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Does Famotidine Enhance Tumor Infiltrating Lymphocytes in Breast Cancer?

Results of a Randomized Prospective Pilot Study

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Thirty patients with breast cancer were prospectively randomized into case and control groups receiving 40 mg famotidine preoperatively for 10–14 days and routine premedication, respectively. Surgical specimens were evaluated objectively for tumor infiltrating lymphocytes in the center and in the periphery of the tumor along with evaluation of metastatic lymph nodes for reactive changes. Ten famotidine-treated cases (67%) showed significant lymphocytic infiltration in the center compared to 4 controls (27%) ($p = 0.03$). Eleven cases (77%) had significant lymphocytic infiltration in the periphery ($p = 0.03$) compared to 5 controls (33%). Considering both sites, lymphocytic response was significant in 9 (60%) cases as opposed to only 3 (20%) controls ($p = 0.03$). This response did not correlate with the stage, grade of tumor or menopausal status of patients in either group. Seventy-eight percent (78%) of the cases showed significant reactive changes in the metastatic lymph nodes as compared to 22% in controls ($p < 0.01$). This study suggests that famotidine enhances tumor infiltrating lymphocytes in breast cancer and might have potential as an immunomodulator. A larger confirmatory study is suggested.

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With newer insights into the immune response against cancer, various immunotherapeutic modalities are being tried to improve survival. Histamine H_2 receptor blockers have been shown to slow down metastatic development and prolong survival in tumor-bearing mice by enhancing the immune response (1, 2). Studies have also indicated that H_2 antagonists improve survival in patients with colorectal cancer when given preoperatively or as postoperative adjuvant therapy (3–6). One of the proposed mechanisms of action of H_2 receptor antagonists is modulation of the local immune response by enhancing the lymphocytic infiltration in the tumor and by enhancing the cytotoxicity of tumor infiltrating lymphocytes (TILs) (3, 7–9). Intense lymphocytic infiltration has been demonstrated to have a positive prognostic value in melanoma, colorectal carcinoma and breast cancer (3, 10–12). In this pilot study we report the effect of a H_2 receptor antagonist (famotidine) on the magnitude of tumor infiltrating lymphocytes in patients with breast cancer.

MATERIAL AND METHODS

Thirty patients with breast cancer admitted for surgery between November 97 and October 99 to the Department of Surgical Disciplines at the All India Institute of Medical Sciences, New Delhi were included in this study.

After admission, written informed consent was taken and the patients were prospectively randomized, using a numbered envelope technique, into famotidine-treated cases and controls. Treatment consisted of oral famotidine at a dose of 40 mg per day, starting 10 to 14 days prior to surgery. On the morning of surgery the patients received 40 mg famotidine, with a sip of water in addition to routine premedication. Controls received routine preoperative medication only.

Surgical specimens were analyzed routinely and adequate sections were taken to include the periphery and center of the tumor. All the dissected lymph nodes were sampled and processed. After formalin fixation, the sections were processed, embedded in paraffin and 5-μ sec-

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tions were stained with hematoxylin and eosin. The sections were evaluated, blind, by a consultant pathologist. The sections were evaluated for histological type (WHO classification), histological grade (Bloom & Richardson) and pathological stage. TILs were analyzed objectively using criteria similar to those of Adams & Morris (3).

Briefly, the criteria were as follows:

- Lymphocytes in the periphery of the tumor (tumor ~ normal breast interface): a count of more than 50 cells per high-power field (HPF) involving more than 50% of the periphery of the tumor was considered significant.
- Focal clusters or diffuse lymphocytic infiltration in the center of tumor (intra ~ tumoral stroma): a count of more than 50 cells per HPF was considered significant.

We attempted to evaluate at least 50% of the tumor/normal breast interface and the tumor stroma, for which more than 50 fields were evaluated in all cases.

Axillary nodes were evaluated for presence of metastasis and reactive changes such as sinus histiocytosis and follicular hyperplasia.

The results were analyzed using Student's t-test for continuous variables and a χ^2 test for non-continuous variables. All patients were followed up in the breast cancer clinic at regular intervals.

RESULTS

The cases and controls were matched for age, menopausal status, stage (TNM) of tumor, histological type, grade and lymph node metastasis (Table 1).

Tumor infiltrating lymphocytes in periphery

Eleven treated cases (73%) had significant lymphocytic infiltration as compared to 5 controls (33%) ($p = 0.03$; Table 2).

Tumor infiltrating lymphocytes in the center

Ten cases (67%) as compared to 4 controls (27%) had significant lymphocytic infiltration ($p = 0.03$; Table 2).

