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Neoadjuvant (Preoperative) Therapy in Breast Cancer

Vladimir F. Semiglazov and Vladislav V. Semiglazov

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1. Introduction

Locally advanced breast cancer (LABC) occurs at presentation in approximately 20-25% of breast cancer patients worldwide, but significantly less in countries with implemented screening programs. LABC refers to large operable (stage IIB, IIIA) or inoperable (stage IIIB, IIIC) tumors, including inflammatory breast cancer. Patients with ipsilateral supraclavicular lymph node involvement previously considered as having metastatic disease are now also included in the category of LABC (stage IIIC). Treatment of LABC has evolved within recent decades. For a long time, mastectomy remained the mainstay of treatment in this group of patients, but long-term local control was disappointingly low, with approximately 50% local recurrences (LR) and only 2% 5-year overall survival (OS). Implementation of postoperative radiotherapy increased local control and survival, but long-term outcomes remained unsatisfactory (35-55% LR and 25-45% five-year OS). Incorporating systemic therapy (be it chemotherapy, hormonal therapy or both) as an adjunct to surgery and/or radiotherapy further improved results. Currently, a combination of systemic therapy with locoregional treatment (surgery and/or radiotherapy) constitutes the standard of care in LABC patients since improving locoregional control is associated with better survival. In patients with stage III breast cancer treated with induction chemotherapy followed by surgery, radiotherapy or a combination thereof, the risk of loco regional recurrence is in the range of 20%. The use of induction systemic therapy results in tumor downstaging, and in selected LABC patients even allows for breast conserving surgery (BCS). However, the safety and efficacy of this approach in LABC have not been verified in randomized studies. Even though locoregional management is an important component of multimodality treatment in patients with LABC, the pattern of local management and factors influencing local treatment strategy in this group are not well recognized (Sinacki et al., 2011). Neoadjuvant therapy is recommended not only for locally advanced and inflammatory breast cancer but also as an option for primary operable disease without compromising long-term outcome (Untch et al., 2011).

2. Neoadjuvant systemic therapy

2.1. Neoadjuvant chemotherapy

Patients presenting with locally advanced primary breast cancer (LAPC) are a heterogeneous group with variable outcomes with regard to local recurrence rates and survival. There is no standard or international agreement on the definition of this type of breast cancer, but one commonly used clinical staging includes patients with large primary tumours greater than 5 cm (T3) or with fixed skin or chest involvement (T4), and/or fixed axillary (N2) or ipsilateral internal mammary lymph node involvement (Mathew et al., 2008). According to TNM staging system proposed by the American Joint Committee on Cancer (AJCC), all of stage III disease is therefore considered locally advanced, as is a subset of stage IIB (T3N0). In addition, inflammatory breast cancer (T4d), with its distinct clinical presentation and worse prognosis, is included within the scope of locally advanced disease. Although the TNM system is not as widely used in some countries, it is generally accepted that locally advanced breast cancers represent those cancers that are difficult to resect with primary surgery either because of their size or extension to chest wall or skin or involvement of regional axillary lymph nodes. Compared to patients with operable primary breast cancer, patients with LAPC are at significantly higher risk of local recurrence and distant metastases and have a worse overall survival; UK figures show that patients with stage II disease have a 10-year survival rate of just under 60%, whereas this is approximately 30% for patients with stage III disease (Mathew et al., 2008).

With the widespread use of breast cancer screening, breast cancers are increasingly being diagnosed at an earlier stage. Because of this, patients with locally advanced breast cancer are less commonly seen than before. Nevertheless, there remains a group of patients who either because they do not seek advice earlier or because the tumour is more aggressive, present with locally advanced disease. Data from the American National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program show that 7% of all breast cancer patients have stage III disease at diagnosis, although this percentage is less than 5% in the screening population. Despite this, patients with LAPC still present a significant clinical problem and exemplify a subgroup of patients where a multidisciplinary approach is particularly important to outcome.

Initially, an aggressive single modality, local therapy approach, was commonly advocated for the treatment of patients with LAPC, either in the form of radical surgery or radiotherapy. This often provided temporary local control, although on follow-up of these patients, the morbidity and recurrence rates were high and survival poor. Multimodal approach is now an established option in most patients with LAPC, especially oestrogen receptor (ER) negative tumours or aggressive ER positive tumours (e.g. some inflammatory cancers). This includes the combination of surgery and radiotherapy for local control and systemic therapy, usually chemotherapy +/- hormone therapy. For others, such as those with strongly hormone receptor positive tumours, local treatments (i.e. surgery +/- radiotherapy) plus endocrine therapy or even primary endocrine therapy may be appropriate options. This may for example be the case in many elderly patients, some of who are medically unfit for surgery.

