Primary systemic therapy in operable breast cancer: clinical data and biological fall-out

M. Maur, V. Guarneri, A. Frassoldati & P. F. Conte*

Department of Oncology and Haematology, University of Modena and Reggio Emilia, Modena, Italy

Primary systemic chemotherapy (PST) was first used in early 1970s for the treatment of locally advanced breast cancer; in this setting primary chemotherapy was administered to allow for radical surgery and the objective response rates were high with a substantial proportion of patients amenable to surgery. On the basis of this activity, PST was subsequently used to treat operable locally advanced or large primary tumors to increase the rate of conservative surgery. First generation clinical trials demonstrated that breast conservation rates were improved, that a proportion of patients experienced a complete pathologic response and that response to PST was a good predictor of long term outcome. Second generation of clinical trials were designed to compare PST to postoperative adjuvant chemotherapy: here again the rate of conservative surgery was significantly improved and the pathologic response rate demonstrated its prognostic value, however no progression free or survival improvement was obtained in comparison with postoperative treatments. Another interesting observation from these trials was that some tumor parameters (histology, grade, hormone receptor status) can predict the likelihood of achieving a pathologic complete response. On the basis of these data, PST can now be considered the standard of care for locally advanced disease, an reasonable option in case of large primary breast tumors not eligible for conservative surgery and an acceptable alternative for all the patients who are candidate to adjuvant treatment. It however clear that PST represents an excellent in vivo model to test new regimens, to evaluate biomarkers with predictive value and to evaluate the treatment induced modifications in tumor biology. Availability of new technologies able to measure the expression of thousands of genes and of new molecularly directed drugs will increase further the interest in this treatment strategy.

Key words: primary systemic therapy, breast conserving surgery, pathological complete response, biomarkers

Introduction

Primary chemotherapy represents the standard treatment in patients with locally advanced breast cancer (LABC), however lessons from trials in LABC have generated interest in the potential use of this approach in earlier stage operable disease [1–3]. Primary systemic therapy (PST) was first introduced into clinical practice in 1970s for non operable and/or inflammatory breast cancers, for operable large breast tumors (T > 5 cm) in the 1980s and for operable small breast cancer (T > 2 cm) more recently [4].

The main aims of PST were to achieve operability in LABC, to improve the breast conservation rate in operable breast disease, and to test the in vivo tumor chemosensitivity and, hopefully, to choose better adjuvant sequential chemotherapy. Moreover, clinical trials demonstrated that PST is an interesting research tool which allows investigators to test new drugs and/or new schedules with a validated surrogate end-point (pathologic complete response, pCR), and represents an ideal model to evaluate the relationships between treatments and tumor biomarkers.

More recently, hormonal treatment has also produced interesting results in the neoadjuvant setting in postmenopausal women with hormonal receptors positive tumors.

Breast conservative surgery: the first goal

Numerous investigators have demonstrated that the rate of BCS is significantly higher in patients treated with PST compared to those who received adjuvant chemotherapy, moreover the risk of ipsilateral recurrence is not increased, while survival is at least as good with neoadjuvant as with postoperative chemotherapy. Non randomised series demonstrated overall response rates from 69%–100%, pathological complete response (pCR) around 10–15 % and high rates of breast conservation ranging from 5% to 36% [5–11].

Several randomized trials comparing PST or different PST regimens and postoperative adjuvant systemic therapy (AST) have confirmed these observations. Makris [12] and colleagues from Royal Marsden Hospital, conducted a randomized trial with eight cycles of mitoxantrone, methotrexate, mitomycin...
plus tamoxifen administered before or after surgery. This trial for the first time demonstrated the 'downstaging' role of PST, with a reduction in the mastectomy rate from 22% to 10% ($P < 0.003$). Luporsi et al. randomized 90 patients with operable breast cancer to six preoperative cycles of FEC100 or ED (epidoxorubicin 100 mg/m$^2$ – docetaxel 75 mg/m$^2$) with a BCS rate of 83% [13]. Mauriac et al. randomized 272 breast cancer patients to receive six courses of pre-operative chemotherapy (3 courses epirubicin, methotrexate, vincristine followed by 3 courses of mitomycin-C, thiopepa and vindesine) versus the same regimen given as adjuvant therapy. Sixty-three per cent of patients treated with PST benefited from BCS, although this rate decreased to 45% after a median follow-up of 124 months [14].

