OXFORD

J Natl Cancer Inst Monogr (2015) 2015(51): lgv023

doi:10.1093/jncimonographs/lgv023

International Expert Consensus on Primary Systemic Therapy in the Management of Early Breast Cancer: Highlights of the Fifth Symposium on Primary Systemic Therapy in the Management of Operable Breast Cancer, Cremona, Italy (2013)

Vito Amoroso, Daniele Generali, Thomas Buchholz, Massimo Cristofanilli, Rebecca Pedersini, Giuseppe Curigliano, Maria Grazia Daidone, Serena Di Cosimo, Mitchell Dowsett, Stephen Fox, Adrian L. Harris, Andreas Makris, Lucia Vassalli, Andrea Ravelli, Maria Rosa Cappelletti, Christos Hatzis, Clifford A. Hudis, Paolo Pedrazzoli, Anna Sapino, Vladimir Semiglazov, Gunter Von Minckwitz, Edda L. Simoncini, Michael A. Jacobs, Peter Barry, Thorsten Kühn, Sarah Darby, Kerstin Hermelink, Fraser Symmans, Alessandra Gennari, Gaia Schiavon, Luigi Dogliotti, Alfredo Berruti, Alberto Bottini

Affiliations of authors: Medical Oncology Unit (VA, ABe), University of Brescia, and Breast Unit (RP, LV, ELS) Spedali Civili Hospital, Brescia, Italy; U.O. Multidisciplinare di Patologia Mammaria, S.S. Terapia Molecolare e Farmacogenomica, AZ. Istituti Ospitalieri di Cremona, Cremona, Italy (DG, AR, MRC, LD, ABo); Departments of Radiation Oncology (TB) and Pathology (FS), University of Texas MD Anderson Cancer Center, Houston, TX; Department of Medical Oncology and Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA (MC); Division of Experimental Therapeutics, Breast Cancer Program, Istituto Europeo di Oncologia, Milan, Italy (GC); Biomarkers Unit, Department of Experimental Oncology and Molecular Medicine (MGD), and Medical Oncology Unit (SDC), Fondazione IRCCS - Istituto Nazionale Tumori, Milan, Italy (MGD); Academic Department of Biochemistry, Biochemical Endocrinology (MD), Department of Surgery, Breast Unit (PB), and The Breakthrough Breast Cancer Research Centre, The Institute of Cancer Research and Breast Unit (MD, GS), Royal Marsden Hospital, London, UK; Department of Pathology, Melbourne University, Parkville, Australia (SF); Molecular Oncology Laboratories, Weatherall Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, Oxford, UK (ALH); Mount Vernon Cancer Centre, London, UK (AM); Section of Medical Oncology, Yale Cancer Center, Yale School of Medicine, New Haven, CT (CH); Memorial Sloan Kettering Cancer Center, New York, NY (CAH); Division of Medical Oncology, Department of Hemato-oncology, IRCCS Policlinico 'San Matteo' Foundation, Pavia, Italy (PP); Dipartimento Medicina di Laboratorio, SC Anatomia ed Istocitopatologia Diagnostica e di Screening, A.O.U. Città della Salute e della Scienza di Torino, Università di Torino, Turin, Italy (AS); N. N. Petrov Research Institute of Oncology, St. Petersburg, Russia (VS); German Breast Group & University of Frankfurt, Neu-Isenburg, Germany (GvM); The Russell H. Morgan Department of Radiology and Radiological Science, Division of Cancer Imaging and Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD (MAJ); Department of Gynecology and Obstetrics, Interdisciplinary Breast Center, Klinikum Esslingen, Germany (TK); Clinical Trial Service Unit, Nuffield Department of Population, Health, University of Oxford, Oxford, UK (SD); Breast Center, Department of Gynecology and Obstetrics (Campus Grosshadern), CCCLMU University Hospital of Munich, Munich, Germany (KH); U.O. Oncologia Medica, E.O. Ospedali Galliera, Genoa, Italy (AG).

Correspondence to: Alberto Bottini, MD, PhD, U.O. Multidisciplinare di Patologia Mammaria, Istituti Ospitalieri di Cremona, Viale Concordia 1, Cremona 26100, Italy (e-mail: a.bottini@ospedale.cremona.it).

Abstract

Expert consensus-based recommendations regarding key issues in the use of primary (or neoadjuvant) systemic treatment (PST) in patients with early breast cancer are a valuable resource for practising oncologists. PST remains a valuable therapeutic approach for the assessment of biological antitumor activity and clinical efficacy of new treatments

in clinical trials. Neoadjuvant trials provide endpoints, such as pathological complete response (pCR) to treatment, that potentially translate into meaningful improvements in overall survival and disease-free survival. Neoadjuvant trials need fewer patients and are less expensive than adjuvant trial, and the endpoint of pCR is achieved in months, rather than years. For these reasons, the neoadjuvant setting is ideal for testing emerging targeted therapies in early breast cancer. Although pCR is an early clinical endpoint, its role as a surrogate for long-term outcomes is the key issue. New and better predictors of treatment efficacy are needed to improve treatment and outcomes. After PST, accurate management of post-treatment residual disease is mandatory. The surgery of the sentinel lymph-node could be an acceptable option to spare the axillary dissection in case of clinical negativity (N0) of the axilla at the diagnosis and/or after PST. No data exists yet to support the modulation of the extent of locoregional radiation therapy on the basis of the response attained after PST although trials are underway.

