Clinics in Surgery

Research Article
Published: 10 Mar, 2020

Safely Avoiding Axillary Lymphadenectomy after Neoadjuvant Chemotherapy for Patients with Proven Axillary Lymph Node Involvement Early Breast Cancer? The French Multicenter Prospective Ongoing GANEA 3 Study

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Abstract

Background and Objective: After Neoadjuvant Chemotherapy (NAC) more than one third of patients presenting with initially axillary node involvement achieved a Pathological Complete Nodal Response (pCR). In this situation, omitting Axillary Lymph Node Dissection (ALND) could enable to decrease post-operative morbidity. GANEA 3 is a prospective multi institutional trial aimed at assessing the feasibility of selecting patients with an initially proven positive axillary node, with a low risk of lymph node involvement after NAC.

Methods: Before NAC, all patients undergo an axillary Ultrasound (US) assessment. A fine needle aspiration of suspicious is performed. Patients with proven axillary lymph node involvement are included. The initially positive axillary lymph node is targeted with a clip under US monitoring. After NAC, surgery of the breast and axilla is scheduled. Surgeon performs three axillary resections: initially involved clipped node, sentinel lymph node biopsy and a complementary ALND. Breast tumour size, (mammography, MRI) breast tumor characteristics, axillary status, before and after NAC are compared. Univariate and multivariate analysis will allow generating a Nomogram able to select patients with the lowest risk of post NAC persistent axillary involvement. Taking into account previous results of post NAC lymph node involvement from GANEA 2 trial, 385 prospectively included patients are required during a period of 3 yrs of inclusion.

Results: Twenty French surgical teams participate in the GANEA 3 trial. The GANEA 3 trial was approved by the national scientific committee and the national ethical committee. Informed consent was obtained from each participating patient. The trial was registered with ClinicalTrials.gov (NCT03630913). At the end of January 2020, one year after the inclusion of the first patient, 125 patients are already included.

Conclusion: GANEA 3 trials will be able to safely identify patients for which ALND could be safely avoided after NAC. It will be an important step of surgical de-escalation after NAC.

Keywords: Breast cancer; Neoadjuvant chemotherapy; Axillary lymph node involvement; Sentinel lymph node biopsy; Pathological complete response

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Received Date: *28 Jan 2020*
Accepted Date: *04 Mar 2020*
Published Date: *10 Mar 2020*

Citation:
Loaec C, Frenel JS, Renaudeau C, Bordes V, Campion L, Classe JM. Safely Avoiding Axillary Lymphadenectomy after Neoadjuvant Chemotherapy for Patients with Proven Axillary Lymph Node Involvement Early Breast Cancer? The French Multicenter Prospective Ongoing GANEA 3 Study. Clin Surg. 2020; 5: 2755.

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Introduction

Most patients treated for a large infiltrative breast cancer receive Neo-Adjuvant Chemotherapy (NAC) in order to increase the likelihood of breast conserving surgery without impact on overall survival [1].

For patients with involved axillary nodes before NAC, almost 22% to 41% are downstaged to a negative axilla after NAC, with a higher rate for patients treated with anti-HER2 therapy making unnecessary a complementary Axillary Lymph Node Dissection (ALND) [2,3].

Whilst initially developed for primary surgery, Sentinel Lymph Node Biopsy (SLN) represents a potential option after Neo-Adjuvant Chemotherapy (NAC) as it reduces the rate of unnecessary ALND. After NAC, in cases of a positive SLN, macro- or micro-metastasis or a mapping failure, an ALND is recommended outside a clinical trial. In cases of a negative SLN the risk of avoiding a systematic complementary ALND is due to the high False Negative Rate (FNR) of SLN technique after NAC, range from 18% to 24% in case of two or one SLN removed [4].

A French trial, GANEA 1, showed that after NAC the FNR of SLN technique varied according to initially axillary lymph node involvement [5].

