2 are the main targets for drug therapy. Repurposing of the current antihistamine drugs can be cost effective, safe medications and allied with lesser adverse effects. Researchers examined Six H1-antihistamines (Cetirizine, clemastine, desloratadine, loratadine, ebastine and fexofenadine) in a nationwide wide cohort study of all Swedish patients with ten types of immunogenic (melanoma, bladder cancer, kidney, prostate, lung, pancreatic, colorectal, breast cancer and Hodgkin lymphoma) and six non-immunogenic (thyroid cancer, liver, ovarian, brain cancer and lymphoma) tumors. The study shows that Desloratadine and loratadine upsurge the survival rate for many tumors by inhibiting the growth tumors and promoting apoptotic cell death. The other H1 receptor antagonist Cloperastine knockdown FGF13 expression which is responsible for anticancer agent cisplatin-resistance and selectively kill HeLa cisR cells. Some findings believe that H1 receptor antagonist should be investigated in randomized clinical trials for immunogenic tumors. These drugs can be curative therapy for several tumors including those prognosis with limited treatment options.

INTRODUCTION TO CANCER

Depending on the type of tumor or sub-types cancer treatment may be strictly limited, besides malignancies as well as dismal prognoses like pancreatic cancer **(Figure 1)** , there is always a requirement for improved and novel anti-cancer medicines . To meet the need for both cost-effectivenesses together time to repurpose the current medications . Histamine H1 receptor targeted by anti-histamine has minimal side effects and is safe as well as tolerated by many individuals creating a brilliant choice for repurposing. For this possible effect, several mechanisms have been suggested as most people thought to be either wholly or partly H1 receptor-independent, including the Lysosomal cell death or immunological pathways . Fenoxifenadine, loratadine, and desloratadine are a few anti-histamines that revealed anti-inflammatory effects , inhibiting the basal signaling of the H1 receptor . To prevent the release of histamine, mast cell membranes are stabilized by desloratadine. The immunoregulatory activity of myeloid-derived suppressor cells along with the Th2-skewing immune response is promoted by histamine . In colorectal cancer, the th1-response has been revealed to be significant for survival. For the survival of breast cancer and malignant melanoma,

loratadine and desloratadine are linked with the improvement previously discovered . In some meta-analyses of data, it was studied whether the related association is seen in several types of the tumor with immune checkpoint inhibitors like anti-PD1 or CTLA-4, to shed more light on potential anti-tumor results of this kind of anti-histamine and whether it can be immunological nature .

PHYSIOLOGICAL ROLE OF MAST CELLS

The important cells of the immune system are known as mast cells which are the hematopoietic cells lineage. They are mainly derived from bone marrow under the impact of the c-kit ligand. Paul Ehrlich first described 130 years ago in his PhD thesis . In the bloodstream, mature mast cells do not circulate when it is under regular condition. The mast cells are normally found in epithelial tissue cells throughout the body, blood cells, smooth muscles, mucous and hair follicles . Mast cells are not found in mineralized bone, cornea and cartilage . The mast cell containing cytoplasm comprises 50 to 200 huge granules that are stored in inflammatory mediators . Outside the granules in the mast cell, the cytoplasm is lipid bodies which are the source of triglyceride-derived arachidonic acid . Mast cells cytoplasm containing few mitochondria, rough endoplasmic reticulum and many unrestricted ribosomes were observed under the electron microscope . The main mechanism of mast cells is IgE-mediated allergenic response through the Fc RI receptor**(Figure 2)** . The mast cell is activated by the most common physiological pathway via IgE/antigen/ Fc RI cross-linking pathway . Fc RI involves α-chain that binds with IgE. IgE antibodies are produced from mature β cells in response to CD4+ Th2 cells . When β cells interact with cytokines like IL-4 the antibody class will switch from IgM to I, mostly found in Fc RI receptors . During degranulation, the activated mast cell produces mediators such as histamine, Leukotrienes, chemokines, and cytokines. Other immune cells such as T cells, eosinophils, monocytes, neutrophils and other pro-inflammatory mediators have recruited these molecules .