Primary (or neoadjuvant) systemic therapy (PST) has become a widely accepted choice to treat patients with locally advanced and operable breast cancer in routine clinical practice. PST may allow many patients with inoperable locally advanced breast cancer to become operable and those with large operable tumors to become suitable for breast conservation. PST may provide early information on treatment induced-antitumor activity and may be a useful tool for switching patients from ineffective therapy (1). Recently the US Food and Drug Administration has released a draft Guidance to Industry, outlining a pathway to accelerated approval for neoadjuvant breast cancer therapies using pathological complete response (pCR) as an endpoint. The association between pCR and outcome is clear for chemotherapy in triple-negative breast cancer and HER2-targeted agents in HER2-positive disease, but might not hold true for other tumor subtypes such as luminal cancers.

This neoadjuvant treatment modal has a major role in clinical research since it offers a unique opportunity to evaluate new agents and to enable predictive biomarker discovery. The rapid assessment of drug efficacy in PST trials could expedite development and approval of treatments for early breast cancer.

Despite these advantages, several drawbacks limit the widespread use of PST in routine clinical practice and the generalizability of the results of PST clinical trials.

To update the role and setting for PST, during "*The Fifth Symposium on Primary Systemic Therapy in the Management of Operable Breast Cancer*" held October 5–7, 2013, in Cremona, Italy, an expert faculty in the areas of medical oncology, breast surgery, radiation oncology, molecular biology, and pathology, provided an overview of recent available data from the most relevant studies and prospective clinical trials of PST in patients with operable breast cancer. At the conclusion of the congress and in the discussion, the panel of experts formulated a declaration of consensus regarding some key issues on the use of PST either in routine practice or clinical research.

This consensus was based on the best available evidence as presented at the 2013 Cremona meeting and reflected by votes recorded for specific questions on selected topics during the following months, according to a modified Delphi process (Table 1). The manuscript was subsequently reviewed and approved by all members of the Panel.

Patient Assessment Before Neoadjuvant Systemic Therapy and Treatment choice

A core biopsy is recommended for histological diagnosis in the initial evaluation of a woman with a suspected breast cancer, after the appropriate breast imaging study. This enables a detailed pathological diagnosis, and clinicians can identify patients who may obtain a significant benefit with specific PSTs (2). In the Panel's opinion, core biopsies are essential either to confirm malignancy and to assess histological grade. The pretreatment biopsy should be tested for hormone receptor (HR) status and HER2 status. Cytological examination is acceptable to confirm metastatic spread in the axillary lymph nodes.

Breast cancer is a heterogeneous disease as demonstrated by microarray-based expression studies. Higher expression of proliferation-related genes, and lower expression of estrogen-related genes are well known to be strong predictors of pCR but worse prognosis after neoadjuvant chemotherapy; immune-related genes and their related protein expression need more validation with regards to their role as predictors of pCR (3). Moreover, gene expression patterns can identify different intrinsic breast cancer subtypes which have a prognostic role (4). Distinct molecular subtypes such as luminal A tumors are associated with a better prognosis and paradoxically with lower rate of pCR following neoadjuvant chemotherapy (5–7).

Recently, a surrogate definition of luminal A-like and luminal B-like subtypes has been proposed on the basis of the immunohistochemistry measurement of estrogen receptor, progesterone receptor, HER2, and Ki67 (8). Patients with tumors classified as luminal A-like in the core biopsy have a lower pCR rate after PST, and the achievement of pCR in these patients had no prognostic impact (2). The Panelists were uncertain on whether the genomic signatures could add clinically useful information to standard immunohistochemistry in the selection of those patients who are candidates for PST.

