Primary systemic therapy in patients with breast cancer: rationale of use and magnitude of evidence

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Primary systemic therapy (PST) is considered part of multimodality therapy for locally advanced breast cancer. More recently, it has also been proposed for the treatment of operable disease. Although no randomized clinical trials have shown a clear survival benefit in comparison with postoperative treatment of early stage disease, several advantages may be depicted with the use of PST. This review focuses on the different considerations that have lead to the rising interest in the use of PST in patients with operable breast cancer and reports new advances on this subject. One of the most investigated topics in the treatment of breast cancer concerns the timing of chemotherapy in relation to surgery. Although postoperative (adjuvant) administration of systemic therapy is still the favorite option in the majority of patients with early stage disease, PST (also called neo-adjuvant, preoperative, induction) is increasingly proposed as a valuable alternative. On the contrary, PST is considered part of the standard care for patients with locally advanced breast cancer. This review focuses on the different considerations regarding the use of PST in patients with operable breast cancer reporting, also, new advances on this subject.

Keywords:
chemotherapy; breast cancer; primary systemic therapy

Primary systemic therapy in locally advanced disease

The use of primary systemic therapy (PST) in mostly inoperable locally advanced breast cancer (LABC) was introduced in the 1970s with the aim of improving operability rate and ameliorating the outcome of this subset of patients. At the time of its introduction, the main concern of PST was the risk of disease progression that could result in patients no longer being able to undergo radical surgery. However, initial clinical studies reported a rate of progressive disease of only 2–3% and gradually demonstrated this fear to be unfounded [1]. Conversely, a high percentage (> 70%) of patients with inoperable breast cancer at baseline experienced an objective (partial or complete) response after PST and could reach loco-regional control.

Although PST is viewed as a standard care for patients with LABC, limited scientific evidence is available to support its use. In fact, only small studies by several groups indicated a prognostic benefit in using preoperative chemotherapy (CT) followed by loco-regional treatment (irradiation and/or surgery) [2–6]. In particular, long-term follow-up data on patients with inflammatory breast carcinoma treated at the M.D. Anderson Cancer Center (TX, USA) showed that with a combined modality approach, a significant fraction of patients (28%) remained free of disease beyond 15 years. In contrast, single-modality treatments yielded a disease-free survival (DFS) of less than 5% [2]. Similar results were obtained in patients with inoperable breast cancer with ipsilateral supra-clavicular node involvement [3]. In this subset of patients, multimodality therapy (induction CT, surgery and/or radiation, post-surgery CT) resulted in a DFS of 32% at 10 years [3]. In addition, the overall response rate (partial and complete responses [CRs]) to PST was about 90%.

Moving towards early stage disease

In 1988, based on hypothetical considerations on tumor cell kinetics [7–9], a randomized clinical trial, the National Surgical Adjuvant Breast and Bowel Protcol (NSABP) B-18 was performed in operable patients to address the question of whether preoperative CT might produce better clinical results when compared with the same CT given after surgery [10]. The rationale for PST relied on the model proposed by Goldie and Coldman that hypothesized the existence of a correlation between the increase of tumor cell population and the expanding number of drug-resistant phenotypic variants [7]. In other words, the early commencement of preoperative CT could lead to easier eradication of neoplastic cells. Furthermore, Fisher and colleagues demonstrated in animal models that the removal of a primary tumor stimulated cell growth of a

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Table 1. Operable breast cancer: randomized trials comparing primary systemic therapy and adjuvant systemic therapy.

Trial	No. of patients		Follow-up (years)	CT (preoperative vs. postoperative)	Breast conservation rate (%) (p value)		DFS (%) (p value)		OS (%) (p value)		Ref.
	Pre	*Post*			*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	
Wolmark *et al.* (2001)	760	763	9.5	AC × 4 (both arms)	67	60	55	53	69	70	[11]
					p = 0.002		p = NS		p = NS		
Mauriac *et al.* (1999)	134	138	10	EVM × 3–MTV × 3 (both arms)	45	-	79	81	55	55	[15]
							p = NS		p = NS		
Broet *et al.* (1999)	200	190	8.5	FAC × 4 (both arms)	-	-	-	-	65	60	[16]
									p = NS		
Van der Hage *et al.* (2001)	350	348	4.5	FEC × 4 (both arms)	37	21	65	70	82	84	[12]
							p = NS		p = NS		
Jakesz *et al.* (2001)	214	209	4	CMF × 3–surg–CMF × 3 (N-) or EC × 4 (N+) vs. surg–CMF × 3–CMF × 3 (N-) or EC × 4 (N+)	67	60	-	-	66	59	[62]
										p = NS	
Gianni *et al.* (2002)	270	622	2	AT–CMF (both arms)	71	35	-	-	-	-	[35]
					p < 0.0001						
Makris *et al.* (1998)	157	152	4	3M/Tam × 4–surg–3M/Tam × 4 vs.surg–3M/Tam × 8	78	89	82	80	78	78	[17]
					p = 0.0004		p = NS		p = NS		

