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Targeted therapy with histamine antagonists - New challenges to fight with breast cancer

**Piotr Więsyk¹, Paulina Oleksa¹, Zuzanna Chilimoniuk¹, Maciej Dobosz¹,
Maciej Sobczyk, Małgorzata Słaboń¹**

1. Students' Research Group at the Department of Family Medicine, Medical University of Lublin

Piotr Więsyk
ORCID ID: <https://orcid.org/0000-0001-6785-6741>
E-mail: piotrwieisyk@gmail.com

Paulina Oleksa
ORCID ID: 0000-0002-3474-6156
E-mail: gp.oleksa@gmail.com

Zuzanna Chilimoniuk
ORCID ID: <https://orcid.org/0000-0001-8261-0192>
E-mail: zuzia_chil@wp.pl

Maciej Dobosz
ORCID ID: <https://orcid.org/0000-0002-4413-3310>
E-mail: macdob.98@gmail.com

Maciej Sobczyk
ORCID ID: <https://orcid.org/0000-0003-1857-2413>
E-mail: maciejso@onet.pl

Małgorzata Słaboń:
Orcid ID: <https://orcid.org/0000-0003-1627-8878>
E-mail: malgorzata.slabon@wp.pl

Abstract

Breast cancer (BC) is currently the most commonly diagnosed cancer in women. BC is most often derived from the epithelial tissue of the mammary gland and is a global problem due to the steady increase in morbidity and mortality in most countries. A particular problem today is the triple negative subtype (TNBC), which accounts for approximately 10-15% of breast cancer cases. BC occurs most frequently in young women and is characterised by various biological characteristics, an unfavourable clinical course and a poor prognosis. Recent studies to detect the effects of histamine receptors on breast cancer have shown that all H1R-H4R receptors are also hyperactive in the cancer microenvironment. Chronically maintaining a high level of histamine in the tumour-affected tissue contributes to increased angiogenesis at this site, induction of cancer cells proliferation and T lymphocyte dysfunction. The rising incidence of breast cancer is contributing to an increasing amount of research into targeted therapies. Studies on the effect of histamine antagonists through H1R-H4R receptors have proven their effectiveness in the treatment of breast cancer. Among those in the study, there was a reduction in tumour growth, cell proliferation and an increase in apoptosis. The use of histamine antagonists also contributed to a reduced risk of death from breast cancer and increased overall survival (OS). Therefore, targeted therapy is needed to improve the prognosis of patients with breast cancer.

Key words: Histamine, Histamine receptor, Breast cancer

1. Introduction and purpose

Breast cancer (BC) originates from the epithelium of the mammary gland [1] and is now the most commonly diagnosed cancer in women [2]. Currently there is a continuous increase in its morbidity [3] and mortality [4]. According to a recent report by the World Health Organisation, in as many as 91 countries, cancer mortality in the under-70s population was the 1st or 2nd cause of death [5]. The high incidence of the disease has contributed to a growing body of research into the possibility of alternative forms of treatment [6]. The triple-negative subtype (TNBC) represents approximately 10-15% of all cases of breast cancer. It is most common in young women and is characterised by different biological features, an unfavourable clinical course and a poor prognosis. This subtype of breast cancer represents an important area of research for a new specific targeted therapy due to the insufficient effectiveness of existing therapies [7,8]. It has been shown that the level of histamine in the affected tissues is an important element, especially in the case of breast cancer, but also of the skin, colon or lung or pancreas. The cancer microenvironment contains a large number of histamine receptors H1R, H2R, H3R and H4R and high histamine concentrations. Therefore, targeted therapy is needed to improve the prognosis of patients with breast cancer. Recently, an increasing number of studies confirm the positive effect of histamine antagonists in the treatment of breast cancer [9].

2. Mechanism of action of histamine and its receptors

Histamine is a biogenic amine that is produced primarily by mast cells and basophils. Platelets, lymphocytes and macrophages are also involved in its production in small amounts. Although histamine is present in the body in relatively low amounts it is probably one of the most pleiotropic molecules currently known in the human [10]. It plays a significant role in inflammatory processes [11], neurotransmission [12], pain perception [13] but is also involved in cancer processes [14], the development and progression of cancer. There are currently four histamine receptors: H1, H2, H3, H4. They are named respectively according to the order in which they were discovered [15]. The enzyme responsible for histamine production is histidine decarboxylase (HDC). Moreover due to the increased expression of the HDC enzyme at the site of cancerogenesis, it is possible that it will be used as a marker in breast cancer [16,17] Additionally histamine is involved in tumour cell proliferation, ageing, and apoptosis which opens up another perspective for the introduction of new cancer therapies using antihistamines [18]. Research confirms that the microenvironment of cancerous tissues contains a high concentration of histamine and the number of H1R-H4R receptors. In addition, their high level may persist up to several months after the excision of the neoplastic lesion [9]. The figure below shows the pleiotropic mechanisms of action of histamine in the tumour-affected tissue.