Anthracycline-taxane-based chemotherapy is the reference regimen both in adjuvant and neoadjuvant settings. However, the optimal sequence of the two drugs is uncertain. Recently, two trials addressed this issue in the PST setting (9,10). In the Neo-tAnGo trial, which recruited 831 patients, paclitaxel administered for four cycles before standard anthracycline chemotherapy (epirubicin plus cyclophosphamide for four cycles) achieved a higher pCR rate compared with the reverse sequence (pCR rate: 20% vs 15%, $P = .03$), although no difference was seen in terms of long-term survival outcomes (9). In the Z1041 trial, 282 patients with HER2-positive breast cancer were randomly allocated to receive either fluorouracil, epirubicin, and cyclophosphamide followed by paclitaxel plus trastuzumab or paclitaxel followed by fluorouracil, epirubicin, and cyclophosphamide, both combined with trastuzumab. There was no difference in the pCR rate between the two arms; asymptomatic decreases in left ventricular ejection fraction during neoadjuvant chemotherapy occurred in similar proportions of patients in each group (10). The sample size of the study was small, and maybe the differences between treatments in terms of cardiac tolerability during neoadjuvant treatment might not have been evident. However, as the effect at the clinical and pathological level was equal between treatments and as the best sequence of anthracyclines and taxanes still remain uncertain, due to the well reported additive cardiac toxicity, trastuzumab should be

Table 1. Summary of most relevant recommendations*

Levels of recommendations	Evidence
A core biopsy is essential for histological diagnosis in the initial assessment of a woman with a suspected breast tumor and to assess histological grade, HR status, and HER2 status	Prospective cohort studies and expert opinion
Cytological examination is acceptable only to verify metastatic spread in the axillary lymph nodes	Expert opinion
It is uncertain whether genomic signatures could add clinically useful information to standard immunohistochemistry in the prediction of patients with higher chance of pathological complete response after neoadjuvant chemotherapy	Expert opinion
The best sequence of anthracyclines and taxanes still remain uncertain in neoadjuvant setting	Randomized clinical trials and expert opinion
Due to its additive cardiac toxicity, trastuzumab should be combined with taxanes and not with anthracyclines	Randomized clinical trials and expert opinion
Current evidence do not support the addition of antiangiogenic agents such as bevacizumab to neoadjuvant chemotherapy	Randomized clinical trials and expert opinion
Platinum-based neoadjuvant therapy could be an option for triple-negative breast cancer	Randomized clinical trials and expert opinion
Dual targeting of HER2 in combination with neoadjuvant chemotherapy is an option for HER2-positive disease	Randomized clinical trials and expert opinion
Neoadjuvant endocrine therapy is an option in patients with HR-positive and HER2-negative breast cancer	Randomized clinical trials and expert opinion
pCR do not satisfy the surrogacy criteria of long-term efficacy of neoadjuvant chemotherapy in unselected breast cancer	Trial-based meta-analyses of randomized clinical trials
pCR can be a valid surrogate of treatment benefit in studies recruiting patients with high-risk triple-negative or HER2-positive breast cancer	Expert opinion
ER-positive status is a negative predictor factor for pCR in HER2-positive breast cancer patients receiving neoadjuvant HER2-targeted therapies plus chemotherapy	Randomized clinical trials and expert opinion
There is not enough evidence to support the in-course change of the initial PST regimen on the basis of the clinical response obtained after two chemotherapy cycles, outside a clinical trial	Expert opinion
Ki67 expression measured either after short-term endocrine therapy or at posttreatment residual disease following neoadjuvant chemotherapy is a valid prognostic parameter, and a potential surrogate parameter of endocrine therapy efficacy	Prospective cohort studies and expert opinion
PEPI score do not provide additional predictive information compared with posttreatment Ki67 alone	Expert opinion
MRI is the reference imaging technique for the assessment of the extension of residual disease after PST	Expert opinion
None of the imaging techniques available (ie, mammography, ultrasound, and FDG PET) provide sufficient accuracy in predicting the pathological residual disease	Expert opinion
Residual disease after PST has a prognostic significance	Prospective cohort studies and expert opinion
No adjuvant chemotherapy is recommended in patients with triple-negative breast cancer having a residual disease in breast or lymph nodes after a full course of neoadjuvant chemotherapy	Expert opinion
There is not enough evidence supporting the omission or limitation of RT for women who achieve a pCR after PST	Expert opinion
SLN biopsy after neoadjuvant chemotherapy is an accurate method of axillary staging; dual tracer detection and removal at least of two SLNs is mandatory to minimize the false-negative rate of the procedure	Prospective clinical studies and expert opinion

*ER = estrogen receptor; FDG = fluorodeoxyglucose; HR = hormone receptor; MRI = magnetic resonance imaging; pCR = pathological complete response, PEPI = preoperative endocrine prognostic index; PET = positron emission tomography; PST = primary (neoadjuvant) systemic therapy; RT = radiotherapy; SLN = sentinel lymph node.

combined with taxanes and not with anthracyclines to avoid any early or late onset possible cardiological complications.

Two randomized studies reported an improvement in pCR rate with the addition of the antiangiogenic agent bevacizumab to standard neoadjuvant chemotherapy in HER2-negative tumors (11,12), but the Panel did not support this combination in clinical practice, since the higher pCR rate observed did not translate into an improved disease-free survival in the GeparQuinto trial after a median follow-up of 3.8 years (13).

