International expert consensus on primary systemic therapy in the management of early breast cancer. Highlights of the fourth symposium on primary systemic therapy in the management of operable breast cancer, Cremona. Italy, 2010.

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Abstract

A panel of international breast cancer experts formulated a declaration of consensus regarding many key issues in the use of primary systemic treatment (PST) either in clinical routine or research practice.

The attainment of pathological complete response (pCR), defined as no residual invasive tumor in the surgical specimens both in breast and in axillary nodes, is one of the main goals of PST and pCR can be used as the primary objective in prospective clinical trials. However, pCR is not a reliable end-point with all treatment approaches and alternatives such as Ki67 index of the residual invasive disease or after 2 weeks of PST are also potential end points.

PST has several advantages: breast conservation and the unique opportunity to obtain information on the interaction between treatment and tumor biology. Changes in tumor biology after PST are an early phenomenon so an additional core biopsy performed after 14 days from treatment start should be considered in clinical trials.

Introduction

Although neoadjuvant systemic therapy is a widely accepted choice to treat patients with locally advanced and inflammatory breast cancer, the sequence of surgery followed by adjuvant therapy in patients with operable disease is still the usual clinical routine. However primary systemic therapy (PST), i.e. a pre-operative treatment for breast cancer in women with operable disease, has many advantages over adjuvant therapy notwithstanding a major role in clinical research.

In order to clarify the role and setting for PST, during "*The fourth symposium on primary systemic therapy in the management of operable breast cancer*" held from the 26th-28th of September 2010 in Cremona (Italy), a faculty comprising experts in the areas of medical oncology, breast surgery, molecular biology, pathology, radiodiagnostics and radiotherapy 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 Cremona meeting and reflected by votes recorded on specific questions at the conference, and reviewed during the weeks immediately afterwards. The manuscript was subsequently reviewed by all members of the panel. The summary of expert recommendations and relevant level of evidence are outlined in Table 1.

Primary systemic therapy in clinical routine

PST should be considered a standard approach in the management of operable breast cancer in routine practice, due to the identical disease free and overall survival compared with adjuvant therapy in several randomized clinical trials and a meta-analysis (1). Most panellists agreed that PST has limited contraindications, i.e. patients with small tumors with low aggressive features for whom systemic chemotherapy would not be a suitable approach. However, if the pre-treatment

information is sufficient to recommend a systemic approach, there is no risk of overtreatment with PST.

Regarding the diagnosis, core biopsy is considered as the reference standard for obtaining sufficient material for tumor diagnosis, treatment decisions and standard and research biological evaluations. PST has a complete response rate of 20-25% or more and a tumor may completely disappear at clinical and imaging reassessment, generating difficulties in its location by the surgeon and subsequently the pathologist. Since surgery is always required, most panellists recommended marking with a coil on a clip all tumors before PST, as per recently published recommendations (2), while a minority of experts suggest to mark selected tumors only: i.e. those with pre-treatment features predictive for high chance of complete response, such as highly proliferating, grade 3, HER2 positive and/or estrogen receptor negative tumors.

Approximately 2-10% of patients are expected to progress during treatment or immediately afterwards. These patients have the poorest prognosis compared with those attaining a disease response or stabilization but they would not represent a significant limitation of PST, since they would have a poor prognosis even if operated on initially, and this information offers the opportunity to consider additional therapies.

The main goal of PST in the past was to obtain a tumor shrinkage rendering the tumor suitable for a conservative surgical approach. The last “Biedenkopf-” guidelines identified three aims of PST: to improve the surgical options, to determine the treatment response, and to obtain long-term disease-free survival (3).

The panel stated that the attainment of pathological complete response (pCR) is an additional main aim, particularly if chemotherapy is employed. Available data are suggestive that pCR can be considered a parameter of efficacy of primary chemotherapy. Therefore, the majority of panellists did not believe that the absence of validation of pCR as a surrogate end point should represent a hindrance for prescribing PST.