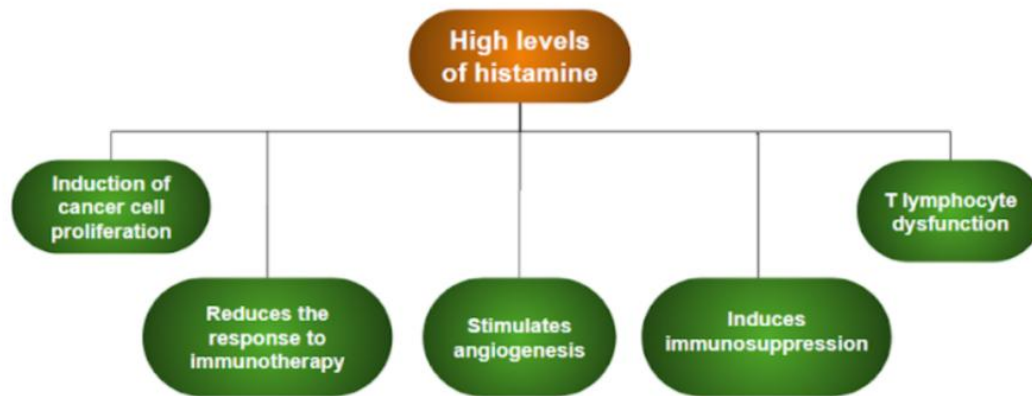


Fig. 1. The influence of high levels of histamine on cancer-related processes

3. Role of Mast Cells:

Mast cells (MC) are derived from hematopoietic stem cells and are primarily characterised by their pleiotropic action [19]. They are a crucial part of the immune response [20]. MCs are involved in inflammatory processes and allergic reactions [21], but it also turns out that they also contribute to processes that protect against cancer and are involved in their development [22]. However, the exact processes involving MC cannot currently be determined. The interference of mast cells in the spread of neoplastic processes occurs through enhanced angiogenesis and increased migration of neoplastic cells as a result of the destruction of the extracellular matrix [23]. Mast cells accumulate in the tumour stroma, influencing the formation of its microenvironment [24]. This is due to their interaction with tumour-affected cells, immune response cells, and the extracellular matrix [25]. According to studies, their increased number within the tumour may be associated with a better or worse prognosis, which depends on the type of tumour and its stage [24]. Extensive research is needed to understand the exact mechanisms of accumulation of mast cells and histamine and its H1R-H4R receptors, which could contribute to alternative forms of treatment for triple-negative breast cancer [26]. It is currently known that increased MC density in axillary lymph nodes in breast cancer has been associated with a better prognosis in many studies [27].

5. Correlation between histamine receptors and breast cancer

The tumour microenvironment in patients with breast cancer is characterised by hyperactivity of the HDC [28] enzyme compared to healthy tissue in the control group. This results in an increase in the level of histamine in the tissue affected by the tumour [29]. Previous studies to detect the effects of histamine receptors in breast cancer have shown that all H1R-H4R receptors are also overactive in the cancer microenvironment [30]. In addition, in mice, the histamine H1R and H2R receptors had a significant role in the progression and induction of breast tumours in mice. A reduction in the incidence of breast tumours has been reported as a result of the administration of H2R antagonists [31,32]. Additionally, H1R [33] and H2R are over productive which has been associated with a worse prognosis for patients[34]. The mechanism of action of H1R antagonists is to reduce cell proliferation. Also by interfering with the cell cycle, by increasing the G0 / G1 phase and reducing G2 / M which suggests that drugs that affect the H1 receptor may contribute to cell death in breast cancer [35]. It is also worth mentioning the EAG1 protein which induces breast cancer cells to the G1 phase of the cell cycle, which leads to carcinogenesis [36]. Some of the H1R antagonists have the ability to bind to EAG1 channels and inhibit the expression of this gene, which reduces the chances of induction of breast cancer [37].

According to the available sources, the unequivocal effect of histamine on the tissues covered by neoplastic cells cannot be determined. The amount of histamine at the site of the neoplasm affects the cell proliferation in breast tumours in different ways. The low amount acting through the H3R receptor limited cell proliferation [38]. Currently, research is mainly being conducted on the effects of the H4R receptor, which was discovered last. It is overexpressed in breast cancer, but also in other cancers, such as lung cancer, gastrointestinal cancer and skin cancer. It plays an important role in the immune response [17,39]. Furthermore, it turns out that the H4R receptor may prove to be a useful marker in monitoring triple negative breast cancer (TNBC). Its increased expression correlated with increased patient survival. It is important to emphasise that there are no specific markers in TNBC at this time [40].