In case of no suspicious axillary lymph node involvement (cN0) before NAC, a meta-analysis of 449 patients from 10 studies showed an Identification Rate (IR) of SLN biopsy of 94% and a FNR of 7% [6]. In a recent retrospective mono-institutional series of 181 T1 to T3 breast cancer patients with an initially negative axilla, were treated with SLN alone after NAC without a complementary ALND. After a median follow-up of 51.1 months, authors described no axillary relapse [7]. The safety of SLN alone after NAC without ALND, for patients with cN0, was confirmed in the French GANEA 2 study, a prospective multi institutional cohort of 418 patients. The 3-years overall survival was 97.2% and the 3-year disease free survival was 97.8% [8].

In cases of cytologically proven node involvement (pN1) before NAC, the recent review of El Hage et al. [9] established a FNR of 14% to 15% with an IR of 89% to 92%. After NAC a FN case corresponds to the persistence of resistant axillary lymph node involvement. Actually, the clinical impact of such a FN rate is almost unknown due to the lack of prospective series. The 2014 American Society of Clinical Oncology recommendations have considered as unacceptable the reported FNR of SLN after NAC, in patients who present with involved axillary nodes [10]. The updated 2017 recommendations specified that performing SLN after NAC in operable breast cancer patients had a moderate strength and an intermediate evidence quality [10].

In order to safely reduce unnecessary ALND, it is necessary to accurately select patients without involved nodes after NAC. The SLN FNR after NAC in patients with initially involved nodes varies according to the number of SLNs resected, the use of the combined SLN detection method (with blue dye and radioisotope), the use of Immunohistochemistry (IHC) and pathological response to NAC [4,11,12].

Recently, it appeared that initially involved axillary node highly reflected the pathological status of the whole axilla. In a recent prospective series of 118 patients with the initially involved node tagged before NAC and resected after NAC within the SLN specimen and a complementary ALND, the SLN FNR decreased from 10.1% to 1.4% when the pathological status of the initially node was taken into account [13]. The GANEA 3 trial is a prospective multi-institutional ongoing trial aimed at identifying patients with initially proven lymph node involvement and receiving NAC, with the lowest risk of SLN FNR after NAC. Secondary objectives are the assessment of radiological axillary status before and after NAC, the feasibility and accuracy of the removal after NAC of the initially involved node, and the usefulness of PET CT in assessing breast and nodal response to NAC.

Patients and Methods

Eligibility criteria are: Age >18 years, biopsy proven primary infiltrative breast cancer, clinical stage T0 to T3, N0-N1, no distant metastasis, proven involved axillary node before NAC, planned neoadjuvant chemotherapy. Exclusion criteria are: Inflammatory breast cancer, pregnancy, no effective contraception or breast feeding, prior ipsilateral axillary surgery, lack of axillary assessment before NAC. Patients fulfilling complete eligibility criteria and no exclusion criteria are included.

Before NAC, prognostic criteria are collected (tumor size, pathological subtype, Hormonal receptor, KI67, HER2 expression, SBR grading). Axillary status was assessed by axillary clinical staging, Axillary Ultrasound Assessment (AUS), and a fine needle aspiration of suspicious nodes in order to select only patients with proven axillary involvement. A node was considered suspicious if it was larger than 1 cm, with irregular cortical thickening, and loss of fatty hilum. Patients with cytologically proven axillary involvement before NAC who signed the consent form were included into the study. A PET CT was then performed and the positive axillary node tagged. Breast tumour size was assessed by Mammography and Breast MRI.

The NAC regimen was left to the discretion of each participating team.

After NAC, breast and axillary response to NAC was assessed by AUS, mammography, breast MRI and PET CT. Breast and axillary surgery was performed during the same procedure four to six weeks after completion of NAC. Breast surgery could be lumpectomy or mastectomy. The size of the breast tumour remaining provided evidence of the breast tumour response to NAC. Axillary surgery provided at least 3 samples: The resection of the initially clipped node, SLN, and a mandatory level I-II ALND (Figure 1). Nodes from the ALND provide evidence of nodal pathological response to NAC, allowing the FN rate of SLN and the impact of the clipped node to be measured. This strategy allows patient with the lowest risk of SLN FN (<1%) to be identified.