Noteworthy, in the subset of patients for whom a high pCR rate is expected, the panel recommended PST as the preferred option. An update of the NSABP B-18 study (4) showed that, although there were no significant differences in OS or DFS overall, women less than 50 years of age seemed to benefit from preoperative versus postoperative chemotherapy. Since younger women are more likely to have estrogen receptor negative tumors and tend therefore to have a higher pCR rate to chemotherapy than older ones, these data suggest there may be a preferential benefit of PST over adjuvant chemotherapy in women with estrogen receptor negative tumors, although this hypothesis has never been proven in a prospective trial. With regards to biological variables, insufficient data are available to assess the role of gene expression profiles to identify those patients who will obtain a pCR after treatment.

The rate of tumor free axillary nodes after PST ranges between 50 and 80 %. Therefore, in these patients full axillary node dissection can be avoided. On the basis of the results of a recent meta-analysis obtained from published studies (5), sentinel node biopsy (SNB) and subsequent sparing of axillary dissection can be used after PST. As recently pointed out (6), the results of SNB after PST are not substantially different from prior multicentre studies evaluating SNB in patients without PST. These data notwithstanding, some panellists still believe that we should wait the results of prospective studies currently ongoing (7) before introducing this procedure in clinical routine.

As PST is a complex approach and has several challenges, an efficient and well-trained multidisciplinary team (surgeons, medical oncologists, radiologists, radiotherapists, pathologists, molecular oncologists/scientists, nurses and psychologists) should be involved. With these considerations in mind, Breast Units offer the optimal organizational model in this respect. It should be noted, however, that standard international guidelines for a Breast Unit are lacking and the prerequisites are still country specific (8). The question of whether PST should be confined in Breast Units or can be administered in Oncology Units divided the panelists, a half of them were in favor of the Breast Units, and a half were not.

Treatment choice and therapy duration

As is the case for adjuvant therapy, pre-treatment clinical, pathological, and biological markers are crucial in selecting the most appropriate PST regimen. The conventional markers like estrogen and progesterone receptors, HER2 expression and Ki67 still drive the selection of the therapeutic approach. New markers as Tau proteins, CA9, p42/44, MAPK, PI3K/pAKT and p95 tumor expression (9) require additional validation before being adopted into clinical standard routine.

pCR rate varies according to the tumor characteristics and treatment. Patients with estrogen receptor positive disease tend to have a poor pCR rate irrespective of whether they are treated with chemotherapy or endocrine therapy. The criteria to be adopted for choosing endocrine therapy or chemotherapy in PST setting have been discussed elsewhere (10). Whether chemotherapy is more active than endocrine therapy in patients with endocrine responsive disease is a controversial issue. In a small randomised clinical trial, primary chemotherapy failed to show a significantly greater pCR rate than primary endocrine therapy (11). These results notwithstanding, data available are not sufficient to state that chemotherapy and endocrine therapy are equally active as primary systemic approaches in endocrine responsive breast cancer.

With respect to treatment duration, chemotherapy should be administered for at least 6 cycles while the optimal duration of endocrine therapy still remains uncertain. In published prospective clinical trials endocrine therapy has been administered for few months (12), so 4 to 6 months is the length of endocrine therapy that has been recommended (9). Many experts, however, agree that a longer duration of endocrine therapy can potentially lead to greater activity. Thus, the panel was divided in this respect, one half of panellists was in favour of an endocrine therapy of 4-6 months duration, and one half suggested longer than 6 months. Whether pCR is dependent upon the number of chemotherapy cycles still remains controversial, data are in favour of an increasing trend until 6 cycles (13) but this trend does not seem to persist with a further number of chemotherapy cycles (14).

A meta-analysis of 7 German randomised clinical trials suggested that estrogen receptor positive tumors benefit from longer neoadjuvant treatment (15), however most panellists believe that these data are insufficient to state that the length of PST should be modulated according the breast cancer subtypes.

