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MINIREVIEW

Past, present and future of primary systemic treatment in breast cancer

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Abstract

Primary systemic treatment is a fundamental part of breast cancer therapy, and it is applied to non-surgical and locally advanced tumours as well as surgical tumours to increase the likelihood of conservative treatment. Its aim is to achieve the best possible survival with better cosmetic results and with the lowest number of treatment-related secondary effects. Before treatment is started, it is necessary to attain the best knowledge of the biological features and locoregional extension of the tumour. To do so, it is necessary to obtain a biopsy of the lesion with a wide bore needle, as well as good radiological knowledge of the disease. Therefore, currently, the use of a dynamic magnetic resonance imaging (MRI) of the breast should be included in all cases. In addition, before it is started, especially in those tumours in which conservative treatment is considered, one or several radiopaque markers should be put into place to make it possible to locate the area to be treated if there is a considerable or complete response. Systemic treatment is mainly based on combined chemotherapy with anthracyclins and taxanes, in addition to some biological agents with demonstrated efficiency for increasing the likelihood of complete disease response (trastuzumab in patients with Her-2/neu overexpression). However, there is room for neoadjuvant hormone treatment, in patients with hormone receptor overexpression, especially in those cases in which chemotherapy is contraindicated as well as in elderly patients with a relatively short life expectancy. The assessment of preoperative treatment should be based on adequate radiological tests, and nowad these should include MRI before taking decisions about adequate surgical treatment. The objective of primary treatment is to be able to increase survival and improve the chances of local treatment in the case of locally advanced treatment, achieving results that are at least equal to those of adjuvant treatment in the case of surgical tumours, but with greater chances of conservative surgery. Although the objective is survival, achieving complete pathological response seems to be a reasonable related objective, although these are more closely linked in some tumour subtypes.

Key words: Breast cancer; Breast carcinoma; Primary systemic therapy; Neoadjuvant chemotherapy; Neoadjuvant therapy

Core tip: Primary systemic treatment is a fundamental part of breast cancer therapy, and it is applied to non-surgical and locally advanced tumours as well as surgical tumours to increase the likelihood of conservative treatment. As in any kind of tumour, an attempt should be made to include these patients in clinical trials to allow us to define the best and earliest individualised treatment strategy for our patients.

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INTRODUCTION

In the specific case of breast cancer, two overriding theories of the biological behaviour of tumors in terms of their mechanisms of metastatic dissemination have predominated over the past two centuries, paving the way for two opposing paradigms: Halsted's mechanistic theory and Fisher's systemic theory. However, observations and evidence from subsequent studies have revealed that an intermediate theory, Hellman's spectrum theory, is more realistic and accounts for the differences observed in different kinds of scenarios[1].

In light of this historical background, the treatment of most malignant tumours is complex and requires interdisciplinary teams of physicians who are specialists in various fields working holistically to control them.

Therefore, breast cancer should be considered as a systemic disease in order to achieve optimal management outcomes, at least from a conceptual point of view. This should be the case even when cancer is theoretically confined to this organ (localized breast cancer) and requires local and systemic treatment for its control.

Systemic adjuvant treatment (hormone therapy, chemotherapy, immunotherapy, biological therapy against a specific molecular target), used to control micrometastatic disease after curative intent surgery, has been proven to reduce recurrence risk by 0.77 and breast cancer mortality by 0.83[2]. This benefit has been attained, although to a varying degree, regardless of axillary lymph node infiltration, the state of the hormonal receptors, the histological subtype, the level of tumour differentiation, or the expression of other predictive response factors (Her-2/neu).

However, for some patients adjuvant treatment is not the best approach and the use of neoadjuvant chemotherapy (primary or preoperative) is preferred before the local treatment of the disease.

Consequently, neoadjuvant treatment has transformed from a treatment for patients with locally advanced breast cancer (making surgery more likely in tumours in which local treatment with curative intent could not be guaranteed), into the treatment used in initially surgical tumours to enable conservative breast surgery. Taking into account that neoadjuvant and adjuvant chemotherapy provide similar benefits in terms of overall and disease-free survival in operable tumours[3], neoadjuvant treatment is currently providing a greater knowledge of the *in vivo* effects of modern treatment options in tumours prior to surgery.

PRELIMINARY TERMINOLOGICAL CONSIDERATIONS

From chemotherapy to systemic therapy

Classically, the systemic cancer treatment was based on the use of chemotherapy, that is, medication against neoplastic tissues with greater or lesser sensitivity and specificity, which directly influences the real achilles heel of this treatment: morbidity associated with the secondary effects of the toxicity of non neoplastic cells and tissues. Nowad, other modalities must be considered which are not related to classical chemotherapy. This is the situation with hormone therapy, which has a fundamental role in the specific case of breast cancer, or with the application of molecular-targeted therapies, through monoclonal antibodies, or immune tolerance induction (or suppression) therapies through vaccines or antibodies. These therapies try to increase effectiveness against different types of cancers by attempting to increase the specificity of treatment and to avoid these secondary effects.

