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Sentinel lymph node biopsy after neoadjuvant systemic chemotherapy in patients with breast cancer: a prospective pilot trial

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ABSTRACT

Introduction. The feasibility and accuracy of the sentinel lymph node biopsy for patients who have received neoadjuvant chemotherapy for the treatment of breast cancer is still controversial. **Material and methods.** Thirty-one consecutive patients with the diagnosis of invasive breast cancer who received neoadjuvant chemotherapy underwent sentinel lymph node biopsy and complete axillary lymph node dissection. **Results.** Sentinel lymph nodes were successfully identified in 26 (83.8%) patients. The node was positive for malignancy in nine (34.6%) patients. Two of the patients with a negative sentinel lymph node presented other positive nodes in the final axillary specimen (false negative rate of 18%). **Conclusions.** The results obtained by our prospective clinical trial do not support the use of the sentinel lymph node biopsy as an accurate procedure to predict the axillary lymph node status.

Key words. Sentinel node biopsy. Neoadjuvant chemotherapy. Breast cancer. Axillary dissection. Prospective clinical trial.

Biopsia de ganglio centinela después de la administración de quimioterapia neoadyuvante en pacientes con cáncer de mama: un estudio piloto prospectivo

RESUMEN

Introducción. *La viabilidad y la precisión de la biopsia del ganglio centinela en los pacientes que han recibido quimioterapia neoadyuvante para el tratamiento del cáncer de mama continúa siendo un tema controversial.* ***Material y métodos.*** *Treinta y un pacientes con diagnóstico de carcinoma invasor de mama, en quienes se administró quimioterapia neoadyuvante, fueron sometidos a biopsia de ganglio centinela y disección axilar.* ***Resultados.*** *El ganglio centinela fue identificado exitosamente en 26 (83.8%) pacientes. El ganglio fue positivo para malignidad en nueve (34.6%) pacientes. Dos de los pacientes con ganglio centinela negativo presentaron ganglios positivos en el espécimen histopatológico final de la disección axilar (porcentaje de falsos negativos: 18%).* ***Conclusiones.*** *Los resultados obtenidos en nuestro estudio clínico prospectivo no apoyan el uso de la biopsia de ganglio centinela como un procedimiento preciso para predecir la positividad de los ganglios axilares.*

Palabras clave. *Biopsia de ganglio centinela. Quimioterapia neoadyuvante. Cáncer de mama. Disección axilar. Estudio clínico prospectivo.*

INTRODUCTION

Management of patients with breast cancer is an ever-changing field in medicine. With the introduction of newer medical strategies surgery has evolved to provide less invasive and less morbid procedures. The sentinel lymph node biopsy is an excellent example of this progress. It has proven to be a reliable technique for patients undergoing a surgical procedure before systemic chemotherapy is administered although more evidence is needed for patients in whom neoadjuvant systemic treatment has been used.

Neoadjuvant systemic treatment is now the standard of care for locally advanced disease and has been considered as a reasonable option for many pri-

mary breast cancers.[1] The aim of this therapy is to obtain freedom from disease and prolong the survival of breast cancer patients.[2] The data shown by the 9 years follow up of the NSABP-18 and 5 years follow up of the NSABP B-27 trials did not demonstrate a significant difference in overall survival relating to all patients who received neoadjuvant systemic therapy compared with those who received adjuvant chemotherapy.[3] Nevertheless, responding to the neoadjuvant chemotherapy and decreasing the size of the primary tumour has demonstrated to increase the rate of breast conservation procedures but not the overall survival.[4,5] The standard schedule of treatment should be an anthracycline-containing combination, sequentially followed by taxane.[6-8]

The utilization of intraoperative sentinel lymph node biopsy was first presented at the World Health Organization's Second International Conference on Melanoma in 1989 by Morton, *et al*. as a way to detect occult lymph node metastasis in patients with melanoma.[9] A 1994 report published by Giuliano, *et al*. described its first use in the management of breast cancer.[10]

Thereafter a number of advantages associated with the use of this technique were described. It has proven to be a less morbid procedure than complete axillary lymph node dissection, costs less, and takes less time to perform.[11] The foremost concerning points regarding its use were the identification and the false negative rates yield by this technique.