The potential role for platinum-based chemotherapy in triple-negative breast cancer has been evaluated in two prospective randomized trials (GeparSixto and CALGB 40603). Preliminary results showed that carboplatin added to a taxane-anthracycline-based regimen improves the pCR rate compared with taxanes and anthracyclines only. The absolute increase of the pCR rate in the carboplatin arm was 16% in the GeparSixto trial (53% vs 37%; $P = .005$) (14) and 13% in the CALGB 40603 trial (54% vs 41%, odds ratio = 1.71; $P = .0029$) (15). It is yet unknown whether this relatively small improvement in the pCR rate could translate into a significant survival benefit in this selected study population; however, the panelists concluded that platinum-based neoadjuvant therapy could be an option for triple-negative breast cancer when a higher response rate could have an impact on the extent of surgery, for example, or when there is a poor clinical response to the standard anthracycline-taxane-based chemotherapy regimen. Moreover, in the triple-negative setting, intensified (dose-dense, high-dose) chemotherapy may represent another therapeutic option which is currently under investigation in prospective trials (16,17).

Information on the germline *BRCA* mutation status as well as on corresponding somatic tumor changes (so-called *BRCA*ness) from the GeparSixto trial were not available yet, but this analysis is in progress. *BRCA1/2* mutation carriers could represent a select population for addition of platinum to standard PST regimens due to the strong biological evidence of high sensitivity of *BRCA*-deficient cells to platinum chemotherapy both in vitro and in vivo and high response rates in a nonrandomized prospective clinical trials. Long-term survival data and subgroup analyses are not yet available in this setting to support a new standard regimen for *BRCA* carriers at this stage; however, this option is enticing to consider when data become available, especially in *BRCA* carriers with triple-negative cancers or with poor response to after standard neoadjuvant chemotherapy regimens.

Dual targeting of HER2 in combination with neoadjuvant chemotherapy is a promising approach for HER2-positive disease. Prospective randomized studies have demonstrated a significant improvement in the rate of pCR with trastuzumab-based systemic therapy plus either lapatinib or pertuzumab (18–20). Moreover, a combined analysis of the neoadjuvant GeparQuattro, GeparQuinto, and GeparSixto trials showed that HER2-positive breast carcinomas carrying a PIK3CA mutation are less likely to achieve a pCR after neoadjuvant anthracycline-taxane-based chemotherapy plus anti-HER2 treatment, even if a dual anti-HER2 treatment is given. Confirmatory data from a prospectively designed trial is needed on role of PIK3CA mutation in HER2 signaling before introduction in clinical practice (21). Breast-conserving surgery rates were also higher in patients treated with these PSTs with an almost 50% conversion rate from breast-conserving surgery-ineligible to breast-conserving surgery-eligible (22). For that reason, at the time of the meeting, most Panelists believed that dual targeting of HER2 is a valid option for clinical practice. More recently, both the NeoALLTO trial (23) and its parallel study in the adjuvant setting, the ALLTO trial, failed to show a significant improvement in long-term clinical outcomes in patients receiving dual HER2 inhibition with trastuzumab plus lapatinib compared with trastuzumab alone. This raises uncertainty about the importance of dual targeting HER2 in neoadjuvant setting particularly if lapatinib is added to trastuzumab. It also challenges the utility of relying on higher pCR rates in the neoadjuvant setting as surrogates for improved long-term outcomes such as disease-free and overall survival. With regards to patients with HR-positive and HER2-positive tumors, the Panel agreed that women with HR-positive and HER2-negative tumors may also be candidates for neoadjuvant chemotherapy, especially in the case of highly proliferating tumors, such as those classified as luminal B-like. Finally, in agreement with the St. Gallen International Expert Consensus (8), the Panel supported neoadjuvant endocrine therapy as an option in patients with HR-positive and HER2-negative breast cancer.

Assessment of Response and Significance of pCR

Response evaluation after PST is an important topic: One of the major advantages of this treatment modality is in fact to obtain a quantifiable evaluation of the sensitivity or resistance of any treated patient to a particular treatment or treatment combination. As inspired by the I-SPY 2 trial, the potential for tumor response (clinical, radiological, or pathological) to predict a reduction in micrometastatic burden might allow the individualization of the proper systemic treatment to administer and the rapid assessment of new targeted agents in well-defined tumors.

pCR, defined as eradication of invasive tumor from both breast and lymph nodes, has been shown to strongly correlate with the patient outcome (24). Nevertheless, pCR did not satisfy the surrogacy criteria of long-term efficacy of neoadjuvant chemotherapy at trial-based meta-analysis level in unselected breast cancer patients (24,25). In agreement with the US Food and Drug Administration (26), the majority of the Panel endorsed pCR as a potential surrogate of treatment benefit (to be considered as the primary endpoint) in studies recruiting patients with high-risk triple-negative or HER2-positive breast cancer. However, significant variability exists in methods of pathological assessment of response to PST, and thus its interpretation for subsequent clinical decisions. Practical methods are needed for standardized evaluation of the post-PST surgical breast cancer specimen, to promote accurate and reliable designation of pCR and meaningful characterization of residual disease for clinical trials are needed. The Panel also acknowledged that the incomplete characterization of long-term toxic effects and uncommon adverse events is of concern for the accelerated approval of new drugs on the basis of the pCR rate.