For all of these reasons, the most appropriate term we should adopt is "systemic therapy" given that it encompasses the different therapeutic modalities, in addition to chemotherapy.

From neoadjuvancy to primary therapy

At first glance the term neoadjuvant therapy was used to refer to the fact that the therapy is administered before other treatments considered as main ones, unlike adjuvant therapy which was assigned after these treatments. Thus, a temporal relationship was explicitly established, involving an implicit subordination of importance between the treatments according to when they were applied. However, two points should be made: firstly the treatment of any type of cancer is usually multimodal, as it should be, with aspects of the treatment targeted at treating the primary tumour and others focussed more on avoiding or treating its dissemination, and which should generally be considered as having a complementary application. The second point refers to the importance of different treatment strategies used in cancer, which are determined by their effectiveness, efficacy (and even efficiency) and are not based on whether they are administered at an earlier or later stage. In this way, the sequencing of the different treatments is a secondary aspect and priority must be given to carrying out the most comprehensive treatment possible: it would be just as pointless to treat the primary tumour without worrying about the occurrence of distant dissemination as it would be to treat the disease as a whole while underestimating the primary focus of the disease thus allowing the persistence or recurrence of locoregional disease which could contribute to a potential focus of future dissemination. Therefore, it would be convenient to sideline the terms referring to the connotations of "main role" or "adjuvancy" of treatment options and to keep to those that refer to temporal sequence (primary).

HISTORY OF NEOADJUVANT CHEMOTHERAPY: THE REASON FOR PRIMARY TREATMENT

Neoadjuvant chemotherapy was first reported in breast cancer in the 1970s as an early-stage treatment for inoperable locally advanced tumours[4] and in several studies

carried out between 1980-1990 which showed an improvement in the surgery rates in these patients, as well as an improvement in their survival rate, so that it became established as part of the initial standard treatment in these patients.

As well as allowing for the surgery of these tumours that were initially non-surgical and improving the survival rate of these patients, it was found that primary chemotherapy could play a role in reducing the initial size of tumours thus making it possible to perform conservative surgery in patients in which mastectomy had initially been established as the surgical treatment. In this situation, it had to be demonstrated that primary chemotherapy was able to achieve the same effects already shown by adjuvant chemotherapy in the reduction of recurrence and overall and disease-free survival[1], and also in the improvement of the percentage of patients in which conservative surgery could be performed.

Many non-randomised studies have investigated the ability of neoadjuvant chemotherapy to increase the possibilities of conservative treatment in surgical breast cancer. Generally, the results obtained in these studies using this kind of chemotherapy achieved clinical response rates of between 67%-85%, with complete pathological responses of nearly 3% and conservative surgery rates of 85%[5-7].

Several studies have prospectively and randomly analysed phase Ⅲ trials on the use of adjuvant chemotherapy compared with the same chemotherapy administered neoadjuvantly in patients with operable breast cancer without revealing any difference in overall survival or disease free survival and achieving a significant increase in the rates of conservative surgery of breast cancer. It is worth highlighting two studies due to their design and the number of patients included: NSABP B-18[8] and EORTC 10902[9].

In the NSABP B-18[8] study, 1523 patients diagnosed with surgical breast cancer (T1-3, N0-1) were randomly administered 4 cycles of chemotherapy with adriamycin and cyclophosphamide (60-600 mg/m^2) as neoadjuvant or adjuvant chemotherapy. A clinical response was achieved in 79% of the patients treated with neoadjuvant chemotherapy, with 36% complete clinical responses and 13% complete pathological responses. What is more, 68% conservative surgeries were achieved in the neoadjuvant chemotherapy arm compared to 60% in the initial surgery arm, especially in patients with tumours greater than 5 cm in diameter.

With more than 15 years of follow-up no differences were found between both groups in terms of survival. An increase in local ipsilateral recurrence was observed in patients receiving primary chemotherapy (10.7 *vs* 7.6) especially in patients under 50 years, which was attributed to the fact that they were not treated with tamoxifen, although this absence of hormone treatment occurred equally in both treatment arms.

In addition, those patients that achieved complete pathological response had a significant improvement in terms of disease-free survival and overall survival compared to those who had residual disease after neoadjuvant chemotherapy.