A large number of studies have assessed the use of neoadjuvant chemotherapy in operable primary breast cancer. Although the results in operable breast cancers suggest that the breast conserving rates can be increased, survival is no different when compared to post-operative adjuvant chemotherapy. However, patients with LAPC often have inoperable disease at diagnosis and the main goal of neoadjuvant treatment is to achieve resectability, either in the form of standard mastectomy or breast-conserving surgery. Furthermore, the clinical and histological response to neoadjuvant chemotherapy has been shown to be important predictors of recurrence and survival in studies of operable breast cancer. Neoadjuvant chemotherapy (NACT) in operable invasive breast cancer (OIBC) has been shown to increase breast conservation surgery (BCS) (Cebrecos et al., 2010). However, chemoresistant and multi focal tumours still require a mastectomy. As a consequence, today global management of these patients may include a breast reconstruction (Monrignal et al., 2011)

2.2. Definition and impact of pathologic complete response on prognosis after neoadjuvant therapy

Neoadjuvant chemotherapy represents an option for patients with early breast cancer when an indication for chemotherapy is given. Pathologic complete response (pCR) has predicted long-term outcome in several neoadjuvant studies and is therefore a potential surrogate marker for survival. However, selected trials comparing different neoadjuvant regimens have failed to demonstrate an association between pCR rate and improved outcome (von Minckwitz et al., 2012)

Methodologic limitations are likely to be the reason for this unexpected discrepancy. First, no standardized definition for pCR exists. Some trials have applied the pCR definition to the breast tumor only, whereas others have included the axillary nodes. Furthermore, some studies have included the presence of focal invasive cancer or noninvasive cancer residuals in their pCR definition whereas others have defined pCR as the complete eradication of all invasive and noninvasive cancer. Second, incidence and prognostic impact of pCR vary among breast cancer-intrinsic subtypes. For example, although patients with luminal A breast cancer show a low pCR rate, their overall prognosis is favorable, whereas patients with triple-negative (TN) breast cancer show a high pCR rate but have an unfavorable outcome (von Minckwitz et al., 2012). Including all intrinsic subtypes might therefore attenuate the prognostic information of pCR.

Pathologic complete response (pCR) defined as no invasive and no in situ residuals in breast and nodes can best discriminate between patients with favorable and unfavorable outcomes. Patients with noninvasive or focal-invasive residues or involved lymph nodes should not be considered as having achieved pCR. pCR is a suitable surrogate end point for patients with luminal B/HER2-negative, HER2-positive (nonluminal), and triple-negative disease but not for those with luminal B/HER2-positive or luminal A tumors (von Minckwitz et al., 2012).

This is, to the best of our knowledge, the first individual patient- based pooled analysis analyzing different pCR definitions for their prognostic impact on survival of patients with breast cancer treated with neoadjuvant anthracycline-taxane-based chemotherapy. The large patient collective included sufficient subpopulations with small residual disease volume (eg,

noninvasive residuals only, focal-invasive disease < 5 mm, or no invasive tumor in the breast but involved lymph nodes). Over the last decades, these subpopulations have frequently been considered to have achieved pCR. However, (von Minckwitz et al., 2012) show that these subpopulations have an increased risk of relapse and sometimes of death as well compared with the group of patients with stage ypT0 ypN0 breast cancer. pCR restricted to this stage showed the lowest adjusted HR for DFS and OS compared with the other definitions (Schott et al., 2012; von Minckwitz et al., 2012) further demonstrate that in subgroups considered to have slowly proliferating tumors, pCR is not associated with prognosis, whereas in subgroups with highly proliferating tumors, pCR can discriminate between patients with good and poor prognosis accurately. The recently proposed clinicopathologic definition of the St Gallen panel nicely recognizes these subgroups. In fact, prognostic impact of pCR is highest in HER2-positive (nonluminal) and TN tumors, where patients achieving pCR show a prognosis comparable to that of patients with luminal A tumors.

Surprisingly, pCR was not prognostic in the luminal B/HER2positive subgroup irrespective of trastuzumab treatment. In this subgroup, pCR rates were low, despite concomitant anti-HER2 therapies, but similar outcomes were observed in the adjuvant trastuzumab studies.

In the research setting, Schott and Hayes (2012) recommend that neoadjuvant trials that are testing classic cytotoxic drugs with pCR as the primary end point should enroll only patients with ER-negative or highly proliferative tumors, given that these are the patients for whom pCR is shown to have prognostic value. In these instances, every body adoption of a uniform definition of pCR, which is substantially clarified by the data from von Minckwitz et al (2012). Uniform definitions for concepts such as pathologic complete response (pCR) can provide a framework for reporting clinical trial results in a coherent manner.

2.3. Neoadjuvant endocrine therapy

Duration of neoadjuvant hormonal treatment for breast cancer in most studies was 3-6 months. The few studies that investigated prolonged treatment with neoadjuvant endocrine therapy suggest that a further reduction in tumour size can be achieved and that even surgery can be withheld for elderly women on continuing hormonal treatment. However, the optimum duration of neoadjuvant endocrine therapy has to be established. For many years, primary systemic (neoadjuvant) therapy has been given before local treatment for women with locally advanced breast cancer in an effort to make such disease operable. Chemotherapy has been the mainstay of this approach, but more recently neoadjuvant endocrine therapy has emerged as an attractive alternative in post-menopausal women with large hormone receptor positive breast cancers. A number of randomized trials (like P024, IMPACT, PROACT) have compared various aromatase inhibitors directly with tamoxifen. An important endpoint in each of these studies has been the rate at which breast conservation has been achieved. The presence of steroid hormone receptors (ER and/or PR) are target for endocrine therapy. Preoperative chemotherapy may be less effective in postmenopausal patients with ER-positive and/or PR-positive tumors at least with respect to doxorubicin-containing or taxane-containing regimens. Pathological complete response (pCR) rates after chemotherapy were significantly higher among patients with tumors that were both ER-negative and PR-