MAST CELL-RELATED DISEASE

Factually, the relation between malignant cells and the TME may result in the progression of tumor growth . The first inflammatory mast cell interacts with entering pathogens are the most important guard of the immune system . It sticks to the phagocyte and executes the innate immunity i.e. Gram-positive and Gram-negative bacteria. The mast cell then initiates its response through the interaction of B cells and T cells, migration, maturation, and the role of dendritic cells . At the site of action, the pro-inflammatory mediators initiate the innate immune response during infection . The mast cells are also engaged in boosting angiogenesis. The pro-angiogenic factors such as VEFG, BFGF, TGF-BETA, TNF-ALPHA and Interleukin-8 are secreted by mast cells. Furthermore, Protease and heparin are discharged by the mast cell which then releases pro-angiogenic factors that bind to heparin. The mast cell release histamine which induces microvascular permeability which in turn induces angiogenesis . The existence of mast cells in the TME is not a fresh finding as Paul Ehrlich previously described them in his doctoral thesis. In certain scenarios depending on the manner of the tumour, mast cells may have an immunosuppressive function by releasing histamine, interleukin-10 and TNF-α. Moreover, mast cells can suppress T cells and NK cells by freeing adenosine into the microenvironment. The penetration of mast cells into the tumour stroma as well as the development and activation of Tregs are stimulated leading to tumour progression . Previous human cell line studies were conducted to aim at the role of mast cells in shaping tumour growth. In patients having non-small lung cancer, mast cells were gathered in the TME both $MC_{TC}$and MC_{T} are rich in tumours . Similar studies were conducted with patients having colorectal cancer, Breast cancer and other numerous cancer in which researcher's observed that high rate of tryptase+ mast cell in the tumour, the PA-2 receptor activated by Tryptase which promotes the progression of cancer . In addition, Histamine promotes cell proliferation by acting on the surface of a tumour expressing H1receptor. In solid tumours like thyroid tumours, high engagement of histamine H1R and H2R results in tumour cell proliferation . This can be controlled by preventing the release of linkage or any substances with respective receptors, for instance, the prevention of histamine linkage to the receptors . In other findings, researchers analyzed the distribution of mast cells around the vessel and gland of gastric carcinoma using computer analysis and it was established that in gastric carcinoma grade II, there is a link between chymase+ mast cells and were located at a shorter distance from the vessel. Meanwhile, targets for new therapeutic approaches are very desirable as mast cells

are involved in several malignant cancer. Concerning the mechanism of mast cell activation, the free light chains have been examined in numerous models. In murine B16F10 melanoma model inhibition of free light chains-mediated mast cell activation reduces tumour growth . The activity of mast cells can be suppressed by using a mast stabilizing agent or indirectly targeting the mediators of the mast cells. For example, an anti-TNF monoclonal antibody targets the TNF as well as anti-histamine medication to inhibit the action of histamine.

CANCER-RELATED INFLAMMATION

The link between inflammation and cancer isn't new, in 1863, Virchow theorized that cancer emerges from the foci of chronic inflammation. In his part, he theorized that some types of irritants and tissue injury enhance cell proliferation . Inflammation is defined as when the body confronts agents like viruses, bacteria or toxic chemicals or suffers an injury, the immune system gets activated . Our immune system sends some responders like Cytokines and inflammatory cells, as well as other white blood cells, produce substances that divide and grow cells, rebuild the tissue and repair the damage. When the injury heals, the inflammatory process ends. In chronic Inflammation, the process of inflammation begins without injury and doesn't stop when needed. It can be caused by a condition such as an abnormal immune response to healthy cells, and persistent infection though it's usually unknown why the inflammation persists. Gradually, chronic inflammation may damage DNA and triggers cancer. For instance, individuals with IBD such as ulcerative colitis and Crohn's disease are at increased risk of colon cancer. In the host, persistent infection causes chronic inflammation because white blood cells and other phagocytes induce DNA damage in the proliferating cells by releasing reactive oxygen and reactive nitrates which are normally released to combat inflammation, then reacts to form mutagenic substance peroxynitrite . Therefore, repeated tissue damage and regeneration in the presence of highly reactive nitrogen and oxygen released by inflammatory cells interact with the proliferating epithelial DNA causing point mutations and deletions, resulting in permanent genomic changes . In cancer development, the role of chronic inflammation is not a minor one. It is believed that one in five cancer caused by inflammation . Pancreatic, colitis and hepatitis are examples of inflammatory diseases that are linked to a greater risk of liver, colon and pancreatic cancer. These diseases cause DNA damage and divide the cells. Chronic inflammation like H.pylori is linked to stomach cancer, whereas hepatitis B and hepatitis C are related to liver cancer . Human herpesvirus 8 is linked with Kaposi sarcoma. People with esophagitis and Barrett's metaplasia along with chronic pancreatitis are at higher risk of oesophageal and pancreatic cancer . A link between chronic asthma and Lung cancer, Foreskin infection and penile Cancer, and Ovarian epithelial infection leads to ovarian cancer, prostatitis infection and prostate cancer are all observed . In the past few years, scientists are focused on the development of anti-malignant drugs, nonetheless, poor responses and chronic toxicity are still in the news. The recent therapeutic approach for cancer therapy is immunotherapy and mast cells represent the essential target for immunotherapy .

