Original Study

A Comparison of Epidemiology, Biology, and Prognosis of Inflammatory Breast Cancer in Japanese and US Populations

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Abstract

This is a comparative study of inflammatory breast cancer in a Japanese population (n = 22) vs. a population in the United States (US) (n = 384) to determine whether there are differences in epidemiologic factors and clinical features. Body mass index (BMI) and nuclear grade were significantly different between the 2 populations. Estrogen receptor (ER) status and race were prognostic factors when populations in Japan and US were combined.

Background: The epidemiology of inflammatory breast cancer (IBC) in East Asia has not been fully investigated. We hypothesized the epidemiologic factors associated with IBC in Japanese populations are different from other populations. To determine this, we conducted a comparison study assessing multiple clinically relevant risk factors. **Patients and Methods:** Patients diagnosed with IBC at St. Luke's International Hospital (SLIH) in Tokyo, Japan, and at the University of Texas MD Anderson Cancer Center (MDA) in Houston, Texas, from 2003 to 2009 were identified via the electronic medical records. Stage IV patients were excluded. Epidemiological, biological, and overall survival (OS) data were collected and compared. After all patient populations were combined, Cox proportional hazard regression analysis was performed. **Results:** Twenty-two patients at SLIH and 384 patients at MDA were identified. No differences were found for IBC between SLIH and MDA regarding age at diagnosis ($P = .898$), hormone receptor status ($P = .144$), overexpression of HER2 ($P = .136$), or OS ($P = .323$), however, BMI ($P < .01$) and nuclear grade (NG) ($P < .01$) in Japanese patients were lower than those of US patients. Cox proportional hazard regression analysis revealed ER status and race were associated with OS. **Conclusion:** Despite the small number of patients enrolled, IBC in a Japanese population demonstrated lower BMI and lower NG than IBC in a US population with no difference in survival. ER status and race were prognostic factors when the 2 populations were combined. To more robustly define IBC among East Asian individuals, we have started to register Japanese patients with an International IBC Registry.

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Introduction

Inflammatory breast cancer (IBC), a form of breast cancer characterized by low incidence, rapid progression, and poor survival, has previously been described in predominantly Western populations.[1,2] Accurate information on IBC is essential for its early detection and treatment, however, its rarity makes large prospective studies difficult. The epidemiologic risk factors influencing IBC in East Asian populations have not yet been fully investigated.

In previous population-based studies, the incidence of IBC varied according to ethnic group.[3-5] In Japan, IBC accounts for approximately 0.09%-2.9% of all breast cancer cases,[6] and represents 5.7% in Tunisia,[7] and 11.1% in Egypt.[5] In addition, there are few established risk factors for IBC, including African-American ethnicity,[3] high body mass index (BMI),[3,8,9] and younger age at disease onset.[3] Because Japan remains a largely homogeneous population with relatively low BMI[10] (http://www.oecd.org/dataoecd/55/2/44117530.pdf page 56-57), previously identified

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risk factors might not be applicable to Japanese or other East Asian populations. We hypothesized that the epidemiological factors associated with IBC in Japan are different than those in other populations. To determine clinical differences of IBC in a Japanese population, we conducted a comparative, hospital-based study using a mixed ethnic population of IBC patients from the United States as a comparison group.

Patients and Methods

Patients

We carried out a retrospective, comparative study of IBC patients identified from St. Luke's International Hospital (SLIH) and the University of Texas MD Anderson Cancer Center (MDA), who presented from 2003 to 2009. For reference, SLIH is a tertiary referral community hospital in Tokyo, Japan, with one of the largest breast cancer centers and in which more than 800 breast surgeries are performed per year. MDA is 1 of 40 National Cancer Institute-designated comprehensive cancer centers in the United States, providing treatment to more than 40,000 patients per year.

Per the 2008 IBC consensus statement, IBC was defined as characterized by rapid onset (progression in 3-6 months) of diffuse breast erythema and edema (peau d'orange), with or without underlying palpable mass, accompanied by pathological confirmation of invasive carcinoma.[11] Clinical stage was classified according to the *AJCC Staging Manual*, 6th edition criteria.[12] IBC is defined as T4d disease categorized at or greater than stage III. Stage IV patients were excluded.

For this study, epidemiological parameters including race, age at diagnosis, menstrual status, BMI, and type of treatment received (chemotherapy, radiation therapy, or surgery) were collected from electronic medical records.

Pathological Analyses

In addition to these parameters, biological data such as hormonal status (estrogen receptor [ER], progesterone receptor [PR]), HER2 expression, and nuclear grade were collected. Nuclear grade was evaluated by at least 2 pathologists.