In the EORTC 10902[9] study, 698 patients diagnosed with breast cancer (T1-4, N0-1) were treated with 4 cycles of 5-fluorouracil, epirubicin and cyclophosphamide (600-60-600 mg/m^2) administered adjuvantly and neoadjuvantly. The response obtained in patients treated with primary chemotherapy was 49% with 4% complete pathology responses. A 23% conservative surgery rate was achieved in patients initially programmed for mastectomy before neoadjuvant chemotherapy.

With a follow-up period of more than 4 years, there were no differences in disease-free survival, overall survival or locoregional recurrence. Significantly, the patients treated with neoadjuvant chemotherapy with complete pathological response had a significant advantage in terms of survival compared to patients with residual disease.

In 2005, Mauri *et al*[10] reported a meta-analysis of 9 randomised studies, including 3946 patients, that faced the same adjuvant and neoadjuvant systemic treatment administered for local treatment (surgery or radiotherapy). There were no differences in terms of survival [RR = 1.00 (95%CI: 0.90-1.12)], disease-free survival [RR = 0.99 (95%CI: 0.91-1.12)] or progression free survival [RR = 0.94 (95%CI: 0.83-1.06)], although there was an increased possibility of local recurrence in patients treated with neoadjuvant chemotherapy [RR = 1.22 (95%CI: 1.04-1.43)], probably because in those patients in which it was administered it was decided not perform surgery and to treat the patients exclusively with locoregional radiotherapy [RR = 1.53 (95%CI: 1.11-2.10)].

Therefore it can be concluded that neoadjuvant chemotherapy is fundamental for the primary treatment of locally advanced tumours, and that in surgical tumours it is an alternative to adjuvant chemotherapy, offering the same survival rate and a comparatively significant increase in conservative treatment rates.

CURRENT SITUATION OF PRIMARY THERAPY: CERTAINTIES AND CONTROVERSIES

Indications

The use of primary systemic therapy is currently indicated in two situations:

The initial treatment of non-surgical locally advanced tumours, before locoregional treatment: (1) for patients with locally advanced or inflammatory tumours, initial systemic treatment allows for the use of subsequent locoregional treatment, which would not have been possible in the first place, and it also provides an added improvement in survival and disease free survival. In these patients, no randomised studies have been carried out for comparing neoadjuvant and adjuvant treatment given that initial surgical treatment is impossible; and (2) in the treatment

of these patients we know that when complete pathological response is achieved there is an advantage in survival compared to when complete response is not attained[11,12].

The initial treatment of tumours in which conservative treatment is considered this should be as a more likely option than radical surgery (mastectomy). In these patients we know that there are similar survival and disease free survival rates in those treated with either neoadjuvant or adjuvant chemotherapy. This means that there is no clear disadvantage for neoadjuvant treatment in terms of locoregional recurrence when it allows for an increase in the possibilities of conservative treatment provided that it is followed by correct hormone treatment and locoregional radiotherapy if required[10].

From a theoretical viewpoint there are advantages to neoadjuvant treatment compared to the adjuvant variety: (1) the possibility of demonstrating the *in vivo* efficacy of the therapeutic agents used by assessing tumour response, offering the theoretical advantage of being able to replace those treatment options that are not useful by others which display a better antitumoral response. However, these "made to measure" treatments have shown no advantage in terms of survival or disease free survival; and (2) identifying biomarkers that allow us to obtain early information about the antitumor activity of the two treatment options would allow us to take faster decisions when we use survival as the fundamental variable.

However, the feasible use of primary systemic treatment could also have disadvantages for initial surgical treatment: It could delay the use of local curative-intent treatment in surgical tumours that could be resistant to systemic treatment. It has been confirmed that this resistance is uncommon but it accounts for around 5% in most studies[8,9,13,14]. It could lead to difficulties for carrying out a correct clinical locoregional staging prior to surgery, preventing the selection of an appropriate systemic treatment or leading to an incorrect disease prognosis being established at a later stage. Nowad, this is less important because initial systemic treatment is very homogeneous from the beginning (with the use of anthracyclines and taxanes) and is mainly based on known biological factors (*e.g.*, the use of trastuzumab/lapatinib in patients with overexpressed Her-2/neu), and additionally we can make accurate locoregional staging through the study of the sentinel node prior to neoadjuvant chemotherapy.