3M: Mitoxantrone, methotrexate, mitomycin; AC: Doxorubicin, cyclophosphamide; AT: Doxorubicin, paclitaxel; C; Tam: Tamoxifen; CMF: Cyclophosphamide, methotrexate, fluorouracil; EC: Epirubicine, cyclophosphamide; EVM: Epirubicine, vincristine, methotrexate; FAC: Fluorouracil, doxorubicin, cyclophosphamide; FEC: Fluorouracil, epirubicine, cyclophosphamide; MTV: Mitomycin C, thiotepa, vindesine; NS: Not significant.

secondary tumor and that this effect could be avoided by the administration of preoperative CT [9]. The NSABP B-18 trial randomized 1523 patients with operable breast cancer (T1-3 N0-1 M0) to receive either four preoperative cycles of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 (AC) or the same CT given after surgery [10]. Results of this trial updated at 9 years of follow-up did not show any significant difference in overall survival (OS) or DFS between the two treatment arms (**Table 1**) [11]. Although these findings contradicted the Goldie–Coldman hypothesis and were initially interpreted as negative, the absence of detrimental effects of PST made this approach feasible and safe as an alternative to adjuvant CT for women with early stage disease. Importantly, the NSABP B-18 trial reported no statistically significant differences between PST and adjuvant CT in the rates of treatment failure at any specific site. Also, a higher rate of breast conserving surgery was observed in patients receiving PST (p = 0.002). In addition, this landmark study was the first to demonstrate an association between observed tumor shrinkage and outcome (DFS and OS). Based on this observation, clinical and pathological response rates to PST are now proposed as surrogate end points to predict long-term survival. In fact, if confirmed by other trials, this could represent an added value of PST, in particular, the response of the primary tumor might be used to test the benefit of new treatments on an individual basis.

Another important study from the European Organization for Research and Treatment of

Cancer (EORTC) randomized 698 patients with operable breast cancer to receive four cycles of fluorouracil, epirubicin and cyclophosphamide either pre- or postoperatively [12]. At a median follow-up of 56 months, no significant difference in terms of survival was observed. However, in a subgroup analysis, clinical node negative patients showed better OS and progression-free survival in the postoperative arm.

Among other randomized clinical trials that tested the effectiveness of PST (**Table 1**), two smaller French studies reported an initial survival advantage for PST [13,14]. However, both these trials had a biased design with imbalances in local as well as in systemic therapy between preoperative and postoperative groups, and therefore could not allow an adequate comparison. In addition, for both these trials the advantage in OS was lost with longer follow-up [15,16], suggesting that PST could delay early death rates without significantly modifying long-term outcome.

Another important trial that provided results similar to NSABP B-18 compared four cycles of preoperative chemo-endocrine treatment (a combination of mitoxantrone and methotrexate ± mitomycin-C and tamoxifen) followed by surgery and then by another four cycles of the same therapy versus all eight cycles of therapy given postoperatively [17]. No statistically significant differences between PST and adjuvant groups were observed in terms of local relapse rate, DFS, or OS.

In summary, no evidence exists indicating any advantage of PST on survival. On the contrary, almost all trials resulted in a statistically significant higher rate of breast conservation among patients that received preoperative CT [18]. A greater use of conservative surgery is usually associated with a small and often not statistically significant, increase in rate of ipsilateral tumor recurrence. This is mainly associated with nodal involvement at diagnosis, minimal tumor shrinkage after PST and multifocal pattern of residual disease [19]. On the other hand, recent trials with new taxane-containing regimens showed an opposite scenario with higher local relapse rate in patients who received postoperative CT [20]. On the basis of the above-mentioned considerations, PST should be proposed to every woman who, although initially a candidate to receive radical mastectomy, desires to have a chance of less extensive surgery. Clearly, PST should not be proposed in cases of *a priori* contraindications for conservative surgery, such as multicentric disease, extensive microcalcifications throughout the breast and coexisting medical conditions that may predispose to radiotherapy injuries.