Scholl et al. randomized 414 patients to receive four or six courses of FAC followed by radiotherapy and surgery or radiotherapy followed by surgery and four courses of the same adjuvant chemotherapy. Similar long term BCS rates were reported [8].

Bonadonna et al. reported a down-staging to less than 2 cm in size in patients with T2–T3 breast cancer treated with three cycles of anthracycline-based neoadjuvant chemotherapy; with BCS rate of 85% (Michelangelo Cooperative Group) [15].

In the EORTC 10902 trial 698 patients with T1c–T4b breast cancer were randomized to four courses of FEC (fluorouracil, epirubicin, cyclophosphamide) before or after surgery. As many as 37% of the patients were down-staged by PST and treated with BCS[5]. In the NSABP-B18 study 1523 patients with T1-3, N0-1 breast cancer were randomized to receive four courses of anthracycline and cyclophosphamide (AC) before or after surgery, and more patients benefited from BCS in PST arm (67.8% versus 59.8%). Interestingly, in this trial ipsilateral breast cancer recurrences rate was twice as great in the preoperative group (14.5% vs. 6.9%, $P = 0.04$); however, when down-staged patients only are analysed, the difference was not statistically significant (7.9% vs. 5.8%, $P = 0.23$). The size of primary tumor and quality of clinical response (complete, partial or minor) correlate with the rate of successful BCS. In the B-18 trial, the patients who received PST may improve their chance for breast conservation by 12.5% if the tumor size is 2 to 5 cm, and by 17.5% if the tumor size is more than 5 cm [16]. The local recurrence rate was as low as 5.6% among patients who achieved a complete clinical response while it was 9.7% among those who did not achieved a complete clinical response. These data support the hypothesis that a poor response to PST is a predictor of poor prognosis and implies a high risk of recurrence irrespective of type of surgery performed.

The ECTO study is a three-arm randomized trial to evaluate the role of paclitaxel in combination with anthracycline in early breast cancer and the role of PST in improving BCS rates. Patients with breast tumor measuring more than 2 cm in size were randomized to receive four cycles of either adjuvant doxorubicin followed by four courses of CMF (A→CMF), adjuvant doxorubicin-paclitaxel followed by CMF (AP→CMF), or preoperative AP→CMF. Axillary clearance and BCS rates were significantly better in PST arm (71% versus 35%, $P = 0.0001$) and 61% versus 38% ($P = 0.0001$) respectively [7].

Jakesz et al. reported a four-year results of Austrian Breast and Colorectal Cancer Study Group (ABCSD) in which more than four hundred patients with T1-3, No-2 breast tumors were randomized to receive four courses of FAC as neoadjuvant or post-operative chemotherapy. A rate of BCS of 66% was reported in PST arm [8].

As in the adjuvant setting where four courses of anthracycline based-chemotherapy are considered an inferior treatment for node positive breast cancer patients, there is an increasing evidence that the use of taxanes in PST provides additional advantages [10, 17–21].

In a recently published meta-analysis, Mauri and co-workers [22] found that PST was associated with an increased risk of loco-regional recurrences (RR = 1.22); this was particularly evident in those trials where, in the neoadjuvant arm, more patients received radiotherapy without surgery (RR = 1.53). An important heterogeneity was observed in the rates of conservative treatment (range 28–89%) after PST. No clear association between the risk of loco-regional recurrences and the use of breast-conserving surgery was found in this analysis.

Based on these data, a slightly increased risk of local relapse after a prolonged follow up in downstaged patients treated with BCS cannot be excluded even if others studies have not raised this issue [13, 23–25]. However, BCS can not be denied to these women and this risk can be minimised with adequate adjuvant hormonal therapy, radiation treatment, and total tumor resection with appropriate margins. Among these high risk populations, young patients with hormone-unresponsive disease, need a close clinical follow up.