In HER2-positive tumors, the addition of HER2-directed therapy (ie, trastuzumab) to neoadjuvant chemotherapy improves both the rate of pCR or the survival outcomes (27,28). This is consistent with the potential surrogate role of pCR for predicting the efficacy of HER2-targeted therapies plus chemotherapy in the PST setting. The pCR rate obtained with trastuzumab plus chemotherapy is significantly higher in patients with HER2-positive, HR-negative tumors (50.3%, 95% confidence interval [CI] = 45.0 to 55.5%) compared with those with HER2-positive, HR-positive disease (30.9%, 95% CI = 26.3 to 35.8%) (24). Based on these data, the Panel concluded that positive estrogen receptor (ER) status should be considered a negative predictor for pCR in HER2-positive breast cancer patients receiving neoadjuvant

HER2-targeted therapies plus chemotherapy. In the neoadjuvant Herceptin (NOAH) randomized study, women achieving pCR after neoadjuvant chemotherapy plus trastuzumab showed a better event-free survival as compared with those achieving pCR after neoadjuvant chemotherapy alone (hazard ratio = 0.29, 95% CI = 0.11 to 0.78, P = .0135). This outcome difference was not evident in patients not attaining pCR (hazard ratio = 0.92, 95% CI = 0.61 to 1.39) (28). These findings add complexity to the interpretation of the significance of pCR as surrogate for survival benefit and raise the question as to whether pCR has a different prognostic significance depending on the type of treatment applied or the baseline prognosis of the treated population (29). The Panel however believed that further confirmation from larger datasets is needed before stating that only women attaining a pCR are those destined to obtain a benefit with chemotherapy plus HER2-directed therapy.

Whatever its definitive biological and clinical significance, pCR is a "late" intermediate endpoint since it can only be assessed only at the end of PST. We hypothesize that an even earlier surrogate may permit a beneficial in-treatment adjustment to the regimen administered. In an unplanned post hoc combined analysis recently published from the GeparTrio trial, a clinical response-guided approach—that is, change of the initial regimen or not on the basis of the clinical response after two chemotherapy cycles—was found superior to the conventional approach in terms of disease-free survival (30). Since the evidence is weak, the Panel did not reach a consensus on the reliability of this approach outside of clinical trial.

Several biological markers (assessing apoptosis or proliferative activity) have been demonstrated to change after PST. Ki67 is the marker mostly used to assess the proliferative activity immunohistochemically and has been extensively studied in neoadjuvant endocrine therapy trials as a biomarker of treatment activity and residual risk of relapse and death. In the Immediate Preoperative Anastrozole, Tamoxifen, or Combined Trial (IMPACT) trial, patients treated with anastrozole had a significant suppression of Ki67 level at both 2 and 12 weeks compared with tamoxifen-treated patients. The change of Ki67 levels between pretreatment and on-treatment biopsies predicted the benefit in disease-free survival observed with anastrozole over tamoxifen in the ATAC adjuvant trial (31). A similar outcome prediction was reported for posttreatment Ki67 in the P024 trial, which randomly compared letrozole with tamoxifen (32). On the basis of the accumulated evidence (31–33), the Panel agreed that Ki67 expression measured either after short-term endocrine therapy or at posttreatment residual disease is a valid prognostic parameter and a surrogate parameter of endocrine therapy efficacy when it is performed in a central laboratory by consistent observers and with established consistency. However, the evidence is not strong enough to conclude that early changes of Ki67 can help clinicians in the decision-making process of changing treatment. The ALTERNATE trial, in which Ki67 level at 4 weeks during neoadjuvant endocrine therapy is used to select patients that should continue anastrozole or fulvestrant from those who should switch to chemotherapy, might provide important insight on this topic (34).

The preoperative endocrine prognostic index (PEPI) is a score integrating posttreatment Ki67 with ER status (assessed by Allred score, 0 or 2 vs 3–8), pathological tumor size and nodal status at surgery following 4 months of endocrine therapy. The prognostic role of the PEPI score was assessed in patients enrolled in the P024 trial and then validated in the IMPACT dataset (32). These data notwithstanding, the Panel was not convinced that additional predictive information compared with posttreatment Ki67 alone can be obtained by using the PEPI score. A prospective trial is ongoing to validate PEPI as a prognostic marker after neoadjuvant endocrine therapy. This trial assess whether adjuvant chemotherapy can be spared in patients with PEPI score of 0 after neoadjuvant endocrine therapy based on their excellent prognosis (34).

