Neoadjuvant chemotherapy in breast cancer

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A CLINICAL EXAMPLE

A 25-year old female came to our Service referred from her surgeon with a diagnosis of breast cancer. Two weeks earlier she had noticed a 5-cm palpable tumor within the upper quadrant of her right breast. An abnormal finding was observed in the mammogram and a biopsy diagnosed invasive breast carcinoma. The surgeon had recommended radical mastectomy, but he explained the patient that she might conserve her breast by using chemotherapy as a first option. We also urged her to consider additional advantages of beginning her treatment with chemotherapy: downstaging the tumor so as to avoid mastectomy, allowing breast conservation, and rapidly assessing the tumor sensitivity to chemotherapy within 4-5 months. The patient accepted the suggestions and received chemotherapy with anthracyclines and taxanes. At the end of the chemotherapy courses, no breast lesion was found in a physical and radiological examination, and breast-conserving surgery with axillary dissection was performed. The patient completed treatment with local radiotherapy. Today, after 4 years of follow-up, this woman is free of disease and healthy.

This is a common situation in women with large breast cancers. Mastectomy is often the only option that is offered to women with large operable tumors, in contrast with women with smaller breast cancers, who are offered breast conservation. Since the loss of a breast is an emotionally disturbing and difficult circumstance for most women, the clinical objective is directed to avoiding unnecessary disfigurement, and maintaining self-esteem, therefore improving the quality of life. This goal can be achieved by reducing tumor size with preoperative chemotherapy, which is delivered before local treatment such as surgery or radiotherapy. This form of treatment is usually referred to as neoadjuvant, preoperative or primary systemic chemotherapy. A panel of international experts recently recommended the term “primary systemic therapy” (PST) instead of neoadjuvant, preoperative or induction therapy because “it takes into account the order of administration, intended subsequent treatment, and efficacy of the systemic intervention”. This review will focus on neoadjuvant chemotherapy, and I will use the term primary systemic chemotherapy (PSC).

INTRODUCTION

PSC was first introduced for patients with inflammatory and locally advanced breast cancer (LABC). The finding that some cases of breast cancer are best treated initially with nonsurgical therapy may be attributed to Haagensen and Stout, who found that patients with any of the following clinical signs had a poor prognosis: extensive edema of the skin, satellite nodules in the skin over the breast, intercostal or parasternal nodules, edema of the arm, proven supravacuicular metastases, or inflammatory-type carcinoma. Initially, these tumors were treated conventionally with radiotherapy and/or surgery, which achieved an optimal local control but eventually resulted in the development of metastatic disease. The first report was prepared by De Lena and colleagues in 1978 as part of a multidisciplinary approach proposed by the Milan Cancer Institute for stage III disease, and reported an overall response rate of 85% with a combination of doxorubicin and vincristine in 152 patients.

WHICH ARE THE ADVANTAGES OF PRIMARY SYSTEMIC CHEMOTHERAPY?

Our first task in the management of the young woman with a breast carcinoma is to explain her that she can be equally treated by either one of two options that differ mainly in the therapeutic sequence. These are either surgery followed by systemic treatment, or with PSC followed by surgery. It is crucial to highlight to the patient that both overall survival (OS) and disease-free survival (DFS) are equivalent in the two options, as has been shown in several randomized trials that compared PSC followed by surgery and surgical resection followed by adjuvant chemotherapy. The largest of these trials is the National Survey Adjuvant Breast and Bowel Project (NSABP-B18), which randomized 1,523 patients with stage I-III breast cancer to receive 4 cycles of standard AC (doxorubicin and cyclophosphamide) given as PSC or adjuvant chemotherapy. No significant differences between groups were found for DFS and OS after a median follow-up of 5 years.

The aims of PSC also need to be singled out to patients. The primary objective is tumor downstaging in order to allow a better cosmetic result in patients who are candidates to breast conservation at the time of diagno-
sis, but also in patients who would otherwise undergo mastectomy due to initial larger tumors. An additional objective is the assessment of tumor sensitivity to chemotherapy within a short period of time (usually 4-5 months) that is much shorter than a follow-up period of at least 5 years required after adjuvant chemotherapy. PSC, like postoperative chemotherapy, has the potential of removing micrometastases and reducing the emergence of drug-resistant mutations.

A potential disadvantage of PSC is the loss of the prognostic information generated by the pathological tumor size and nodal status. However, a retrospective study from the MD Anderson Cancer Center showed that the pathologic nodal status after PSC can be used as a prognostic marker of long-term outcome. Recently, two important multicenter phase III trials have shown the benefits of adding taxanes to anthracycline-containing regimens in node-positive breast cancer patients. If this is confirmed in ongoing trials with node negative tumors, the loss of this prognostic information when patients receive PSC will not be important because all patients with early breast cancer will be treated with taxanes and anthracyclines.