negative compared with patients whose tumors had any (even low) expression of steroid hormone receptors (Colleoni et al. 2004, 2008). In the ECTO I trial, pCR after neoadjuvant chemotherapy was observed in 42% of women with ER22 negative tumors, compared with 12% in the ER-positive group (Gianni et al. 2009). In the NSABP B-27 study, ER-negative tumors had higher rates of pCR than ER-positive tumors when treated with neoadjuvant AC, as well as when treated with AC followed by docetaxel (Bear et al., 2006). Before our trial there were few, if any, direct comparisons of primary neoadjuvant endocrine therapy with primary neoadjuvant chemotherapy in patients with hormone-responsive breast cancer.

This was an open-label, randomized phase 2 trial of once-daily endocrine therapy (exemestane or anastrozole) or chemotherapy (doxorubicin and paclitaxel, every 3 week for 4 cycles) in postmenopausal women with primary ER-positive breast cancer. A total of 239 patients with ER-positive and/or PgR-positive breast cancer (T2N1-2, T3N0-1, T4N0M0) were randomly assigned to receive neoadjuvant endocrine therapy (ET) [anastrozole 1 mg/day or exemestane 25 mg/day for 3 months, 121 patients] or chemotherapy (CT) [doxorubicin 60 mg/m² with paclitaxel 200 mg/m², four 3-week cycles, 118 patients]. All patients were considered to be ineligible for breast-conserving surgery (BCS) at enrollment. After BCS all patients received radiotherapy (50 Gy in 25 fractions). The median follow-up time was 5.6 years.

The primary efficacy end point was already reported (Semiglazov et al., 2007). Overall response (OR=CR+PR) was similar in the endocrine therapy group (65.5%) compared with chemotherapy group (63.6%; $p>0.5$). Interim analysis of this trial showed similar objective response in patients who were receiving exemestane and in patients who were receiving anastrozole. It allowed us to review and to analyze dates on all patients who were receiving aromatase inhibitors in the endocrine therapy group. There was a trend toward higher overall rates of OR and breast-conserving surgery among patients with tumors expressing high levels of ER (Allred score ≥ 6) in the endocrine therapy compared with the chemotherapy group (43% vs 24%, $p=0.054$).

After completing neoadjuvant treatment, 31 patients (13%) did not undergo surgical resection: 12.3% of patients who were receiving endocrine therapy and 13.5% of patients who were receiving chemotherapy. Twenty-two patients did not receive surgery because of disease progression. These patients were switched to the other study therapy: patients initially treated with endocrine therapy received chemotherapy, and patients treated with chemotherapy received endocrine therapy. Progressive disease was observed in 9% of patients who were receiving endocrine therapy and 9% of patients who were receiving chemotherapy ($P>0.5$). Stable disease was seen in 21% of patients who were receiving endocrine treatment and 26% of patients who were receiving chemotherapy.

Analysis of BCS rates according to pretreatment characteristics showed a non-significant trend towards increased BCS in patients with clinical stage T2, ER+/PgR+, 70 years and older ($p=0.054-0.088$) receiving neoadjuvant endocrine therapy.

The rate of BCS was particularly marked in patients receiving endocrine therapy, who achieved a clinical response. There was no significant difference between endocrine therapy

(ET) and chemotherapy (CT) relative to the incidence of locoregional recurrences and distant metastases (8.2% and 7.6%, $p=0.99$; 14.8% and 15.2%, $p=0.83$, respectively). There was no significant difference in DFS through 5 years of follow up between the 121 patients who received neoadjuvant endocrine therapy and 118 women who received chemotherapy: 71.0% and 67.7% ($p>0.5$). After a median follow up of 5.6 years 35 events had been reported in the endocrine group (24 in 66 patients who underwent mastectomy and 11 in 40 patients who underwent BCS). 5-year DFS was 63.6% after mastectomy and 72.5% after BCS ($p=0.076$). The incidence of commonly reported adverse events was higher in patients receiving chemotherapy. No serious adverse events were reported in patients receiving endocrine therapy. Six patients receiving chemotherapy experienced febrile neutropenia leading to treatment interruption. No deaths occurred during the preoperative therapy. Our trial has shown that preoperative endocrine therapy with aromatase inhibitors offers the same rate of overall objective response, breast-conserving surgery, 5-years DFS as chemotherapy in postmenopausal patients with ER-positive tumors. The frequency of adverse events was higher among patients who were receiving chemotherapy. Endocrine treatment was well tolerated. Preoperative endocrine therapy with aromatase inhibitors is a reasonable alternative to preoperative chemotherapy for postmenopausal women with ER-positive disease in clinical situation in which the low toxicity of the regimen is considered an advantage. According St.Gallen recommendation (Goldhirsch et al., 2009) neoadjuvant endocrine therapy without chemotherapy was considered reasonable for postmenopausal patients with strongly receptor-positive disease. If used, such treatment should be considered for a duration of 5-8 months or until maximum tumour response.