Presently, there is no recommended regimen for PST and the choice of agents, number of cycles and schedules of treatment are mainly based on results obtained in the adjuvant setting. For example, the knowledge that four cycles of anthracycline-based therapy could be a suboptimal treatment for node-positive patients, as well as the evidence of a clinical benefit with the addition of taxanes can not be ignored in the preoperative setting. In fact, although preliminary and based on observations on surrogate end points, these findings have also been observed in patients who received PST. In particular, either a longer treatment duration or the addition of taxanes resulted in a higher rate of pathological complete response (pCR), the main candidate as a surrogate marker of long-term survival [21–25]. According to these remarks, one proposed option is to start with a short anthracycline-based therapy and to tailor the additional treatment on the basis of the obtained response (i.e., additional cycles of the same therapy in responding patients or the use of potentially noncross-resistant regimens in nonresponders). However, this is an important open issue that merits further investigation in future large trials.

Therefore, although the patient should be informed about the absence of evidence of a survival benefit, advantages related to improvement of operability and to the availability of an *in vivo* test of chemosensitivity deserve to be discussed. In fact, the use of PST as a clinical research model alternative to trials in the adjuvant setting demonstrates several advantages [26]. First, PST allows the tumor size to be readily monitored while the patient is undergoing treatment (*in vivo* measure of chemosensitivity). Second, potential molecular tumor and/or patient discriminants could be identified and correlated with tumor response to therapy. Taken together, these benefits may be translated in time sparing (few months vs. years) and sample size reduction (hundreds vs. thousands of patients) in the conduction of clinical trials regarding anticancer agents (**Table 2**).

To date, several questions remain regarding the best treatment for patients with early operable breast cancer [27,28]. These especially concern the role of taxanes, the importance of therapy duration and the value of dose density.

Specific trials exploring these topics were recently published whereas others are still ongoing. We report below the main studies, using them as examples to emphasize the different

Table 2. Advantages of primary systemic therapy versus adjuvant therapy as a clinical research model.

	Primary systemic therapy	Adjuvant therapy
Sample size required	Hundreds of patients	Thousands of patients
Time to results	Few years (with the use of surrogate end points)	An average of 10 years
Evaluation of response	Possible	Impossible
Translational research	Feasible	Difficult

approaches used in PST trials compared with trials of adjuvant therapy.

What is the benefit of using taxanes?

In the adjuvant setting, four randomized clinical trials have been reported regarding the addition of taxanes to anthracycline-based regimens [29–32]. Among them, two have examined four courses of paclitaxel after four cycles of AC [29,31], with CALGB 9344 showing a survival benefit at 5.5 years of follow-up (risk reduction: 18%) [29]. Unfortunately, these trials have some drawbacks in their design, such as the imbalance between treatment arms with regard to duration (four vs. eight cycles), the choice of a 'weak' reference arm (four cycles of AC), the concomitant use of tamoxifen and the absence of a prospective stratification for hormonal receptor status [27,28].

The Breast Cancer International Reserach Group (BCIRG) 001 trial compared a taxane–anthracycline combination (TAC) regimen (docetaxel, doxorubicin, cyclophosphamide) with the widely used standard regimen of 5-fluorouracil, doxorubicin and cyclophosphamide, known as FAC. A recent update of the study was presented at the 2003 San Antonio Breast Cancer Symposium [32]. After a median follow-up of 55 months, DFS and OS advantages were seen with the taxane-based therapy. Although these findings are encouraging and support the use of taxanes as a reasonable therapeutic option in the adjuvant setting, mature data with longer follow-up of these and other trials are awaited to draw definitive conclusions about this topic.

In the meantime, results coming from studies of PST are providing further interesting infomation on the value of taxane-based therapy for the treatment of early stage (operable) breast carcinoma (**Table 3**).

The NSABP B-27 trial assigned patients to receive either four cycles of AC followed by surgery, or four cycles of AC followed by four cycles of docetaxel and then surgery, or four cycles of AC followed by surgery and four cycles of adjuvant docetaxel. Preliminary results indicated that the sequential use of docetaxel after AC provided a significantly higher complete clinical response rate (63.6 vs. 40.1%, $p < 0.001$) and pCR rate (26.1 vs. 13.7%) compared with AC only [25]. No statistically significant increase in breast conservation rate was observed with the addition of preoperative docetaxel (63.7 vs. 61.6%, $p = 0.33$) but this finding was not surprising given the high clinical response rate (85%) obtained after four cycles of AC.