Ki67 assessed on residual tumor following neoadjuvant chemotherapy is a prognostic parameter (35); however, there was no consensus among panelists as to whether Ki67 assessed after chemotherapy is also a good surrogate of treatment efficacy.

The optimal assessment of residual disease following PST is important in assisting in the surgical management of these patients with breast cancer. The panel agreed that magnetic resonance imaging is the reference imaging technique for the assessment of the extension of residual disease after PST. The diagnostic role of magnetic resonance imaging could be improved by ^{18}fluorodeoxyglucose (FDG) positron emission tomography (36). However, in the Panel's opinion all of the imaging techniques available (ie, mammography, ultrasound, and ^{18}FDG-positron emission tomography) have limitation in predicting the pathological residual disease. As far as the assessment of tumor shrinkage after PST is concerned, the accuracy of magnetic resonance imaging is clearly superior to mammography; however, only a weak superiority over ultrasound and even clinical palpation was reported (37). The use of early evaluation of response (eg, after 1 month or two cycles of treatment) with imaging techniques such as magnetic resonance imaging or FDG-positron emission tomography is currently under investigation in PST setting as a possible early classifier of responders versus nonresponders with subsequent changes in systemic treatment.

Management of Patients After Neoadjuvant Chemotherapy

Some controversy exists about the postsurgical approach in women who have received PST. This is true both for patients achieving a pCR and for those with evidence of residual disease. A valid tool to predict disease recurrence after primary chemotherapy beyond pCR would be helpful in clinical decision making. Residual cancer burden index is a validated predictor of distant relapse in patients with residual tumor in the surgical specimen (38). The pathological variables included in the residual cancer burden index are the bidimensional diameters of the primary tumor bed, the proportion of primary tumor area containing invasive carcinoma, the number of positive lymph nodes, and the diameter of the largest nodal metastasis. Each of these parameters was independently associated with distant disease-free survival in the developmental cohort of 241 patients treated with taxane-anthracycline-based chemotherapy (38). Posttreatment Ki67 can also predict the clinical outcomes after neoadjuvant chemotherapy, particularly in HR-positive disease where the prognostic impact of pCR is limited (35). Although eradication of axillary lymph node metastases with neoadjuvant chemotherapy was reported being associated with improved clinical outcome even in the presence of residual tumor in the breast (39), the Panel believed that residual disease in the breast still had a prognostic relevance.

Recently, a combined analysis of two NSABP trials with a total of 3088 patients showed a lower risk of locoregional recurrence in patients responding to neoadjuvant chemotherapy and not treated with radiotherapy to the chest wall and regional lymph nodes (40). Currently, a prospective randomized trial (NSABP B-51/RTOG 1304) addresses the issue of whether

locoregional radiotherapy improves the clinical outcomes of patients with lymph node-positive breast cancer who become lymph node-negative at surgery after PST (41). Pending these results, the majority of the Panel did not endorse the omission or the limitation of radiotherapy for those women who achieve a pCR after PST.

The Panel was uncertain about the optimal management of patients with triple-negative breast cancer having a residual disease in breast or lymph nodes after a full course of neoadjuvant chemotherapy with regards to further systemic therapy. No recommendations were offered. This unmet clinical need is currently being addressed in a number of prospective clinical trials that are in progress.

Management of Axillary Lymph Nodes

Two important prospective studies assessing the reliability of sentinel lymph node (SLN) surgery after neoadjuvant chemotherapy were published in 2013 (42,43). This approach has the potential advantage of reducing the number of patients who require axillary lymph node dissection and the extent of locoregional radiotherapy in those who are downstaged by PST. The American College of Surgeons Oncology Group (ACSOG) Z1071 trial prospectively assessed the false-negative rate (FNR) of a standardized SLN biopsy procedure in 689 women who converted from clinical node-positive (cN1) to clinical node-negative (cN0) after neoadjuvant chemotherapy. The SLN detection rate was 92.7% (95% CI = 90.5 to 94.6%) and the FNR was 12.5% (95% CI = 9.4 to 16.7%), just above the 10% FNR rate that was selected as the primary endpoint (42). The FNR was lower in patients for whom both blue dye and radiolabeled colloid were used to identify SLN (10.8%), and in patients with more than two SLN identified.

The SENTINA trial enrolled patients with both cN0 and cN1 breast cancer and who were candidates for neoadjuvant chemotherapy. The SLN detection rate was quite high before any PST in cN0 patients (99.1%) and lower in women who converted from cN1 to cN0 (80.1%). In the latter group the FNR was 14.2% (95% CI = 9.9 to 19.4%), a value that is less favorable compared with the FNR reported in patients who undergo primary surgery (43).