2.4. Neoadjuvant therapy in HER2+ breast cancer

Amplification or overexpression, or both, of human epidermal growth factor receptor-2 (HER2, also known as ERBB2), a transmembrane receptor tyrosine kinase, is present in around 22% of early breast cancers, 35% of locally advanced and metastatic tumours, and 40% of inflammatory breast cancers, and is associated with aggressive disease and poor prognosis (Ross et al., 2009). Patients with HER2-positive locally advanced or inflammatory breast cancer are therefore in particular need of effective treatment. Trastuzumab (Herceptin, Roche, Basel, Switzerland), a recombinant humanized monoclonal antibody that targets HER2, has efficacy as monotherapy (Baselga et al., 2005) and improves results of chemotherapy in patients with HER2-positive metastatic (Slamon et al., 2001; Marty et al., 2005) and early operable breast cancer (Smith et al., 2007; Romond et al., 2005; Slamon et al., 2005). It is widely approved for use as monotherapy and in combination with chemotherapy or hormone therapy in these patients, but not specifically in those with locally advanced or inflammatory breast cancer. In a pilot study, anthracycline and paclitaxel were successfully combined with trastuzumab in patients with metastatic disease (Bianchi et al., 2003). To reduce the risk of cardiac toxic effects, only three cycles of doxorubicin were given in the pilot study, which corresponds to a cumulative dose of 180 mg per m² of body surface area (Gianni et al., 2009). No patient developed symptomatic cardiac dysfunction, although four patients (of 16) had reversible asymptomatic decreases in left ventricular ejection fraction to 50% or lower.

The neoadjuvant Herceptin (NOAH) study was designed to assess efficacy of neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone in patients with HER2-positive locally advanced or inflammatory breast cancer. The NOAH study randomized 228 patients with centrally confirmed HER2+ locally advanced breast cancer to a chemotherapy regimen consisting of 3 cycles of doxorubicin plus paclitaxel (AT); 4 cycles of paclitaxel (T); and 3 cycles of cyclophosphamide, methotrexate, and fluorouracil (CMF), with and without trastuzumab. The addition of trastuzumab significantly improved overall response rate (81% vs 73%, $P=0.18$) and pCR rates (43% vs 23%, $P=0.002$) (Gianni et al., 2010).

The primary objective was to compare event-free survival, which was defined as time from randomization to disease recurrence or progression (local, regional, distant, or contralateral) or death from any cause, in patients with HER2-positive disease treated with and without trastuzumab.

Trastuzumab significantly improved event-free survival in patients with HER2-positive breast cancer (3-year event-free survival 71% [95% CI 61-78; n=36 events] with trastuzumab, vs 56% [46-65; n=51 events] without; hazard ratio 0.59 [95% CI 0.38-0.90]; $p=0.013$). Trastuzumab was well tolerated and, despite concurrent administration with doxorubicin, only two patients (2%) developed symptomatic cardiac failure. Both responded to cardiac drugs. The results of the NOAH study have shown that in patients with HER2-positive locally advanced or inflammatory breast cancer, addition of 1 year of trastuzumab (starting as neoadjuvant and continuing as adjuvant therapy) to neoadjuvant chemotherapy improved overall response rates, almost doubled rates of pathological complete response, and reduced risk of relapse, progression, or death compared with patients who did not receive trastuzumab. Investigators recorded a benefit of trastuzumab in all 1 subgroups tested, including women with inflammatory disease (27% of HER2-positive patients) who benefited substantially from trastuzumab (Baselga et al., 2005; Semiglazov et al., 2011)

The results of the NOAH study consolidate those of other studies of trastuzumab in the neoadjuvant setting. In these mainly non-randomised studies, pathological complete response rates (variously defined) ranged from 17% to 73%, and were better than they were in historical or concurrent HER2-negative controls (Gluck et al., 2008; Untch et al., 2008). One randomised trial in patients with operable non-inflammatory disease was stopped early when the pathological complete response rate in the trastuzumab group was more than twice as high as that of the control group (65% vs 26%) (Buzdar et al., 2005). Patient numbers in this study were small, but preliminary results from another randomized study also show a doubling in pathological complete response rate in the trastuzumab group. These response rates to primary systemic therapy are a surrogate for relapse-free and overall survival in patients who were unselected for HER2 status.

Despite concurrent use of doxorubicin, paclitaxel, and trastuzumab in the NOAH trial, incidence of symptomatic cardiac failure was low (<2%) and less than was expected (2.8- 4.1%) on the basis of adjuvant trials in which trastuzumab was given concurrently with paclitaxel after completion of doxorubicin and when trastuzumab was given as monotherapy after completion of a range of cytotoxic regimens (2%). These findings support the accumulating

evidence that trastuzumab can be given concurrently with anthracyclines with a low frequency of symptomatic cardiac dysfunction, provided that low cumulative doses or less cardiotoxic anthracyclines are used, and careful cardiac monitoring is done.

The addition of trastuzumab to neoadjuvant sequential anthracycline-taxane chemotherapy (with and without capecitabine) was also investigated in the phase III GeparQuattro study, and led to a doubling of pCR rates (31.8% vs 15.4%, $P < 0.001$) (Von Minckwitz et al., 2008). With the emergence of lapatinib (Tykerb), a dual tyrosine kinase inhibitor against HER1 and HER2, the CALGB is conducting a randomized phase III trial to evaluate paclitaxel with trastuzumab or lapatinib, or both in the preoperative setting. Several other trials are ongoing to evaluate these 2 drugs in the neoadjuvant setting, including Neo-ALTTO (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimization) in phase III and CHERLOB in phase II.