PHYSIOLOGICAL ROLE OF HISTAMINE

The endogenous biogenic amine histamine is synthesized in the presence of the amino acid L-histidine **(Figure 3)** . Initially, histamine was recognized as a mediator of allergies. In early 1932, scientists discovered its role in the modulation of allergic reactions. Subsequently, researchers have established that histamine is a mediator of autoimmune conditions, hematopoiesis and gastric acid secretion . Histamine is circulated throughout the tissues and is mainly concentrated the in lungs, skin, gastrointestinal tract, mast cells, basophils, neurons and parietal cells. A large amount of histamine in granules is delivered by basophils and mast cells and is linked with chondroitin-4-sulfate and anionic proteoglycans heparin . The key reason that triggers the histamine is an allergic reaction where B cells are first activated and form plasma cells which release a large amount of antibodies. The activation of IgE triggers the mast cell to release granules rich in histamine **(Figure 4)** . Histamine-N-methyl transferase which is responsible for the degradation of histamine in epithelial cells of the airway and diamine oxidase present in the liver, kidney, small intestine mucosa, eosinophils, placenta and skin are the two major pathways that metabolized 97% of the synthesized histamine . Histamine part in allergic disease and autoimmune has an important role in numerous pathological and physiological progressions, specifically in chronic urticaria due to histamine release from basophils

and circulating IgE antibodies against FcεRIα and IgE . Allergic rhinitis, Atopic dermatitis, allergic rhinitis, anaphylaxis and bronchoconstriction are other examples of allergic and autoimmune diseases . Lately, histamine confirmed as a serious factor in interaction with infiltrating immune cells and tumour tissues, where the mechanism of the immune system containing histamine allows malignant cells to escape. Various in vitro and in vivo studies of human cell lines of cancers such as lymphoma, breast cancer, ovarian cancer, etc. have shown clear participation of histamine in malignant cell proliferation .

SIGNALLING PATHWAY OF HISTAMINE RECEPTORS

Histamine bind to a different type of histamine G-coupled protein receptors and exerts its action. The four histamine receptors which are identified by researchers are H1, H2, H3 and H4 **(Figure 5)** , where the first two receptors i.e. H1 and H2 are important targets for clinically effective drugs. In some human tumours, these histamine receptors are recognized by genomic-based methods for example colorectal cancer, melanoma, and breast cancer, vaginal, cervical and ovarian cancer. The H1 receptors are on smooth muscles, endothelial cells, as well as brain and, are also found in peripheral nerve endings and mediate vascular permeability at the site of inflammation. H1 receptor activation causes anaphylactic reactions such as bronchoconstriction, hypotension, flushing and tachycardia . When histamine bind to the H1 receptor in the brain elevates other things like wakefulness and appetite suppression. In the peripheral nerve, histamine mediates stimulation which leads to pain and itching sensations. The H2 receptors are mainly located in gastric parietal cells and cause gastric secretions. In histaminergic neurons, H3 receptors are mostly found which regulate 5-HT3, dopamine, Norepinephrine, Acetylcholine and histamine. Its mRNA is situated in the peak of the spinal cord, bone marrow and peripheral hematopoietic cells play a vital role in the variation of myoblast and promyeloblast along with chemotaxis .

PHARMACOLOGICAL ROLE OF ANTI-HISTAMINE

Antihistamines are a class of medications that can block a variety of histaminic activities. To cure allergies and skin disorders Phenbenzamine became the first anti-histamine utilized in humans as it was produced in 1937 by Bovet and Staub . The first-origin antihistamines also recognized as classic anti-histamines, contain low molecular mass, are extremely lipid soluble, simply cross the blood-brain barrier and express high affinity to the brain having H1-receptors, triggering sedation, incoordination, absence of attentiveness and in few Cases causes anxiety and excitement These first-generation of antihistamines are inexpensive than the second generation having shorter life span, requiring numerous regular dosage . Apart from them inhibiting the central part as well as peripheral H1 receptors, H1 antihistamines also obstruct the action of muscarinic and adrenergic receptors which cause bronchial and oral secretions to dry out, urinary retentiveness, cardiac infraction, vague sight and low blood pressure . Newer antihistamines also called as 2^{nd} generation antihistamine, have been established in the first 1980s to diminish the unexpected effects **(Table 1)** . They possess high meticulousness for the H1 receptor and subtle affinity for muscarinic along with adrenergic receptors . Unlike 1^{st} antihistamines, 2^{nd}antihistamines are extremely molecular mass, fat-soluble combined with a subtle affinity for brain Histamine 1-receptors, with no systemic result. To refine clinical trial efficacy and decrease the unexpected effects, 3^{rd} generations were developed having effective metabolites of 1^{st}-generation anti-histamines . The new class of anti-histamines validate clinical benefits and are cardio-toxic free, drug contraction and CNS results. H2 antagonist medications are normally used in the therapy of peptic ulcers, increase gastric acidity happened in gastroesophageal reflux disease as well as in the prophylaxis of conditions. Although the safety and proper use of antihistamines are not properly understood, these are mainly prescribed medications for progenies and mature persons .