WHAT IS THE ROLE OF PRIMARY SYSTEMIC CHEMOTHERAPY IN INOPERABLE BREAST CANCER?

Inoperable breast cancer is usually defined as a tumor that may not be removed with surgery as a first-line treatment option. These tumors are generally described as stage IIIIB in the TNM classification, and include tumors from the T4 class, any N classes, M0, and any T class with N3. In addition, although N2 tumors can be surgically removed at the time of diagnosis, this is not done in general.

Initial trials of PSC were conducted in stage III breast carcinoma, which includes both operable (IIIA) and inoperable tumors (IIIB). In almost every report, most patients achieved significant shrinkage of the primary tumor and axillary nodes (60% to 80%) in. However, the percentages of operability after PSC in IIIB tumors are usually not reported. In most of these trials, the authors reported the feasibility and safety of breast conservation for locally advanced breast cancer (IIIA) after PSC, which varied markedly between institutions (27% to 90%). It is very unusual to find a trial where PSC is only applied to patients with stage IIIB tumors.

WHAT IS THE ROLE OF PRIMARY SYSTEMIC CHEMOTHERAPY IN OPERABLE BREAST CANCER?

The use of PSC has been progressively extended to stage I and II breast cancers. The majority of phase III trials of PSC in operable breast cancer included stage I-III tumors, and therefore their results are sometimes difficult to interpret. Therefore, many authors describe the median tumor size, the tumor range and the clinical nodal status (palpable or non-palpable nodes) at the time of diagnosis in order to provide a better approach to the clinical characteristics of the whole population. The success in treating tumors with a median size of 4.5 cm is different from that found with larger tumors (for example, a median tumor size of 7 cm), since smaller lesions are more likely to shrink than large tumors.

The impact of PSC on breast conservation for patients with small operable breast cancer is likely to be small. Morrow et al reviewed 356 stage I and II breast cancer patients treated between 1988 and 1993. In this retrospective study, the addition of PSC to the treatment slightly increased the optimal breast conservation rate from 77.5% to 81%. In the NSABP B-18 study, the breast conservation surgery rate increased by an absolute percentage of 8% with PSC (60% to 68%) of. Nevertheless, PSC has had an impact on the management of operable disease. Besides improving cosmetic results, PSC allows the assessment of tumor response to treatment. If the tumor does not respond to a specific regimen, appropriate changes can be introduced in the chemotherapeutic regimen. Monitoring response to PSC can also be a challenge. Chemotherapy-induced fibrosis is difficult to differentiate from residual tumor, and clinical measurements may be inaccurate. This is a problem often found with smaller tumors. At the present, no radiological tools have been shown more accurate than others for differentiating residual tumors.

WHAT IS THE ROLE OF PATHOLOGIC COMPLETE RESPONSE?

Clinical response is often selected as the primary endpoint in PSC, but pathologic complete response (pCR) should possibly be the main goal, since this is a more accurate predictor of improved outcome and prolonged survival of an individual patient. The best survival rates are observed in patients with complete eradication of tumor in both the breast and axillary lymph nodes and the best regimen should achieve the highest rate of tumor eradication in both sites.

A known problem found in trials with PSC is that several divergent classification systems for pathologic results are used. In my opinion, the most complete pathologic evaluation of response is that prepared by Miller and Payne, since it considers pathologic remission in both the breast and axillary lymph nodes, and differentiates true negative nodes from those that were initially positive but later responded to PSC.
WHAT IS THE ROLE OF PREDICTIVE FACTORS FOR RESPONSE TO PRIMARY SYSTEMIC CHEMOTHERAPY?

One of the advantages of PSC is the access to tumor specimen before chemotherapy through biopsy or trucut in order to determine biological markers such as hormonal receptors, Her2 receptor, proliferation index and p53 expression. These specific biological markers need to be correlated with response to treatment in order to be able to identify a series of tumors with a high probability of responding to a specific regimen and thus be cured. However, these findings are not definitive, as the trial results have proven inconclusive and often contradictory; this may be due to several factors related to trial design (e.g., retrospective studies, heterogeneous population, the use of different assays and regimens, and the fact that biological markers need to be correlated with response to treatment).
markers are sometimes correlated to pCR and other times to clinical response) (table 1). Recently, microarray studies are beginning to identify a group of genes correlated with the best response to treatment\(^ {56,57}\).

