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ORIGINAL ARTICLE

Identification of patients with hormone receptor-positive breast cancer who need adjuvant tamoxifen therapy for more than 5 years

Chiao-En Wu [a], Shin-Cheh Chen [b], Hsien-Kun Chang [a], Yung-Feng Lo [b], Swei Hsueh [c], Yung-Chang Lin [a,*]

[a] *Division of Hematology-Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan, Taiwan*
[b] *Division of Breast Surgery, Department of General Surgery, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan, Taiwan*
[c] *Department of Pathology, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan, Taiwan*

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Background/purpose: Extended hormonal therapy with tamoxifen for > 5 years has improved disease-free survival (DFS) and overall survival (OS) in hormone receptor (HR)-positive breast cancer patients. The aim of this study was to identify the HR-positive breast cancer women who need adjuvant tamoxifen for > 5 years.
Methods: Between 1990 and 2004, 1104 HR-positive breast cancer patients who had received tamoxifen treatment at our institution and had been disease free for at least 6 years were included in this analysis. Univariate and multivariate analyses of prognostic factors for late recurrence were performed using the binary logistic regression model.
Results: During a median follow-up period of 10.9 years after surgery, 70 patients died and 99 showed recurrence. In multivariate analysis, age < 40 years ($p < 0.001$) and lymph node metastasis ($p < 0.001$) were associated with higher rates of recurrence. We stratified patients into high-risk (age < 40 years or positive lymph node status, 536 patients) and low-risk (age > 40 years and negative lymph node status, 566 patients) groups. The recurrence rates were 14.6% and 3.5% in the high-risk and low-risk groups, respectively. Patients in the high-risk group had poorer disease-free survival ($p < 0.001$) and overall survival ($p = 0.010$) than those in the low-risk group.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

* Corresponding author. Division of Hematology-Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou, 5 Fushing Street, Gueishan Township, Taoyuan County 333, Taiwan.
E-mail address: yclinof@adm.cgmh.org.tw (Y.-C. Lin).

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Conclusion: Our findings suggest that HR-positive breast cancer women either aged < 40 years or with positive lymph node status were justified in continuing with tamoxifen therapy for > 5 years.

Introduction

Breast cancer is a heterogeneous, phenotypically diverse disease composed of several biologic and molecular subtypes that have distinct behaviors and responses to various therapies. Hormonal receptor (HR)-positive [positive for estrogen receptor (ER) and/or progesterone receptor (PR) expression] breast cancer is the most common type of breast cancer. A robust response to various types of endocrine therapy is the dominant feature of HR-positive breast cancer; endocrine therapy is indispensable for the treatment of this subtype of breast cancer.

Adjuvant tamoxifen therapy for 5 years has resulted in reduced recurrence and mortality in premenopausal and postmenopausal women with both node-negative and node-positive, HR-positive breast cancer.[1] To achieve the maximal efficacy of adjuvant endocrine therapy, adjuvant tamoxifen beyond 5 years has been studied for decades. However, early studies recruited relatively few patients and the results of these studies were inconclusive.[2–5] Nonetheless, adjuvant 5-year tamoxifen therapy has been the standard treatment for early HR-positive breast cancer in past decades.

Recently, both extended therapy with tamoxifen[6,7] and sequencing therapy with letrozole in postmenopausal women[8] after the completion of 5 years of treatment with tamoxifen have resulted in an improvement in disease-free survival (DFS) and overall survival (OS). However, a meta-analysis of five trials reported that extended adjuvant tamoxifen could not reduce recurrence or all-cause death in unselected breast patients.[9] Extended tamoxifen treatment could increase the risk of endometrial cancers and thromboembolic diseases, which may compromise the decrease in breast cancer mortality in HR-positive breast cancer patients;[6,7] this raises the question of which patient subgroups have a higher risk of recurrence after 5-year tamoxifen treatment and would benefit more from an additional 5-years of endocrine therapy. Therefore, the identification of risk factors that can predict disease recurrence beyond 5 years after 5-year tamoxifen therapy for HR-positive breast cancer may provide additional supporting evidence for the optimal treatment for those premenopausal patients. Hence, we sought to retrospectively review our database of HR-positive breast cancer patients who had completed adjuvant tamoxifen therapy and who were free of disease recurrence 6 years postsurgery to identify possible risk factors that result in a higher risk of late recurrence and mortality.

Materials and methods

Patients

Between 1990 and 2004, all breast cancer patients who underwent breast cancer surgery at Linkou Chang Gung Memorial Hospital (CGMH), Taoyuan, Taiwan were registered in the CGMH breast cancer databank. Data on patient demographics, tumor characteristics, surgical procedures, adjuvant chemotherapy, radiotherapy, hormonal therapy, disease status, and survival outcomes were retrospectively collected. The present analysis enrolled stage I–III HR-positive breast cancer patients undergoing curative surgery with or without adjuvant chemotherapy followed by adjuvant tamoxifen therapy. Patients who were free of disease 6 years after their surgery, regardless of the duration of their tamoxifen therapy, were included for analysis. Before 1998, the HR status was examined by using a cytosol charcoal absorption assay, whereas immunohistochemical staining was used to determine HR status thereafter. As human epidermal growth factor-2 (HER-2) staining was not available prior to 2000, HER-2 expression data were not used. This retrospective analysis was approved by the Institutional Review Board of CGMH.

Treatment

All patients underwent primary surgery consisting of either modified radical mastectomy (MRM) or partial mastectomy (PM) with axillary lymph node dissection. Adjuvant radiotherapy was administered to patients who received PM or who had pathological stage T3 disease, or more than three axillary lymph node metastases.[10] Adjuvant chemotherapy was administered to high-risk patients, such as high-risk node-negative or node-positive cancer. Chemotherapy regimens were administered at the physician's discretion and patients' preference; for example, intravenous cyclophosphamide, methotrexate, and 5-fluorouracil (CMF), cyclophosphamide, epirubicin, and 5-fluorouracil (CEF) or CEF regimens followed by taxanes were utilized in node-positive disease in accordance with the contemporary international consensus. Adjuvant endocrine therapy consisted of tamoxifen (20 mg per day) for 2–5 years; prior to1996, 2 years of tamoxifen treatment was the common duration of treatment. After the completion of surgery, chemotherapy and radiotherapy, the patients were followed-up at the outpatient department with a physical examination every 3 months for the first 2 years, every 6 months for the next 3 years, and every 12 months thereafter; breast mammography or ultrasonography every 12 months; chest radiography every 12 months; and a complete blood count, biochemical tests, and measurements of the serum levels of carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3) every 6 months for the first 3 years and every 12 months thereafter. Other examinations, such as bone scanning and abdominal ultrasonography, were performed at the physicians' discretion. Medical information was obtained by a periodic review of the charts and by telephone interviews. The cut-off (data-lock) follow-up time-point was July 2012.