ROLE OF ANTI-HISTAMINE IN NUMEROUS CANCER

Various epidemiological studies explored the link between cancer and allergy over years. Furthermost, the studies are mainly retrospective and the association between cancers together with allergies remains vague. Moreover, in cancer, the role of histamine and its receptor is still blurred . Previously, in several cancer cells, many studies were fixated on the expression of histamine receptors which may promote or inhibit cancer. What impact does histamine signaling carry on TAM activity and anti-tumor immunity? Earlier studies

focussed on the H1-anti-histamines effective suppression of cancer. However the researchers found that the genetic expression was related to the proportion of tumor-linked macrophage inflammation in the TMA . To fight cancer our immunotherapy turns the immune system by stimulating T cells for identification and executing unwanted tumour cells. Unluckily, in every patient, it is unsuccessful, as tumours can become resistant to T-cell attacks. A paper was published in cancer cell reports which state that an increased level of histamine H1receptor (HRH1) in tumour environment dysfunction T cells . Mechanistically, activated HRH1 macrophages factionalize towards M2- like immunosuppressive phenotype with high expression of immune checkpoint VISTA and exhibit T cell dysfunction. Using the inhibitory receptor proteins as well as soluble protein molecules, TME containing histamine may reduce the CD8+T ability to combat tumors. The gene fingerprint of TME shifted towards theM1 macrophage due to H1R deficiency together with CD8+T cell destruction decreased The treatment of antihistamines reverse the macrophage immunosuppression revitalized the T cell cytotoxic function and revived the response to immunotherapy **(Figure 6).** A team of cancer researchers in Texas approached their first quest by distinguishing the consumed drugs in combination with immune checkpoint inhibitors that can influence the response of patients in the treatment of cancer. By retrospectively, scanning of patient's data receiving immunotherapy together with 40 common drugs like aspirin, antibiotics and hydrocortisone, found that lung cancer and melanoma patients taking an antihistamine such as fexofenadine, loratadine and cetirizine had higher survival rates . Cancer treatment options are restricted depending on the kind or sub-type, likewise, new and improved anti-cancer medications are always needed for malignancy with dismal prognoses similar to pancreatic cancer . Cancer treatment often develops resistance towards anti-cancer agents. The researcher also showed that overexpression of fibroblast growth factor 13gene (FGF13) also known as FGF homologous factor 2 (FHF2) creates resistance towards Cisplatin of protein in HeLa CisR cells. The H1 receptor antagonist Cloperastine knockdown FGF13 expression which is responsible for anti-cancer agent cisplatin-resistance and selectively kills HeLa cisR cells . Repurposing the existing medication can be done to fulfil that requirement in both a time and low-cost manner . Antihistamines aiming at histamine receptor H 1 make brilliant aspirants for drug reuse for cancer treatment, they are harmless medications with less adverse outcomes that are well accepted by maximum individuals, and data that they may be helpful against many emerging cancer . Many systems have been anticipated for this possible impact most are believed to be histamine receptor H 1 independent, either wholly or partly , either involving lysosomal cell loss or pathways related to immunological . Particular anti-histamines, like desloratadine, fexofenadine and loratadine, have been exposed to carry anti-inflammatory results , which are assumed to hinge on their potent inverse histamine agonist, inhibiting histamine receptors (h1) containing basal signalling pathway . To prevent the release of histamine, the mast cell membrane can also be stabilized by Desloratadine . Histamine endorses the immunoregulatory action of myeloid-derived suppressor cells and the Th2-skewing immune reaction . The combination of anti-histamine with checkpoint blocker boosted the survival and therapeutic efficacy over checkpoint blockade in both pre-clinical models of breast cancer and melanoma . To evaluate the tumour progression researcher used pre-clinical models of allergic disease. The growth of tumours and levels of histamine escalated after the introduction of allergies in the body. Nonetheless, the effects may be reversed with anti-histamine therapy. Their pre-clinical outcomes proposed that the anti-histamine can enhance the response to immunotherapy, particularly those with increased levels of histamine in the blood. They are focused on finding anti-histamine approaches with minimal side effects and working on prospective clinical trials to study the combination of anti-histamine and checkpoint inhibitors in cancer patients .

