Enhancing immunotherapy efficacy with the use of Antihistamines in cancer patients-A review of published studies

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Background

Histamine, released during allergic reactions and by tumor cells, impairs the response to immunotherapy. However, antihistamines have been shown to improve immunotherapy outcomes in cancer patients due to their ability to counteract histamine-H1 receptor signaling that promotes cancer progression. In allergic reactions, histamine is released by mast cells and basophils due to allergen-triggered IgE-Fcε receptor 1 crosslinking. Tumor cells themselves can also generate histamine. Tumor-associated macrophages (TAMs) are the primary cell type expressing histamine H1 receptors (H1R). Activation of H1R in TAMs leads to several effects: (1) transformation of TAMs towards an M2-like phenotype based on gene expression; (2) initiation of calcium release inside cells; (3) elevation of VISTA molecule on the cell surface; (4) suppression of CD8+ T cell activity, including the release of interferon-gamma (IFN-g) and perforin-1 (PRF-1), achieved through VISTA's interaction with its putative receptor, P-selectin glycoprotein ligand-1 (PSGL-1) on T cells. These outcomes of histamine's actions contribute to tumor growth and hinder the body's response to immunotherapy using anti-PD-1 and anti-CTLA-4 monoclonal antibodies (mAb). H1-antihistamines obstruct histamine binding to H1R on TAMs, thereby mitigating the previously mentioned tumor-promoting consequences of histamine. Consequently, the use of H1-antihistamines enhances the immune response against tumors and augments the effectiveness of immunotherapy (figure 1) (1). In addition, M1 macrophage polarization may be induced by H1-Antihistamin through the interferon-gamma pathway. This effect may synergize with the immunotherapy of advanced cancers such as melanoma

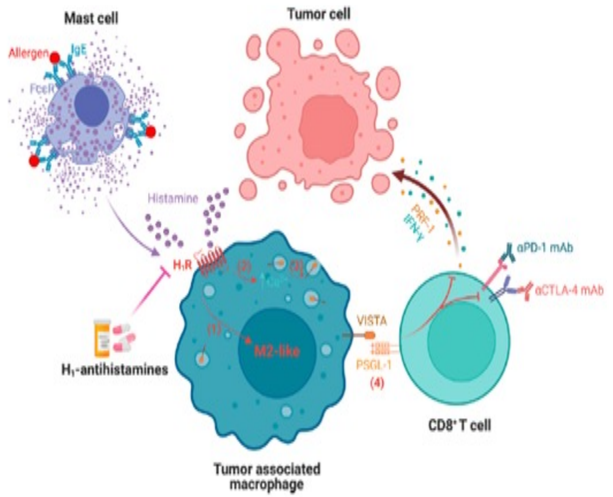

Figure 1. illustrates the impact of H1-antihistamines on various aspects of immune response and cancer treatment.

Methods

Study Purpose	Evaluate published results of the effect of cationic amphiphilic antihistamines in patients receiving immune checkpoint inhibitors (ICIs)	Review published results to evaluate the use of antihistamine to see whether improved survival can be seen in tumors with and without a known response to immune checkpoint therapy, such as anti-CTLA-4 or anti-PD-1	Assess the publication to evaluate the effect Of cationic amphiphilic antihistamines on lung cancer patients receiving ICIs	Analyze the publishes results to evaluate additive effect of anti-PD-1 agents (by promoting M1 macrophage polarization) and cetirizine in patients with advanced melanoma
Study Design	-Retrospective propensity score-matched cohort study at two tertiary referral centers in Taiwan between 2015 and December 2021 - 734 ICI treated patients (68 cationic and 68 non-cationic antihistamin) Adult patients diagnosed with stage IV cancer(mostly lung) and treated with at least two cycles of ICI+ cationic H1 antihistamine (cyproheptadine(mostly prescribed), and ebastine , desloratadine) vs non antihistamine users -Antihistamine use was defined as any prescription of antihistamines given within 30 days of immune checkpoint blockade - Validated clinician-anchored and radiology data to evaluate tumor response	- Nation-wide cohort of all 429,198 Swedish patients - Use of six common H 1 -antihistamines (cetirizine, clemastine, desloratadine, ebastine, fexofenadine and loratadine) - Ten types of immunogenic (gastric, colorectal/anal, pancreatic, lung, breast, prostate, kidney, and bladder cancer, melanoma and Hodgkin lymphoma) and six non-immunogenic (liver, uterine, ovarian, brain/CNS, and thyroid cancer and non-Hodgkin lymphoma) -The most common antihistamine used was cetirizine with 8,606 users, followed by desloratadine (8,269 users), clemastine (8,167 users) and loratadine. (5,957 users), and 396,667 pts are non-users. - Follow up 2006-2019 - Analyses of use of all six antihistamines were done using Cox regression model with time to tumor-specific death	- Two Retrospective cohort studies in Taiwan - 336 lung cancer patients receiving ICIs - 294 antihistamine users (43 cationic amphiphilic and 222 non-cationic amphiphilic) and 42 non-antihistamine users. - Antihistamines subclassified into cationic amphiphilic and non-cationic amphiphilic according to their lipophilic properties	- A retrospective study was carried out in Naples, Italy - 121 adult patients with metastatic melanoma IIIb–IV, treated with an anti-PD-1 concomitantly with cetirizine on the day of immunotherapy - Anti-PD1 medications: Pembrolizumab or Nivolumab in 1st (mostly) or 2nd line of the treatments - Cetirizine had been used as a premedication on the day of immunotherapy (10 mg once) - Cetirizine treatment was used concomitantly with anti-PD-1 in 71/121 patients, in 49/88 patients naïve to checkpoint inhibitors , and in 22/33 patients pretreated with ipilimumab (named pretreated thereafter) - A transcriptomic analysis was performed on blood samples obtained at baseline and after 3 months of treatment - Evaluate patients from July 2014 -2018 - Evaluation of outcomes via RECIST 1.1 criteria
Outcomes	- Primary outcome: OS - Secondary outcomes: PFS	-Improved survival	- Disease progression - PFS	- PFS - OS
References	2	3	4	5