Trastuzumab (H) in combination with chemotherapy improves outcomes in patients with HER2-positive breast cancer and is integral to the standards of care for these patients. However, in some patients disease progression still occurs. Pertuzumab (P) and trastuzumab (H) target different epitopes of HER2, and their use in combination has demonstrated improvement in response rates. NEOSPHERE study (Gianni et al., 2011) assessed the efficacy and safety of pertuzumab added to trastuzumab-based neoadjuvant chemotherapy in women with HER2-positive operable, locally advanced/inflammatory breast cancer who had not received prior cancer therapy.

Patients ($n = 417$) with HER2-positive (IHC3+ or IHC2+ and FISH/CISH+) breast cancer were randomized 1:1:1:1 to receive 4 neoadjuvant cycles of docetaxel (T) plus H, THP, HP or TP. Pertuzumab (P) was given at a loading dose of 840 mg and 420 mg maintenance, trastuzumab (H) at a loading dose of 8mg/kg and 6 mg/kg maintenance, and docetaxel (T) at 75 mg/m² with escalation to 100 mg/m² if tolerated in a 3weekly schedule. The primary endpoint was pCR in the breast.

About 40% of patients had locally advanced/inflammatory breast cancer and approximately 50% were ER/PR negative. THP combination (docetaxel + trastuzumab + pertuzumab) significantly improved the pCR rate compared with TH (docetaxel + trastuzumab) alone: 45.8% (95% CI 36.1-55.7) vs 29.0% (95% CI 20.6-38.5), $P = 0.0141$. Patients receiving THP (docetaxel + trastuzumab + pertuzumab) had the highest pCR rate regardless of ER/PR status, although the greatest treatment benefit in all 4 arms was observed in ER/PR-neg patients. The chemotherapy-free HP (trastuzumab+pertuzumab) arm achieved a pCR rate of 16.8%. THP (docetaxel + trastuzumab + pertuzumab) had a similar safety profile to TH. The incidence of AEs was lowest in the HP (trastuzumab+pertuzumab) arm.

Thus, the addition of pertuzumab to trastuzumab-based neoadjuvant chemotherapy resulted in a significant improvement of the pCR rate with no new safety signals of concern. Pertuzumab and trastuzumab have complementary mechanisms of action as pertuzumab inhibits HER2:HER3 heterodimerisation, thereby providing a potential mechanism to overcome tumour escape. These results support the rationale for a planned Phase III, double-

blind, placebo-controlled trial evaluating pertuzumab added to standard trastuzumab-based therapy in women with HER2- positive breast cancer.

Dual HER2 inhibition is being examined in neoadjuvant and adjuvant settings. The Neo-ALTT0 (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) study showed that the addition of lapatinib plus trastuzumab to neoadjuvant chemotherapy resulted in a higher pathologic complete response rate compared with the addition of trastuzumab or lapatinib monotherapy (51.3% v 29.5% v 24.7%, respectively; $P < .01$). Also objective (clinical) response rates at 6 weeks with anti-HER2 therapy alone were 67.1%, 30.2%, and 52.6%, respectively; those at surgery after 18 weeks of neoadjuvant anti-HER2 therapy plus chemotherapy were 80.3%, 70.5%, and 74.0%, respectively, suggesting that the combination is beneficial in the neoadjuvant setting (Baselga et al., 2012; Blackwell et al 2010-2012).

Despite the dramatic improvement in the outcome of HER2+ breast cancers since the widespread use of HER2-directed therapies, such as trastuzumab, patients continue to develop recurrences and disease progression. The mechanisms of intrinsic and acquired resistance to trastuzumab are likely multifactorial and are being exploited by the use of novel targeted agents in clinical development. The phosphoinositide-3-kinase (PI3K) pathway plays a key role in resistance to trastuzumab through increased signaling through upstream growth factor receptors, PTEN mutations, and other mechanisms, and therefore, is an excellent target for drug development in patients with trastuzumab-resistant, HER2+ breast cancers. Available clinical trials demonstrate encouraging activity of mTOR inhibitors in combination with trastuzumab monotherapy or trastuzumab-based chemotherapy in patients with HER2+ metastatic breast cancer pretreated with trastuzumab with or without lapatinib. The results of early-stage clinical trials are currently being confirmed in 2 large phase III trials (Brachman et al, 2009; Vazquez-Martin et al, 2009). Other agents, targeting the PI3K pathway, are in early clinical development for HER2+ breast cancers.