ROLE OF ANTI-HISTAMINE IN COLORECTAL CANCER

Colorectal cancer is a disease where the healthy lining of the rectum or colon spreads out of control afterward it forms a tumor, and this growth is called a polyp. Colorectal cancer is one of the primary causes of cancer-related mortality in the world . CRC is accountable for more than 600,000 mortality yearly and occurrence rates are rising mainly in the advancing nations. Epidemiological, as well as laboratory surveys, suggest that environmental factors such as western style dietary habits, tobacco smoking, and absence of physical actions are measured as risks for CRC. The molecular pathology of CRC involves pro-inflammatory conditions to stimulate the tumor's malignant progression, and attack in addition to metastasis . It is well-

identified that patients with IBD are at greater risk of CRC. Infection involves relations between countless immune cells, inflammatory cells, chemokines, cytokines, and pro-inflammatory mediators which may lead to signaling regarding tumor cell proliferation also attack . An article published online on January 2011 stated that the third-generation compound oxaliplatin is the key agent for the management of colorectal cancer. When Patients were treated with Oxaliplatin it caused hypersensitivity reactions. Hypersensitivity reaction to Oxaliplatin developed one of the followings symptoms and was considered a manifestation of a severe allergic reaction like pulmonary erythema, Urticaria, tachycardia, angina, wheezing, facial or tongue edema, Dypsenea hypertension, Hypotension, respiratory arrest, diffuse erythroderma, anaphylaxis, seizure or death. So they conducted a retrospective cohort study of patients having advanced colorectal cancer who received modified FOLFOX 6 . A premedication routine was given to the patients with dexamethasone 8 mg and Granisetron 3 mg for the first five cycles of FOLFOX 6. Cohort 1 received the first pre-medication from the sixth cycle. Cohort 2 received a modified version of premedication i.e. diphenhydramine 50mg orally, followed by granisetron 3 mg, dexamethasone 20 mg and famotidine 20 mg. The researcher's then compared the incidence of hypersensitivity reactions, duration of the treatment and reasons for treatment withdrawal between two cohort studies . A total of 181 patients were studied in the cohort, they found out that in cohort one 16 patients developed hypersensitivity reactions (20%) and in cohort two 7 patients developed hypersensitivity reactions (7.0%). In cohort one other than a progressive disease, they discontinued the treatment in 20% of patients due to neurotoxicity as compared to cohort two . It was concluded that high doses of dexamethasone and antihistamine remarkably decrease Oxaliplatin related hypersensitivity reactions . So this effective approach should be considered for all patients receiving FOLFOX . A randomized phase II clinical trial was conducted to study the effect of the given drug Levocetirizine on patients having colorectal cancer and how it affects the tumour response to Capecitabine and bevacizumab . The second-generation drug H1 antihistamine Levocetirizine with anti-inflammatory and IL-8 suppression properties. A chemotherapy drug Capecitabine blocks tumour growth by disrupting the DNA- RNA synthesis and restoring cell division. On the other hand, the monoclonal antibody bevacizumab blocks tumour growth by inhibiting the growth of blood vessels that feed those. Patients having colorectal cancer may develop resistance towards the bevacizumab effects. To overcome the anti-angiogenic therapy resistance 47 patients volunteered in the trial. Arm A volunteered 23 patients, where Levocetirizine was started after starting the chemotherapy. Arm B volunteered twenty-four patients, where Levocetirizine was started prior to the chemotherapy. In arm, A median time progression was 3.4 months whereas in arm B it was 3.5 months. It was then concluded that 50% of the patients had progressive disease and 62% of patients had stable disease in both arms as a great response. There was no provable difference between the two arms, but patients with the stable disease showed a decreased level of IL-8 as compared to the patients with the progressive disease in the analysis of cytokine .

ROLE OF ANTI-HISTAMINE IN BREAST CANCER

Breast cancer occurs when a healthy cell grows out of control and forms a tumor and it can spread to other parts of the body. About 1 in 8 women are diagnosed with cancer in their lifetime. Breast cancer develops inside the milk ducts which is called Ductal Carcinoma (DCIS). When abnormal DCIS cells spread to surrounding tissue is known as Invasive Ductal Carcinoma (IDC). An abnormal cell may also develop into lobules called Lobular Carcinoma in Situ (LCIS) and are not cancer, when it spreads to the surrounding tissue then it becomes cancer called Invasive Lobular carcinoma. As an inflammatory environment maintained in tumours, an anti-inflammatory medication may be useful in Cancer treatment . H2- anti-histamine has shown promising results in cancer treatment. Investigators showed a link with improved survival in melanoma by using H1- antihistamine. Six antihistamines namely, cetirizine, desloratadine, ebastine, fexofenadine, clemastine and loratadine were investigated by researchers in a nation-based study of all 61,627 Swedish women identified with breast cancer from 2006-2013. By using Cox regression models both pre- and post-diagnostic antihistamine use was analysed. Based on subgroup and age oestrogen receptor status and menopausal status were executed. Within the patient population based on safety and current use scientists found that desloratadine users had improved survival rates including loratadine users compared to non-users, irrespective of menopause status, oestrogen receptor status and patient age. Other antihistamines

