The Breast xxx (2016) 1–4

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Viewpoints and debate

SINODAR ONE, an ongoing randomized clinical trial to assess the role of axillary surgery in breast cancer patients with one or two macrometastatic sentinel nodes

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ARTICLE INFO

Article history:
Received 29 March 2016
Received in revised form
14 June 2016
Accepted 15 June 2016
Available online xxx

Keywords:
Breast cancer
Sentinel lymph node biopsy (SLNB)
Axillary lymph node dissection (ALND)
Overall survival (OS)
SINODAR ONE

ABSTRACT

Sentinel lymph node biopsy alone is the current surgical axillary treatment for early-stage breast cancer patients with a negative sentinel lymph node (SLN). The possibility to omit axillary dissection also in presence of positive SLNs has been promoted by the American College of Surgeons Oncology Group (ASOCOG) Z0011 randomized trial. Several limitations and evidences of potential selection bias made this trial fairly controversial. Stronger evidence than currently available is needed on the safety of foregoing axillary dissection in well-defined populations of patients with positive SLNs. The Italian multicentre SINODAR ONE randomized trial here presented was designed with this aim.

Introduction

Sentinel lymph node biopsy in the settings of negative SLNs: guidelines

The minimally invasive procedure of SLNB has replaced axillary lymph node dissection (ALND) in SLN-negative breast cancer (BC) patients, based on randomized trials [1–5] demonstrating that SLNB is as effective as ALND to achieve disease control, does not compromise survival even at the long term [6,7] but improves patients' quality of life [2,8]. In the last revision of the Clinical Practice Guidelines on the use of SLNB in early-stage BC made by the Update Committee of the American Society of Clinical Oncology, the first recommendation specifies that "*Women without sentinel lymph node metastases should not receive axillary lymph node dissection*" [9].

Sentinel lymph node biopsy in the settings of positive SLNs: advocacy from the ACOSOG Z0011 trial

Complete axillary dissection has remained the standard procedure when the SLN is metastatic. However, this recommendation starts being challenged based on the following considerations: the SLN is the only site of axillary metastases in ≈40% of the cases [10,11]; observational studies showed that loco-regional failure rate is low in SLN-positive patients not undergoing ALND [12,13]; distant metastases are unlikely to originate from metastatic axillary nodes [14]; adjuvant therapies are increasingly tailored according to biological features and markers of the tumor rather than the extent of axillary disease [15].

In this line, the ACOSOG Z0011 trial has set the ground for introducing ALND omission in the surgical management of SLN-positive patients. In this trial, patients with 1–2 metastatic SLNs were randomized to ALND or no further axillary surgery. Results showed that axillary dissection did not provide outcome advantage with respect to loco-regional recurrence [16] and survival [17]. However, these conclusions are questionable due to various study limitations and selection bias: the study was underpowered because of premature enrollment ceasing; median follow-up was short (≈6 years); ≈18% of all patients were lost to follow-up; 25%

Abbreviations: ALND, axillary lymph node dissection; ACOSOG, American College of Surgeons Oncology Group; BC, breast cancer; BCS, breast-conserving surgery; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; OS, overall survival; WBI, whole-breast irradiation.

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http://dx.doi.org/10.1016/j.breast.2016.06.016
0960-9776/

did not meet the eligibility criteria of 1–2 positive SLNs; only 60% presented SLN macrometastases.

Need for stronger evidences: expectations from the SINODAR ONE randomized trial

Despite some clinical relevance, the Z0011 trial is not a practice-changing study; it is premature to extrapolate the findings beyond the study population which included essentially patients at low risk: tumor ≤2 cm (T1, 70% of the cases), SLNs with only micrometastases (40%), one single SLN involved (65%), positive hormonal receptors (>80%).

Thus, additional large-scale randomized studies are needed, presenting specific selection criteria based on uniform clinico-pathological parameters and using surgical procedures and therapeutic protocols precisely defined. Long-term follow-up (>5 years for all patients) and limited rate of patients lost to follow-up (≤5%) would also be mandatory. With these considerations in mind, the Clinical Institute Humanitas of Milan (Italy) promoted the Italian multicentre SINODAR ONE clinical trial here described.

Patients and methods

SINODAR ONE is a prospective non-inferiority randomized study aimed at assessing the therapeutic role of ALND in patients with macrometastatic SLNs candidate for breast-conserving surgery (BCS) or mastectomy (Fig. 1).