The overall identification and false negative rates for sentinel lymph node biopsy analyzed by three separate meta-analyses of patients who did not received preoperative chemotherapy were 96%, 97%, 96% and 7.3%, 5% and 4% respectively. In two of the three meta-analyses the analyzed data revealed an inverse correlation between the false negative rate and the number of patients.[12-14]

Nowadays, the number of patients treated with neoadjuvant chemotherapy has increased considerably. As a result, surgeons began to question if these patients would benefit from the use of the sentinel lymph node biopsy technique to avoid axillary lymph node dissection. Most of the studies done to validate its use have been small single-center trials, obtaining controversial results. The false negative rates reported range from 0 to 33 per cent.[15,16] In the study that reported 33 per cent false negative rate, the presence of clinically positive lymph nodes before chemotherapy (present in 43% of the patients) did not predict which patients would subsequently have a false negative sentinel lymph node biopsy. Nevertheless, larger tumor size (T3) was associated with an increased false negative rate.[16]

A study designed to evaluate the efficacy of this procedure in patients with documented positive axillary lymph node in whom neoadjuvant chemotherapy was administered at the MD Anderson Cancer Center, concluded that the status of the sentinel lymph node cannot be used as a reliable indicator of the presence or absence of residual disease.[17]

A meta-analysis that included 21 studies with a total combined study population of 1,273 patients found an identification rate of 91 per cent with a 95 per cent confidence interval of 88 to 94 per cent, the sensitivity of the procedure was estimated to be 88 per cent with a 95 per cent confidence interval of 84 to 91 with a false-negative rate of 12 per cent.[18] However in this meta-analysis, the 21 trials analyzed varied considerably in entry criteria, chemotherapy regimen, and technique used to assess the axillary status. Trials that achieved a false negative rate lower than 10 per cent had less than 40 patients each, thus we consider, these results should be taking cautiously since the variability makes them difficult to interpret.

The objective of the present study was to prospectively analyze the identification and false negative rates of Sentinel Lymph Node Biopsy in patients who received neoadjuvant chemotherapy for invasive breast carcinoma.

MATERIAL AND METHODS

Inclusion and exclusion criteria

The patients with diagnosis of invasive breast cancer who were arranged to receive neoadjuvant chemotherapy followed by surgical excision of the tumour at the National Institute of Medical Science and Nutrition in Mexico City were enrolled in this trial. Palpable axillary adenopathies after the administration of neoadjuvant chemotherapy as well as a known allergy to the isosulfan blue dye were exclusion criteria. Thirty-one patients underwent sentinel lymph node biopsy and complete axillary lymph node dissection. Informed consent was obtained and signed by all patients.

Surgical technique

The surgery performed was either a modified radical mastectomy or a breast conserving procedure, depending on the characteristics of the tumour and patient's preference. Sentinel node biopsy was per-

formed followed by axillary dissection of the lymphatic levels I and II in every case.

After induction of general anesthesia 3 to 5 mL of 1% Isosulfan blue dye were injected in the subaerolar area of the tumour bearing breast 15 minutes before the sentinel node identification and biopsy were performed. In a few patients, radioactive colloid was used as well; in which cases 1.0 mCi of Technetium-99 sulfur colloid was injected just around the tumour, or in case of a non palpable lesion, in the quadrant involved one to two hours before the operation was performed. Lymphoscintigraphy to exclude extra-axillary location of sentinel lymph nodes was not used in any case. Intraoperative identification of sentinel nodes was achieved either by visual recognition of blue stained nodes or using a Gamma-detecting probe (Neoprobe 2000© Johnson & Johnson, Cincinnati OH, USA).

RESULTS

An attempt to identify and remove the sentinel lymph node was performed in 31 patients. The combination of radioactive colloid and isosulfan blue dye was employed in four patients. Isosulfan blue dye alone was applied in the rest. The median patient age was 43 ranging from 24 to 78 years. Mean tumour size before chemotherapy was 4.8 cm (1.7-15 cm) and 21 patients (67.7%) had tumours larger than 4 cm. The chemotherapy administered was FAC (5-FU, adriamycin and cyclophosphamide) in 22 patients (70.9%) and FEC (5-FU, epirubicin and cyclophosphamide) in nine patients. Previous to the administration of chemotherapy 14 patients (45.1%) presented palpable ipsilateral axillary adenopathies.

The sentinel lymph node was successfully located in 26 of 31 patients for an overall identification rate of 83.8 per cent. Among the five patients in whom sentinel lymph node was not found, four (80%) had tumours larger than 4 cm. Comparison of tumor size, clinically positive axilla before chemotherapy and localization technique in patients in whom the sentinel lymph node was identified *vs*. those in which was not was performed. Mean tumour size was 4.6 cm in patients in the group where sentinel node was identified *vs*. 5.52 cm in the group in which it was not identified ($p = 0.36$). Clinically positive axilla was recorded in 11 patients (42.3%) *vs*. three patients (60%) respectively ($p = 0.09$).

Regarding the localization technique, combined radiotracer and blue-dye was used in four patients: three (11.5%) from the group in which the sentinel node was identified, and one (20%) from the group in which sentinel node was not identified. This difference did not reach statistical significance ($p = 0.27$).

