Original Article

The Effect of Perioperative Cimetidine on the Outcomes of Stage 2 Melanoma

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Abstract

Objectives The use of immunotherapies in the treatment of melanoma has significantly improved the survival of patients with advanced disease. Historically, histamine has been implicated in the pathogenesis of several cancers. Cimetidine does play a role in modulating the immune system and was advocated as an immunotherapeutic agent since the 1970s. Cimetidine has been showing promise in conjunction with standard care in many cancers in vitro and in vivo. However, its effects in melanoma have not been explored yet. Our study was designed to determine if cimetidine taken in the perioperative period improves the disease-free survival (DFS) or overall survival in patients with the American Joint Committee on Cancer, seventh edition (AJCC 7) stage 2 melanoma.

Materials and Methods We have reviewed all the patients with stage 2 melanoma in our center in a retrospective cohort to assess the difference in survival between patients who received H2 blockers in the perioperative period and those who did not.

Statistical Analysis and Results Thirty-two patients were included in the analysis. Nine of 32 patients received H2 blockers in the perioperative period. All the patients were males except for one female in the control group (4.3%). The age in the analyzed population ranged between 51 and 92 years; the median age was 70 years (mean: 71; standard deviation: 10). The median overall survival of the patients who received H2 blockers was 112.7 months and it was 77.2 months for those who did not receive H2 blockers. There was no difference in DFS between the two groups ($p = 0.5395$), and there was no difference in the overall survival ($p = 0.4770$). The cumulative dose was strongly correlated with the overall survival in the patients who received H2 blockers ($r = 0.8341$, $p = 0.0196$).

Conclusion Despite having a small treatment group, we were able to detect a strong correlation between the cumulative dose of H2 blockers received and the overall survival.

Keywords

► cancer
► cimetidine
► immunotherapy
► melanoma
► stage 2

Introduction

Invasive melanoma is the most common cause of skin cancer deaths,[1] and is currently the fifth most commonly diagnosed cancer in the United States.[2] Nevertheless, mortality from invasive melanoma is declining because of the advent of new treatments. Because of the presence of histamine 2 (H2) receptors on tumor cells, cimetidine, a H2 blocker, has been studied in vitro and in vivo and shown to inhibit tumor cell growth and to increase overall survival in humans when used as adjuvant therapy after resection in patients with colorectal cancer.[3,4]

Materials and Methods

This is a retrospective cohort study designed to compare the overall survival and disease-free survival (DFS) in patients with stage 2 melanoma exposed to H2 blockers during the perioperative period of melanoma resection. To be included in the H2 blocker perioperative use, the H2 blocker had been taken prior to the operation and continued for at least 2 weeks after the resection. The cumulative dose was calculated as the total dose of H2 use since the start of medication. Patients in our facility either received cimetidine or ranitidine during that period, so we converted the doses of cimetidine to the equivalent therapeutic doses of ranitidine. All the records for patients who underwent melanoma resection at the Veterans Affairs Amarillo Health Care System were reviewed between the period of 1996 and 2008. The seventh edition of the American Joint Committee on Cancer (AJCC) was used to stage the melanoma as it was the staging system used during the period of this study. Patients older than 18 years with stage 2 disease at initial diagnosis were included in the final analysis.

Records were then followed up to January 2022, last available record, or patient death whichever came first to assess for disease recurrence and death. Patients with H2 who received and did not receive H2 blockers during the perioperative period were compared. The DFS was calculated from the initial date of tissue diagnosis until recurrence. Overall survival was assessed from the date of initial tissue diagnosis to death or to the last date of contact. GraphPad Prism version 9.4.0 statistical software was used for analyzing the data. The Kaplan–Meier method and log-rank test survival analyses were performed in addition to Pearson's r test to assess for the correlation between the cumulative dose of H2 blockers and the time to recurrence or death. None of the included patients were lost to follow-up. Two patients were removed from the Pearson's correlation and plot because of missing dosing data.

Results

Patients' demographics and treatment characteristics are described in ►Table 1. A total of 32 patients were included in the analysis. Nine patients received H2 blockers in the perioperative period and 23 patients did not. The median DFS for both groups was difficult to calculate because in both groups, the probability of DFS exceeded 50% throughout the entire follow-up period. The median overall survival of the patients who received and did not receive H2 blockers was 112.7 months and 77.2 months, respectively.

There was no difference in the DFS between the two groups ($p = 0.5395$; ►Fig. 1), and there was no difference in the overall survival ($p = 0.4770$; ►Fig. 2). The cumulative dose was strongly correlated with the overall survival in the patients who received H2 blockers ($r = 0.8341$; $p = 0.0196$; ►Fig. 3).

Discussion

Using Pearson's correlation to correlate the cumulative dose of the medication, we were able to uncover a relationship between the cumulative dose used and the overall survival. Patients who received a larger cumulative dose had better disease-free duration. Some patients in the group died prior to recurrence and the time to death was used as an endpoint for this plot. This suggests that there could be a dose-related effect on the immunomodulatory effect of the H2 blockers. Despite the bright outlook of this analysis, this does not prove that there is an improved DFS by itself.