The benefit obtained with the addition of docetaxel was paid with some increase in toxicity (febrile neutropenia: 21 vs. 7%).

As the data on DFS and OS will mature, the NSABP B-27 trial is expected to provide important information about the prognostic value of giving further therapy (docetaxel) to specific subgroups of patients, such as those experiencing a response to preoperative therapy.

Although not yet formally published, similar results to those of the NSABP B-27 were observed in the German Pre-operative Adriamycin Docetaxel (GEPARDUO) trial where the sequential 24-week schedule of AC followed by docetaxel (the same regimen of the NSABP B-27 trial) provided a pCR rate of 22.4% with a breast conservation rate of 74.9% [33].

Another study by the Aberdeen Breast Group randomized patients who had obtained a clinical CR or a clinical partial response after four cycles of CVAP (cyclophosphamide 1000 mg/m^2, vincristine 1.5 mg/m^2, doxorubicin 50 mg/m^2, prednisolone 40 mg for 5 days) to receive either four additional cycles of CVAP or four additional cycles of docetaxel 100 mg/m^2 [34]. All nonresponders to initial CVAP were treated with four additional cycles of docetaxel. In total, 162 patients were enrolled and about 65% experienced a response after four cycles of CVAP. The patients who were randomized to receive four additional cycles of docetaxel showed a higher objective response rate (85 vs. 64%, $p = 0.03$)

Table 3. Selected randomized clinical trials with taxane-based primary systemic therapy.

Study	Taxane-based PST	Breast conservation rate	pCR rate	Ref.
NSABP-B-27	AC × 4–Docetaxel 100 mg/m^2 x 4	63.7%	26.1%	[24]
GEPARDUO	AC × 4–Docetaxel 100 mg/m^2 x 4	74.9%	22.4%	[32]
Aberdeen Breast Group	CVAP x 4–Docetaxel 100 mg/m^2 × 4	67%	31%	[33]
ECTO	A 60 mg/m^2, P 200 mg/m^2 x 4–CMF × 4	71%	23%	[34]

AC: Doxorubicin and cyclophosphamide; CVAP: Cyclophosphamide, vincristine, doxorubicin, prednisolone; A: Doxorubicin (adriamycin); P: Paclitaxel; CMF: Cyclophosphamide, methotrexate, 5-fluorouracil.

and a higher pCR rate (31 vs. 15%, p = 0.06) than those randomized to further four cycles of CVAP (intention to treat analysis). On the other hand, the nonresponders to initial cycles of CVAP obtained a final clinical response rate of 46% after treatment with docetaxel. After a follow-up of 5 years, a statistically significant advantage was observed in terms of OS (93 vs. 78%) in favor of patients randomized to receive docetaxel. Based on the results of the Aberdeen Breast Group study, the sequential addition of docetaxel seems to be clinically valuable in responders as well as nonresponders to previous anthracycline-based therapy. Moreover, these findings support the hypothesis that the addition of the taxane and not the duration of CT is of major importance in determining a therapeutic benefit.

Among the studies evaluating the role of paclitaxel in the PST setting, the trial known as European Cooperative Trial in Operable Breast Cancer (ECTO) randomized 1355 women with primary tumor (T) > 2 cm breast cancer to adjuvant doxorubicin (A, 75 mg/m^2 every 21 days [Q21] x 4) followed by intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) x 4, or adjuvant doxorubicin (60 mg/m^2) and paclitaxel (200 mg/m^2 over 3 h Q21d x 4) followed by CMF (AT-CMF), or preoperative AT-CMF [35]. Preliminary results on 892 evaluable patients were presented in abstract form and showed a statistically significant increase in conservative surgery after PST (71 vs. 35%, p < 0.0001). CT was well-tolerated and rarely caused febrile neutropenia (A-CMF: 5%; AT-CMF: 9%).

An interesting recently published Phase II trial was conducted in patients with HER-2 positive Stage II/III breast cancer [36]. Forty patients received PST sequentially with trastuzumab (4 mg/kg x 1, then 2 mg/kg/wk x 11) in combination with paclitaxel (175 mg/m^2 every 3 weeks × 4), followed by breast surgery and then four cycles of AC. A pCR rate of 18% was observed. The treatment was feasible and no patients developed symptomatic heart failure. This pilot study also showed that up-front therapy with trastuzumab and paclitaxel is possible before anthracycline-based therapy, providing an alternative to the ongoing trials in which the sequence anthracyclines followed by trastuzumab is adopted as adjuvant therapy. In turn, earlier administration of trastuzumab for early stage breast disease could be expected to provide more benefits as demonstrated in the advanced setting [37,38].