In view of these results, most Panelists considered SLN biopsy after neoadjuvant chemotherapy an accurate method of axillary staging, but they suggested the use of dual tracer and the removal at least of two SLNs to minimize the FNR. Conversely, there was no consensus on whether SLN surgery could be avoided in the presence of cytologically positive axillary lymph nodes which become negative after PST.

Conclusions

The neoadjuvant approach offers the opportunity to evaluate new treatment options in a faster way and with fewer patients than large adjuvant trials. New trial designs like window-of-opportunity trials or postneoadjuvant trials provide a platform to identify tumor sensitivity or to overcome tumor resistance at an early tumor stages (44). Results from a recent meta-analysis questioned the value of pCR after PST as a surrogate endpoint of treatment efficacy in patients with “lower-risk” breast cancer (25). This may limit the use of PST in operable breast cancer in routine clinical practice. However, the PST approach is preferred for the management of “higher-risk” triple-negative and HER2-positive breast cancers where residual disease has a more adverse prognosis, and could be advantageous in appropriately selected subgroups of patients.

PST remains a potent model for the evaluation of new agents and the development of early surrogate markers of response are a research priority.

References

1. Berruti A, Brizzi MP, Generali D, et al. Presurgical systemic treatment of nonmetastatic breast cancer: facts and open questions. *Oncologist*. 2008;13(11):1137–1148.
2. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol*. 2012;30(15):1796–1804.
3. Gianni L, Zambetti M, Clark K, et al. Gene expression profiles in paraffin-embedded core biopsy tissue predict response to chemotherapy in women with locally advanced breast cancer. *J Clin Oncol*. 2005;23(29):7265–7277.
4. Sotiriou C, Pusztai L. Gene-expression signatures in breast cancer. *N Engl J Med*. 2009;360(8):790–800.
5. Glück S, de Snoo F, Peeters J, Stork-Sloots L, Somlo G. Molecular subtyping of early-stage breast cancer identifies a group of patients who do not benefit from neoadjuvant chemotherapy. *Breast Cancer Res Treat*. 2013;139(3):759–767.
6. Rouzier R, Perou CM, Symmans WF, et al. Breast cancer molecular subtypes respond differently to preoperative chemotherapy. *Clin Cancer Res*. 2005;11(16):5678–5685.
7. Balmativola D, Marchiò C, Maule M, et al. Pathological non-response to chemotherapy in a neoadjuvant setting of breast cancer: an inter-institutional study. *Breast Cancer Res Treat*. 2014;148(3):511–523.
8. Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. *Ann Oncol*. 2013;24(9):2206–2223.
9. Earl HM, Vallier AL, Hiller L, et al. Effects of the addition of gemcitabine, and paclitaxel-first sequencing, in neoadjuvant sequential epirubicin, cyclophosphamide, and paclitaxel for women with high-risk early breast cancer (Neo-tAnGo): an open-label, 2×2 factorial randomised phase 3 trial. *Lancet Oncol*. 2014;15(2):201–212.
10. Buzdar AU, Suman VJ, Meric-Bernstam F, et al. Fluorouracil, epirubicin, and cyclophosphamide (FEC-75) followed by paclitaxel plus trastuzumab versus paclitaxel plus trastuzumab followed by FEC-75 plus trastuzumab as neoadjuvant treatment for patients with HER2-positive breast cancer (Z1041): a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2013;14(13):1317–1325.
11. von Minckwitz G, Eidtmann H, Rezai M, et al. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. *N Engl J Med*. 2012;366(4):299–309.
12. Bear HD, Tang G, Rastogi P, et al. Bevacizumab added to neoadjuvant chemotherapy for breast cancer. *N Engl J Med*. 2012;366(4):310–320.
13. von Minckwitz G, Loibl S, Untch M, et al. Survival after neoadjuvant chemotherapy with or without bevacizumab or everolimus for HER2-negative primary breast cancer (GBG 44-GeparQuinto)†. *Ann Oncol*. 2014;25(12):2363–2372.
14. von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. *Lancet Oncol*. 2014;15(7):747–756.
15. Sikov WM, Berry DA, Perou CM, et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). *J Clin Oncol*. 2015;33(1):13–21.
16. Moebus V, Jackisch C, Lueck HJ, et al. Intense dose-dense sequential chemotherapy with epirubicin, paclitaxel, and cyclophosphamide compared with conventionally scheduled chemotherapy in high-risk primary breast cancer: mature results of an AGO phase III study. *J Clin Oncol*. 2010;28(17):2874–2880.
17. Martino M, Bottini A, Rosti G, et al. Critical issues on high-dose chemotherapy with autologous hematopoietic progenitor cell transplantation in breast cancer patients. *Expert Opin Biol Ther*. 2012;12(11):1505–1515.
18. Guarneri V, Frassoldati A, Bottini A, et al. Preoperative chemotherapy plus trastuzumab, lapatinib, or both in human epidermal growth factor receptor 2-positive operable breast cancer: results of the randomized phase II CHERLOB study. *J Clin Oncol*. 2012;30(16):1989–1995.
19. Baselga J, Bradbury I, Eidtmann H, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. *Lancet*. 2012;379(9816):633–640.
20. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012;13(1):25–32.
21. Loibl S, von Minckwitz G, Schneeweiss A, et al. PIK3CA mutations are associated with lower rates of pathologic complete response to anti-human epidermal growth factor receptor 2 (her2) therapy in primary HER2-overexpressing breast cancer. *J Clin Oncol*. 2014;32(29):3212–3220.
22. Ollila DW BD, Cirrincione C, Carey LA, et al. Impact of neoadjuvant chemotherapy plus HER2-targeting on breast conservation rates: surgical results from CALGB 40601 (Alliance). *J Clin Oncol*. 2013;31(suppl 15):501.