Selection of patients who are candidates for primary treatment

The following patients are candidates for this treatment: (1) patients diagnosed with non-surgical locally advanced breast cancer: tumours greater than 5 cm in diameter (T3), or attached to the thoracic wall (T4a), or with skin ulceration or satellite lesions (T4b), or both (T4c); axillary lymph nodes attached to each other (N2); supraclavicular lymph node involvement (N3); inflammatory tumours (T4d); (2) patients diagnosed with surgical breast cancer, to increase the chances of conservative surgery. Traditionally, a 3 cm tumour diameter has been accepted as the cut-off point although some studies have included tumours of 2 cm. From a practical point of view this treatment can be offered to all patients who have an a priori disproportion between the tumor and breast size which presupposes mastectomy or a poor cosmetic result after initial conservative treatment; (3) patients contraindicated against surgery and in whom surgery should be delayed: a recent acute myocardial infarction, a recent cerebrovascular accident, pregnancy, *et al*; and (4) fragile elderly patients in which surgery would involve too high a risk and who could benefit from initial medical treatment.

Diagnosis and staging in patients before systemic therapy

Initial diagnosis should be carried out before starting primary systemic treatment and preferably through biopsy using a wide bore needle rather than a fine needle, located either by palpation or, better still, guided by ultrasound. In addition to confirming the existence of tumor invasion, this biopsy should provide enough tissue for the study of estrogen, progesterone and Her-2/neu receptors, as well as other biological markers that could be used in other research studies.

Initial staging should make use of the TNM system, and the "c" prefix is advised in pretreatment staging and "y" in pathological staging after surgery. For the assessment of lymph node staging it is recommended to use the "c" when assessment is clinical or radiological, "f" if it included fine needle aspirations and "sn" if a study of the sentinel gland has been carried out.

All the patients should have had a thorough physical examination, at least one bilateral mammography exam, a breast ultrasound analysis, and correct systemic staging, above all in the case of locally advanced tumours to rule out distant metastasis.

LOCOREGIONAL STAGING

Assessment of the primary tumour

Before beginning primary chemotherapy a locoregional analysis should be carried out which should include a physical examination, a bilateral breast analysis, a breast ultrasound study, and in addition, the lesion should be located with a radiopaque (clip) marker which makes it possible to locate the lesion after chemotherapy in preparation for surgical treatment when there is a complete clinical response[15,16].

Magnetic resonance imaging (MRI) provides high definition anatomical images of the breast and the tumour, as well as the dynamic study of the uptake and elimination of contrast making it possible to define the existence of other tumour foci not seen using conventional analyses (multicentricity and multifocality). In addition, it allows for a better definition of possible chest wall involvement. However, although its sensitivity is greater than that of other radiological techniques, its specificity is not so sharp, so that it identifies suspicious lesions that are not malign, often leading to overtreatment.

Currently, a histological analysis is recommended (taking a biopsy with a fine or wide bore needle) of the potentially malignant lesions identified using MRI, if these findings alter the plan initially set out. These lesions could be located using guided ultrasound (second-look)[17] or otherwise using a MRI-guided biopsy, for which there are specific kits available[18].

The positioning of a radiopaque marker could be done at the time of the ultrasound-guided histological diagnosis, when the need for neoadjuvant treatment is initially considered. Alternatively, it can be done at a second stage, before beginning treatment or once it has been started and treatment response has been seen, although in the latter case it is important to closely monitor the response to avoid the disappearance of the lesion before being marked. It is particularly useful for locating the area for carrying out conservative surgical treatment if a complete clinical and radiological response is achieved, and to guide the pathologist in the search for tumor remnants and to identify microscopic disease persistence or a truly complete pathological response[1,19].

Axillary lymph node assessment

It is particularly important to carry out axillary lymph node assessment before the start of neoadjuvant chemotherapy in those patients who are surgical from the outset, although it can also be beneficial in selected cases for some patients with locally advanced disease.

Its utility is guaranteed because it allows for patient prognosis as well as the choice of chemotherapy for treatment (*e.g.*, the addition of taxanes to the anthracyclins if there is lymph node affectation).

However, this need could change in the years to come, especially if we take into account that the addition of taxanes seems to be beneficial to the adjuvant treatment of patients with negative lymph nodes. In addition, the prognostic and therapeutic assessment of the disease increasingly depends on biological factors analysed in the primary tumour rather than on classical prognostic factors such as axillary lymph node infiltration.

This assessment can be carried out through physical examination, axillary radiological examination (mainly ultrasound) and fine needle aspiration of the suspicious lesions, but clearly the best assessment is achieved through selective analysis of the sentinel node. These techniques have a sensitivity of between 70% and 90%, but this is lower where axillary involvement is due to micrometastasis.

Selective analysis of the sentinel node

It is debatable whether the sentinel node should be studied before or after chemotherapy in patients with operable breast tumours with clinically negative lymph nodes if they are going to be treated using primary systemic treatment[20].

The analysis of the sentinel node after neoadjuvant chemotherapy is made difficult by the fact that it is identified to a lower extent, probably due to structural changes in lymphatic drainage brought about by chemotherapy, and a greater percentage of false negatives due to chemotherapy response.