which were consumed by survival users experienced change compared to non-users . The TMC engage in a huge role in the progression of cancer. Throughout the metastatic period, the malignant cells familiarize themselves with the TMC and activate pathways to promote tumor growth by using local signals. In the breast cancer progression, TAK-1 activating cytokines are present in TMC, higher level of interleukin-1 has been linked with the aggressive proliferation of breast cancer . The latest verdict has shown that the anti-histamine drug Loratadine can also have anti-inflammatory properties even though the exact mechanism is still unknown. In this researchers investigated if loratadine can be used as an anti-inflammatory drug through in-vitro and in-vivo experiments using macrophage cell lines. Later it was concluded that loratadine exhibits anti-inflammatory action in macrophage cell lines, specifically inhibiting the AP-1 signaling pathway and targeting TAK-1**(Figure 7),** and suppressing AP-1 transactional activity. In this manner, it reduces the pro-inflammatory mediator's expression together with MMP3, MMP1, and MMP9 . The researchers believe further studies of H1-antihistamine use needs to be conducted for survival in breast cancer .

ROLE OF ANTI-HISTAMINE IN MELANOMA

A serious type of skin cancer melanoma also known as melanocytes releases melanin. It may also form rarely in our eyes as well as inside our body, for example, nose and throat. The exact cause of melanoma is unknown, but it may increase the risk of melanoma if the individual is exposed to UV sunlight or any lamp. It occurs mostly in people under the age of 40, mainly in women. The melanoma signs and symptoms such as a change in an existing mole or the development of any fresh pigmentation . In a research letter published in the journal allergy, Investigator reported that ordinary allergy medication loratadine and desloratadine can be linked with improved survival in patients with melanoma . Previously it was found that similar antihistamines have shown survival gains and increasing evidence of H1 antihistamines inhibiting malignant growth and encouraging cell death in several tumors. The same concerns were shown for malignant melanoma, hence researcher investigated six anti-histamines namely, cetirizine, loratadine, desloratadine, clemastine, fexofenadine and ebastine . From big registers i.e. cancer register, drug register, and causality register information were matched of Swedish patients who were diagnosed with melanoma in 2006-2014 (n= 24,462), among these 1,253 were antihistamine users. A total of 395 patients were taking desloratadine, 324 patients taking cetirizine, and loratadine patients taking 251 whereas other anti-histamine were given to a few individuals. The follow-up studies were finished in December 2018, after observation researchers found a link between improved survival for malignant melanoma patients taking desloratadine and loratadine between the age group of 65 and older patients not using antihistamine medication. These can also help in advanced stages of cancer as the verdicts are stimulating, moreover, the medication has no practical side effects. To understand the mechanism of action, suitable dose for humans, and optimum treatment period the investigator team is currently planning animal studies and randomized studies .

ROLE OF ANTI-HISTAMINE ON NON-SMALL LUNG CANCER

NSLC is one the most threatening and common cancer, like all cancer it starts at the cellular level and causes abnormal malignant cancer in the lungs and quickly spreads and reproduce out of control . The majority of patients are detected only after cancer spread beyond the primary site. Treatment of Patients is mostly a combination containing platinum-based therapy and microtubule-distributing the most advanced cancer-required resistance to therapy, though there are other challenges for NSLC . To explore more options related to the treatment of NSLC, the investigator examined 72 CAD drugs based on their profile on clinical safety and capacity to prevent sphingomyelinase for cytotoxicity archive against NSLC cells and found many CAD anti-histamine inducers for lysosomal destabilization. In Denmark between 1995 and 2011, Researchers executed a cohort study on the outcome of CAD anti-histamine used on the mortality of patients identified with non-localized cancer. Loratadine and astemizole the most commonly prescribed CAD anti-histamine was linked with notably decreased all cause of mortality among patients having non-localized non-small lung cancer or any non-localized cancer while it was compared with non-CAD antihistamine. Another CAD anti-histamine ebastine showed a related tendency. Within six months after the diagnosis patients with non-localized cancer were stratified (2002-2012) according to the evidence of chemotherapy (registered N=34,394 or non-registered N=42,267). The most commonly prescribed CAD anti-histamine loratadine revealed statistically notably