A recent trial has shown that, in postmenopausal women with estrogen-receptor (ER) positive breast cancer, four months of preoperative letrozole was more effective than tamoxifen in terms of objective responses and rate of BCS [26]. In the IMPACT trial, 330 postmenopausal women were randomized to receive preoperative tamoxifen, anastrozole or the combination of both. There were no significant differences in OR between the three arms however, among patients requiring mastectomy at baseline, 44% received BCS after anastrozole compared with 31% of patients after tamoxifen. Moreover anastrozole seemed to be more active than tamoxifen in HER-2 positive tumors: the objective response rate was 58% for anastrozole compared with 22% for tamoxifen ($P = 0.10$) [27].

**primary versus post-operative treatments: same efficacy but possibility to identify who benefit. pCR as a surrogate end-point of survival**

In the second generation trials, the main objective was to compare the PST to classical adjuvant chemotherapy in terms of disease free survival (DFS) and overall survival (OS). The clinical complete responses (cCR) ranged from 6.6% to 33%, while non significant differences in DFS and OS were observed [8, 9, 13, 28]. The first two studies, published by Mauriac [14] and Scholl [8], reported a significant benefit of PST on DFS and OS but, after a longer follow up, this survival advantage had disappeared. These preliminary exciting results were the basis for the subsequent trials. Bonadonna et al. [15] reported their large experience in a series of 536 patients with tumors > 2.5 cm, treated in two prospective non-randomized trials: 8-year DFS and OS (54% and 69% respectively) were comparable to
historical adjuvant chemotherapy controls. The ABCSG Trial 07 [8] was a comparison between a pre and post-operative ‘sandwich’ therapy and adjuvant chemotherapy alone. After preoperative CMF OR and pCR were 69% and 6%, respectively, with more BCS being performed in this arm. With a follow-up of 4 years RFS was significantly worse in the ‘sandwich’ arm, although OS were similar. In the NSABP-B18 study, overall response, cCR and pCR were 80%, 36% and 9% respectively; no significant difference was reported in OS (80% versus 79.6%) and DFS (67% versus 66%); it was also demonstrated that the achievement of a pathologic response in the breast was a predictive factor for disease-free and overall survival [6]. In the EORTC 10902 trial overall response, cCR and pCR were 49%, 7% and 4% respectively. At a median follow up of 56 months, there was no significant difference in terms of OS (82% in PST group and 84% in the postoperative arm, HR 1.16, P = 0.38) [9]. Recently the Royal Marsden Hospital has reported that good clinical responders (patients with cCR or residual thickening only) achieve superior overall survival at 10 years compared to poor clinical responders [29].

All these data indicate that the quality of clinical and pathological response is an important prognostic factor. The early assessment of response might provide useful information on primary treatment resistance, but the optimal method to assess response to neoadjuvant chemotherapy is unclear. The only parameter consistently related with survival is the pCR rate which is however a relatively late finding. Many different grading system for pathological response have been proposed. The NSABP evaluates response in the breast only and pCR is defined as no invasive tumor in the breast independently from the nodal status [6]. On the contrary, the M. D. Anderson group requires the absence of invasive tumor both in breast and axillary lymph nodes to define a pCR [30]. The most stringent definition of pCR, including no viable infiltrating cancer cells in the breast plus negative axillary nodes, provides a better discrimination. In fact several trials have demonstrated a better DFS and OS in patients who obtained an axillary pCR, in comparison to those who did not achieve this status, irrespectively of the response in the breast [23, 30–37].

### pCR rates with different chemotherapy regimens

Depending on the chemotherapy regimen and the schedules used, the objective response rates can be as high as 70–90%, with up to 20–40% of the patients having a complete clinical remission [38, 39]. The number of chemotherapy courses may have a significant impact in the neoadjuvant setting. Reitsamer et al. [40] conducted a randomized study to compare 3 cycles of epipodophyllotoxin/docetaxel to 6 cycles of the same regimen prior to surgery in forty-five stage II and III breast cancer patients. A pCR was achieved in 10% and 36% of the patients after 3 or 6 cycles respectively (P = 0.045). In the ECTO study the complete CR rate was 27% after four courses of AP (doxorubicin/paclitaxel) and increased to 52% after four CMF courses [7]. Similarly Roumieu and coworkers reported better pCRs and RRs with six versus four preoperative cycles of AP (24% versus 17%; 32% versus 20%) [41].