The potential advantages of the analysis of the sentinel node before chemotherapy include the prevention of these confusions caused by the chemotherapy itself, together with the guarantee of the appropriate choice of systemic treatment and the correct subsequent locoregional treatment after it has been completed, preventing unnecessary axillary lymph node dissections or reducing the volume of locoregional radiotherapy.

However, this procedure involves subjecting the patient to two operations and only on a few occasions will it modify the type of chemotherapy that will be received; systemic treatment usually includes anthracyclins and taxanes for achieving the best possible response and this is mainly decided upon according to the studies of biological markers in the biopsy of the primary tumour.

A systematic review of 27 studies including 2148 patients subjected to a selective biopsy of the sentinel node after chemotherapy confirmed that the lymph node was identified in 91% of patients (95%CI: 88-93) and the false negatives were 10.5% (95%CI: 8.1-13.6)[21]. This study concluded that during surgery of the primary tumour and after neoadjuvant chemotherapy, the sentinel node is a useful tool for considering post chemotherapy treatment.

Few data are available comparing the pre and post chemotherapy procedure. In a series of cases in which the first 31 were carried out after chemotherapy and a further 58 before, it was found that in 99% *vs* 87% the sentinel node was identified and there were false negative rates of 0% *vs* 16% (pre *vs* post)[22].

No data are available for comparison of the biopsy before and after neoadjuvant chemotherapy over a prolonged follow-up period making the treatment of choice a matter of opinion. While there are data that lead us to believe that this analysis is a useful tool after chemotherapy, doing it beforehand is going to bring about a more precise knowledge of the situation and will allow for maximum subsequent locoregional treatment (axillary radiotherapy).

Systemic staging

In addition to the locoregional staging (axillary and primary tumour) previously reported, before beginning treatment it is necessary to perform a correct systemic staging of the disease. As a general rule, and following the recommendations of the published guidelines, it would be enough to test surgical tumours using adequate anamnesis, a thorough physical examination, radiography of the thorax and a comprehensive medical analysis including bone and hepatic biochemical tests. Analysis with computerized axial tomography, bone scintigraphy or even positron emission tomography (PET) or PET with computed axial tomography (PET/CAT) would be performed when considered necessary due to any alterations in the previous test results.

In the case of locally advanced tumours, and given that the possibilities of distant dissemination from diag-

nosis are higher, computerized axial tomography would be indicated from the beginning, leaving bone scintigraphy and PET/CAT for those situations in which it was considered as a clinical recommendation or there were suspicious alterations in the tests previously carried out.

Choice of neoadjuvant treatment

There are many possible treatment options with neoadjuvant intent: hormone therapy, targeted therapeutic treatment, to name a few, but the treatment of choice is mostly going to be based on polychemotherapy.

Neoadjuvant hormone therapy

Most of the studies published on primary systemic treatment are based on combination chemotherapy, but recent studies with neoadjuvant hormone therapy are being reported, especially in elderly patients or in those in which for some reason the chemotherapy is considered as an unacceptable treatment option.

Most of the studies carried out are about tamoxifen, although in recent years data is becoming available on studies with aromatase inhibitors.

In 2009, Syed *et al*[23] published a study in ASCO comparing treatment with adjuvant tamoxifen after surgery or tamoxifen administered exclusively without surgery, in 1031 elderly patients with operable breast tumours. The 5-year survival rate was greater in those patients treated with surgery than in those that were only treated with tamoxifen (95% *vs* 85%) in patients between 70 and 80 years of age, but survival was the same in those over 80 years (90% for both), and it was concluded that in these patients with a short life expectancy exclusive administration of tamoxifen could prevent surgical treatment.

Few data are available comparing hormone therapy with neoadjuvant chemotherapy.

A randomized phase Ⅱ study compared 3 mo treatment with exemestane or anastrozol with 4 cycles of chemotherapy with adriamycin and paclitaxel in 121 postmenopausal patients with positive hormone receptors. There were no differences in median time until response (57 d *vs* 51 d), complete pathological response (3% *vs* 6%) or clinical response (67% and 62% in exemestane and anastrozol *vs* 63% in chemotherapy). No differences were found regarding conservative breast surgery (33% *vs* 24%) or locoregional recurrences (3.3% *vs* 3.4%)[24].

No differences were found in either premenoupausal patients in complete response or clinical response or in type of surgery when faced with exemestane and goserelin treatment with 4 cycles of epirubicin-cyclophosphamide followed by 4 cycles of docetaxel[25].

In general and with the data available until now it could be said that the preference for neoadjuvant chemotherapy over hormone therapy is reserved for patients in which chemotherapy is not indicated and in which surgery is not the only initial option (patients with locally advanced or surgical tumours contraindicated for surgery and chemotherapy).

