RESEARCH COMMUNICATION

Clinical Characteristics of Triple-negative Breast Cancer: Experience in an Asian Developing Country

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Abstract

Introduction: Triple negative (TN) breast cancers are defined by a lack of expression of oestrogen, progesterone, and HER2 receptors. They tend to have a higher grade, with a poorer outcome compared to non-TN breast cancers. Objective: The aim of this study is to determine the incidence of TN breast cancer in an Asian country consisting of Malays, Chinese and Indians, and to determine the factors associated with this type of breast cancer. Results: The incidence of TN breast cancer in the University Malaya Medical Center is 17.6%. There is no significant difference amongst the Malays, Chinese and Indians. In bivariate analysis, TN breast cancer was significantly associated with younger age and Grade 3. However, in multivariate analysis using logistic regression, TN breast cancer was only associated with Grade 3. Conclusion: The incidence of TN breast cancer in our study is similar to other studies, and associated with a higher grade.

Key Words: Triple negative breast cancer - hormone receptors - HER2 over-expression -prognostic factors - ethnicity

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Introduction

Triple-negative breast cancer is characterized by a lack of expression of estrogen receptor (ER), progesterone receptor (PR), and HER2/neu. It is noted to be a clinicopathologic entity with aggressive behavior and poorer prognosis. Standard therapy is associated with high relapse rates, and the most appropriate treatment is as yet unknown (Cleator et al., 2007).

The objective of this study is to determine the incidence of triple negative breast cancer in a multiethnic population of Malaysian women presenting with breast cancer at the University Malaya Medical Centre, and to investigate the differences in the patients' demography and tumour characteristics between triple negative (ER & PR & HER-2/neu negative) and non- triple negative breast cancer patients.

Materials and Methods

We conducted a retrospective review of 1147 patients with newly diagnosed breast cancer treated in the University Malaya Medical Center from January 2005 to December 2007. The patients' age at onset, self-reported race, stage of disease, size, tumour grade, histology and lymph node status were evaluated from pathological and clinical reports. The patients were staged according to the American Joint Commission on Cancer (AJCC) Cancer Staging Manual 6th Ed (Grene et al., 2002). We excluded 151 patients where the ER, PR and HER2 status was not available in the patient records, and the final analysis was conducted on 996 patients. We conducted binary logistic regression analysis to determine the independent predictors of triple negative breast cancer.

ER, PR and HER2 status were determined by immunoperoxidase staining of the tumour. ER and PR were considered negative if staining of the tumour cell nuclei were less than 10%. HER2 was assessed through immunohistochemistry (IHC) and based on a staining intensity, was classified as negative, 1+, 2+ or 3+. Only a report of negative or 1+ was taken as HER2 negative. FISH (Fluorescene in situ hybridization) was not carried out as it was not available in our institution

Determination of ER and PR (by IHC) has been carried out since 1996 in the University Malaya Medical Centre, and although the pathology laboratory started HER2 testing in 2000, it initially has problems with standardization, and it was not until 2005 when the test became more reliable. Hence, the period of this study was from 2005-2007, and outcome data is not yet available. The aim of this preliminary report is to study the incidence of triple negative breast cancer in a multi-ethnic Asian developing country and the factors associated with this subtype.

Results

The majority of patients treated at this centre (68.9%) were Chinese, with 17.3% Malays, 12.0% Indians and 1.8% other races (mixed race and Eurasians). The patients'

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Table 1. Clinicopathological Characteristics of Triple Negative Breast Cancer Cases

Parameter		Triple-ve (%)	Others (%)	p-value
Age	Less than 40	32 (25.0)	93 (75.0)	0.01
	40 and above	143 (16.4)	728 (83.6)	
Race	Malays	30 (17.4)	142 (82.6)	0.45
	Chinese	124 (18.1)	562 (91.9)	
	Indians	16 (13.3)	104 (86.7)	
	Others	5 (27.0)	13 (73.0)	
Histology	IDC	146 (16.8)	724 (83.2)	0.09
	Non IDC	29 (23.0)	97 (77.0)	
Stage	1-2	136 (17.2)	653 (82.8)	0.53
	3-4	39 (19.1)	165 (80.9)	
Size	2 cm and less	53 (15.5)	290 (84.5)	0.39
	2-5 cm	81 (18.7)	353 (81.3)	
	>5 cm	35 (19.6)	144 (80.4)	
Grade	1	6 (10.5)	51 (89.5)	<0.01
	2	38 (10.2)	335 (89.8)	
	3	99 (40.7)	144 (59.3)	
Lymph node status (N)	Involved	78 (17.3)	372 (82.7)	0.83
	Uninvolved	96 (17.8)	442 (82.2)	

ages at presentation ranged from 22 to 88 years old with a mean of 53.3 years. A significant proportion of patients were less than 50 years old, and notably, 125 (12.6%) patients were less than 40 years old. The majority of patients (87.3%) had infiltrating ductal carcinoma and 45.5% had lymph node involvement. Nearly 20% of patients had tumour size greater than 5 cm. The majority of patients had high grade tumours; (Bloom and Richardson classification) 47.9% grade 2 and 44.7% grade 3. Three percent of patients had stage 0 disease, 25.7% stage 1, 50.8% stage 2, 14.7% stage 3 and 5.8% stage 4. We found that overall 175 (17.6%) patients had triple negative breast cancer, and we have compared the demographic and clinicopathological features of patients with triple negative and non-triple negative breast cancers (Table 1). From bivariate analysis, triple negative breast cancer patients were significantly associated with younger age i.e. less than forty years old (p=0.012) and higher tumour grade (grade 3) (p<0.001). Although not statistically significant, there was a trend for the tumours which are diagnosed at later stages and at larger sizes to be triple negative. Indians also tended to have a lower incidence of triple negative breast cancers compared to the Chinese and Malays.