Another important advance to improve the pCR rates is the addition of taxanes to anthracycline-based chemotherapy. An increase in clinical responses and/or pCR rates has been reported in several trials with the addition of taxanes [13, 20, 22, 42–46, 66] (Table 1).

Our group has evaluated the impact of a dose-dense chemotherapy on pCR rate in patients with locally advanced breast cancer (LABC) treated with a combined modality therapy. A total of 150 patients with stage IIIA/IIIB breast disease were randomized to receive three courses of induction chemotherapy and three courses of adjuvant chemotherapy every three weeks or every two weeks with G-CSF support. No difference in clinical (62.3% versus 61.6%) and pCR rates (2.6% versus 4.1%) after induction chemotherapy were observed between the two arms; however accelerated chemotherapy reduced the duration of the combined-modality program (6.1 versus 4.6 months) with no additional toxicities [2].

More recently, other trials have investigated the role of dose-dense regimens. The AGO group randomized 631 patients to either four courses of epirubicin-paclitaxel every three weeks or biweekly epirubicin for three cycles followed by biweekly paclitaxel with G-CSF support. Preliminary data showed a improved pCR rate in the intensive arm (18% versus 10%, P = 0.03) [18]. The GEPARDUO study compared an anthracycline-cyclophosphamide regimen followed by docetaxel (ACx4 followed by D×4) with a dose-dense biweekly AD with G-CSF support for four cycles; higher pCR rates were seen in the sequential arm (22.4% versus 11%, P < 0.001) [46]. At present, in spite of the promising results, the dose-intensified schedules cannot be considered standard treatment and further investigations should be encouraged particularly in patients with aggressive tumors.

### Table 1. Anthracycline versus anthracycline+taxane-based regimens: response rate and pCR

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Regimen</th>
<th>RR%</th>
<th>pCR%</th>
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<tbody>
<tr>
<td>Luporsi et al.</td>
<td>90</td>
<td>6 FEC100 vs. 6 Epi/docetaxel</td>
<td>72 vs. 84</td>
<td>24 vs. 24</td>
</tr>
<tr>
<td>Diers et al.</td>
<td>247</td>
<td>4 AC vs. 4 AP</td>
<td>83 vs. 66</td>
<td>16 vs. 10</td>
</tr>
<tr>
<td>Buzdar et al.</td>
<td>147</td>
<td>4 FAC vs. 4 P</td>
<td>79 vs. 80</td>
<td>17 vs. 8</td>
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<td></td>
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<td>(P = NS)</td>
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<tr>
<td>Semiglazov et al.</td>
<td>103</td>
<td>4 FAC vs. 4 AP</td>
<td>82 vs. 84</td>
<td>9.6 vs. 25 (P = 0.003)</td>
</tr>
<tr>
<td>Heys et al.</td>
<td>162</td>
<td>8 CVAP vs. 4 CVAP + 4 D</td>
<td>64 vs. 94 (P &lt; 0.002)</td>
<td>16 vs. 34 (P = 0.04)</td>
</tr>
<tr>
<td>NSABP B-27</td>
<td>2411</td>
<td>4 AC vs. 4 AC + 4 D</td>
<td>40 vs. 63.6 (P &lt; 0.001)</td>
<td>13.7 vs. 26.1 (P &lt; 0.001)</td>
</tr>
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Another interesting strategy is the sequential administration of active agents versus concomitant treatments. Green and co-workers have shown a higher response rate using weekly paclitaxel rather than a 3-weekly schedule followed by four cycles of FAC [47].