What about dose-density?

One of the strategies to achieve a greater response to anticancer therapy is by increasing the dose-density. It has been shown that a given dose of CT always kills a certain fraction of exponentially growing cells. Based on the Norton and Simon model of cancer growth [39], it has been hypothesized that more frequent administration of CT could be more effective in minimizing tumor regrowth between two cycles.

Recently, Citron and colleagues demonstrated that dose-dense postoperative CT significantly prolongs DFS and OS in operable, node positive breast cancer [40].

Similarly, the dose-dense approach has been investigated in the neoadjuvant setting. In a European Organization for Research and Treatment of Cancer, National Cancer Institute of Canada and Swiss Group for Clinical Cancer Research (EORTC-NCIC-SAKK) Phase III trial [41], patients (n = 448) with LABC were randomized to receive 6 preoperative courses of

either CEF (cyclophosphamide 75 mg/m^2 orally days 1 to 14; epirubicin 60 mg/m^2 days 1 and 8; fluorouracil 500 mg/m^2 days 1,8 and Q28d) or dose-dense epirubicin (120 mg/m^2); cyclophosphamide (830 mg/m^2 on day 1 followed by Q14d) (EC) with granulocyte-colony stimulating factor (G-CSF). After a median follow-up of 5.5 years no significant differences were seen in PFS (34 vs. 33.7 months in CEF and EC group respectively) and OS (5-years survival rate of 53 and 51% in CEF and EC group respectively).

In another trial [42], patients with LABC (n = 150) received 3 courses of induction FEC (fluorouracil 600 mg/m^2, epirubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2 day 1) followed by local therapy and subsequent adjuvant CT with one course of FEC in alternation with one course of CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, fluorouracil 600 mg/m^2 day 1) for a total of six courses. They were randomized to receive CT either every 3 weeks (conventional schedule) or every 2 weeks (dose-dense schedule). No differences in terms of pCR rates, of 5 years DFS nor of OS were observed.

In the GEPARDUO randomized trial [33], 4 courses of preoperative dose-dense AT (doxorubicin 50 mg/m^2, docetaxel 75 mg/m^2 Q2 weeks with G-CSF) were compared with eight courses of sequential AC–T (four cycles of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 Q3 weeks followed by four cycles of docetaxel 100 mg/m^2 Q3 weeks) in stage II–III breast cancer patients (n = 913). pCR was significantly higher in the sequential, nondose-dense arm (22.4 vs. 11.5%). It should be noted that the treatment period is shorter (8 weeks vs. 24 weeks) and the cumulative dose of doxorubicin and docetaxel is lower (200 mg/m^2 vs. 240 mg/m^2 and 300 mg/m^2 vs. 400 mg/m^2 respectively) in the dose-dense arm.

Overall, these studies do not show a superiority for the dose-dense approach. However, accelerated schedules provide the opportunity of integrating sequential regimens in a reasonable duration of preoperative treatment.

Importance of assessing response

Conventionally, the assessment of tumor response after PST is made by documenting pathological changes in the neoplastic mass and lymph nodes. However, such changes are only apparent at the end of the entire program of planned CT.

Instead, it seems crucial during the administration of PST to accurately assess tumor response. Intermediate evaluation could lead to early discontinuation of an ineffective regimen and could potentially predict a final response to PST. Moreover, preoperative assessment is fundamental to plan a conservative surgical treatment. The pathological measurement of tumor diameter in surgical sample is considered the gold standard with which to compare the accuracy of clinical and radiological assessments.

Detection of residual tumoral mass by means of mammography (Mx), ultrasound (Us) or physical examination is probably limited by the development of CT-induced fibrosis and regressive changes that hamper the ability to precisely determine the border between neoplastic and normal tissue. Magnetic resonance imaging (MRI) is expected to offer a more accurate measure since it is based not only on morphological features but also on characteristics of contrast enhancement.

Davis and colleagues compared the accuracy of MRI, Us and Mx for measuring the largest diameter of residual tumor after PST with respect to pathological evaluation. MRI showed the highest correlation coefficient with pathological measure (r = 0.98), while Mx and Us reported a correlation coefficient of 0.46 and 0.47 respectively [43]. Similarly, Weatherall and colleagues showed that MRI correlates to histological measurements better than Mx and physical examination (r = 0.93 vs. 0.63 vs. 0.72 respectively) [44]. In another small study by Rosen and colleagues, MRI was superior to physical examination (r = 0.75 vs. r = 0.61) although the difference was not statistically significant [45].

