Impact of antihistamines use on immune checkpoint inhibitors response in advanced cancer patients

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Abstract

Background

Histamine and H1 receptor play a crucial role in the tumor microenvironment. Preclinical data showed that concomitant use of antihistamines and immune checkpoint inhibitors (ICIs) may increase the effect of ICIs. This study aimed to evaluate impact of antihistamines on oncological outcomes of ICIs.

Patients and Methods

This retrospective study was conducted in a tertiary cancer center. Advanced cancer patients treated with ICIs were included in this study.

Results

A total of 133 patients receiving ICIs in the metastatic setting were included. Melanoma (33.1%) was the most common tumor type. The most common ICI was nivolumab (63.2%). Fifty-five (38.4%) patients received antihistamines concomitantly with ICIs. The most common antihistamine was pheniramine (85.5%). The median progression-free survival (PFS) (8.2 vs. 5.1 months, log-rank \(p = 0.016\)) and overall survival (OS) (16.2 vs. 7.7 months, log-rank \(p = 0.002\)) were longer in patients receiving antihistamines concomitantly with ICIs. In multivariate analysis, PFS (Hazard Ratio (HR) = 0.63, 95% CI:0.40–0.98, \(p = 0.042\)) and OS (HR = 0.49, 95% CI:0.29–0.81, \(p = 0.006\)) were also better in those patients after adjusting for confounding factors, such as performance status, bone or liver metastasis, and concurrent chemotherapy.

Conclusion

This study suggested that antihistamines may enhance the efficacy of ICIs in patients with advanced cancer. If validated in prospective trials, antihistamines and ICIs combinations might be new options to improve oncological outcomes.

Introduction

The treatment armamentarium for patients with cancer has been expanding over the last decades. In this context, the immunotherapy era started with the approval of ipilimumab as a monoclonal antibody against CTLA-4 in 2011\(^1,2\).

Anti-programmed death-1 (PD-1), anti-programmed-death ligand-1 (PD-L1), and anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) drugs are well-known immune checkpoint inhibitors (ICIs)\(^3\). Despite their considerable effect on particular cancer types, such as melanoma, renal cell cancer, and non-small cell
lung cancer, subgroups of patients do not respond effectively to the treatment with ICIs⁴. The rate of tumor infiltration by cytotoxic T lymphocytes, expressions levels of TGFB1⁵, mismatch repair genes status⁶, expression levels of PD-L1 on tumor microenvironment, tumor-infiltrating lymphocytes (TIL)⁷, somatic mutation and neoantigen synthesis, tumor mutation burden (TMB)⁸, and gut microbiota⁹ are the most researched topics. In this context, studies on finding new biomarkers to elucidate resistance mechanisms against ICIS are continuing. Furthermore, recent studies showed that histamine levels were found to be increased in plasma and cancerous tissue due to increased histamine synthesis from the cancer cells¹⁰. Histamine binds to the HRH1 receptor located on the surface of tumor-associated macrophages (TAMs) and contributes to the tumor progression by suppressing CD8 T lymphocytes¹¹. In parallel to this knowledge, Li et al. showed that H1-antihistamines might increase the effect of immunotherapy responses in cancer patients¹².

This study aimed to assess the effect of concomitant use of antihistamines with ICIs in advanced cancer patients treated with ICIs.

**Methods**

This study was approved by the local ethical committee, and it was conducted in accordance with the “Declaration of Helsinki”.

**Patients and Data**

This retrospective study was conducted in a tertiary cancer center in Turkey. All patients treated with ICIs were screened from inception to September 2021. Patients receiving ICIs in the metastatic setting were included in this study.

Patients’ clinicopathological data (e.g., age, sex, Eastern Cooperative Oncology Group performance score, type of ICI, treatment line of ICI, initial and ending time of ICI, cancer diagnosis, drugs, dates of progression and death) were extracted from the electronic hospital records.

**Statistical Analysis**

Descriptive analyses were done by using median (interquartile range (IQR)), mean (standard deviation), and percentages for continuous and categorical variables. Chi-square or Fisher’s exact tests were used for comparing categorical variables. Overall survival (OS) was defined from the initiation of ICIs to death and progression-free survival (PFS) was defined from the initiation of ICIs to disease progression or death, whichever occurs first. Survival outcomes were calculated by using the Kaplan-Meier estimates and survival curves were compared by using the log-rank test. Cox’s proportional hazard model was structured by using the statistically significant in univariate analysis. SPSS 27.0 for Mac (IBM Corp., Armonk, NY, USA) and R Studio (version 1.4.1106) were used for statistical analyses.
Results

Baseline Characteristics

A total of 133 patients were included in the study. The median age was 62 (IQR:55-69) years. Two-thirds of the patients were male. ECOG performance score was 0 or 1 in most patients (87.2%). Melanoma (33.1%) was the most common tumor type, followed by renal cell carcinoma (RCC) (27.8%), non-small cell lung cancer (NSCLC) (24.8%), small cell lung cancer (SCLC) (7.5%), and other tumor types (e.g., urothelial, gastrointestinal system malignancies) (6.8%). The most used ICI was nivolumab (63.2%), followed by pembrolizumab (15%), ipilimumab (12.8%), and atezolizumab (9%). Most patients (76.7%) received ICIs in the second-line or later in the metastatic setting. Lung was the most common metastatic site (58.6%) and central nervous system (CNS) metastasis was observed in 18 patients (13.5%). Fifty-five (38.4%) patients received antihistamines concomitantly with ICIs. The most common antihistaminic was pheniramine (n=47, 85.5%), followed by cetirizine (n=4, 7.3%), desloratadine (n=3, 5.4%), and fexofenadine (n=1, 1.8%). All baseline characteristics of patients are shown in Table 1.

