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Original Article

Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer. Its relation with molecular subtypes☆

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ABSTRACT

Objective: To evaluate the influence of the molecular subtype (MS) in the Sentinel Node Biopsy (SNB) technique after neoadjuvant chemotherapy (NAC) in women with locally advanced breast cancer (BC) and a complete axillary response (CR).
Material and methods: A prospective study involving 70 patients with BC treated with NAC was carried out. An axillary lymph node dissection was performed in the first 48 patients (validation group: VG), and in case of micro- or macrometastases in the therapeutic application phase (therapy group: TG). The patients were grouped according to MS: 14 luminal A; 16 luminal B HER2−; 13 luminal B HER2+; 10HER2+ non-luminal; 17 triple-negative.
Results: SNB was carried out in 98.6% of the cases, with only one false negative result in the VG (FN = 2%). Molecular subtype did not affect SN detection. Despite the existence of axillary CR, statistically significant differences were found in the proportion of macrometastasis (16.7% vs. 35.7%, $p = 0.043$) on comparing the pre-NAC cN0 and cN+. Breast tumor response to NAC varied among the different MS, this being lowest in luminal A (21.5%) and highest in non-luminal HER2+ group (80%). HER2+ and triple-negative were the groups with the best axillary histological response both when there was prior clinical involvement and when there was not.
Conclusions: Molecular subtype is a predictive factor of the degree of tumor response to NAC in breast cancer. However, it does not affect SNB detection and efficiency. SNB can also be used safely in women with prior node involvement as long as a complete clinical and radiological assessment is made of the node response to NAC.

La biopsia del ganglio centinela después de quimioterapia neoadyuvante en el cáncer de mama. Relación con los subtipos moleculares

Palabras clave:
Ganglio centinela
Quimioterapia neoadyuvante
Cáncer mama localmente avanzado
Subtipo molecular
Estadificación axilar

RESUMEN

Objetivo: Evaluar la influencia del subtipo molecular (SM) en la biopsia del ganglio centinela (BGC) tras quimioterapia neoadyuvante (QTN) en cánceres de mama (CM) localmente avanzados y respuesta completa axilar (RCA).
Material y métodos: Estudio prospectivo de 70 CM tratadas con QTN para cirugía conservadora. Se realizó linfadenectomía axilar en 48 pacientes (fase validación), y en caso de micro o macrometástasis (fase terapéutica). Clasificadas según el SM: 14 luminal A, 16 luminal B HER2-, 13 luminal B HER2+, 10 HER2+ no-luminal, 17 triple-negativo.
Resultados: La BGC se realizó en el 98.6% de los casos, con un falso negativo en la fase de validación (FN = 2%). El SM no influyó en la detección del GC. A pesar de existir RCA, al comparar los cN0 y cN+ preQTN, encontramos diferencias significativas en la proporción de macrometástasis (16,7% vs. 35,7%, p = 0,043). La respuesta completa del tumor mamario tras QTN varió estadísticamente entre los SM, siendo la más baja los luminal A (21,5%) y la más alta los HER2+ no-luminal (80%). El HER2+ y el triple negativo fueron los grupos con mejor respuesta patológica axilar tanto si existía afectación clínica previa o no.
Conclusión: El SM es un factor predictivo del grado de respuesta tumoral a la QTN en el CM pero no influye en la detección y la eficacia de la biopsia del ganglio centinela. Es seguro utilizar la biopsia del ganglio centinela también en mujeres con afectación ganglionar previa siempre que se realice una completa evaluación clínica y radiológica de la respuesta ganglionar a la QTN.

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Introduction

Sentinel lymph node biopsy (SLNB) is currently the technique of choice in lymph node staging of early stage breast cancer.[1–4] However, its utility, efficacy and safety in large advanced tumors has been questioned because axillary metastases may be found in 50–60% of the patients with clinically negative axilla.[5–7]

With the use of neoadjuvant chemotherapy (NCT) it is possible to reduce the size of the tumor and even eliminate all the tumor cells, thereby facilitating conservative surgery in women in whom mastectomy is the only surgical option. With the same conservative approach it is again possible to perform SLNB in patients undergoing NCT with the aim of avoiding axillary lymph node dissection without therapeutic repercussions. However, recently published results have demonstrated uncertainty regarding when SLNB should be carried out, with variable false negative result rates (10–30%) and differing pros and cons for doing SLNB pre- or post-NCT, particularly in patients with clinical axillary involvement prior to NCT.[8–10]

The aim of this study was to present a prospective evaluation of our experience in the application of SNLB after NCT in patients with and without previous axillary involvement and evaluate the relevance of the molecular subtype of primary breast cancer in the SLNB technique and in tumor response to NCT.