There was no statistical difference when survival was compared between the two groups due to the lack of power

Table 1 Demographics

	H2 blockers not used ($n = 23$)		H2 blockers used ($n = 9$)	
Age (y)	72.9		67.2	
Gender				
Male	22	95.7%	9	100.0%
Female	1	4.3%	0	0.0%
Smoking	15	71.4%	6	75.0%
Alcoholism	2	10.0%	2	25.0%
Secondary cancer	5	21.7%	0	0%
Use of chemotherapy	1	4.3%	2	22.2%
Use of radiotherapy	0	0%	1	11.1%

Note: The distribution of characteristics among the treatment and control groups.
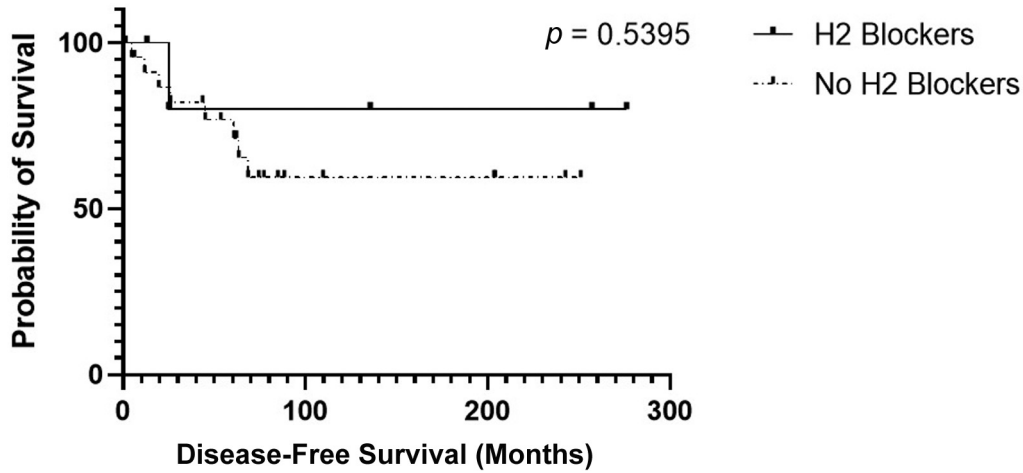
Fig. 1 Disease-free survival of patients who received H2 blockers (*solid line*) versus patients who did not (*dotted line*).
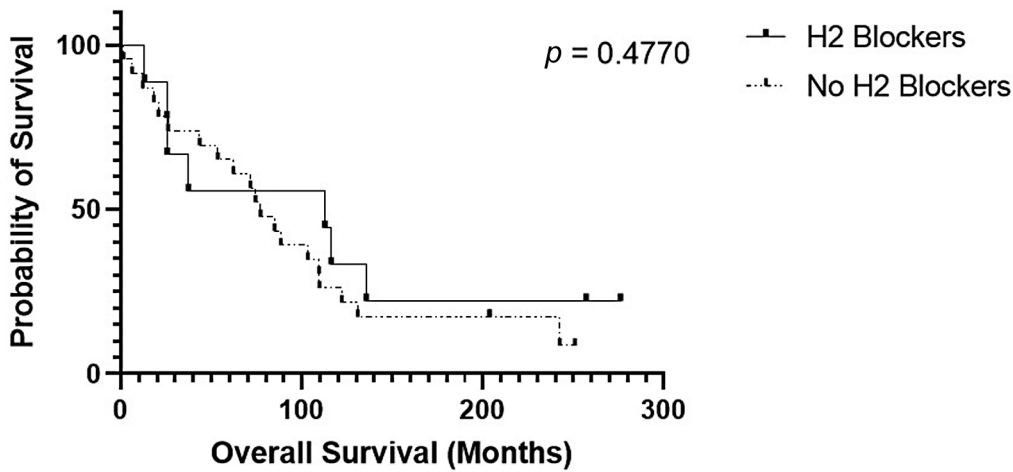

Fig. 2 Overall survival of patients who received H2 blockers (*solid line*) versus patients who did not (*dotted line*).

to detect differences given the small number of patients in our study. However, the DFS curves diverge, suggesting a possible difference in the outcomes of disease recurrence

Fig. 3 Overall survival in days plotted against cumulative dose of ranitidine equivalent.

between the two groups. This is consistent with observed dose-related responses to H2 blockers.[4] The overall survival curves were not different between the groups. We believe that the reason for that is the low overall mortality of patients with stage 2 disease. In a similar fashion, other studies showed a significantly improved survival in patients with melanoma who received antihistamines.[5,6] While the mechanism of action of these agents differs from the mechanism of action of H2 blockers, it confirms that histamine has a strong role in modulating the immune system.[7] To conclude, the benefit of H2 blockers should be further explored by using larger controlled trials to assess its effectiveness.
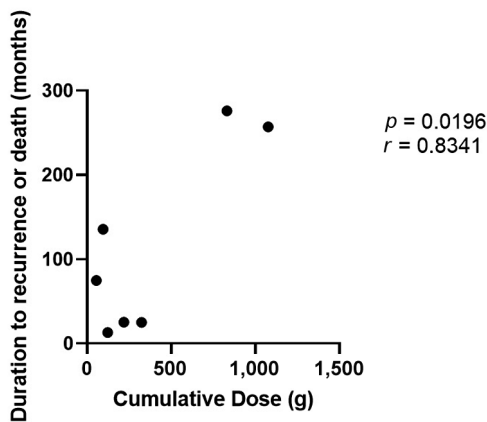
Limitations

The sample size in this study was small, most of the patients were males, and only few patients were taking H2 blockers in the perioperative period. This made our study underpowered to detect a difference in survival. Advanced age of many patients at diagnosis might have contributed to the low

power of our study. Different kinds of H2 blockers were used among the patients who received H2 blockers in the perioperative period, and this might have affected the results of the study. The cumulative dose did not take into consideration whether the H2 blocker was started long before the operation as long as the medication was taken during the perioperative period.

Conclusion

This study suggests that there might be a significant difference in the DFS of patients who are put on H2 blockers perioperatively, and there seems to be a correlation between the cumulative dose used and DFS. Further studies are needed to delineate the efficacy of this readily available treatment in melanoma patients.

Conflict of Interest
None declared.

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