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Original article

Pathological complete response in invasive breast cancer treated by skin sparing mastectomy and immediate reconstruction following neoadjuvant chemotherapy and radiation therapy: Comparison between immunohistochemical subtypes

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ABSTRACT

Context: Even if neoadjuvant chemotherapy (NACT) and oncoplastic techniques have increased the breast conserving surgery rate, mastectomy is still a standard for multifocal or extensive breast cancers (BC). In the prospect of increasing breast reconstruction, an alternative therapeutic protocol was developed combining NACT with neoadjuvant radiation therapy (NART), followed by mastectomy with immediate breast reconstruction (IBR). The oncological safety of this therapeutic plan still needs further exploration. We assessed pathological complete response (pCR) as a surrogate endpoint for disease free survival.

Methods: Between 2010 and 2016, 103 patients undergoing mastectomy after NACT and NART were recruited. After CT and RT were administrated, a completion mastectomy with IBR by latissimus dorsi flap was achieved 6 to 8 weeks later. pCR was defined by the absence of residual invasive disease in both nodes and breast. Histologic response was analyzed for each immunohistochemical subset.

Results: pCR was obtained for 53.4% of the patients. This pCR rate was higher in hormonal receptor negative (HER2 and triple negative) patients when compared to luminal tumours (69.7% vs 45.7%, p=0.023).

Discussion: The pCR rate found in this study is higher than those published in studies analyzing NACT (12.5%-27.1%). This can be explained by the combination of anthracycline and taxane, the use of trastuzumab when HER2 was overexpressed but also by RT associated to NACT.

Conclusion: Inverting the sequence protocol for BC, requiring both CT and RT, allows more IBR without diminishing pCR and should therefore be considered as an acceptable therapeutic option.

1. Introduction

Even though breast-conserving surgery (BCS) has extended in the last decades with the development of oncoplastic techniques and neoadjuvant chemotherapy (NACT) [1,2], mastectomy is still a standard for multifocal or extensive tumors. This mutilating surgery is difficult to accept for many women, and has a negative impact on their psychosocial well-being and their sexuality [3].

Skin-sparing mastectomy with immediate breast reconstruction (SSM-IBR) has been developed, allowing better aesthetic outcome as well as better acceptance of the amputation [4–6]. However surgeons are often reluctant to perform IBR due to the risk of necrosis, often considered being at high level. Risk factors for IBR complications are now well known and include smoking, diabetes, obesity, history of breast augmentation and radiation therapy [7,8].

In order to allow more women to access SSM-IBR, without compromising neither the oncological safety nor the esthetic

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outcome, an alternative treatment sequence protocol was developed for patient requiring both chemotherapy (CT) and radiation therapy (RT). Since the beginning of the 1990's, after NACT and neoadjuvant radiation therapy (NART), some selected patients with invasive breast cancer can undergo a completion surgery combining SSM with IBR. The feasibility of this innovative sequence protocol has been demonstrated [9–11].

When regarding the oncological safety of a neoadjuvant treatment, the pathological complete response (pCR) is considered as a valid surrogate endpoint for disease-free survival (DFS) [12]. In addition, it has been demonstrated that the clinico-pathologic subtype of the tumor has an impact on the pCR rate after exclusive NACT [13].

In order to assess the oncological safety of inverted sequence protocol, we analyzed the pCR rate according to tumor subtypes for patients having completed NACT and NART, prior to mastectomy.

2. Patients and methods

Between august 2010 and february 2016, 196 women, from 4 different centers, were consecutively included in our study. We retrospectively identified all patients undergoing a mastectomy with IBR after NACT and NART, by using each institution's database. In order to be suitable for analysis the NACT and NART had to be decided upfront or at the end of CT. Patients having initially been treated with BCS with invaded margins were excluded of the study (n = 93). Indeed an unsuccessful attempt of BCS could increase the pCR rate by reducing the tumor's volume. Other exclusion criteria were: metastatic disease, a history of breast surgery, and major breast ptosis (grade 3). A total of 103 patients required a mastectomy without previous BCS and were therefore analyzed (Fig. 1).

Diagnostic work-up included clinical examination, mammography and ultrasonography. Most patient had a breast MRI. All tumors were staged with a core-needle biopsy. Pre treatment hormone receptors (HoR) were assessed by a validated immunohistochemistry (IHC). For HoR, cases with 10% or more positive staining for estrogen and/or progesterone receptors were considered as positive. Tumors with an expression of Ki67 > 20% were considered as proliferative. HER2 status was documented using IHC and fluorescent in situ hybridization (FISH) when needed. HER2 was considered overexpressed in case of IHC 3+ or 2+ and FISH amplification. Lymphovascular invasion and Ki67 were determined prior to treatment for most patients. An initial evaluation of the disease extension was systematic, using PET-CT or CT associated to bone scintigraphy.