23. de Azambuja E, Holmes AP, Piccart-Gebhart M, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. *Lancet Oncol*. 2014;15(10):1137–1146.
24. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet*. 2014;384(9938):164–172.
25. Berruti A, Amoroso V, Gallo F, et al. Pathologic complete response as a potential surrogate for the clinical outcome in patients with breast cancer after neoadjuvant therapy: a meta-regression of 29 randomized prospective studies. *J Clin Oncol*. 2014;32(34):3883–3891.
26. Prowell TM, Pazdur R. Pathological complete response and accelerated drug approval in early breast cancer. *N Engl J Med*. 2012;366(26):2438–2441.
27. Buzdar AU, Valero V, Ibrahim NK, et al. Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: an update of the initial randomized study population and data of additional patients treated with the same regimen. *Clin Cancer Res*. 2007;13(1):228–233.
28. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet Oncol*. 2014;15(6):640–647.
29. Montemurro F, Di Cosimo S. Pathological complete response in breast cancer patients receiving neoadjuvant chemotherapy. *Breast*. 2014;23(5):690–691.
30. von Minckwitz G, Blohmer JU, Costa SD, et al. Response-guided neoadjuvant chemotherapy for breast cancer. *J Clin Oncol*. 2013;31(29):3623–3630.
31. Dowsett M, Smith IE, Ebbs SR, et al. Short-term changes in Ki-67 during neoadjuvant treatment of primary breast cancer with anastrozole or tamoxifen alone or combined correlate with recurrence-free survival. *Clin Cancer Res*. 2005;11(2, pt 2):951s–958s.
32. Ellis MJ, Tao Y, Luo J, et al. Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. *J Natl Cancer Inst*. 2008;100(19):1380–1388.
33. Dowsett M, Smith IE, Ebbs SR, et al. Prognostic value of Ki67 expression after short-term presurgical endocrine therapy for primary breast cancer. *J Natl Cancer Inst*. 2007;99(2):167–170.
34. Goncalves R, Ma C, Luo J, Suman V, Ellis MJ. Use of neoadjuvant data to design adjuvant endocrine therapy trials for breast cancer. *Nat Rev Clin Oncol*. 2012;9(4):223–229.
35. von Minckwitz G, Schmitt WD, Loibl S, et al. Ki67 measured after neoadjuvant chemotherapy for primary breast cancer. *Clin Cancer Res*. 2013;19(16):4521–4531.
36. Partridge SC, Vanantwerp RK, Doot RK, et al. Association between serial dynamic contrast-enhanced MRI and dynamic 18F-FDG PET measures in patients undergoing neoadjuvant chemotherapy for locally advanced breast cancer. *J Magn Reson Imaging*. 2010;32(5):1124–1131.
37. Marinovich ML, Houssami N, Macaskill P, et al. Meta-analysis of magnetic resonance imaging in detecting residual breast cancer after neoadjuvant therapy. *J Natl Cancer Inst*. 2013;105(5):321–333.
38. Symmans WF, Peintinger F, Hatzis C, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol*. 2007;25(28):4414–4422.
39. Hennessy BT, Hortobagyi GN, Rouzier R, et al. Outcome after pathologic complete eradication of cytologically proven breast cancer axillary node metastases following primary chemotherapy. *J Clin Oncol*. 2005;23(36):9304–9311.
40. Mamounas EP, Anderson SJ, Dignam JJ, et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. *J Clin Oncol*. 2012;30(32):3960–3966.
41. White J, Mamounas E. Locoregional radiotherapy in patients with breast cancer responding to neoadjuvant chemotherapy: a paradigm for treatment individualization. *J Clin Oncol*. 2014;32(6):494–495.
42. Boughey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA*. 2013;310(14):1455–1461.
43. Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. *Lancet Oncol*. 2013;14(7):609–618.
44. Gampenrieder SP, Rinnerthaler G, Greil R. Neoadjuvant chemotherapy and targeted therapy in breast cancer: past, present, and future. *J Oncol*. 2013;2013:732047.