**WHAT IS THE ROLE OF TAXANES IN PRIMARY SYSTEMIC CHEMOTHERAPY?**

The introduction of taxanes has had a great impact on the management of breast cancer during the last decade. Taxanes induce cytotoxicity through tubulin stabilization and cell cycle arrest, and they also promote apoptosis and inhibit angiogenesis\(^ {36}\). Docetaxel and paclitaxel are related but not identical drugs. For example, docetaxel has a longer plasma half-life and longer intracellular retention time compared with paclitaxel. In addition, docetaxel is a more powerful tubulin assembly promoter and microtubule stabilizer. Taxanes also differ in doses and dosage schedule. An anthracycline regimen such as AC, FEC or FAC generally achieved pCR rates of 9% to 13%\(^ {5-7}\). The taxanes have allowed to go beyond this range, and this is very relevant due to the better outcome of patients with no evidence of disease in breast and axilla at the time of definitive surgery.

The rationale for combining a taxane and an anthracycline is based on the efficacy of both drugs alone, not on any evidence for preclinical synergy. Therefore, the aim is to determine the most effective combination therapy. Several phase II trials have been conducted with combinations of either docetaxel or paclitaxel with an anthracycline as PSC (tables 2 and 3).

**Paclitaxel plus anthracycline trials**

To date, only one randomized study reported as abstract evaluated the addition of paclitaxel to an anthracycline-containing regimen\(^ {51}\). This phase II trial included 105 patients with locally advanced breast carcinoma and gave them 4 cycles of doxorubicin 60 mg/m\(^2\) plus paclitaxel 200 mg/m\(^2\) every 5 weeks, or 4 cycles of standard FAC (fluorouracil 600 mg/m\(^2\), doxorubicin 60 mg/m\(^2\), cyclophosphamide 600 mg/m\(^2\)) every 3 weeks. The preliminary results reported in 2002 at the SABCS identified a trend towards a higher overall clinical response with the doxorubicin-paclitaxel regimen (84% versus 75%). However, a statistically improved pCR was found with the combination arm compared with FAC (25% versus 10%; p=0.005). Other randomized trials administered paclitaxel in both treatment arms, and hence the results concerning the benefits of adding a taxane to anthracylines were more inconclusive. An innovative phase III trial by Green compared 5-weekly versus weekly paclitaxel regimen followed by 4 cycles of FAC as PSC in stage I-III breast cancer patients\(^ {52}\). The paclitaxel doses were higher in patients with positive palpable nodes. In summary, the rates of pCR improved significantly in patients receiving the weekly regimen compared with patients receiving standard 5-weekly treatment (28% versus 14%; p<0.01). The ECTO (European Cooperative Trial in Operable Breast Cancer) is an ongoing randomized trial\(^ {29}\) that includes two arms with coadjuvant chemotherapy and a third arm with AT (doxorubicin 60 mg/m\(^2\) plus paclitaxel 200 mg/m\(^2\) every 3 weeks) followed by sequential CMF every 4 weeks for 4 cycles. Preliminary results in 270 patients receiving PSC showed a pCR of 23%. The only factors predictive of pCR by multivariate analysis were absence of estrogenic receptor expression.

But, in order to ensure that the addition of a taxane increased pCR compared to an ACR (anthracycline-containing regimen), the design of this randomized trial should include a control arm with anthracyclines and a study arm with the combination. The only two trials with this design used docetaxel as taxane\(^ {53,54}\).

**Docetaxel plus anthracycline trials**

The NSABP B27 study\(^ {55}\) is the largest and most complete trial evaluating the role of sequential docetaxel following standard AC in patients with stage I-III breast carcinoma. The patients included were randomized to one of the following groups:

1. Four cycles of AC (doxorubicin 60 mg/m\(^2\) plus cyclophosphamide 600 mg/m\(^2\)) every three cycles.
2. Four cycles of AC followed by 4 cycles of docetaxel 100 mg/m\(^2\) every three weeks.
3. Four cycles of AC followed by surgery and then 4 cycles of docetaxel 100 mg/m\(^2\) every three weeks as coadjuvant chemotherapy.

The primary objectives of NSABP B27 included DFS and OS. The preliminary results were presented at the San Antonio Breast Cancer Symposium in 2001 and published in rapid report format at the Journal of Clinical Oncology 2005. A total of 2,500 patients were enrolled in the trial, and most of them (70%) were node-negative at the time of diagnosis. In patients who received AC followed by docetaxel as PSC, the overall response rate was 90% compared to 85% in patients with AC alone. The pCR in the breast was 26% in the sequential arm and 14% in the group with AC (p<0.001). Overall 41% of patients in the sequential arm had histologically positive nodes after PSC compared to 49% in the AC group. However, a longer follow-up period is necessary to confirm whether the addition of docetaxel further improved DFS and OS.