Immunohistochemical (IHC) localization of ER, PR, and HER2 was scored in a semiquantitative fashion, incorporating the intensity and distribution of receptor-specific staining. At SLIH, ER and PR status were evaluated using the Allred score. At MDA, samples from primary tumors were considered positive for ER or PR if $\geq$ 10% of cells demonstrated nuclear staining on IHC analysis.

For HER2, the percentage of HER2 tumor cell positivity was graded on a scale of 0 to 3. For IHC analysis, scores of 0 or 1+ HER2 status was considered negative, and a score of 3+ HER2 was considered positive. For IHC analysis, scores of 2+ according to fluorescent in situ hybridization, which quantitatively measures HER2 gene amplification, was used. Samples were considered positive for HER2 gene amplification with a HER2/CEP17 ratio $\geq$ 2.2.

Statistical Analyses

Patient and tumor characteristics were tabulated and then stratified and compared between hospitals (SLIH vs. MDA). The χ^2 test was used for comparisons of categorical data, and the *t* test was used to compare means of continuous data. Before using the *t* test, the normal distribution of data was verified using graphical methods, including histograms and normal plots; the equal variances assumption was verified using the *F* test.

The follow-up cutoff for this data set was May 1, 2011. Overall survival was calculated from the date of diagnosis to the date of death from any cause or to the last follow-up. Patients who were still alive at the time of last follow-up were censored. Disease-free survival was calculated from the date of diagnosis to the date of recurrence. The Kaplan-Meier approach was used to analyze survival estimates, and the log-rank test was used to compare across groups. After the 2 populations were combined, Cox proportional-hazard analysis was used to identify a subset of significant prognostic variables that were related to overall survival. *P* values were 2-sided, and a value $< .05$ was considered to be statistically significant. All analyses for this study were performed using SPSS 18.0J (SPSS Japan, Tokyo, Japan).

Results

Between 2003 and 2009, 22 and 384 patients were diagnosed with IBC at SLIH and MDA, respectively. All patients were women. Characteristics of these patients are shown in Table 1.

At SLIH, all patients were Asian. At MDA, 11 patients (2.9%) were Asian, 290 patients were Caucasian (75.5%), 40 patients were African-American (10.4%), and 38 patients were Hispanic (9.9%). The mean age at IBC diagnosis was 51 years (SD, 10.5) at SLIH and 50 years (SD, 11.3) at MDA ($P = .898$). Mean BMI was 22.5 (SD, 3.3) and 30.9 (SD, 8.0) at SLIH and MDA, respectively ($P < .01$). Fifty percent (11/22) of patients were postmenopausal at SLIH, compared with 51.8% (199/384) at MDA ($P = .898$).

At SLIH, 17 patients (77.3%) received chemotherapy, 20 patients (90.9%) underwent surgery, and 13 patients (59.1%) received radiotherapy. At MDA, 278 patients (72.4%) received chemotherapy, 355 patients (92.4%) underwent surgery, and 294 patients (76.6%) received radiation therapy (chemotherapy, $P = .618$; surgery, $P = .792$; radiotherapy, $P = .063$).

At both hospitals, IBC was more likely to be hormone-negative. ER- and PR-negative cases comprised, respectively, 36.4% (8/22) and 54.5% (12/22) at SLIH vs. 52.1% (200/384) and 65.1% (250/384) at MDA (ER, $P = .144$; PR, $P = .215$). At SLIH, HER2-positive cases comprised 27.3% (6/22) of IBC cases, and HER2 positive cases comprised 31.5% (121/384) at MDA ($P = .136$). A significant difference in nuclear grade was seen between SLIH and MDA with Grade 3 seen in 22.7% (5/22) at SLIH and in 70.8% (272/384) at MDA ($P < .01$). Median follow-up was 3.1 years at SLIH and 2.5 years at MDA ($P = .139$). Median overall survival of patients was 4.2 years at SLIH and 4.2 at MDA ($P = .323$) (Fig. 1). Median disease-free survival was 6.0 years at SLIH and 2.1 years at MDA ($P = .317$) (Fig. 2).

We performed Cox proportional hazard regression analysis after all patients were combined. The analysis revealed that ER status was a prognostic factor ($P = .002$). More interestingly, race was also associated with overall survival ($P = .032$) (Table 2). Caucasian and African-American individuals were found to have increased risk of death compared with Asian individuals (hazard ratio [HR], 2.3 for Caucasian [$P = 0.03$]; HR, 4.2 for African-American [$P < .01$] individuals).