inverse linked with mortality, a lowered record of Chemotherapy and HRs among loratadine users . The appropriate dosage of loratadine and astemizole results in lower plasma concentrations than those essential for the prevention of NSLC cell growth or survival in vitro. Therefore, it was observed that CADS alone does not cause anti-cancer side effects, sooner it was evaluated that it was caused by the combined effect of low concentration of CAD anti-histamine and chemotherapy . It was reported that in chemotherapy MDR1-mediated resistance is one of the big long terms for this patient group, at micro molecular concentration it was reported that some CAD anti-histamine reverted MDR1-mediated resistance. Therefore, they tested CAD anti-histamine whether it can sensitize MDR1-expression NSLC to chemotherapy. As the MDR1 expression was not detectable they created an MDR-variant of A459 cells by continuous treatment with increasing the concentration of vinorelbine. Loratadine, ebastine and astemizole re-sensitized the obtained A549-MDR cells even at 500 nM also Terfenadine did in 1nμ . It was also informed that astemizole and Terfenadine prevent the efflux action of MDR1 at IC_{50} of 1.4 and 1.3 μM, correspondingly. Investigator also tested other CAD anti-histamine drugs namely, loratadine and ebastine to examine the similar concentration relevancy for re-sensitization. Later, it was shown that Loratadine and ebastine failed to inhibit the activity of MDR1-action but they can revert the drug resistance by specific mechanisms . After all the data collected by researchers suggested that inexpensive and safe CAD anti-histamine can be used in cancer treatment and might boost the anti-neoplastic reaction to chemotherapy specifically in the situation of micro-tubule drugs. Scientists are now looking forward to doing more pre-clinical and clinical studies shortly for advanced cancer therapy with antihistamines .

ROLE OF ANTI-HISTAMINE IN PROSTATE CANCER

In the prostate gland, cancer cell starts to grow in an uncontrolled manner, it is mostly found in males and create some fluid that is part of semen. The cell of the prostate gland appear smaller than normal and found signs of inflammation in that location which is called Proliferative inflammatory atrophy. Though it is not cancer it is linked directly to prostate cancer . The catalytic component of polycomb repressive complex 2 and a histone lysine methyl transferase, enhancer of zester homolog 2 (EZH2) has been examined as a chromatin regulator and for the most part in cancer it is mutated . The Polycomb group proteins form repressive complexes (PRCs) with varied and preserved proteins that achieve their purpose as central epigenetic modifiers and transcriptional regulators in several cellular methods, involving cell cycle, cell differentiation, DNA injury repair, renewal of stem cell, and progression as well as the development of disease . Many studies have reported that EZH2 overexpression boosts cancer cells' proliferative possessions while striking down EZH2 could encourage apoptosis and autophagy in cancers. Notably, the new indication discloses that H3K27 plays a crucial role in epigenetics . Groups of scientists have reported that EZH2 is a biomarker of destructive prostate together with breast cancer. The expression range of EZH2 is deeply immersed in the development of prostate cancer. While in benign cells EZH2 expression is undetectable, EZH2 mRNA as well as protein levels are elevated in progressive cancers. In prostate and breast cancer, EZH2 overexpression indicates an increased opportunity for metastasis and adverse clinical prognosis . In the quest for novel therapy plans for progressive cancers, EZH2 grants be a hopeful treatment target. Remarkable labor has been made to produce little molecule inhibitors opposite to EZH2. The first identified EZH2 inhibitor 3-deazaneplanocin A (DZNep) targets S-adenosyl-L-homocysteine hydrolase (SAH), a cofactor known to be essential for EZH2-dependent methylation . DZNep reduces the EZH2 protein range, but it is not a perfect EZH2 inhibitor due to its non-specific inhibition of histone methylation and extreme toxicity in animal models . Therefore, we testify that a second-generation antagonist of the histamine H1 receptor ebastine, which has been widely assessed for its toxicity combined with safety and is approved for anti-allergy therapy in several European countries, could be reutilized for cancer treatment by aiming EZH2 in cancer . Many investigators stated that the biomarker EZH2 is aggressively high in prostate cancer progression. In benign cells, the EZH2 expression is low and untraceable. The protein levels and mRNA of EZH2 are high in progressive cancer . It was found that the Increase possibility of metastases is due to overexpression of EZH2 expression in prostate cancer. EZH2 stands as a hopeful therapeutic target in the hunt for new therapeutic strategies for progressive cancer. Newly, many anti-histamine medications turned out to successfully prevent malignant tumor progression. In addition to the anti-histamine medication, astemizole revealed that it can disturb

the EZH2-EED relation and introduce degradation of EZH2. Sadly, astemizole was discontinued since it can cause ventricular arrhythmia. During the search for further anti-histamine drugs were examined to observe the possible decrease in EZH2 protein levels in malignant cells . Ebastine is a new EZH2 inhibitor by targeting specifically the EZH2 transcription and decreases the EZH2 protein level and trimethylation H3K27 in several cancer cell lines at below concentration 10 μmol/L. Impairment of progression of cancer, migration done by ebastine. After the therapy with ebastine medication, it released the neoplastic things of these malignant cells, signifying that EZH2 is independent of its enzymatic progression which is the main target for Ebastine. Furthermore, tumor growth and progression are successfully reduced by ebastine therapy and improved the progression-free existence in patients derived drug resistance-castration prostate cancer in xenograft mice model. Researchers established that ebastine is a safe and effective anti-cancer medication for patients with advanced cancer by affecting the EZH2 oncoprotein .