2.5. Triple-negative breast cancer

Triple-negative (ER-negative, PgR-negative, and HER2 receptor-negative) breast cancers (TNBC) account for approximately 15% of all breast cancers and, though in and of itself it is a heterogeneous group, it often exhibits an aggressive phenotype with a generally poor prognosis. Unlike HER2+ or hormone receptor- positive breast cancers, triple-negative tumors lack an established therapeutic target and though initially responsive to many standard treatment regimens, progression and recurrence can be rapid and refractory to alternative approaches. Loss or inactivation of breast cancer type 1 (BRCA1) leads to defects in certain DNA repair pathways. Most BRCA1 mutant breast cancers lack ER, PgR, and HER2 expression, and this association has raised the question of defective BRCA1 function in sporadic (non-familial) TNBC (Sorlie et al., 2003). This led to the hypothesis that triple-negative tumors may be more sensitive to DNA damaging agents, such as platinum. A retrospective analyses of patients with triple-negative breast cancer who received taxane/platinum-based primary chemotherapy demonstrated an overall response of 39% (Uhm et al., 2009), while studies of platinum monotherapy or combinations in the neoadjuvant set-

ting have produced pCR rates of 22%-50% (Garber et al., 2006; Chang et al., 2008; Byrski et al., 2009; Schott et al., 2011).

3. Molecular profiling in prognosis and patient selection for neoadjuvant systemic therapy

Gene expression profiling with the use of DNA microarrays has added valuable information to our understanding of breast cancer biology. In the seminal work of Perou et al. (2011) the ability to interrogate thousands of genes at the same time was translated into a "molecular portrait" of each tumor sample studied, and the concomitant analysis of the individual molecular portraits of breast cancer tumor samples made the definition of molecular subtypes of breast cancer possible (Perou et al., 2011). In order to analyze this large quantity of information (thousands of genes per sample evaluated), a hierarchical clustering method was used to group genes according to similar patterns of expression. The proposed molecular classification of breast cancer was divided into five classes: luminal-A, luminal-B, basal-like, HER2-positive and normal-like tumors (Sotiriou et al., 2003; Sorlie et al., 2003). Subsequently, the correlation between molecular subtypes and clinical data have shown a significant difference in overall survival between the subtypes.

Despite this progress, the clinical applicability of molecular classification is limited by the tight correlation between the molecular subtypes and currently available immunohistochemical markers (ER, PR, HER2, Ki67) (Sotiriou & Pusztai, 2009). For example, the molecular subtype HER2-positive is clinically detected by IHC or fluorescent in situ hybridization (FISH) according to published guidelines (Sauter et al., 2009). Although a good correlation has been established between the molecular subtype HER2 and clinically assessed HER2-positive breast cancer, the opposite is not true, because 30% of HER2-positive breast cancers are molecularly characterized as luminal-B (Cheang et al., 2009). Luminal-A and luminal-B molecular subtypes are, by definition, hormone receptor positive tumors, but the distinction between these two subtypes is controversial.

One of the proposed clinical definitions characterizes luminal-A and luminal-B tumors using hormone receptor status, HER2 status and the Ki67 index (percentage of Ki67-positive nuclei by IHC). Luminal-A is defined as being ER- and/or PR-positive, HER2-negative and Ki67-low (Ki67 index < 14%). Luminal-B is defined as ER- and/or PR- positive, HER2- negative and Ki67-high (Ki67 index > 14%). Another luminal-B subtype has also been proposed, namely luminal HER2 enriched, with tumors being ER- and/or PR- positive, HER2-positive and Ki67-high (ki67 index > 14%) (Perou, 2011).

Study Jinno et al (2011) was to evaluate the clinical utility of breast cancer intrinsic subtypes in the prediction of pathological complete response (pCR) in a cohort of breast cancer patients receiving neoadjuvant chemotherapy.

Patients with stage II/III breast cancer received 4 cycles of chemotherapy XT (capecitabine 1650mg/m² on days 1-14 and docetaxel 60mg/m on day 8 every 3 weeks), followed by 4 cy-

cles of FEC (fluorouracil 500 mg/m², epirubicin 90mg/m², cyclophosphamide 500mg/m²). Immunohistochemical (IHC) analysis of ER, PgR, HER2, EGFR, cito-ceratine 5/6, and Ki67 was performed in core needle biopsy samples at baseline. Tumors were classified as luminal A (ER+ and/or PgR+, and Ki67<20%), Luminal B (ER+ and PgR+, and Ki67 > 20%), Luminal-HER2 (ER+ and/or PgR+, and HER2+), HER2-enriched (ER- PgR-, and HER2+), or triple-negative (ER-, PgR-, and HER2-). Triple-negative tumors with and without EGFR+ and/or cito-ceratine 5/6+ were further classified as basal-like and non-basal-like TN (NBTN), respectively. Pathologic complete response (pCR) was defined as no microscopic evidence of residual viable tumor cells, invasive or noninvasive, in all resected specimens of the breast. Twenty-six (31.3%) patients were classified as luminal A, 12 (14.5%) were luminal B, 15 (18.1%) were luminal-HER2, 9 (10.8%) were HER2, 10 (12.0%) were basal like, and 11 (13.3%) were NBTN. The overall response rate was 90.4%, including a complete response in 30 patients and a partial response in 45 patients. The overall pCR rate was 15.5% (12/83). The highest pCR rate (40.0%) was observed in patients with basal-like tumors. In triple-negative patients, basal-like patients showed significantly higher pCR rate than NBTN patients (40.0% vs. 9.1%, $p = 0.01$). There were no cases with pCR in a cohort of luminal HER2 subtype patients. A higher proportion of luminal B patients had 1 pCR than luminal A patients (25.0% vs. 3.8%, $p = 0.01$). Data indicate that breast cancer subtypes are useful predictive biomarkers of pCR in breast cancer patients treated with neoadjuvant systemic chemotherapy.