The node was positive for malignancy in nine patients (34.6%). The sentinel node was the only positive node in one patient (3.8%). Two of the patients with a negative sentinel lymph node presented other positive lymph nodes in the final histopathologic specimen, with a false negative rate of 18 per cent and a sensitivity of 81 per cent.

Clinical response subsequent to the administration of systemic chemotherapy was as shown: complete response was observed in 13 (41.9%) patients, partial response in 12 (38.7%) patients and stable or progressive disease in six (19.3%) patients.

DISCUSSION

The Sentinel Lymph Node biopsy has become the standard of care for patients who have not received preoperative chemotherapy.[19] It has proven to be an accurate technique to predict the presence of lymph node metastasis, reducing the morbidity associated with a complete axillary lymph node dissection. Nevertheless, its use for patients who have received neoadjuvant systemic chemotherapy is still controversial. Most of the studies designed to validate this novel application for the technique have been small single-institution series. The results obtained by the largest clinical trial, the NSABP-B27, demonstrated favorable results with an identification rate of 84.8 per cent and a false negative rate or 10.7 per cent. However the study's primary aim was to determine whether the administration of taxotere plus Adriamycin and Cyclophosphamide (AC) would prolong survival compared with AC alone and not the accuracy of the sentinel lymph node biopsy in this setting.[20]

The controversial results obtained by the different clinical trials prompted us to initiate a prospective pilot clinical trial, specifically designed to elucidate the accuracy of the sentinel lymph node biopsy after the administration of systemic neoadjuvant chemotherapy.

The rationale behind the sentinel node biopsy technique is based on the systematic way in which lymphatic drainage takes place. However the use of systemic neoadjuvant chemotherapy may cause excessive fibrosis of the tumour and lymphatics with the potential obstruction of lymphatic channels with cellular material or tumour emboli, thus disrupting the usual anatomical pathway.[21]

It is not biologically plausible that the ordered process in which malignant cells migrate and invade the lymphatic nodes is the same in which systemic chemo-

therapy exerts its cytotoxic effects; thus making it unlikely that the nodes will respond to therapy and regress in the inverse way they became affected.

The overall identification rate seen in this trial (83.8%) is significantly lower than the one observed previously at our institution. A prospective trial design to validate the sentinel lymph node biopsy technique at our institution showed an overall identification rate of 100 per cent and no significant difference between the use of Isosulfan blue dye and Technetium-99.[22] The previously mentioned study demonstrates that the volume of patients at our institution is large enough to give us the necessary experience in order to have a high identification rate and a low false negative rate. The decrease in the identification rate observed between the trials performed at the same hospital by the same surgeons could be partially explained by the larger size of the tumor,[23] and the structural changes produced by the chemotherapy on the tissue.

In patients who have been prearranged to receive neoadjuvant chemotherapy followed by the surgical excision of the tumor it has been suggested that sentinel lymph node biopsy could be performed before the administration of chemotherapy, thus avoiding its deleterious effects on the axillary tissue by the time the biopsy is taken. Women with evidence of positive axillary lymph nodes should undergo axillary lymph node dissection during the surgical procedure after the completion of neoadjuvant chemotherapy. The disadvantage of this approach, however is that these women would need to undergo at least two surgical procedures: The sentinel lymph node biopsy before chemotherapy and then, resection of their breast tumour plus axillary dissection in case of a previous positive sentinel node. In fact the axillary lymph node metastases may have been eradicated by the chemotherapy, thus ruling out the need for axillary node dissection.[24]

The false negative rates reported in the literature range from 0 to 33 per cent.[15,16] The low false negative rates reported by some trials is derived from a miss calculation of this rate; using the total number of patients biopsied as the divisor instead of using only the patients in whom a positive lymph node has been obtained. The results of our trial show an 18 per cent false negative rate using only the patients with positive lymph nodes to calculate it.

CONCLUSIONS

Although this is a prospective trial, we are aware of the limitations of the study. Because of the small number of patients it is difficult to drawn definitive conclusions. However the high number of false negative results obtained does not support the use of the sentinel lymph node biopsy as an accurate procedure to predict the axillary lymph node status in patients who have received neoadjuvant systemic chemotherapy.

The current National Comprehensive Cancer Network (NCCN) guidelines do not recommend its use, (recommendation category 3, there is major NCCN disagreement that the recommendation is appropriate) reflecting the need of larger prospective clinical trials. The use of this approach should be restricted to clinical trials.

At our institution, because of the controversial results regarding the use of SLNB in patients who have received neoadjuvant chemotherapy, we currently perform SLNB before neoadjuvant chemotherapy is administered.

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