ROLE OF ANTI-HISTAMINE IN OVARIAN CANCER

The reproductive organ ovary is located in the female body and produces eggs for reproduction. Ovarian cancer indicates any malignant tumor growth that starts with the ovary. In females, specifically in the United States, it is 7^{th} most common cancer . Despite having advanced ovarian cancer therapy, the mortality rates keep on increasing. It is becoming a clinical priority as researchers are still exploring strategies to improve the survival rates of ovarian cancer. The allergy medication anti-histamine is repurposed as it gained more interest and many laboratory studies are testifying the effects of anti-neoplastic. Lately, it was discovered that CAD anti-histamine is linked with a decrease in mortality percentage among patients with progressive cancer . This verdict encouraged them to examine the potential effects of CAD anti-histamine on ovarian cancer patients, so they conducted a nationwide cohort study of patients suffering from ovarian cancer. The researchers found all women between 34-84 years with a case of ovarian cancer during 2000-2015, in their cohort studies total of 5075 female patients' participated. One or maybe more filled anti-histamine recommendation around six months of diagnosis of cancer and onset of follow-up was considered . The follow-up stage begins 1-year baseline or a three-year baseline with the cancer diagnosis and is terminated until the person died, relocates or the study ended (Dec 31, 2016) whichever happens first. For ovarian cancer, Cox regression models were used by researchers to approximate HRs ratio with 95% confidence intervals. After therapy with clinically applicable doses of 8 anti-histamine cell viability assay was conducted to examine the cell death in three ovarian cancer cell lines. In their cohort study, compared to the non-CAD anti-histamine user was linked with a reduction rate estimated at around 20-35% in ovarian cancer. As it was evaluated that CAD is the group of compounds that gather in acidic lysosomes and induce permeabilization of the membrane of the lysosomal, preceding cell death. Cancer-specific toxicity has been shown by CAD anti-histamine in many in vivo and in vitro studies. Particularly in tumour lysosomes which tumours acidic tumours, CAD antihistamines are gathered up to 1000 folds. It was also hypnotized that CAD antihistamine may revert the multidrug resistance in ovarian cancer cell lines including other cancer cell lines. As the reporters at the end concluded that in a nationwide cohort study at the current dosage with CAD characteristic of anti-histamine the pieces of evidence suggested that patients can get prognostic benefits in patients with ovarian cancer. Recent CAD anti-histamine is well tolerated, inexpensive and have no toxicity and are already commonly used in cancer patients. CAD anti-histamine may become promising therapy for ovarian cancer patients and researchers should further know more about the benefits of CAD anti-histamine .

CONCLUSION

The drugs which are used to cure runny noses and watery eyes throughout the allergy season may also treat tumour progression in cancer. Anti-histamines contain certain anti-cancer properties that hinder a type of cell which decreases the body's potential to fight the malignant tumour. Many cancers such as colorectal cancer, breast cancer, prostate cancer, ovarian cancer and melanoma found aggressively high levels of histamine receptors. The findings of particular studies estimated on cancer cell growth besides the impact of mast cell mediators recommended that in future cancer therapeutics, mast cells could be a positive target because as inhibition of these mediators prevents cancer growth, inhibition of pro-inflammatory mediators by degranulation of mast cell. In cancer therapy, Compared to chemotherapeutic agent antihistamines are

a lot safer and have low toxicity. It is redeemed to learn the promising effect of the most common over-the-counter medication anti-histamine. The researchers are thrilled to know more about the connection between inflammation and cancer. However, more investigation is needed to determine whether anti-histamine can be used effectively in cancer treatment. Although it's not the time to use anti-histamine in cancer prevention, still need to read and research more suppressor cells as their product can become immunotherapy targets for cancer. It is important to shed light on the precise concentration of histamine receptors in different areas as well as the kinds of tumors and their activation in certain tumor growth by estimating them in vitro and in vivo studies before recommending anti-histamine as a new cancer medication to cancer patients. Recent studies suggest that researchers should be open-minded about examining the immune process or mechanism superficially.

Abbreviations

AP-1	Activator protein 1
BFGF	Basic fibroblast growth factor
CAD	**C**ationic Amphiphilic Antihistamines
Fc RI	Fc Epsilon R1
IBD	Inflammatory bowel disease
IgE	Immunoglobulin E
IgM	Immunoglobulin M
IL-4	interleukin 4
IL-8	Interleukin 8
MMP3 MMP1 and MMP9	Matrix metalloproteinase
TAK-1	TGFbeta Activated Kinase 1
TGF-β	Transforming growth factor-beta
Th2	T helper type 2
TME	Tumour Microenvironment
TNF-α	Tumour necrosis factor-alpha
VEGF	vascular endothelial growth factor
VISTA	V-domain immunoglobulin suppressor of T cell activation

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