Patients fulfilling all eligibility criteria (Table 1) are randomly assigned (1:1ratio) to either removal of ≥10 axillary level I/II non-sentinel nodes followed by adjuvant therapy (standard arm) or no surgical intervention on the axilla but only adjuvant therapy (experimental arm). The study population includes patients aged 40–75 years presenting an unifocal infiltrating carcinoma ≤5 cm and 1–2 SLNs with macrometastasis. We chose to exclude patients aged <40 years for ethical reasons: BC occurrence at lower age is often associated with hereditary pattern; tumors in young patients are frequently HER-enriched, ER-negative, triple negative, of high grade or with lymphatic/vascular invasion, all parameters possibly contributing to poorer prognosis in terms of overall survival (OS) and early disease recurrence [18]. The choice of adjuvant therapies is guided by the biological and pathological features of the tumor and International Guidelines, and includes chemotherapy, endocrine therapy and/or HER-2 targeted treatment as appropriate. Patients undergoing BCS also receive whole-breast irradiation (WBI). Radiotherapy is performed according to the individual standard institutional regimen (mostly standard tangent fields). Since randomization is stratified by center, statistical evaluations of the outcome will take into account eventual between-center variability by including the participating centers as an independent variable. Primary endpoint is OS. Secondary endpoints are loco-regional recurrence-free survival and distant disease-free survival. Patients will be followed-up for at least 5 years. Overall, the recruitment of 2000 patients will be necessary to assess the hypothesis that OS is not worse in the arm not receiving axillary surgery compared with the standard arm, given a margin Δ of non-inferiority of 4% and assuming a 5 y-OS of 85% in the standard arm.

All surgical procedures and clinical treatments used in this trial are conducted in accordance with the International Good Clinical Practice Guidelines and the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Statistical analyses will be performed both on the Intention-To-Treat and the Per-Protocol populations.

Table 1
Enrollment criteria.

Eligibility
- Age ≥40 and ≤75 years
- Invasive breast carcinoma (cytology/core biopsy assessment)
- Unilateral and unifocal lesion
- Tumor size ≤ 5 cm (cT1-2) (ultrasound/mammography assessment)
- Clinically negative axillary nodes (N0) (ultrasound assessment)
- No more than 2 sentinel lymph nodes proven metastatic (histological assessment)
- Involved SLN(s) with macrometastsis foci (≥2 mm)
- No distant metastasis (M0)
- No neoadjuvant therapy
- No previous invasive breast carcinoma
- Signed and dated written informed consent
Exclusion
- Ongoing pregnancy or breast-feeding
- Inflammatory breast cancer
- In situ breast carcinoma
- Synchronous contralateral breast carcinoma
- Comorbidity possibly preventing adjuvant therapy
- Disease, comorbidity or psychological conditions preventing the compliance to a regular follow-up
- Previous neoplasm within the 3 years preceding randomization (with the exception of in situ carcinoma of the cervix, basalioma and spinocellular carcinoma of the skin)

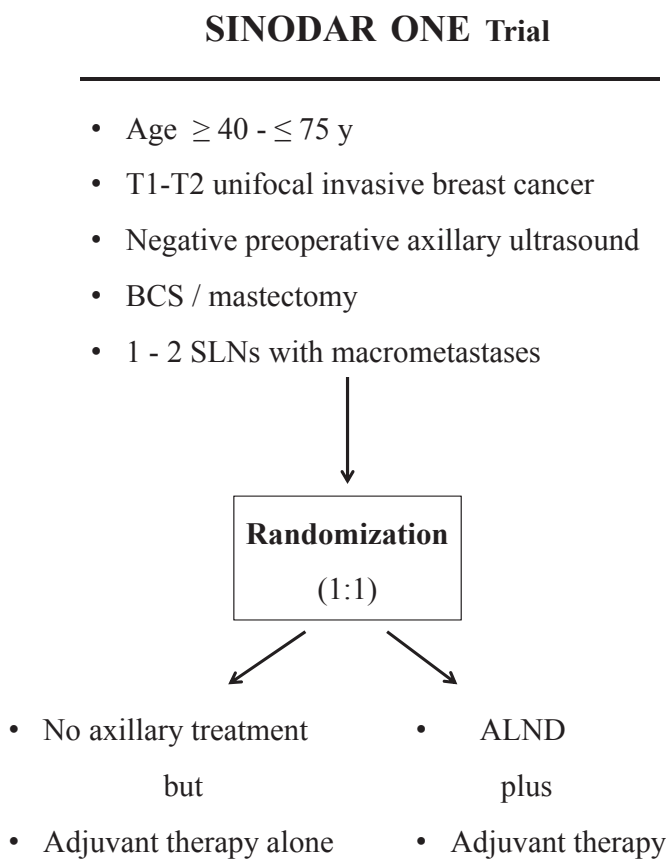

Fig. 1. SINODAR ONE trial: study design. BCS, breast conserving surgery; SLN, sentinel lymph node; ALND, axillary node dissection.

Results

SINODAR ONE was launched on April 2nd 2015 and patient recruitment is expected to end by March 31st 2018. Twenty-six centers have already adhered to the trial upon approval from their local Ethical Committee. Other 10 centers are awaiting the decision of their respective Committee and should shortly start being operative.

Please cite this article in press as: Tinterri C, et al., SINODAR ONE, an ongoing randomized clinical trial to assess the role of axillary surgery in breast cancer patients with one or two macrometastatic sentinel nodes, The Breast (2016), http://dx.doi.org/10.1016/j.breast.2016.06.016