Report

Correlation of Fcγ receptors on peripheral blood mononuclear cells and survival in patients with metastatic breast cancer

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Summary

Patients with carcinomas have elevated levels of Fc receptors for IgG (FcγR) on their peripheral blood mononuclear cells (PBMC). The purpose of the present study was to determine whether there is a correlation between FcγR levels on PBMC and survival in patients with metastatic breast cancer. Binding assays were performed on PBMC using 125I-labeled fibrinogen complexed with rabbit IgG (or as a control F(ab′)2) anti-human fibrinogen. Twenty-two metastatic breast cancer patients had significantly (p<0.001) elevated FcγR levels as compared to either 22 breast cancer patients receiving adjuvant chemotherapy following mastectomy without clinical evidence of tumor, or to 34 non-malignant controls. Significantly more metastatic patients with elevated FcγR levels died at 6 months (p<0.001) as compared to those with low levels. A direct correlation between FcγR levels and hazard probability was found (correlation coefficient = 0.3321, p<0.005). These results raise the possibility that FcγR levels on PMBC from metastatic breast cancer patients may be clinically useful as a prognostic marker of disease activity.

Introduction

Prognosis for survival of breast cancer patients depends on the clinical staging and levels of estrogen and progesterone receptors on the primary tumor cells (1). Recently there have been numerous reports of immunoassays for cancer attempting to correlate an immunologic marker with the staging or prognosis of cancer. For example, increased proportions of peripheral blood mononuclear cells (PBMC) or T cells with Fc receptors for IgG (FcγR) have been demonstrated in patients with breast cancer (2, 3), other carcinomas (4–6), and lymphoproliferative malignancies (7). Furthermore, a direct correlation between tumor mass and/or extent of tumor and the level of FcγR has been reported in patients with breast cancer (2, 3), neuroblastoma (8), and nasopharyngeal carcinoma (9). The purpose of the present study was to determine whether the levels of FcγR on PBMC from metastatic breast cancer patients could be used as a prognostic marker for survival.
Materials and methods

Patients

Twenty-two patients with metastatic breast carcinoma were studied. The median age was 58, with a range of 35 to 71 years. Nine patients were pre-menopausal and 13 were post-menopausal. Seventeen were estrogen receptor (ER) positive, ten of which were progesterone receptor (PR) positive as well. One patient was PR positive and ER negative. At the time blood was drawn for the FcyR assay, ten patients had bone metastases, four had lung and bone metastases, and eight had liver metastases with or without other metastases. The median time from surgery to the detection of the first metastases was 17 months (range of 10 to 22 months). The median time from detection of the first metastases to blood drawing was 12 months (range of 9 to 14 months). Treatment before and after the time blood was drawn for the FcyR assay was varied and included hormonal or cytotoxic chemotherapy with or without palliative radiotherapy.

Twenty-two patients receiving adjuvant chemotherapy for breast cancer were also tested. The median age was 55, with a range of 29 to 70 years. Six patients were pre-menopausal and 16 were post-menopausal. Nineteen were ER positive, 15 of which were PR positive as well. All patients had undergone a work-up consisting of chest X-ray, bone and liver scans, and blood chemistries following surgery, and were without clinical evidence of metastases at the time blood was drawn for the FcyR assay. The median time from surgery to blood drawing was 6 months (range of 4 to 13 months). Sixteen patients who were classified as having T1 or T2 tumors with N1 or N2 axillary lymph nodes and who had undergone a modified radical mastectomy were receiving 5-fluorouracil and melphalan when blood was drawn for the FcyR assay. Six patients with T3 tumors with N0, N1, or N2 axillary nodes with prior mastectomy had received tangential radiation to the chest wall and were receiving 5-fluorouracil.

Three groups of female patients without cancer served as controls: 16 healthy volunteers (median age 33 years old, range of 25–53), 11 patients with atherosclerotic heart disease and/or hypertension (median age 67 years old, range of 61–82), and seven patients with rheumatological diseases (three with systemic lupus erythematosus and one each with scleroderma, rheumatoid arthritis, vasculitis, or mixed connective tissue disease) (median age 48 years, range of 27–62).

FcyR assay

PBMC were separated from 20 ml of heparinized venous blood by Ficoll-hypaque centrifugation, washed three times, stored overnight at 4°C in RPMI 1640 with 10% heat-inactivated fetal calf serum, washed, and resuspended in Hank’s balanced salt solution (HBSS) at a concentration of 1 × 10⁷ cells/ml. A complex of rabbit IgG anti-human fibrinogen, or (as a control) rabbit F(ab')₂ anti-human fibrinogen, and 125I-fibrinogen at a molar ratio of 1:2 was prepared as previously described (10). 10⁶ PBMC were dispensed in PVC U-shaped multwell plates which had been precoated with a solution of 1% bovine serum albumin (BSA)/HBSS. The cells were spun and an excess of 125I-labeled immune complex containing 50–100 × 10³ counts per minute (cpm) was added. The cells were resuspended, incubated for 30 min at 4°C, and washed three times with 1% BSA/HBSS. The plates were dried and cell-bound radioactivity was determined in each well. There was a linear curve of cell-bound radioactivity versus the log of cell number from 2 × 10⁵ to 3 × 10⁶ PBMC per well. Accordingly, the assay was always performed using 1 × 10⁶ PBMC per well. Specific binding for each patient was calculated from the net cpm, after subtracting the radioactivity of the non-specific binding of 125I-labeled fibrinogen complexed with F(ab’), from the cpm of 125I-labeled fibrinogen complexed with IgG. Results are represented as the percent binding, which is the ratio of the specific binding of each patient divided by the total counts per minute of 125I-labeled fibrinogen-IgG complex added to each well.