Insufficient data are also available on whether additional chemotherapy is needed after a full treatment of six preoperative cycles followed by surgery in those without pCR, since no randomised trials have addressed this issue. The panel consensus is that no further cycles are needed unless less than 6 cycles were given as PST.

Response definition

Since an important goal of PST is achieving of pCR, a careful definition of pCR is mandatory. On the basis of the results of 2 studies (16,17) showing that residual *in situ* carcinoma do not alter the patient prognosis as opposed to pCR, the majority of panelists believe that *in situ* carcinoma can be included in the definition of pCR (2). More data on this topic are underway from the German neoadjuvant metaanalysis (14, 15). The two possible definitions are i) no residual invasive cancer in the breast and in the axilla or ii) no residual invasive tumor in the breast and in the axilla, but presence of *in situ* carcinoma in the breast (2).

The entire tumor bed removed at surgery should be pathologically examined. The panel considered histology and immunohistochemistry as the best methods for detecting residual disease. In the opinion of many panelists hormone and growth factor receptors should be repeated on any residual tumor in clinical routine, this procedure, however, still remain controversial due to uncertainties about the interpretation of discordant results since no assay is 100% accurate and the absence of demonstrations that further adjuvant therapies should be based on tumor characteristics at residual disease to PST. Residual cancer burden calculated as a continuous index combining pathologic measurements of primary tumor (size and cellularity) and nodal metastases (number and size) was recently found a significant predictor of RFS (18). Thus, quantification of residual disease can be a

further early predictor of treatment efficacy in cases in which a pCR was not attained. Different systems are currently used to categorize the residual disease after PST in breast cancer (19-20) and a prognostic comparison of these classifications on a large number of patients is needed.

Clinical response should be assessed using RECIST criteria. Clinical palpation still remains the reference method in clinical routine practice, sonography is an excellent and reliable technique. Magnetic resonance imaging (MRI) was considered the most accurate method by most panelists. Data are also needed to assess the role of nuclear medicine imaging techniques such as positron emission tomography (PET) in defining response to PST. On the basis of the results of GeparTRIO (14), the panel agreed that clinical and sonographic response can be considered an early predictor of pCR; MRI was the best tool for assessing early clinical response, although this is not recommended in routine clinical practice.

Beyond pCR, the treatment-induced changes in proliferative activity are a promising surrogate parameter of endocrine PST efficacy (21), since pCR is not common in this patient group (12). The majority of panelists agreed that Ki67 expression is the best available marker to assess the changes in proliferative activity after PST. Ki67 assessment is considered a reproducible method whilst the additional role of other proliferative markers such as cyclin D1 and E is uncertain. In the opinion of most panelists, published data are strong enough to state that Ki67 assessed after primary endocrine therapy is a marker of long term clinical outcome and warrants validation as a surrogate end point. Conversely, the question of whether an early increase in Ki67 expression during treatment should be considered a sign of treatment failure that may lead to a change of the therapy has divided the panelists, half of them being uncertain and among those favorable no consensus was obtained about the most appropriate cut-off of increase. This controversial issue needs therefore further studies.

PST in clinical trials

PST is a useful tool in the early development of new drugs to be used in early breast cancer and is the best model to identify oncogenic pathway signatures as a guide to develop new targeted

therapies. In addition, PST offers the unique opportunity to collect tumor samples at diagnosis and after treatment thus allowing acquisition of important information on the interaction between treatment and tumor biology. Changes in tumor biology have been repeatedly found to be an early phenomenon (22,23), in some cases only a few days being long enough to show a significant change, so sample collection at baseline and definitive surgery is no longer considered optimal and at least one additional biopsy is needed in the interval between diagnosis and final surgery. However, no guidelines have been formulated up to now to recommend what is the most appropriate time to perform intermediate biopsies.