According Sanpaolo et al (2011) study, breast cancer subtype seems a prognostic factor of breast cancer specific survival and distant metastases rates, but not of local relapse rate. Patient could be submitted to conservative surgery, if feasible, but considering the differenced in survivals, patients with worse prognosis should receive more aggressive adjuvant treatment.

The goals of neoadjuvant therapy of breast cancer have significantly changed and evolved since it was firstly applied to women with inoperable locally advanced and inflammatory breast cancers in the early 1970's. The extended indication to allow more breast conserving surgery has widened the application of neoadjuvant treatments and provided evidence for the association between favorable long term outcome and intermediate endpoints, like pathologic complete response (pCR) after chemotherapy or decreased tumor proliferation measured by Ki87 after endocrine therapy. A key question is whether pCR and Ki87 can take the role of qualified and validated surrogate markers of drug efficacy, so that any difference in survival between treatments disappeared after adjustment for the intermediate endpoint. The recent improvements in understanding the molecular basis of breast cancer heterogeneity has provided a new level of complexity but also an outstanding conceptual framework for interpreting the role of pCR as potential surrogate marker, and has made clear that the biologic meaning of pCR is different in different molecular subtypes, and that different molecular subtypes will require different intermediate surrogate endpoints. The validation of the intermediate surrogates markers of efficacy would dramatically change the landscape of development of new drugs for early breast cancer and do provide the rationale for a comparative analysis of the intermediate endpoint instead of the final survival endpoint. The feasibility of this major paradigm shift from large and lengthy adjuvant clinical

trials to smaller and faster neoadjuvant trials is still the topic of discussion, and will be addressed by regulators, biostatisticians, translational scientists and oncologists.

4. The surgical aspects of neoadjuvant therapy

4.1. The surgical management of patient who achieve a complete pathological response after neoadjuvant therapy

Neoadjuvant systemic treatment (NST) is the standard treatment for locally advanced breast cancer (BC) and a standard option for primary operable disease. This analysis aimed to identify whether breast cancer patients receiving radiotherapy alone following a complete clinical remission (cCR) to neoadjuvant chemotherapy had a worse outcome than those treated with surgery.

We identified 8 studies of NST where breast cancer patients who achieved a cCR were eligible for different types of local management: radiotherapy only or surgery. Primary outcomes were loco-regional recurrence, distant disease free survival (DDFS), overall survival (OS) (Semiglazov, 2008; Clouth et al., 2007; Ring et al., 2004; Smith et al., 2002).

We performed subgroup meta-analyses for the primary outcomes on the basis of local management. Heterogeneity between the risk ratios for the same outcome between different studies was assessed by use of the chi-square-based Q statistic.

Rates of pathologic complete response (pCR) range from 25% to 35,8% of patients who had a cCR. If a cCR is considered as a "test" of pCR then the positive predictive value of cCR in all eligible trials was low (range from 29.9% to 35%). For surgery and no surgery (radiotherapy alone) groups respectively there were no significant differences in DDFS (summary risk ratio [RR]=0.94, 95% confidence interval [CI]=0.91- 1.07) or OS (RR= 1.00, 95% CI=0.99- 1.12). But there was trend towards increased loco-regional recurrences for the radiotherapy only group (difference in favor to surgery range from 11% to 20%; RR= 1.53, 95% CI= 1.11- 2.10; P=0.02).

In patients achieving a cCR to neoadjuvant chemotherapy, radiotherapy alone achieve survival rate as good as with surgery, but with higher local recurrence rate. A prospective randomized trial addressing the need for surgery after cCR would seem reasonable in patient with magnetic resonance or positron emission tomography-defined complete remissions.

4.2. Role of sentinel node biopsy after neoadjuvant systemic therapy

The surgical management of patients presenting early stage breast cancer (T1- T2) and clinically negative lymph nodes (NO) has long included both primary tumor resection and level I/II axillary lymph node dissection (ALND). This last procedure has been largely substituted by the sentinel lymph node biopsy (SLNB) which is nowadays recommended by most clinical guidelines for this subgroup of patients. Indeed, the well documented accuracy of SLNB in predicting the axillary status implies that, in these patients, a negative sentinel lymph

node (SLN) is considered sufficient to rule out metastases in other axillary nodes and to avoid axillary dissection. Several randomized clinical trials have further indicated that SLNB and ALND are comparable in terms of overall survival and incidence of nodal failure (Canavese et al., 2011).

Over the years, neo-adjuvant chemotherapy (NAC) has become the preferred treatment for patients with operable locally advanced breast cancer, in an attempt to reduce the tumor mass and to favor breast-conservative surgery over mastectomy. In addition, NAC has been shown to down-stage the axillary status in some 30-40% of the patients treated. Based on the SLNB validation studies mentioned above, it would be reasonably legitimate to introduce the SLNB procedure also in the context of NAC. However, one frequent adverse effect of NAC is the anatomical alteration of the lymphatic drainage, with lymphatic vessels disrupted by tumor, inflammation or fibrosis, or blocked by necrotic and/or apoptotic cells; in addition, NAC could induce a non-uniform tumor regression in the axillary nodes, being most effective in some nodes but not in others.