In contrast with previously reported favorable results, Rieber and colleagues demonstrated that MRI is unreliable in determining the size of residual tumor [46]. Interestingly, early size reduction analyzed by MRI after the first CT course predicts response to PST [47]. However, the CT-induced regressive changes also decrease the MRI precision, and in fact the highest correlation between MRI and histological measurements has been reported in cases of either no response or pCR [48].

An additional promising method to assess therapeutic response at an earlier stage in the preoperative treatment regimen is positron emission tomography (PET). In particular, PET is a functional imaging technique that allows the evaluation of *in vivo* cellular glycolysis by

labelled glucose analogue [18F]-fluorodeoxy-D-glucose ([18F]-FDG). In practice, a decline in the tumor glucose metabolism (i.e., reduction in the rate of [18F]-FDG uptake) has been observed to be associated with a higher probability of pathological cancer response to a variety of CT agents [49,50]. However, although the use of [18F]-FDG PET seems to be worthwhile in the early prediction of response to PST, some studies were not able to validate this approach [51]. Additional studies with adequate sample size are therefore needed.

Treatment with PST can result in a broad spectrum of histopathological modifications in tumor mass, ranging from complete disappearance of carcinoma to no change. Between these extremes there are different markers of antiblastic exposure. Essentially, there may be evidence of macroscopic or only microscopic neoplastic tissue. In addition, fibrosis (resembling scar tissue) and cytonuclear changes may be the features of drug-induced regressive changes.

Several different scores have been proposed to report pathological response after PST [52–54]. In order to compare the results of different studies, mainly in the field of translational research, homogeneous methods for pathological response evaluation should be considered.

As previously discussed, pCR to PST is now considered a strong predictor of long-term outcome [11,55]. Several biological markers have been investigated as potential predictive factors of pCR. In particular, absence of hormone receptors in pre-treatment neoplastic samples has been associated with a higher rate of pCR [56,57]. In addition, among the other tumor characteristics, high histological grade and Ki-67 expression have been reported to correlate with pCR rate [56,58].

Highlights

- No evidence by randomized clinical trials exists about superiority or inferiority of primary systemic therapy versus adjuvant therapy in terms of disease-free survival or overall survival for patients with early stage breast cancer.
- Primary systemic therapy is a valuable alternative to adjuvant therapy for breast cancer patients who desire to have more chances of breast conservation surgery.
- No standard regimens of primary systemic therapy exist but recommended therapy should include anthracyclines and/or taxanes for at least four to six cycles.
- Primary systemic therapy is a valuable clinical model to test new anticancer agents or regimens.
- Pathological complete response (CR) rate is expected to be used as a surrogate end point in substitution of long-term survival.
- Recent studies with the sequential use of anthracyclines and taxanes provided the highest rate of pathological CR.

Expert opinion

In summary, several trials are published and others are ongoing regarding the use of PST in early stage breast cancer patients. Caution is needed in comparing results of these studies because of confounding factors, such as differences in patient populations, initial tumor burden, duration of therapy, definition of pathological response and concomitant use of CT and hormonal therapy.

Nonetheless, most of the recent trials reported a high rate of pCR after treatment with sequence or a combination of anthracyclines and taxanes. If the pCR rate is confirmed to be a reliable predictor of survival, long-term results of these trials should demonstrate an important clinical benefit.

In addition, if the above assumption is correct, PST may be expected to become the best and fastest clinical model to test novel agents or regimens in patients with breast cancer.

Finally, pre-treatment sampling of the primary tumor for new molecular technology (i.e., gene expression or proteomic analysis) could identify more precocious predictors of response to PST [59–61], providing a very useful guide for therapy selection on an individual basis.

Five-year view

The next 5 years will hopefully answer several open questions about PST for breast cancer. The long-term data of NSABP B-27, GEPAR-DUO, and ECTO trial will clarify the role of taxanes in PST. In addition, the issue of the optimal schedule of PST will also be addressed.

The novel biological molecules are expected to be integrated in PST regimens in order to test their efficacy for the treatment of early breast cancer. The translational research in PST trials and the introduction of modern molecular technologies such as proteomics or genomics, will provide interesting opportunities to identify new predictive and prognostic factors. This will help to tailor the best regimen for the individual patient.

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