Hormone treatment is an alternative to surgery in tumours in elderly patients with a relatively short life expectancy.

Among the hormone treatments available, the treatment of choice is aromatase inhibitors rather than tamoxifen, given that there are data showing that the responses are more frequent and the possibilities of conservative treatment are higher, although it is not clear that this will lead to an increase in survival[26-29].

It is also unclear how long treatment should last, but in the absence of progression, most studies suggest between 3-4 mo, and it would seem to be reasonable to continue until month 6 or more if there is a response before surgery, to later complete 5 years of adjuvant treatment.

Primary chemotherapy

As we have already seen, neoadjuvant chemotherapy achieves the same overall and disease free survival as the same schemes administered adjuvantly, with an increase in the possibilities of conservative breast surgery. However, there are data pointing towards an increased possibility of local relapse, although they are not conclusive.

The treatment of choice is based on the principle that the chemotherapy that is efficient in adjuvant treatment has a similar efficacy in neoadjuvant treatment, and therefore there is no reason to use different schemes.

In locally advanced non-surgical tumours and those surgical ones in which an increase in conservative surgery is sought after, obtaining a maximal response is a reasonable objective, and this is achieved by combining anthracyclins and taxanes[30-34], whether simultaneously or sequentially (Table 1).

It is generally recommended to administer all the planned chemotherapy before the surgical procedure, if there is no evidence of progression, to maximse clinical response or complete pathological response.

In those patients contraindicated for the use of anthracyclins the exclusive use of taxanes or the combination with capecitabine or vinorelbine could be a valid option.

It is not clear whether the schemes with increased dose density (the same dose of chemotherapy in shorter periods of time) could improve the data of the conventional schemes. Along these lines, the GerparDuo study randomized 913 patients with T1-3N0-2 breast cancer in 4 cycles of chemotherapy with adriamycin and docetaxel every 14 d and compared them with 4 cycles of AC every 21 d followed by 4 cycles of docetaxel every 21 d. The data were favourable for sequential treatment (in other words, with a lower dose density) with greater pathological responses and a higher level of conservative surgery[35].

There are data supporting the use of dose-dense treatments especially in patients with negative hormone receptors, given that in a published meta-analysis, these treatments, used adjuvantly or neoadjuvantly, could be associated with better overall and disease free survival

Table 1 Chemotherapy schemes used in neoadjuvant treatment, with category-1 evidence and that can be used in neoadjuvant treatment

Ref.		Chemotherapy scheme	Drugs/dose
Martin *et al*[70]		CAT	Docetaxel 75 mg/m^2 *iv* on day 1 Doxorubicin 50 mg/m^2 *iv* on day 1 Cyclophosphamide 500 mg/m^2 *iv* on day 1 Cycled every 21 d for 6 cycles (all cycles are with filgrastim support)
Citron *et al*[71]	Non-trastuzumab containing regimens	Dose-dense AC followed by paclitaxel every 2 wk	Doxorubicin 60 mg/m^2 *iv* on day 1 Cyclophosphamide 600 mg/m^2 *iv* on day 1 Cycled every 14 d for 4 cycles Followed by paclitaxel 175 mg/m^2 as a 3 h *iv* infusion on day 1 Cycled every 14 d for 4 cycles (all cycles are with filgrastim support)
Henderson *et al*[72]		AC followed by weekly paclitaxel	Doxorubicin 60 mg/m^2 on day 1 Cyclophosphamide 600 mg/m^2 *iv* on day 1 Cycled every 21 d for 4 cycles Followed by paclitaxel 80 mg/m^2 as a 1 h *iv* infusion weekly from day 1 for 12 wk
Jones *et al*[73]		CT	Docetaxel 75 mg/m^2 on day 1 Cyclophosphamide 600 mg/m^2 *iv* on day 1 Cycled every 21 d for 4 cycles (all cycles are with filgrastim support)
Romond *et al*[74]	Trastuzumab containing regimens	AC followed by weekly paclitaxel concurrent with trastuzumab	Doxorubicin 60 mg/m^2 *iv* on day 1 Cyclophosphamide 600 mg/m^2 *iv* on day 1 Cycled every 21 d for 4 cycles Followed by Paclitaxel 80 mg/m^2 as a 1 h *iv* weekly for 12 wk With Trastuzumab 4 mg/kg *iv* with first dose of paclitaxel Followed by Trastuzumab 2 mg/kg *iv* weekly to complete 1 yr of treatment Cardiac monitoring at baseline, 3, 6, and 9 mo
Robert *et al*[75]		TCH	Docetaxel 75 mg/m^2 *iv* day 1 Carboplatin AUC 6 *iv* on day 1 Cycled every 21 d for 6 cycles With Trastuzumab 4 mg/kg in week 1 Followed by Trastuzumab 2 mg/kg for 17 wk Followed by Trastuzumab 6 mg/kg *iv* every 3 wk to complete 1 yr of trastuzumab therapy Cardiac monitoring at baseline, at 3, 6, and 9 mo