The oncological management of each patient was decided by a multidisciplinary committee according to the French national guidelines. Each patient was given an individualized care plan.

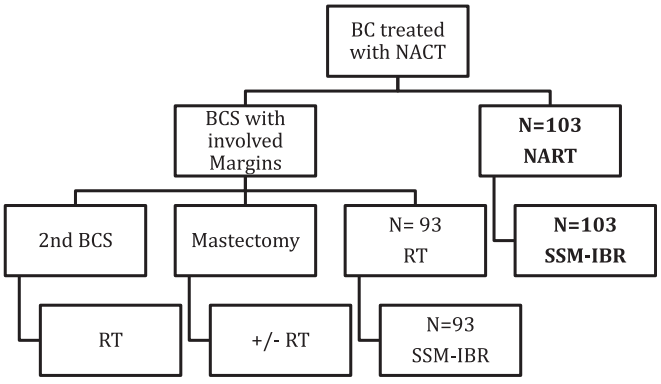

Fig. 1. Flow diagram.

The axillary lymph node staging was different between the oncological teams. Depending on the physical examination, the surgeons could achieve the nodal staging through fine needle core biopsy, sentinel node biopsy (SNB), initial axillary node dissection (iALND) or completion ALND (cALND). When a biopsy was positive, the patient had either iALND, cALND, or could be included in a multicentric national prospective survey assessing the impact of ALND for node biopsy (SERC study). Post therapeutic SNB was not considered to be a valid therapeutic option.

NACT was indicated in case of high-risk features: large tumor size non-eligible for initial BCS (>20 mm), SBR grade 3 or Ki67 > 20%, initial nodal involvement, HoR-negative tumor or HER2 overexpression. Fifty-four patients (52.4%) received 3 cycles of FEC (5FU, epirubicin, cyclophosphamide) followed by 3 cycles of docetaxel, and 43 (41.7%) were treated with 4 cycles of FEC followed by 4 cycles of docetaxel. Six patients (5.8%) had another chemotherapy protocol. When HER2 was overexpressed, trastuzumab was added to the neoadjuvant treatment and continued for a total of 12 months.

Performing NART followed by SSM-IBR rather than BCS was decided by the surgeon and the patient at the end of NACT. A re evaluation of the disease was made with clinical examination and imagery. The decision was based on the initial tumor size, tumor multicentricity, the tumor-breast size ratio, and the patient's choice.

RT was completed with the same guidelines than a post mastectomy radiation therapy (PMRT). Clinical Volume Target (CTV) and dose administrated was determined according to the initial clinical tumor size, the localization of the disease, the lymph node involvement, and the lympho-vascular invasion. Conventional fractionation was used in all patients (2 Gy per fraction, 5 times a week) for a total of 50 Gy on the breast (without boost) and 46 Gy on regional nodes when required.

The surgical procedure was completed 6–8 weeks after the end of RT. SSM was combined with IBR by latissimus dorsi musculocutaneous flap with or without additional silicone implant. SSM was completed by most surgeons through a peri-areolar incision. An adrenaline serum could be used to diminish blood loss therefore facilitating subcutaneous scissor dissection. When required, cALND was performed during the same surgical act, using the same or a different incision.

No central pathology review was carried out for this analysis. In accordance with the criteria of the BIG-NABCG, pCR was defined as the absence of residual invasive cancer on evaluation of the complete resected breast and on all sampled axillary lymph nodes, regardless of the presence of in situ carcinoma. Five simplified breast cancer intrinsic subtypes were determined according to clinic-pathologic criteria (HoR, HER2 status, SBR grade and Ki67 documented on pre treatment biopsy) [14]:

- Luminal A (HoR-positive/HER2-negative/grade 1–2),
- Luminal B (HoR-positive/HER2-negative/grade 2 and Ki67 > 20% or grade 3),
- Luminal B-HER2 (HoR-positive/HER2-positive/all grades),
- HER2 positive (HoR-negative/HER2-positive/all grades),
- Triple negative (HoR-negative/HER2-negative/all grades).

When Ki 67 was not available from the collected data, we used the SBR grade to classify tumor into intrinsic subtype as suggested by the St Gallen 2011 consensus [15].

All statistical analysis was performed using SPSS 16.0 statistical software. χ^2 test and fisher exact test were used to examine differences between categories. $P < 0.05$ was considered to indicate a statistically significant difference.