Survival Outcomes and Safety

The median follow-up was 22.5 (95% Confidence Interval (CI): 17.6-27.4) months. The median PFS (8.2 vs. 5.1 months, log-rank $p=0.016$) and OS (16.2 vs. 7.7 months, log-rank $p=0.002$) were longer in patients who received antihistamines concomitantly with ICIs (Figures 1 and 2). In multivariate analysis, concomitant use of antihistamines and ICIs was associated with better PFS (Hazard Ratio (HR)=0.63, 95% CI:0.40-0.98, $p=0.042$) and OS (HR=0.49, 95% CI:0.29-0.81, $p=0.006$) after adjusting for confounding variables (i.e., ECOG performance score, presence of liver or bone metastasis, and concurrent chemotherapy) (Table 2).

Any grade adverse events (AEs) were observed in 12 patients. The rates of AEs were similar in patients receiving antihistamines and those not receiving antihistamines (10.9% vs. 7.7%, $p=0.552$).

Discussion

In this study, we showed that patients with metastatic cancer treated with ICIs had better survival outcomes when they concomitantly used antihistamines and ICIs. Indeed, our findings were consistent with Li et al. They showed that concomitantly using ICIs and antihistamines was associated with improved survival outcomes in patients with melanoma or lung cancer. They also concluded that histamine and HRH1 were responsible for increased immunosuppression against tumor cells in the tumor microenvironment. Indeed, these findings supported that allergic reactions and tumor growth might share a similar immune process. Histamine and HRH1 play a significant role in allergic reactions. In this context, Li et al. found that histamine, mainly produced by tumor cells, and HRH1 on TAMs suppressed immune response against cancer cells.
In the study of Li et al., improved survival outcomes were more prominent in patients with melanoma or lung cancer\(^ {12}\). In our study, we included all cancer subtypes. However, most patients had melanoma or lung cancer (65.5%) and this might explain the better survival outcomes with the concomitant use of ICIs and antihistamines in our study. Of note, second-generation antihistamines were evaluated in the study of Li et al.\(^ {12}\) However, most patients received first-generation antihistamines in our study. It should be noticed that the main difference between first- and second-generation antihistamines is that the brain-blood barrier permeability of second-generation antihistamines is low\(^ {13}\). At that point, it should be questioned whether the concomitant use of ICIs and antihistamines are effective in patients with brain metastasis. Due to the small number of patients in each subgroup, we did not perform a subgroup analysis. However, 13.5% of all patients had CNS metastasis in our study.

Except for the combined use of ICIs and antihistamines, a retrospective study showed that concurrently antihistamine use in melanoma patients improved survival outcomes\(^ {14}\). Similar to these findings, survival outcomes were better in breast cancer patients who received antihistamines. On the other hand, the relation between allergy and cancer development has not been elucidated yet. There were conflicting results about the different cancer subtypes\(^ {15}\). For instance, the presence of asthma was associated with lung cancer development. Conversely, pancreatic cancer or glioma risk was lower among patients with allergy\(^ {15}\). As mentioned above, combined use of ICIs and antihistamines reduced mortality and tumor growth, especially in patients with melanoma or lung cancer. Decreased risk of death was observed in patients with colon cancer, but it was not statistically significant. The authors thought that it might be caused by the small number of patients with colon cancer receiving antihistamines\(^ {12}\). However, it should be kept in mind that conflicting results about the allergy and tumor growth in different tumor subtypes might have led to this result.

There are some limitations in our study. First, patients received first and second-generation antihistamines in our study. Second, it was shown that blood histamine levels and tumor burden were correlated in cancer patients, but we could not measure histamine levels in blood or tumor tissue because of being a retrospective nature of our study. Third, we did not evaluate the duration of antihistamine use, which might have an impact on our findings. Fourth, we had a heterogenous population and all patients using ICIs, regardless of tumor and ICIs type, were included in this study.

**Conclusion**

In conclusion, we showed that receiving first or second-generation antihistamines concurrently with ICIs was associated with better survival outcomes in advanced cancer patients. In this context, our findings support conducting further prospective studies.

**Declarations**

**Conflict of interest:** All authors declare no conflict of interest.
References


Tables

Tables 1-2 are available in the Supplementary Files section.
Figure 1. Kaplan-Meier Estimates of Overall Survival According to Antihistamine Use

(Abbreviations: CI=Confidence Interval, OS=Overall Survival *The p-value was calculated by the log-rank test.)

Figure 1

See image above for figure legend
**Figure 1.** Kaplan-Meier Estimates of Progression-Free Survival According to Antihistamine Use

*(Abbreviations: CI=Confidence Interval, PFS=Progression-Free Survival *The p-value was calculated by the log-rank test.)*

**Figure 2**

See image above for figure legend

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- table1.png
- table2.png