Enhancing immunotherapy 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, and approximately 2-5% of IgE-Fc 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 toward a M2-like phenotype based on gene expression; (2) inhibition of calciton release inside cells; (3) elevation of VISTA molecule on the cell surface; (4) suppression of CD8+ T-cell activity, including the release of interferon-γ (IFN-γ) and programmed death-ligand 1 (PD-L1), 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 monomolecular antibodies (mAbs). H1R-antagonists obstruct histamine binding to H1R on TAMs, thereby mitigating the previously mentioned immunosuppressive 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, macrophage polarization may be induced by H1-Antihistamin through the interferon-γ–macrophage pathway. This effect may synergize with the immunotheroapy of advanced cancers such as melanoma.

Figure 1. Illustrates the impact of histamine-H1 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 antihistamines 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

Study Design
Retrospectively propensity score-matched cohort study to two tertiary referral centers in Taiwan between 2015 and December 2021: 734 ICI treated patients (68 cationic and 66 non-cationic antihistamines) Adult patients diagnosed with stage IV cancer (mostly lung) and treated with at least two cycles of ICIs-cancer H1 antihistamine (ciprofibrate/propranolol), and pseudoephedrine/dextroantihistamines

Antihistamine use was defined as any prescription of antihistamines given within 30 days of immune checkpoint blockade.

Validated clinician-analyzed and radiology data were evaluated to evaluate tumor response

Outcomes
Primary: OS; Secondary outcomes: PFS

Results

Outcome: End point results

1. Antihistamine users had a longer mOS and mPFS

2. Among antihistamine users, cationic amphiphilic antihistamines had a longer OS and PFS than non-cationic antihistamines.

3. The use of cationic amphiphilic antihistamines before the initiation of ICIs was not associated with a decreased risk of mortality or disease progression

4. H1 Antihistamines (mostly desloratadine) are associated with an improved survival for all immunogenic tumors vs non-immunogenic ones

5. Antihistamine use did not have a significant effect on overall survival of patients treated with immune checkpoint inhibitors

6. Antihistamines were used concomitantly with anti-PD-1 for 71/121 patients, in 49/88 patients naive to checkpoint inhibitors, and in 22/23 patients pretreated with pembrolizumab (n=17) and nivolumab (n=5) for management and morbidity of treatment

7. Concomitant antihistamines were used in 33 lung cancer patients receiving Pembrolizumab or Nivolumab in 1 (mostly) or 2 lines of the treatments

8. Cytokine had been used as a premedication on the day of immunotherapy (10 mg once)

9. Antihistamine use was improved by concomitant with anti-PD-1 in 71/121 patients

Conclusions: The findings from these studies collectively indicate that certain antihistamines, particularly those with cationic amphiphilic properties like cetirizine, desloratadine, and loratadine improve on activity of immunotherapy. These antihistamines appear to influence macrophage polarization, inhibit histamine-induced immune suppression, and enhance immune response among cancer patients receiving immunotherapy. This suggests a potential role for antihistamines in improving the outcomes of cancer immunotherapy treatments, particularly in cases of 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.

References

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