Results

Outcome/ End point results	Statistics		
A: Antihistamine users had a longer mOS and mPFS B: Among antihistamine users, cationic amphiphilic antihistamine users had a longer OS and PFS than non-cationic amphiphilic antihistamine users C: The use of cationic amphiphilic antihistamines before the initiation of ICIs was not associated with a decreased risk of mortality or disease progression	A: Antihistamine user's vs non- users	- OS (median 24.4 vs. 6.4 months, p = 0.002) - PFS (median 8.2 versus 4.1 months, p = 0.049)	2
	B: Cationic amphiphilic vs non-cationic amphiphilic antihistamine users	- OS (24.8 versus 10.4 months; P=0.018) - PFS (10.6 versus 4.93 months; P=0.004)	
	C: Patients who had received cationic amphiphilic antihistamines before the initiation of ICI vs non-users	- OS (19.5 vs 19.3 months; P=0.89) - PFS (7.7 vs 6.0months; P=0.92)	
H1 Antihistamines (mostly desloratadine) are associated with an improved survival for all immunogenic tumor's vs non-immunogenic ones	Immunogenic (Desloratadine)	Hodgkin lymphoma Improved survival HR:0.40 (0.10-1.62) 95% CI	3
	Non-immunogenic (Desloratadine)	Non- Hodgkin lymphoma Improved survival HR:1.18 (0.93- 1.50) 95% CI	
A: Antihistamine vs. non-antihistamine have less disease progression and more PFS B: Cationic amphiphilic antihistamine vs. non-cationic amphiphilic antihistamine have less disease progression and more PFS	A1: Disease progression A2: PFS	A1:HR (95% CI): 0.67 (0.45-0.99), P=0.049 A2: PFS (median 8.2 vs 4.1 months, p = 0.049	4
	B1: Disease progression B2: PFS	B1:HR (95% CI) : 0.48 (0.32-0.73), P=0.001 B2: PFS (median 17.5 vs 6.2 months, p < 0.001	
A: Patients treated with cetirizine concomitantly with an anti-PD-1 agent had significantly longer PFS and OS in comparison with those not receiving cetirizine. B: The expression of specific Marker of M1 macrophage, was increased in patients receiving cetirizine with anti-PD1	A: cetirizine concomitantly with an anti-PD-1 vs no-cetirizine	- mean PFS: 28 vs 15 months, HR 0.46, 95% CI: 0.28–0.76; p = 0.0023) - mean OS was 36 vs 23 months, HR 0.48, 95% CI: 0.29–0.78; p = 0.0032)	5
	B: M1 macrophage interferons	- CCL8 interferon (rho = 0.32; p = 0.0111), IFIT1 interferon (rho = 0.29; p = 0.0229)	

Conclusion:The findings from these studies collectively indicate that certain antihistamines, particularly those with cationic amphiphilic properties like cetirizine, desloratadine, and loratadine improves on activity of immunotherapy. These antihistamines appear to influence macrophage polarization, inhibit histamine-induced immune suppression, and enhance overall survival among cancer patients receiving immunotherapy. This suggests a potential role for antihistamines in improving the outcomes of cancer immunotherapy treatments, particularly in cases of lung cancer and other cancers where histamine-related immune responses play a significant role. Further research is warranted to explore the precise mechanisms and clinical implications of these findings.

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