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Original research article

Clinicopathological features and prognosis of triple negative breast cancer in Kuwait: A comparative/perspective analysis☆

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ABSTRACT

Aim: The aim of this study was to determine the incidence of TNBC in Kuwait, to analyze the clinicopathologic features and prognosis of this type of breast cancer, and compare it with reports from other regions of the world.

Background: Triple negative breast cancer (TNBC) is defined as a subtype that is negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2). There is a growing evidence of the heterogeneity of such entity on the molecular level that may cause discrete outcomes.

Methods: We analyzed the clinicopathologic features of 363 TNBC cases which were diagnosed in Kuwait from July 1999 to June 2009. The disease-free survival (DFS) and overall survival (OS) were analyzed by Kaplan–Meier method. Comparison was done with reports from USA, Europe, Middle and Far East.

Results: Among 2986 patients diagnosed with breast cancer in Kuwait, 363 patients (12.2%) were TNBC. The median age was 48 years, 57.2% had lymph nodes (LN) metastasis, 56.9% were of grade III tumor and 41.9% had stage II disease. 81% developed recurrences and 75% of deaths occurred by 2.5 years after treatment. There is marked variation of clinicopathologic features according to country of patients' cohort.

Conclusion: The incidence of TNBC in our study is similar to other studies. TNBC patients showed an early major recurrence surge peaking at approximately year 2.5. Regional variation of clinicopathologic features indicates a need for molecular studies to define underlying molecular features and its impact on survival.

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1. Background

Breast cancer (BC) is increasingly recognized as a heterogeneous disease exhibiting substantial differences with regard to biological behavior and requiring distinct therapeutic interventions. Steroid hormone receptors (HR) such as estrogen receptor (ER) and progesterone receptor (PR) in concert with the oncogene ErbB-2/human epidermal growth factor receptor 2(HER-2) are critical determinants of these BC subtypes.[1–6] Triple-negative breast cancer (TNBC) is characterized by a lack of expression of both ER and PR as well as HER-2. A recent analysis indicates that TNBC carries a distinct molecular profile when compared with HR-positive BC.

A breast cancer classification emerged in the scientific scene based on gene expression profiles. The subgroups (luminal, HER2, normal breast and basal-like; BLBC) have distinct gene expression patterns and phenotypical characteristics. TNBC shares phenotypical features with basal-like breast cancer, which is in turn the most aggressive and with worse outcome.[7–11] However, the molecular classification of breast cancer has not led to changes in treatment recommendations and should yet be considered investigational, as the clinicopathological entities defined by the use of common immunohistochemistry (IHC) methods still represent the base for such recommendations.[12]

In Kuwait, a trend of presentation of breast cancer at earlier age was documented.[13] This carries a risk of having more patients with TNBC (that is known to be more common at young ages). Many reports from different countries across the world documented different clinicopathological features that may be different by ethnicity.

2. Aim

The aim of this study was to determine the incidence of TNBC in Kuwait. In addition, analysis of the clinical and pathologic features of TNBC patients in Kuwait as well as the prognosis of this type of breast cancer was documented. Third, these findings were compared with reports representing different ethnic and demographic populations over the world.

3. Patients and methods

This is a retrospective analysis of the patients who attended the Kuwait Cancer Control Center (KCCC) for treatment or follow-up of breast cancer. Based on the Hospital cancer registry, medical files of all patients diagnosed with breast cancer in the period from July 1999 to June 2009 were reviewed. For all patients, the pathology was reviewed to confirm the diagnosis and the hormonal receptor and Her-2-neu status. Pathological diagnosis was based on biopsy from the primary breast lesion even in the context of cases presented with metastasis. We analyzed the clinicopathologic features of 363 triple negative cases which were diagnosed in this period. The TNM staging was based on pathologic findings in patients who had undergone upfront surgical treatment, while it was clinical and radiologic staging in patients who had received neoadjuvant chemotherapy. The disease-free survival (DFS) and overall survival (OS) were analyzed by the Kaplan–Meier method.

ER and PR were assessed using immunohistochemical staining for quantitative and qualitative assessment. Negativity was defined as absent IHC stain in all the examined tissue, i.e. 0%. Her-2-neu scores of 0 and 1 were considered negative, and a score of 3 was considered positive.[14] Score of 2 was considered equivocal and FISH was considered. Ki67 was considered positive if it was more than 10%.

Follow up of patients was scheduled to be every 4 months for the first 2 years post-treatment, every 6 months for the next 3 years then annually. Follow up was by clinical examination and annual mammography. Follow up duration was 41.9 months in average (range 1–131 months). Studies from the USA, Europe, Lebanon, Korea and Japan were reviewed.[23–30]

4. Results

4.1. *Clinical features*

During the period from July 1999 to June 2009, 2980 patients were documented to have breast cancer in KCCC. Out of them, 363 patients (12.2%) were confirmed to have a triple negative disease. Patient characteristics are summarized in Table 1. The mean age was 48 ± 11.7 years for the study population. Median age at the first birth was 23 ± 5.3 years.

4.2. *Pathological features*

Tumor characteristics are summarized in Table 1. Sixty two percent had T1-2 tumor and the mean tumor volume was 3 cm. Majority of cases had node negative (42.8%) and 24.1% had N1 disease. N2-3 disease was the rule in 33.1%. Her-2-neu was negative by IHC staining in 87.6% while FISH was needed to confirm diagnosis in 45 patients.

Treatment modalities are summarized in Table 2. It should be mentioned that, in our patient cohort, 51 patients had not received chemotherapy at all during their treatment course.

4.3. *Pattern of failure Table 3*

There were 100 documented recurrences in our study population. The most common site of recurrence was local recurrence in 10.7% of cases (39% of all recurrences) followed by bone and lung metastasis that occurred in 7.7% of cases each (28% of all recurrences each). Liver metastasis was documented in 5.2%, brain metastasis in 3.8%, and contra-lateral breast recurrence in 2.2%, (19%, 14%, 8% of all recurrences, respectively) (Table 3).

4.4. *DFS and OS (Fig. 1)*

Excluding patients presented with metastatic disease, most of recurrences happened in the first 2–3 years i.e. 81% of recurrences occurred by 2.5 years after treatment. DFS was 76.6%