Pathology

No intra operative pathological examination is performed. Clipped nodes and SLNs are sent to the pathologist separately from ALND specimens. Paraffin embedded SLNs were serially sectioned and stained with Hematoxylin and Eosin (HE). If no metastasis was detected, further IHC analysis was performed. The size of the largest nodal metastasis was recorded using the definition of the AJCC staging system 6th edition [14]. SLNs with metastasis of any size were considered positive including those only detected by IHC. The clipped node is treated as a SLN. Nodes from ALND are bisected and stained using H &E. A positive ALND node corresponds to a macro-metastasis (>2 mm).

Statistical analysis

Assuming that the GANEA 3 strategy could shift the False Negative (FN) rate (π) of tumour-involved SLN detection from 14% to <1%, we required 180 pN+ patients to reject the hypothesis π=14% using a Mc Nemar chi^2 test, if the true FN rate is <1% with a power =80% and α=5%. Based on the GANEA 2 study where about 60% of patients after NAC had a residual axillary nodal disease and with 20% missing data, 375 patients should be included.

Results

The GANEA 3 trial was approved by the 2017 French national

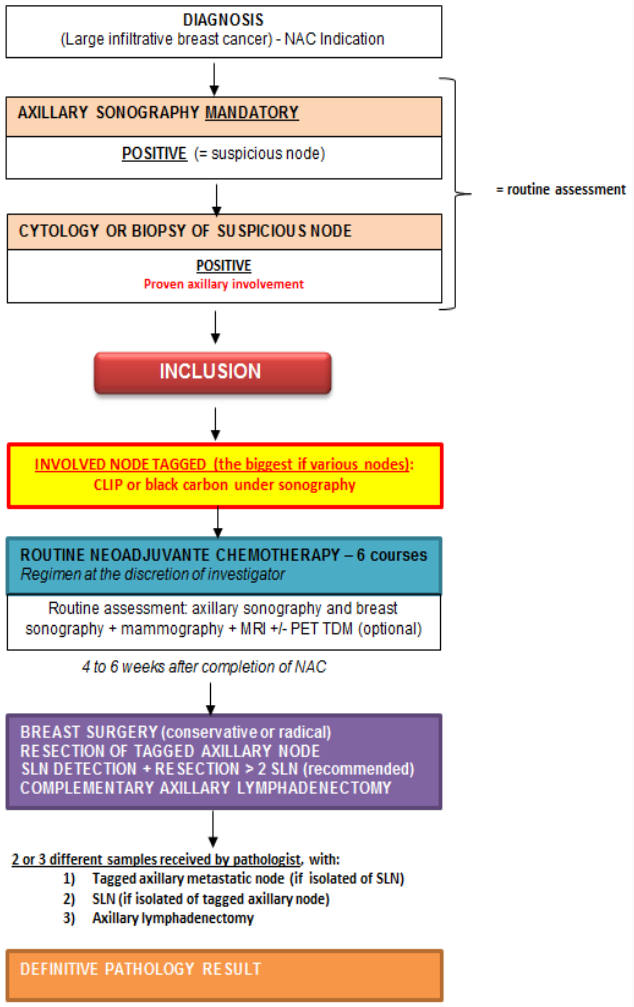

Figure 1: GANEA 3 study design.
SLN: Sentinel Lymph Node; NAC: Neoadjuvant Chemotherapy

scientific committee and ethical committee. GANEA 3 was registered with ClinicalTrials.gov (NCT03630913). Twenty French institutions agreed to participate and to include patients in the trial over a 36 months period.

During the recruitment period each patient treated for an operable breast cancer with NAC in participating institutions will be offered to participate in the trial. For each included patient the study ends 60 days after surgery.

Results from the GANEA 3 trial will guide changes in the international guidelines for axillary surgery strategy for patients with initially involved nodes treated with NAC, safely sparing unnecessary ALND in selected patients.

Conclusion

Currently, patients with initially involved axillary nodes treated with NAC could undergo an ALND, unnecessary in case of complete pathologic response, or a SLN biopsy with the high of FNR and unknown clinical consequences.

The GANEA 3 trial is aimed at defining a group of patients with a low risk of pathological nodes after NAC, with a complete pathological response in initially positive node and SLN, in order to safely spare them an unnecessary ALND.

Ethical Approval

The GANEA 3 trial was approved by the 2017 French national scientific committee.

Funding

This research received financial support from the French National Institute of Oncology (National Program for Hospital Clinical Research 2017.