Nevertheless, the panel stated that tumor sample collection at baseline, after 14 days and at the end of treatment is the best protocol to be performed in a PST prospective clinical trial. In addition, some panelists suggest flexible evaluations depending on the agent e.g. DNA repair studies would need much shorter time frame. Core biopsies are more reliable also for intermediate biological evaluations.

Since pCR is considered by the panel a surrogate marker of chemotherapy (plus/minus targeted therapy) efficacy, it is a valid primary end-point not only for phase II but also for phase III PST trials.

The identification of early changes in the expression of molecular biomarkers after treatment makes PST the ideal approach for planning the so-called "window of opportunity" studies that have a molecular change as primary end-point. Standard guidelines for study design are required however.

Changes in soluble biomarkers after PST do not provide complementary information with respect to tissue biomarkers. Similarly, circulating tumor cell (CTC) counts and CTC molecular characterization before and after treatment have not provided up to now sufficient data to consider this method useful in the clinical management of patients having PST. Further studies are required to define its role in this setting.

Anti-angiogenic agents are increasingly being employed in PST regimens in prospective clinical trials. However, their role is being debated after concerns were raised regarding anti-angiogenics in

the metastatic setting. Commonly adopted response criteria may not be the best way to monitor the activity of these dugs. Several methods have been proposed and MRI and PET scan have provided the most interesting data. The majority of panelists suggest MRI plus or minus PET scan a useful approach, but a clear consensus to formulate a recommendation was not obtained.

The panel recognized that PST studies are increasing in complexity and there is a need to a dialogue with human ethics committees that will allow more access of clinical samples for research with a view that this approach will lead to more accurate and useful biomarkers to improve patient management.

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Table 1: summary of most relevant recommendations.

Recommendations	*Evidence*
PST is a standard option in the management of breast cancer with operable disease in clinical routine	Superimposable survival of primary versus adjuvant systemic therapy in randomised clinical trials and a meta-analysis
Surgery is always necessary in case of clinical complete response, so the tumor size should be assessed and marker coils or clips used prior to PST	Expert opinion
The few patients who progress after PST do not represent a significant limitation for this approach, because this provides an opportunity to introduce additional therapy	Expert opinion
The attainment of pathological complete response (pCR) is one of the main goals of primary chemotherapy	Expert opinion
Primary chemotherapy should be administered for 6 cycles with current agents	Level 1 a evidence metaanalysis
In the patient subset in which a high pCR rate is expected, PST is the preferred option in clinical routine.	Expert opinion
Residual invasive tumor after chemotherapy has to be removed surgically and the entire tumor bed should be pathologically examined	Expert opinion
Magnetic Resonance Imaging is superior to clinical palpation in defining clinical response	Prospective case series
Ki67 is a good marker available to assess the changes in proliferative activity of hormone receptor positive tumors after primary endocrine treatment.	Expert opinion
Ki67 assessment is reproducible	Expert opinion
Ki67 assessed after endocrine therapy is a marker of long term clinical outcome	Randomized clinical trial in which the prognostic role of Ki67 was a secondary aim
PST is a useful tool in the early development of new drugs to be used in early breast cancer and is the best model to identify oncogenic pathway signatures as a guide to develop new targeted therapies.	Expert opinion
Tumor sample collection at baseline, after 14 days and at the end of treatment is the current optimum protocol to be performed in a PST prospective clinical trial.	Expert opinion
pCR is a valid primary end point for phase II and III PST trials.	Expert opinion
The identification of early changes in the expression of molecular biomarkers after treatment makes PST the ideal approach for planning the so called “window of opportunity” studies that have a molecular change as primary end-point.	Expert opinion

The combination of chemotherapy and targeted agents (monoclonal antibodies, thirosine kinase inhibitors) significantly increases pCR	Prospective randomized trials
There is a significant correlation between pCR and long term outcome for PST with chemotherapy and targeted therapy	Follow up from large randomized trials with chemotherapy and targeted therapy

Abbreviations: PST = Primary Systemic Therapy; pCR = pathological complete response