LYMPHOCYTOPENIA AFTER MODIFIED RADICAL MASTECTOMY IN PATIENTS WITH LYMPH NODE METASTASES ☆

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Subjects: Patients with lymph node metastases.
Abbreviations: WBC = White blood cells; POD = post operative days.

Abstract

In patients with cancer, the number of circulatory lymphocytes decrease and the in vitro proliferative response is impaired. The hypothesis has been advanced that both the degree of lymphocytopenia and recovery times are individually well correlated with the magnitude of surgical damage. We retrospectively studied whether the changing pattern of circulatory lymphocytes in patients with breast cancer differs peri-operatively between the lymph node-positive and node-negative groups. We re-emphasized in the present report that the number of circulatory lymphocytes is a simple and useful prognostic parameter after surgical intervention.

Eighty-nine female patients who underwent modified radical mastectomy with lymph node dissection (Kodema’s method) at Omiya Medical Center, Jichi Medical School, from 1991 to 1995 were retrospectively studied to compare the changing pattern of the peri-operative number of circulatory lymphocytes. Thirty-one patients with lymph node-positive (n = 31), and fifty-eight were lymph node-negative (n = 58). The survival rates of these patients were confirmed during 1998.

There are no statistically significant differences in the surgical parameters between the two groups. Recovery from lymphocytopenia was notably longer in the lymph node-positive patients on post-operative days one and seven. However, in both patient groups, the number of circulatory lymphocytes was markedly reduced immediately post-operatively but returned to the pre-operative level on post-operative day 14. No significant difference was seen in the changing patterns of peripheral neutrophils and C-reactive protein.

These observations suggest that the immune surveillance system of patients with a potentially poor prognosis may be easily disturbed by surgical intervention and may thus result in delayed recovery. The changing pattern of circulatory lymphocytes in patients with breast cancer should be reconsidered as a simple prognostic parameter, especially after surgical intervention.
Introduction

When compared with people who do not suffer from cancer, patients with breast cancer have significantly impaired cell-mediated immune responses (Whittaker and Clark, 1971). Although there is no significant decrease in the number of circulatory lymphocytes in patients with benign or early malignant breast disease, the number of lymphocytes in the advanced stages of cancer does decrease and the in vitro proliferative T cell response in impaired as well (McCluskey, Toy et al., 1983). The mechanisms of this lymphocyte impairment remain unclear. On the other hand, surgical damage immediately depresses the host immune surveillance system, which sometimes leads to a poor prognosis in these patients (Kawahito, Kobayashi et al., 1998; Kobayashi and Yamouchi, 1997). The number of peripheral lymphocytes decreases immediately after surgery. This decrease is due to fatty acid synthetase (Fas) mediated apoptosis. The recovery time of surgical damage (Kobayashi and Yamauchi, 1997). The changing pattern as regards the number of circulatory lymphocytes in patients with cancer may possibly be a prognostic parameter following surgical intervention, as has been shown previously in cases of open heart surgery (Kawahito, Kobayashi et al., 1998).

We retrospectively compared alterations in the number of circulatory lymphocytes peri-operatively between lymph node-positive and lymph node-negative patients with breast cancer. Although hematologic parameters are routinely measured intraoperatively, the differentiation of white blood cells (WBCs) and changes in the lymphocyte count are not usually considered to be meaningful parameters. In the present report, we wish to emphasize that the practicality of this simple parameter is of great current interest among surgeons (Kobayashi, 1998; Kowahito, Kobayashi et al., 1998; Kobayashi, Yamauchi, 1987; Yamauchi, Kobayashi et al., 1998).

Materials and Methods

Eighty-nine female patients (29 to 86 years old) with breast cancer underwent a modified radical mastectomy with lymph node dissection (Kodama’s method) between September 1991 and December 1995 in our center. Patients who received pre-operative chemotherapy or irradiation were excluded from the present study. Post-operative histologic examinations revealed that 58 patients had no lymph node metastases (lymph node-negative).
node-negative group) and 31 patients had lymph node metastases (lymph node-positive group).