These events could prevent a proper diffusion of the scintigraphic tracer during lymphatic mapping, in the one hand, and contribute to a reduction in the rate of successful SLN identification and, more importantly, an increase in the rate of false-negative SLN. Therefore, the demonstration of the feasibility and accuracy of SLNB after NAC is of major interest since in the future responders to NAC who would be down-staged to a negative nodal status (NO) could be spared a complete axillary dissection and the immediate sequelae of axillary surgery. Two large NSABP trials have incorporated SLN biopsy either before chemotherapy (B-32, 5536 patients) or after NAC (B-27, 428 patients) and report comparable mapping success (97% vs 89%) and false negative rates (9.8% vs 9.3%) for combined blue dye and radioactivity.

There is a current SNB trial looking at SNB before and after neoadjuvant systemic therapy in Germany called SENTINA (Kuehn et al., 2009). This is a four arm study. Patients who are clinically node-negative have SLNB prior to NAC. Those who are SLNB negative at diagnosis have no further axillary procedure after NAC whereas those who are SLNB

Positive proceed after NAC to a further SLNB and axillary dissection. Clinical node-positive patients have primary systemic therapy and those that are clinically node-negative go on to have SLNB and axillary lymph node dissection, whereas those who are clinically node-positive undergo axillary lymph node dissection alone. Over 600 patients have been enrolled to date. The study design is somewhat complex but will add to the body of knowledge on the value of ALNB after NAC

Dixon and Cody (2010) recommend that all patients at diagnosis have axillary ultrasound and that any suspicious nodes should be submitted to fine needle aspiration cytology or core biopsy. Those who appear to be node-negative on the basis of clinical exam, imaging, and needle biopsy should have SLN biopsy post-NAC, at the same time as their breast surgery, to assess the extent of any remaining disease. Those with proven axillary node metastases at diagnosis should also be considered for SLN biopsy post-NAC. For patients with triple-negative or HER2-positive disease there is a more than 50% chance that all involved

nodes will be sterilized by NAC +/- trastuzumab. This contrasts to patients with ER-positive disease who have an approximate 4% rate of axillary node sterilization. These data can be used to inform patients at the outset of treatment as to the possible surgical options for the axilla after NAC. For patients with involved nodes at diagnosis who have a complete clinical and imaging response in the axilla, SLN biopsy is reasonable post-NAC and ALND can be avoided if the SLN is negative. For the remaining patients whose nodes remain positive post-NAC (less than half of those with triple-negative or HER2-positive cancers, and over 95% of those with ER-positive disease), ALND should remain the standard of care.

So intra-operative lymphatic mapping and SLNB are nowadays part of the standard management of patients with early-stage breast cancer and clinically negative axillary nodes. Based on the present results, this procedure is feasible and is an accurate predictor of the axillary nodal status also when it is performed after NAC in patients with locally advanced breast cancer. However, before introducing SLNB as a routine procedure in the context of NAC, clinical trials will have to demonstrate that overall survival and disease-free survival do not worsen when ALND is not performed in the subset of post-NAC SLN-negative patients, thus leaving behind down-staged axillary nodes.

5. Conclusion

The neoadjuvant (preoperative, primary) use of cytotoxic, hormonal, and/or trastuzumab therapy effectively reduces tumor burden in the breast and the axilla without compromising survival. The risk of local recurrence is determined by the initial clinical stage and the pathologic stage after neoadjuvant therapy. Neoadjuvant therapy is indicated in patients with inoperable tumors or if BCT is desired by patients with large tumors otherwise requiring mastectomy. Patients with multicentric tumors generally will not become candidates for BCT with this approach. Initial multidisciplinary evaluation is important. The tumor site should be marked before treatment (eg, by clipping) to allow tumor localization at surgery. Multiple imaging studies are not needed during treatment unless there is concern about disease progression. Surgery is necessary in all patients, even those with a complete clinical response. Any residual palpable or imaging-detected lesions should be removed, but the entire initial tumor volume does not need to be resected in tumors showing a reduction in size. The optimal timing of sentinel lymph node biopsy in relation to neoadjuvant systemic therapy in patients with a clinically lymph node-negative axilla is uncertain at this time, and further study is required. The identification rate of the sentinel lymph node appears to be lower after neoadjuvant therapy, but some patients may avoid axillary lymph node dissection because of downstaging. Ultrasonography of the axilla in clinically lymph node-negative patients is useful in identifying pathologically lymph node-positive patients at presentation. In some cases, knowledge of the pretreatment lymph nodal status is useful for radiation planning. In patients with lymph node-positive disease at presentation who become clinically lymph node-negative after treatment, axillary dissection is recommended because of the high false-negative rate of SNB in this circumstance. Postoperative radiation therapy is recommended for all patients treated with breast-conserving surgery and for all

patients with initially lymph node-positive disease or with locally advanced disease treated with mastectomy.

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Author details

Vladimir F. Semiglazov¹ and Vladislav V. Semiglazov²

1 Petrov Research Institute of Oncology, Russia

2 St.Petersburg Pavlov Capital Medical University Russia, Russia

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