**pCR: beyond anthracycline-taxanes**

The incorporation of new cytotoxic agents might further improve the activity of anthra and/or taxane based PST. Several phase II trials have evaluated gemcitabine-containing doublets or triple regimens with promising clinical and pathological response rates and manageable toxicities. Gomez et al. reported a high response rate (overall OR 95%, cCR 18%) with moderate hematological and non-hematological toxicity using the combination of gemcitabine (1200 mg/m²) given on day 1 and 8 and doxorubicin (60 mg/m²) on day 1 [48].

More recently, we have shown that the combination of gemcitabine plus epirubicin and taxol (GET) is feasible and extremely active in metastatic breast cancer [49, 50]. Based on the high overall and complete response rates obtained with this regimen, we have designed a phase II trial to evaluate the activity of GET as PST in operable breast cancer. Forty-three patients with stage II–III A breast cancer were treated with gemcitabine 1000 mg/m² on days 1 and 4, epirubicin 90 mg/m² on day 1 and taxol 175 1000 mg/m² as a 3-h infusion on day 1 every 21 days for six cycles. The overall clinical response was 87.8%, with 26.8% complete responses. A pCR in the breast was observed in six patients (14.6%); 15 patients (36.6%) had negative axillary lymph nodes [51]. Schmid and co-workers recently reported the results of a phase II trial with gemcitabine, non-pegylated liposomal doxorubicin (NPDL) and docetaxel in early breast cancer patients. Forty-four patients with stage II or III breast cancer were treated with NPDL (60 mg/m²) and docetaxel (75 mg/m²) on day 1 and gemcitabine as 4-h infusion (350 mg/m²) on day 4. Treatment was repeated every 3 weeks for a maximum of 6 cycles. All patients received recombinant granulocyte colony-stimulating factor. The clinical response rate was 80%; BCS was performed in 19 out of 20 patients with a initial tumor size of less than 3 cm and in 14 patients (70%) with a tumor size ≥ 3 cm. Seven patients had histologically-confirmed complete response (pCR 17.5%). A grade 3–4 neutropenia occurred in 61% and a grade 3–4 non-hematological toxicity in 10% of patients respectively [52]. Estevez et al. published preliminary results of a phase II and pharmacogenomic study on biweekly docetaxel (65 mg/m²) and gemcitabine (2500 mg/m²) as neoadjuvant chemotherapy in stage II and III breast cancer patients; chemotherapy was administered every two weeks for six cycles; prophylaxis with growth factors was allowed. After surgery patients received four courses of AC. A cDNA microarray study was performed to correlate pre-treatment gene expression profile with clinical and pathological responses. The overall RR was 79%, with six complete responses and one pCR. Breast conservative surgery was performed in 61% of patients. Grade 3–4 neutropenia was observed in 11% of cycles [53]. Schneeweiss and others reported results of a phase I/II study of gemcitabine/epirubicin/docetaxel (GEDoc), with prophylactic filgrastim in 77 patients. Dose-limiting toxicities were grade 3 febrile neutropenia and grade 3 diarrhea at the fourth dose level of GEDoc tested (gemcitabine 800 mg/m² day 1 and 8, epirubicin 90 mg/m² day 1 and docetaxel 75 mg/m² day 1). As assessed by ultrasound, overall 92% of patients responded (26% complete response), and 79% of patients received breast-conserving surgery; the pathological complete response rate was 26% [54].

**PST: not only chemotherapy**

A part from chemotherapy, PST is the ideal setting to test targeted drugs because of the availability of tumor tissue before, during and after treatment. Primary trastuzumab-based therapy has been evaluated in pilot studies for HER2 over-expressing stage II or III breast cancer in combination with non-doxorubicin-containing regimens; in these studies, pCR rates have ranged from 19% to 35% [55–60]. Buzdar et al. [61] have recently published results of a randomized trial in HER2 positive operable breast cancer: forty-two patients were randomly assigned to either four cycles of paclitaxel followed by four cycles of fluorouracil, epirubicin, and cyclophosphamide or to the same chemotherapy with simultaneous weekly trastuzumab for 24 weeks. pCR rates were 25% and 66.7% for chemotherapy and trastuzumab plus chemotherapy respectively (P = 0.02). After 34 patients had completed therapy, the trial’s Data Monitoring Committee stopped the trial because of superiority of trastuzumab plus chemotherapy. The safety of this approach is not fully established, however no clinical congestive failure was observed.