Material and methods

We performed a prospective single center study of all consecutive patients with breast cancer treated with NCT from January 2007 to December 2012 with the aim of carrying out conservative breast surgery. The SLNB was done post-NCT in all the patients, with axillary lymph node dissection in the first 48 patients in the validation phase (VP) and in 22 patients in the therapeutic phase (TP) with metastasis (macrometastasis or micrometastasis).

Initial staging of the breast cancer

The patients were classified according to the international TNM classification and local and regional staging was carried out by physical examination of the breast and axilla in addition to mammography, ultrasonography and magnetic resonance. Ultrasound-guided thick needle tumor biopsy was performed, which also allowed placement of a marker coil to help in radiologic control following NCT and to guide ultrasound-guided surgery in patients with complete clinical response. In cases with axillary lymph nodes suspected of malignancy, ultrasound-guided aspiration puncture was performed. Distant staging was undertaken by chest X-ray, abdominal ultrasonography and whole body bone scintigraphy.

Molecular classification of breast cancer

We determined the following biological and molecular tumor markers: estrogen receptors (ER), progestagen receptors (PR), protein p53, the Ki-67 index, human epidermal growth factor receptor-type 2 (HER2), e-cadherin and cytokeratin-19 (CK-19). Positivity of HER2 was confirmed by fluorescence in situ hybridization (FISH). The patients were classified into 5 groups according to the practical clinical guidelines for breast cancer of the ESMO (European Society of Medical Oncology)[11] as follows: luminal A (ER positive, HER2-negative, low Ki-67 index <20%, PR positive >20%); luminal B HER2-negative (ER positive, HER2-negative, high Ki-67 index>20% or PR <20%); luminal B HER2-positive (ER positive, HER2-positive, any Ki-67 index, any PR); HER2-positive (not luminal: ER negative, PR negative); and triple negative (ductal: ER negative, PR negative, and HER2 negative).

Neoadjuvant chemotherapy

The NCT schedule was based on the biological-molecular characteristics of the tumor and the physical characteristics of the patients. In general, patients with HER2 positive receptors confirmed by the FISH molecular study received a regimen with paclitaxel (taxol®) at a weekly dose of 80 mg/m^2, for 12 weeks, followed by 4 cycles of FEC (600 mg/m^2 of 5-fluoracyl, 90 mg/m^2 of epirubicin, and 600 mg/m^2 of cyclophosphamide) administered every 21 days. From the beginning this was accompanied by trastuzumab (herceptin®) weekly at an initial dose of 4 mg/kg, followed by 2 mg/kg which was maintained for one year.

Patients with HER2 negative receptors first received 4 cycles of FEC at the previously mentioned doses over 3 weeks followed by docetaxel (taxotere®) at a dose of 100 mg/m^2 (4 cycles every 21 days) together with a colony stimulating factor (neupogen®).

Clinical-radiological response to NCT

Physical examination of the breast and axilla was performed on each visit for NCT. On finishing the NCT, mammography, ultrasonography and magnetic resonance of both breasts and axilla were carried out. Clinical and radiological response at the level of the breast and axilla was established in three groups as: complete, partial, or no response. In cases with axillary involvement prior to the NCT and without complete response, SLNB is not indicated, and complete axillary lymph node dissection was performed.

Breast surgery

In all the cases the objective was to perform conservative surgery of the breast. If this was not possible, and if requested by the patient, mastectomy was followed by immediate reconstruction of the breast. Tumorectomy was done in all the interventions taking advantage of the marker coil placed at diagnosis. In cases of partial response, intraoperative ultrasonography and the macroscopic study established the resection limits at >3 mm.

Axillary staging

The SLNB was carried out using the combined radiotracer plus dye technique. In cases with partial response the radiotracer was injected peritumorally; in cases with complete response the injection was performed in the quadrant in which the lesion was located. The dose used was 74–111 MBq of ^{99m}Tc-colloidal rhenium sulphide (nanocis®) or ^{99m}Tc-albumin nanocolloid (nanocoll®). Preoperative scintigraphy was performed in all the cases: the day prior to surgery in 27 cases and on the same day of the surgery in 43. In the operating room and under anesthesia a periareolar injection of 2 ml of isosulfan blue (lymphazurin®) was made followed by breast massage to facilitate lymphatic drainage. Lymph nodes were considered to be anything with significant activity using the gamma detector probe (europrobe®) and/or blue dye. In addition, intraoperative examination of the axilla was performed with resection of any suspicious lymph node regardless of its radioactivity or staining. Histopathological analysis of the sentinel lymph nodes (SLN) was done using the OSNA method of cytokeratin-19 amplification which allows complete analysis of the SLN and specifies the presence of micro- or macrometastasis. To make optimal use of the time in the operating room the SLN were first resected and then local treatment of the breast tumor was carried out. The axillary lymph node dissection was done in the VP and in the TP in patients with