When we considered TILs in both center and periphery, 9 cases (60%) as against 3 controls (20%) had significant lymphocytic infiltration ($p = 0.03$; Table 2). No correlation was found between TIL density and menopausal status ($p = 0.83$ and $p = 0.43$), stage ($p = 0.79$ and $p = 0.6$) or grade ($p = 0.28$ and $p = 0.47$) in the treatment group and the control group, respectively.

Reactive changes in the lymph nodes

In the treatment group, 7 out of 9 patients with metastatic lymph nodes (78%) showed reactive changes compared with 2 out of 9 (23%) in the control group ($p < 0.01$). The uninvolved lymph nodes in both groups were similar with respect to reactive changes.

Follow-up: At a mean follow up of 9 months (2–14 months) for cases and 8 months (2–18 months) for controls one patient in the famotidine-treated group suffered a recurrence while one patient in the control group died of metastasis; another two patients developed distant metastases.

Table 1

The demographic data

	Cases (n = 15)	Controls (n = 15)	p-value
Mean age in years (range)	45 (28–60)	48 (36–70)	0.71
Menopausal status			
Premenopausal	7	8	0.71
Post menopausal	8	7	
Stage			
1	0	0	0.71
2a	5	8	
2b	7	6	
3a	3	1	
3b	0	0	
Type			
IDC(NOS)[1]	14	12	0.24
Lobular	0	2	
Mucinous	0	1	
Cribriform	1	0	
Grade			
I	1	2	0.54
II	8	8	
III	6	3	
Not graded (lobular)	0	2	
Lymph node metastasis			
Present	9	9	0.38
Absent	6	6	

[1] Infiltrating duct carcinoma (not otherwise specified).

DISCUSSION

Our study suggests that famotidine enhances lymphocytic infiltration in breast cancer. There is experimental evidence to suggest that histamine plays an important role in tumor development. High levels of histamine and histidine decarboxylase have been demonstrated in tumor interstitium (13–15). In addition, high levels of histamine have also been identified in human skin, rectal and breast cancer (16–19). Both H_1 and H_2 receptors have been demonstrated in benign breast lesions, and 75% of malignant lesions have H_2 receptors (18). In a recent study evaluating the concentration of histamine in breast cancer, it was concluded that the

Table 2

Significant lymphocyte infiltration in the two groups

TIL	Cases	Control	p-value
Periphery	11 (77%)	5 (33%)	0.03
Center	10 (67%)	4 (27%)	0.03
Both periphery and center	9 (60%)	3 (20%)	0.03

concentration of histamine in breast cancer was sufficient to inhibit the lymphocytic function and could be immunosuppressive locally (16). Histamine induces immunosuppression by inhibiting lymphocyte migration (16, 20) and reducing the lytic ability of cytotoxic T lymphocytes (9). Histamine also inhibits the natural killer cell activity (21, 22). These actions are mediated by H_2 receptors (9, 23) and can be reversed by H_2 receptor antagonists (3, 9, 23). The immunoprotective action of H_2 receptor antagonists has been demonstrated in a number of studies. The mechanisms include reduction of postoperative immunosuppression by improving the cell-mediated immunity (24–27) and enhancing the local immune response by augmenting the tumor infiltrating lymphocytes (3). This immunostimulatory effect of H_2 antagonists has also translated into better survival in experimental and clinical studies in gastric and colorectal cancer (1–3, 5, 6, 28, 29). Both cimetidine and famotidine (1–3, 6, 8) enhance the lymphocytic activity and inhibit tumor growth.

Tumor infiltrating lymphocytes have been reported to be of prognostic significance in breast cancer (1, 3, 10–12). Various studies have shown that the presence of lymphocytic infiltration correlates with improved survival rates in breast cancer (10, 11, 16). Thus enhancement of lymphocytic infiltration may lead to improved survival for these patients.

We have shown that famotidine given preoperatively increases the TILs in breast cancer. This may have a potential value in improving the outcome of these patients. We have also found that famotidine significantly increases the reactive changes in the form of sinus histiocytosis and follicular hyperplasia in lymph nodes involved by the tumor. The exact significance of this finding is not known. However there are reports in the literature suggesting that the presence of sinus histiocytosis in lymph nodes correlates with a more favorable prognosis (10, 30). It has been suggested that H_2 receptor antagonists may be more effective in patients with the advanced stage of disease since these are the patients with maximum immunosuppression (5). However, the TIL response in our study was not related to the stage or grade of the tumor. The short follow-up time does not allow evaluation of survival.

SUMMARY

This pilot study suggests that famotidine increases tumor infiltrating lymphocyte concentration in breast cancer—a finding that should be confirmed by a more extensive study with a longer follow-up. In addition, a comparison with known prognostic factors should be undertaken in order clearly to define the impact of famotidine and TILs on the prognosis of breast cancer.

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