CAT: Docetaxel, doxorubicin and cyclophosfamide; AC: Doxorubicin plus cyclophosfamide; CT: Docetaxel plus cyclophosfamide; TCH: Docetaxel, cyclophosfamide plus trastuzumab.

rates[36]. However, it would be necessary to gather data from well-designed phase Ⅲ studies to consider dose-dense treatments as a standard treatment.

Positive Her-2/neu tumors

The addition of trastuzumab to patients with an overexpression of Her-2/neu has demonstrated a survival benefit both in the context of adjuvant therapy as well as in advanced disease.

In the same way, the use of trastuzumab is recommended in the neoadjuvant treatment of Her-2/neu positive patients given that it increases the possibility of complete responses. There are phase Ⅲ studies comparing the addition of trastuzumab to neoadjuvant chemotherapy (NOAH[37], GeparQuattro[38]). In both cases the addition of trastuzumab significantly increases the chances of a complete pathological response (43% and 31.7% compared to 23% and 15.7% respectively), without any changes in the survival rate or percentage of patients treated with conservative surgery.

A meta-analysis has been carried out comparing the addition of trastuzumab to schemes without it, including 5 studies with 515 patients and the conclusion is similar to the previous one: a significant increase in the chances of achieving a complete pathological response without adding toxicity or changing the likelihood of carrying out conservative treatment[39].

Lapatinib, a biological drug with anti thyrosin-kinase activity, achieves results that are similar to those of trastuzumab when it is used in an isolated way and associated with chemotherapy, according to the results reported in ASCO in 2012. Both drugs achieve similar complete response rates, regardless of the status of the hormone receptors. However, the addition of them does not increase the percentage of pathological responses[40].

The results of the Neo-ALTTO study, however, contradict the previous results, showing that the addition of trastuzumab and lapatinib to neoadjuvant paclitaxel significantly increases the percentage of complete pathological response (51.3% in combined treatment compared with 29.5% and 24.9% with trastuzumab and lapatinib as single treatments, respectively)[41], although with greater toxicity.

The addition of pertuzumab, another anti-Her2/neu antibody, to trastuzumab and docetaxel as a neoadjuvant treatment significantly increases the chances of pathological responses by nearly 45.8% (according to the results of a randomized phase Ⅱ study), compared to trastuzumab and docetaxel on their own[42].

The use of any of these drugs is still not recommend-

ed (lapatinib or pertuzumab) as a standard treatment with neoadjuvant intent.

Triple negative tumours

Although many studies suggest that the percentage of complete pathological response is greater in triple negative patients than in the rest, it remains unclear whether this produces some kind of benefit in these patients. In fact, in spite of the increase in complete response these patients still have a poor prognosis with lower expectations in terms of survival.

There are no specific defined treatment schemes for these patients although there are data suggesting promising results using derivates from platinum[43] PARP inhibitors (especially in patients with the BRCAs mutation) and antiEGFR1 drugs.

The current recommendations are to use the same treatments that are used for the rest of the patients, although this is undoubtedly a fertile area for specific clinical trials which are likely to change the treatment used in the near future.

Other biological treatments

The addition of bevacizumab (an anti VEGF antibody, with mainly antiangiogenic activity) to chemotherapy in negative Her-2/neu patients has revealed contradictory results. In the GeparQuinto[44] study, with 1948 patients, bevacizumab was able to increase the percentage of complete pathological responses in triple negative patients but not in patients with an overexpression of hormone receptors. However, the NSABP B-40 study[45] on 1206 patients achieved the opposite effect, producing an increase in pathological responses in patients with an overexpression of hormone receptors but not in triple negative patients.

Therefore, until more substantial results are obtained, its use is not recommended in this context.

Tailoring

In spite of the advantage of neoadjuvant treatment for checking the *in vivo* sensitivity of certain drugs (so that a change in the chemotherapy scheme could provide advantages in the case of progressive disease or limited response), this benefit has not been demonstrated in the only phase Ⅲ study carried out with this objective.

In the GeparTrio[46] study on 2070 patients treated using the CAT scheme (cyclophosphamide, doxorubicin and docetaxel), those who do not achieve a response of at least a 50% reduction in tumour size are randomized to continue with CAT or to receive treatment with vinorelbine and capecitabine, and do not achieve any differences in response according to ultrasound tests, complete pathological responses or percentage breast conservation.