**PST: an in vivo model to incorporate biomarkers in the decision making process**

PST offers the possibility to perform biological studies on the primary tumor and to better understand mechanism of response and chemoresistance. Many predictive factors of response have been studied and several authors have reported that hormone receptor negativity, high histological grade and ki-67 levels correlate with pCR, while the predictive value of HER2 expression, bcl-2 and p53 status is still unclear [30, 62–71]. Mathieu et al. [65] demonstrated that the poor responsiveness of lobular breast carcinoma (ILC) to PST may be explained by its biological profile. ILC was an independent predictor of a poor clinical response: histological and biological factors predicting a lower pCR (histological grade, ER, Ki67 and p53 status) are more frequent in ILC than in infiltrating ductal carcinoma (IDC). In the EORTC 10994 trial the predictive value of p53 was assessed in patients with breast cancer randomised to two neoadjuvant anthracycline-based regimens with different dose-intensities. In the multivariate analysis, p53 positivity was associated with a shorter progression free survival (HR=1.96, P = 0.0008) and a shorter OS (HR 0.54, P = 0.0045) [67]. Billgren and co-workers [68] reported a lower risk of progression after a 25% decrease of Ki-67 after PST (recurrences 21% versus 65%; P = 0.003). Faneyte [69] has recently reported that response to PST is predicted by tumor size, estrogen receptor status, proliferation index, and p53 status. The same findings were shown by Burcombe et al. [70]. A total of 118 patients with
T2-4, N0-1 primary breast cancer received six cycles of anthracycline-based PST. Diagnostic biopsies and post-chemotherapy surgical specimens were stained for ER, PgR, HER-2 and Ki 67. Clinical, radiological and pathological response rates were 78.7% and 38% (pCR 8%) respectively. Median Ki-67 index was 24.9% before and 18.1% after treatment (P = 0.02); the median reduction in Ki-67 index after treatment was 21.2%. Tumors displaying >75% reduction in Ki-67 after chemotherapy were more likely to achieve a pathological response (77.8% versus 26.7%, P = 0.004). We have previously reported in locally advanced breast cancer studies that inhibition of tumor proliferation after PST predicts a better outcome [3]. Recently, we have reported that the expression of hormonal receptor status and nuclear grading were not modified by chemotherapy. A statistically significant difference between Mib-1 at baseline and at definitive surgery was observed: Mib-1 ≥ 20% in 71.4% of the patients versus 28.6% at surgery (P < 0.05). Her-2 neu expression was also modified by chemotherapy even if the difference was not significant (21% versus 10.5%) [51]. Petit et al. reported a comparative value of tumor grade, hormonal receptors (HR), Ki-67, HER-2 and topoisomerase II alpha status as predictive markers in breast cancer patients treated with neoadjuvant anthracycline-based chemotherapy. In the multivariate analysis, the absence of HR expression and Ki-67 ≥ 20% were predictive for a clinical complete response. A high tumor grade was a predictive for a pCR. Overexpression or amplification of HER2 or Topoisomerase II alpha were not predictive of response [71]. NSABP-B27 is attempting to assess the changes in tumor biomarker expression (estrogen and progesterone receptors, proliferation markers, p53, bcl-2, HER2/neu oncoprotein etc.) and whether these variations can be correlate with tumor response and long-term outcome.

Novel technologies such as gene profiling and proteomics may improve our understanding of response and resistance, and hopefully, by identifying who will respond, will allow a tailored PST. Some groups have recently demonstrated that the response to neoadjuvant chemotherapy results in alterations in gene expression [72–74].

In conclusion, PST has now an established role in the management of locally advanced and operable breast cancer. Ongoing trials will answer a number of important questions such as the best regimen, the potential survival benefit for subgroups of patients, the optimal loco-regional treatment (surgery followed by radiotherapy or radiotherapy alone etc.), the possibility to administer postoperative adjuvant therapies tailored on the observed response in neoadjuvant setting.

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references