During the study, mice lacking the H4R receptor had significantly less tumour growth and percentage of CD4+ tumour-infiltrating T cells. However, the number of Natural Killer cells increased. In this regard a key role for targeted therapy in triple-negative breast cancer is probably to be played by the H4R receptor [39].

6. Effect of histamine antagonist on breast cancer

Histamine has been shown to play an important role in breast tumour growth and tumour cell proliferation in several mouse studies. It was possible to establish that the main mechanism acted through the H2R and H4R. Moreover, by administering H2R antagonists to mice, it was possible to reduce tumour growth and cell proliferation [27,41]. However, when Cimetidine (H2R antagonist) was tried on breast cancer patients, it did not improve prognosis [42]. H2R and H4R receptors are involved in the regulation of both CD4+ and CD8+ T lymphocytes. According to a breast cancer study, increased CD4+ lymphocytes in patients led to reduced overall survival (OS). Increased OS in patients was correlated with a low CD4/CD8 ratio as a result of the administration of H4R antagonist [43].

It's also worth mentioning that another study confirming the beneficial effects of histamine on reducing tumour size is one conducted on mice. Mice in this study were exogenously administered histamine dihydrochloride (HDC) which is an immunomodulator that affects the activity of the immune system. This increases the effectiveness of interleukin-2, which stimulates the immune system to attack cancer cells. Mice were administered the exogenous route of histamine dihydrochloride three times a week, resulting in a remarkable reduction in tumour size as compared to the control trial [44]. In addition, it has been shown that antagonists of the histamine H1R receptor limit cell growth and contribute to increased apoptosis through ERK activation in vitro in various tumour cell lines [45,46]. Moreover, these mechanisms only take place in the primary and HER2 breast cancer cells [47]. Among the drugs affecting the H1 receptor, desloratadine and loratadine play a crucial role, increasing survival in women with ER (-) and ER (+). The desloratadine and ebastine are also noteworthy due to the results which indicated a reduced risk of death from breast cancer in women before and after menopause [48]. The study of Astemizole, which is an H1R antagonist, also proved to be noteworthy. Through the mechanisms presented in Fig.2, it contributes to the increased survival of patients with breast cancer [35].

Fig.2 Mechanisms of action of Astemizole (H1R antagonist)

7. Combination therapy & histamine

Currently, a growing number of studies are aiming to find combination therapies associated with histamine antagonists but the main difficulty with finding an appropriate treatment is that histamine antagonists do not always improve patient outcomes when administered alone. However, the synergistic action of some of the drugs such as cetirizine with thalidomide makes it possible to reduce angiogenesis and tumour size. Moreover, neither of these drugs, when administered alone, had an effect on angiogenesis or reduction of tumour size [49]. The combination of immunotherapy with antihistamine in the treatment of triple-negative breast cancer also brings positive results through an immunostimulating effect and leading to the normalisation of the micro-environment of neoplastic cells [50]. It is also worth mentioning that high levels of histamine contribute to disorders of T lymphocyte function, induction of immunosuppression and increased resistance to immunotherapy. Recently it has been proven that pharmacological maintenance of histamine at a low level using histamine antagonists acting through H1R brings better results of immunotherapy in cancer patients [51]. Phagocytes inhibit signal transmission to NK cells, which accelerates neoplastic processes. However, this process is prevented by the administration of histamine with interferon-alpha, contributing to the killing of tumour cells by NK [52].

Besides this, research is also being conducted on the effect of histamine of radiotherapy. The results indicate that histamine can block epithelial-to-mesenchymal transition events in infiltrated tumour cells. This is another alternative treatment pathway suggesting the usefulness of using histamine in the treatment of breast cancer by radiotherapy [53].

SUMMARY:

At present, we do not know the complicated mechanisms of action of drugs affecting H1R-H4R receptors on the proliferation and proliferation of neoplastic cells in breast cancer. At this point in time, many research results are controversial and inconclusive. Drugs that interact with H1R-H4R receptors have different effects depending on tumour type and stage. Therefore additional multiple studies are necessary. Histamine is known to play an important role in the tumour microenvironment, which affects the subsequent prognosis of patients. The search for new alternative methods may contribute to increased 5-year survival in triple-negative breast cancers. Continued research on the histamine H4R receptor seems promising. Its overexpression is associated with a better prognosis of patients. It may prove to be particularly useful as a prognostic marker in

triple negative breast cancer, which so far does not have any specific markers of its own. Work on an effective drug in the treatment of breast cancer should be continued due to the fact that antihistamines have a high level of safety and have a low cost of production.

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