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In order to examine whether erbB-2 protein overexpression influence the survival and tamixifen response in ER positive node negative breast cancer, 937 patients were examined from NSABP trial B-14. No such effect was found.

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Annual Report

Title: Custom tailoring chemotherapy with erbB-2

Summary:
In order to examine the effect of erbB-2 protein overexpression on prognosis and the therapeutic response of clinical breast cancer, we proposed to examine archival materials available from four finished clinical trials from National Surgical Adjuvant Breast and Bowel Project. These trials were selected to specifically address following questions; 1) Is erbB-2 an important prognostic indicator for node-negative ER positive breast cancer? 2) Is erbB-2 an indicator for tamoxifen resistance? 3) Is erbB-2 an important prognostic indicator for node-negative ER negative breast cancer? 4) Is erbB-2 indicator for poor response to MF adjuvant regimen? 5) Is erbB-2 an indicator for poor response to MF but not to CA regimen? During the first project year, 937 cases from NSABP protocol B-14 were examined for erbB-2 expression. 18% of the cases showed overexpression of erbB-2 protein as measured by immunohistochemical staining. The analysis of B-14 showed no positive correlation between erbB-2 and survival outcome of the patients ($p=0.3$ for disease free survival, $p=0.6$ for overall survival), neither response to tamoxifen therapy. Multivariate analysis with other factors indicate that % S-phase, tumor size, PgR, and nuclear grade are independent predictors of DFS. All but nuclear grade predict for survival. This data is consistent with our previous finding that erbB-2 is not prognostic on its own in node-negative breast cancer patients. In addition, the data demonstrates that erbB-2 does not influence the tumor response to tamoxifen. For node positive patients to address questions #3 to 5, cases from B-11 and 12 will be examined during project year 2. Blocks from these trials have been obtained from NSABP and currently being cut for staining.

Introduction

Treatment of breast cancer has been revolutionized through three important stages. First was the development of surgical techniques to remove cancer tissue which improved the survival of patients dramatically. Second stage was the use of systemic adjuvant therapy (tamoxifen for estrogen receptor positive tumors and chemotherapy for estrogen receptor negative tumors). The final revolution was the early detection through aggressive screening program. Through these revolutionary stages, there has been significant improvement in the survival of patients with breast cancer. However, we still did not obtain 100% cure of breast cancer even with early detection. Thus, about 30% of early invasive breast cancer will still recur within 10 years after surgery and radiation. Additional systemic therapy will reduce this recurrence rate to about 20%. This moderate benefit brings significant dilemma for clinical practice. Thus probably only small subset of patients respond to systemic therapy. It would make no sense to give toxic systemic therapy to treat the tumors when we know that it will not respond to such treatment. However, there has been no proven way to predict the response to systemic therapy so that we have to treat all of them with systemic therapy to achieve that 10% gain. If we develop simple, inexpensive, and reliable ways to predict the tumor response to specific types of systemic treatment, we can eventually custom tailor systemic treatment for each patient so that we will have more significant improvement in treatment results without causing unnecessary toxicity. Our data together with others strongly suggest that we can use one marker to predict treatment response. This marker - erbB-2 protein - can be detected by extremely simple and inexpensive method (immunohistochemical staining) using even archival materials (this ability gives tremendous advantage in studying large number of clinical samples with long follow up period). The proposed studies are designed to confirm the use of erbB-2 as a predictor of treatment response to certain systemic treatment regimens. If validated through this study, this will be the beginning of the fourth revolution in breast cancer treatment - namely custom tailoring of systemic treatment.

erbB-2 is a cell membrane receptor protein which is thought to play an important role in breast cancer cell growth control. About 15 to 30% of breast cancer has increased amount of this protein and this correlates with increased growth potential of the tumor cells. When tumor cells have increased levels of erbB-2 protein, it can be easily detected with immunohistochemical staining method utilizing specific antibodies made against erbB-2. Thus we are able to screen archival specimens from already finished clinical trials such as NSABP trials to effectively study the role of erbB-2 in breast cancer.

Our project involves screening of archival specimens from patients enrolled in four different NSABP clinical trials to address following questions;

1. Is erbB-2 an important prognostic indicator for node-negative ER positive breast cancer?
2. Is erbB-2 an indicator for tamoxifen resistance?
3. Is erbB-2 an important prognostic indicator for node-negative ER negative breast cancer?
4. Is erbB-2 indicator for poor response to MF adjuvant regimen?
5. Is erbB-2 an indicator for poor response to MF but not to CA regimen?

Body:

During the first project year, we have examined 937 cases of node negative estrogen receptor positive breast cancer patients enrolled in NSABP project B-14. This trial was examined to answer the above mentioned questions #1 and #2. This group of 937 patients represent 35% of the entire study population. Detailed statistical analysis showed that this 937 cases are representative of the entire 2661 patients in the trial. Thus there was no bias in patient selection that could influence the analysis of the result. Although the 937 cases represent only 35% of the initial study population, this is the largest study ever performed for node negative ER positive group of patients with unified treatment. In addition to erbB-2 staining, following data were available for analysis; histopathological parameters including tumor size and nuclear grading, progesterone receptor status, DNA ploidy and S-phase measurement by flow cytometry, and survival outcome. Flow cytometric data was available from 759 (29%) of the cases. Univariate analysis showed that there were no significant differences in either disease free survival ($p=0.3$) nor survival ($p=0.6$) according to erbB-2 status. Patients with high S-phase had worse survival ($p=0.001$). Results from multivariate analysis (Cox model) indicate that % S phase, tumor size, progesterone receptor, and nuclear grade are independent predictors of disease free survival. All but nuclear grade predict for survival. In addition benefit from tamoxifen therapy was evidenced in any subgroups examined including erbB-2, tumor size, and S-phase. **Thus we failed to identify any subgroup in ER positive tumors that may not benefit from tamoxifen treatment.** This is a very important clinical observation, since the data suggest that all ER positive node negative tumors should receive tamoxifen, since there is no predictive marker for response.

During the first year, blocks from other clinical trials (NSABP B-13, B-11, and B-12) were obtained and have been cut for erbB-2 staining. The staining will be carried out through second project year.

Conclusions:

The conclusion from project year one can be summarized as follows:

1. erbB-2 is not a prognostic factor in node-negative, ER positive breast cancer.
2. erbB-2 does not predict poor response to tamoxifen in this group of patients.
3. Although other markers such as S-phase fraction can predict survival outcome, they do not predict response to tamoxifen.
4. Currently there is no marker that can be used to select patients who might not respond to tamoxifen therapy.

Additional studies which will be conducted during second project year will address following questions.

1. Is erbB-2 an important prognostic indicator for node-negative ER negative breast cancer?
2. Is erbB-2 indicator for poor response to MF adjuvant regimen?
3. Is erbB-2 an indicator for poor response to MF but not to CA regimen?