For multivariate analysis using logistic regression, triple negative breast cancer patients was associated only with a high tumour grade (p<0.001, OR-3.0, CI 2.00-4.48).

Discussion

The triple negative subgroup of breast cancer has been reported to have different incidence amongst different ethnic groups and have been associated with lower disease-free survival, a higher predisposition to visceral metastases and poorer outcome when compared to other subtypes of breast cancer (Bauer et al., 2007; Dent et al., 2007; Lund et al., 2008). For example, in a study of triple negative breast cancer in a large multi-ethnic population, Bauer and colleagues (2007) studied a total of 6,370 women identified as having triple negative breast cancer from the California Cancer Registry and compared it with 44,704 women with non-triple negative breast cancer, and found that women with triple negative breast cancer were more likely to be under age 40 years old (OR 1.53), and non-Hispanic Black (OR 1.77) or Hispanic (OR 1.23), and also from the lower socio-economic group. Regardless of stage at diagnosis, women with triple negative breast cancer had poorer survival than those with non- triple negative breast cancer, and non-Hispanic black women with late stage triple negative breast cancer had the poorest survival of only 14%.

The overall rate of triple negative breast cancer in our centre (17.6%) is comparable with the results from different population and ethnic groups, where rates of 11.2% amongst 1601 cases in Canada (Dent et al., 2008) and 16.3% amongst 1944 cases in the United Kingdom in predominantly Caucasian populations (Rakha et al., 2007) to 14% amongst 1552 cases in Japan (Nishimura and Arima, 2008) and 17% amongst 1132 cases in China (Liu et al., 2008) have been reported. Notably, the rate of triple negative breast cancer amongst the Chinese in our cohort (18.1%) is similar to that seen in the Chinese population in China (Liu et al., 2008) .

Triple negative breast cancer has been associated with high grade tumours, larger size, and later stages at presentation (Rakha et al., 2007; Liu et al., 2008; Reis-Filho and Tutt, 2008). Intriguingly, although the tumour grades, size, stage and stage at presentation of breast cancer in our cohort is similar to that that has been reported amongst African Americans (Deshpande et al., 2008) and all of these factors are associated with higher triple negativity status, we have not observed the higher rate of triple negative breast cancer that has been reported in African Americans (29.3%) in our Asian cohort (Lund et al., 2008). Moreover, in our study on the three main racial groups in Malaysia, there appears to be no significant racial difference in the incidence of triple negative breast cancer. There is a lower incidence of triple negative breast cancers in Indian women, which is consistent with the later mean age of onset of breast cancer amongst Indian women compared to Malay and Chinese women, although the significance of this has not yet been determined.

Although triple negative breast cancers have been associated with lower disease-free survival, a higher predisposition to visceral metastases and poorer outcome when compared to other subtypes of breast cancer (Bauer et al., 2007; Dent et al., 2007; 2008; Lund et al., 2008), a study of triple negative breast cancer in Chinese women did not find a significantly poorer outcome and suggested that triple negative disease in Chinese may not be associated with a poorer outcome as reported in Caucasians (Yin et al., 2008).

Given that there appears to be a poor prognostic subgroup of breast cancer that is associated with the triple negative status, it is critical that we understand the molecular characteristics of this subgroup of breast cancer and determine accurate markers which may be used in the identification of and treatment selection for this poor prognostic group. Clearly, there are significant overlap between triple negative breast cancers and basal-like

breast cancers (Kreike et al., 2007) but they are not synonymous (Rakha et al., 2007). Notably, at least by gene expression profiling, up to 71.5% of triple negative breast cancers were basal-like, while conversely, by pathological staining, 76.9% of basal-like breast cancers was triple negative (Bertucci et al., 2008). Moreover, histologically and transcriptionally, triple-negative breast cancers and basal breast cancer cancers have many similarities to BRCA1-associated breast cancers, which suggests that dysfunction in BRCA1 or related pathways occurs in these subsets of breast cancers (Cleator et al., 2007; Reis-Filho and Tutt, 2008). At least by immunohistochemistry, the poor prognosis basal-like and/or triple negative breast tumours may be better identified by staining for a five-marker panel comprising ER, PR, HER2, Cytokeratin (Ck) 5/6, and epidermal growth factor receptor (EGFR) (Cheang et al., 2008). Triple negative breast cancers are also associated with expression of p53 and P-cadherin (Rakha et al., 2007; Lund et al., 2008; Nishimura and Arima, 2008).

There is currently no specific systemic regimen recommended for the treatment of triple-negative breast cancers, and despite treatment with standard dose anthracycline-based chemotherapy, the clinical outcome of triple negative and bilateral cancers remains poor (Tan et al., 2008). Alternative chemotherapeutic regimens and/or novel therapeutic approaches are warranted, with new efforts focused on targeting specific molecular features of these cancers, including the EGFR receptor and BRCA1 status (Cleator et al., 2007).

In conclusion, the incidence of triple negative breast cancer in this predominantly Asian population is comparable to reported data in other populations, and there is no significant difference in incidence between the Malays, Chinese and Indians. Consistent with other studies, it is associated with a younger age and a higher grade of tumour in bivariate analysis, but in multivariate analysis, higher grade appears to be the only important association

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