An important caveat of this trial is that the advantage of the sequential arm may be due to differences in the number of administered cycles (4 in the AC arm and 8 in the sequential arm) and not due the addition of
docetaxel *per se*. Fortunately, this question may be answered by the phase III Aberdeen trial. This is a very important trial that assesses the benefits of sequential docetaxel after an anthracycline-containing regimen. Its interesting design included three arms. Stage I-III breast cancer patients initially received 4 cycles of CVAP (cyclophosphamide, vincristine, doxorubicin, and prednisonone) every 5 weeks and were then clinically evaluated:

1) Patients responding to CVAP were randomized to receive 4 additional cycles of CVAP or 4 cycles of docetaxel 100 mg/m² every 5 weeks.
2) Non-responding patients received 4 cycles of docetaxel 100 mg/m² every 5 weeks.

Clinical response in the Aberdeen trial was again assessed at the end of cycles and prior to definitive surgery. From July 1996 to March 1999, 162 patients were included in the trial. The median tumor size was 4.9 cm and 64% of patients were negative for palpable nodes. The overall clinical response was 66% in the 162 patients after the first 4 CVAP cycles. The most relevant results were significant improvements in both overall clinical response rate and pCR with sequential docetaxel compared with patients receiving 8 CVAP cycles (94% versus 66%; *p*=0.001 and 15% versus 50.8%; *p*=0.04, respectively). The pCR value was again referred to pathologic results in the breast only. The locally metastatic tumor in the involved axillary nodes of randomized patients with docetaxel had a similar rate of pathologic response (15% versus 14%) compared to patients with 8 cycles of CVAP. An important conclusion from this trial was that tumors showing a reduction in size after 4 cycles of an anthracycline-containing regimen (i.e., complete or partial response) did not benefit from additional cycles of the same regimen. In fact, these tumors could be better treated by shifting to a non-cross-resistant regimen or drug such as docetaxel.

**CONTROVERSIES CONCERNING THE USE OF PRIMARY SYSTEMIC CHEMOTHERAPY**

There are many unanswered questions on the use of PSC in breast cancer. From my point of view, the most important are the following:

1) What is the correct number of cycles? The results suggest that the more cycles are administered, the higher is the rate of pCR achieved. Most recent large-scale trials are using 6 or 8 cycles and are achieving better results than historic controls.

2) How can we ensure clinical response to treatment? Physical examination is the first approach in the evaluation of tumor response, but its accuracy is low. Two thirds of patients with clinical complete response have residual microscopic disease at the time of definitive surgery. Several trials evaluating the role of RNM and PET in PSC are ongoing.

3) What is the role of sentinel lymph node biopsy after PSC? Experience with this technique has shown that the main predictor of success with the procedure is the surgeon’s experience with the technique. Some trials have evaluated the role of sentinel lymph node in PSC, with controversial results. The problem is that PSC may cause disappearance or regression of metastatic disease in some nodes (e.g., sentinel lymph nodes) but not in others. Additional trials are needed to answer the ongoing controversy regarding optimal treatment for sentinel lymph node after PSC.

**CONCLUSIONS**

Taking into account what we presently know about neoadjuvant chemotherapy in breast cancer, the following conclusions may be drawn:

The use of PSC is increasing, but some women still undergo mastectomy recommended by the surgeon. Many of these women might wish to avoid mastectomy, and this may be possible using primary systemic chemotherapy. The use of PSC provides the opportunity for breast conservation and thus improves the patients’ quality of life. Women with breast cancer should be aware of the two options currently available for treating this disease: surgery followed by adjuvant chemotherapy or PSC followed by surgery. These options have similar DFS and OS. By knowing the advantages and disadvantages of these two alternatives, breast cancer patients may have a chance of conserving their breasts.

The main goal of neoadjuvant trials should be a complete pathologic response rather than a complete clinical response. This pCR has to be evaluated by a universal pathologic classification and, at the present time, the most complete one is the Miller and Payne classification.

With regard to the best chemotherapy regimen, anthracycline-containing regimens followed by sequential docetaxel has shown to be the most effective regimen. This has been proven in the largest and best designed neoadjuvant trials. Finally, non-cross resistant chemotherapy regimens should be offered in the adjuvant setting to improve clinical outcome.
References


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