Peripheral blood samples were drawn into EDTA tubes at five time points: admission (pre-operative), 1 hour post-operatively (POD-0), and at 6 a.m., on the 1st, 7th, and 14th post-operative days (POD-1, POD-7 and POD-14). An auto-analysis system (Microx Heg-120, Omrun, Mie, Japan) was used for counting peripheral WBCs and lymphocytes in the blood samples. Data were expressed as the mean ± the standard error of the mean (± SEM) for each study group. Statistical analysis was performed using Mann-Whitney's U-test, and the results were considered significant if p < 0.05.

Results

The mean patient age, operation time, and blood volume loss in the lymph node-negative group were, respectively, 54.4 ± 1.6 years old, 193.0 ± 6.4 minutes, and 260.5 ± 24.7 g. In the lymph node-positive group, these parameters were 52.5 ± 2.4 years old, 178 ± 9.1 minutes and 232.2 ± 24.1 g, respectively. There were no significant differences between the two groups.

Post-operative changes in the circulating lymphocyte count are shown in the Figure. In the lymph node-negative and the lymph node-positive groups, the pre-operative lymphocyte counts were 1687 ± 57.6/mm³ and 1671 ± 88.3/mm³, respectively. There were no significant pre-operative differences between the groups. Although the number of lymphocytes decreased markedly on POD-0 in each group, there were no significant differences between the groups. Both groups recovered gradually on POD-1 and POD-7. On POD-1 (1260.0 ± 90.7/mm³ and 1468.1 ± 67.5/mm³) and POD-7 (1276.4 ± 76.6/mm³ and 1639.7 ± 101.3/mm³), the number of lymphocytes was more decreased in the lymph node-positive group than in the lymph node-negative group (p = 0.0451 and p = 0.0239, respectively).

The data obtained from the lymph node-positive group on POD-7 also showed that the level of circulatory lymphocytes in patients with more than three positive lymph nodes tended to be lower than in patients with one to three positive lymph nodes (1221.1 ± 90.0/mm³ vs. 1332.2 ± 55.0/mm³, respectively). However, these measurements returned
Figure: Changes in the percentage of the level of peripheral lymphocytes after modified radical mastectomy. The results are expressed as a percentage of the pre-operative level (mean ± SEM). Open circles indicate the lymph node-negative group without axillary lymph node metastasis; closed circles indicate the lymph node-positive group. *p = 0.0451, **p = 0.0239.
to pre-operative levels and no significant difference was seen in the lymphocyte levels between the lymph node-negative and lymph node-positive groups on POD-14 (1687 ± 61.2/mm³ and 1711 ± 78.3/mm³ respectively). Other hematologic parameters such as peripheral neutrophils and C-reactive protein did not differ between the groups.

At the end of December 1998, all patients of the lymph node-negative group survived, but two had disease recurrence. In contrast, six patients in the lymph node-positive group died of cancer and five patients had bone or liver metastases or both.

Discussion

Metastasis to be axillary lymph nodes reflects the prognosis of patients with breast cancer. Patients in the lymph node-negative group have a good prognosis, whereas patients in the lymph node-positive group are likely to experience disease recurrence even after the lesions are curatively removed. In the preceding studies of cardiac surgery, we showed that the degree of lymphocytopenia correlated with the severity of surgical damage (Kobayashi and Yamauchi, 1997). Therefore, delayed recovery from lymphocytopenia might be a reliable prognostic indicator after surgical stress (Kawahito, Kobayashi et al., 1998).

In the present study, we compared the changing pattern of the number of circulatory lymphocytes between patients with and without lymph node metastasis who underwent modified radical mastectomy. Pre-operatively, there was no significant difference between groups in the number of lymphocytes. In addition, there was no difference on POD-0 between the lymph node-positive and lymph node-negative groups. However, the recovery time necessary for the lymphocyte count to return to normal was markedly longer in the lymph node-positive group, which in general had a worse prognosis than the lymph node-negative group. Recent surgical studies have focused on the measurement of inflammatory cytokines as an indicator of surgical damage (Yamauchi, Kobayashi et al., 1998). However, simpler parameters obtained from routine data still need to be re-examined (Kobayashi, 1998; Yamauchi, Kobayashi et al., 1997). The molecular mechanisms of the down-regulation of circulatory lymphocytes, especially of the CD4⁺ cell population, after surgical intervention will be the focus of future studies.
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References