Another one of the issues to be taken into account within systemic treatment tailoring is to know if it makes sense to prolong this treatment once surgery has been performed and a partial response has been achieved, whether this is a result of the initial treatment or of an alternative type of treatment.

It might be thought that systemic treatment is not the most appropriate strategy and further treatment or another kind of treatment could increase efficacy, or alternatively, that the limited response or the lack of response to the systemic treatment is a reflection of the fact that we are facing a tumour with a worse prognosis which is therefore less chemosensitive.

Until now, no study has demonstrated that the administration of any kind of systemic treatment after standard preoperative treatment improves the prognosis of these patients.

Outside of a clinical trial no recommendation has been made for additional systemic treatment following surgery, after standard preoperative treatment.

Assessment of treatment response

The assessment of treatment response involves the assessment of clinical response as much as pathological response after surgery. Both prognostic factors are related to survival.

It is vital to carry out an exhaustive clinical follow up during systemic treatment because although a change in systemic chemotherapy in the absence of treatment response has not proven to be useful[36], clinical disease progression or the absence of response is enough to postpone systemic treatment and to consider immediate adequate locoregional treatment.

The clinical and radiological response should be made according to the RECIST criteria[47,48], so that a bidimensional assessment of the lesions can be made. Complete clinical response can be defined as the disappearance of the tumour in both the breast and the axillary lymph node through physical examination and radiological tests.

The traditional methods for examining the breast (physical examination, mammogram and ultrasound) have a limited ability to assess response and are not very closely correlated with pathological response[49].

However, dynamic MRI has been better correlated with pathological response in many studies and in one meta-analysis[50]. In spite of its increased sensitivity compared to other techniques it has more false positives and overestimates the occurrence of residual disease after systemic treatment[51].

By carrying out early dynamic MRI after initiating chemotherapy it is possible to distinguish respondent patients (in whom there is an early-onset decrease in contrast enhancement compared to levels in previous tests), from non-respondents, in whom this enhancement is maintained or increased[52].

MRI can also underestimate the result of chemotherapy revealing residual disease or disease which is very unresponsive to treatment, and this seems to be especially related to the use of taxanes in the chemotherapy regimes'[53].

Although MRI can provide underestimations or overestimations of response to chemotherapy, currently it is undoubtedly the radiological method of choice for assessing neoadjuvant treatment response.

In those patients studied given MRI after systemic treatment, the possibility of overestimating the disease should be assessed before planning surgical treatment given that conservative surgery would become less likely in patients who could potentially receive this kind of surgery[54].

Pathological response

Although complete clinical response (disappearance of the tumour in the physical examination and radiological tests) and complete pathological response (the absence of a viable invasive tumour, depending on the accepted definition in the surgical sample) have been related with disease prognosis, there is no clear correlation between them, and approximately a third or more of the patients with complete clinical response have a viable tumour in the surgical sample[55].

In most of the initially reported studies, a significant reduction in tumour size was achieved making conservative treatment more likely, but this had no correlation with disease-free or overall survival.

Achieving complete pathological response is a very important surrogate marker for determining the efficacy of preoperative treatment and it has been correlated in several studies and a recent meta-analysis[56] with better results in disease survival and it is considered as a marker of systemic disease chemosensitivity.

The definition of complete pathological response varies among the reported studies. In some studies complete response has been considered as the absence of tumour cells in the primary tumour area and in the axillary node areas, whereas in other studies where it has been argued that the existence of a ductal tumour does not affect disease-free or overall survival[57], it is defined as the persistence of a non-invasive tumour. Some studies go further separating complete response in the primary tumour and in the axillary lymph node.

Although there is disagreement over complete response in the literature, it is currently thought that obtaining complete pathological response is a predictive factor, independent of disease-free and overall survival in the multivariate analysis[7].

Furthermore, the persistence of residual disease in the lymph nodes is a factor of worse prognosis than disease persistence in the primary tumour[58].

The likelihood of achieving complete response varies according to tumour biology, so that tumours with Her-2/neu overexpression and negative receptors can achieve up to a 45% chance of complete response (defined as an absence of tumour invasion) compared to those that have hormone overexpression but no Her-2/neu receptors in whom only 9% attain a complete response[59] (without trastuzumab).

In addition, complete pathological response capacity or long term survival prognosis also appears to depend on the tumour subtype, so that, complete response is the best predictor of disease-free survival especially in patients with positive hormone receptors[46].

Predictive response factors

Several predictive response factors related to achieving complete response have been reported, and therefore they are related to chemosensitivity, but they are currently still not recommended for selecting individualised systemic treatment.

We know that tumours that do not express hormone receptors or only express a few of them such as luminal B subtype and tumours with a high percentage of Ki67 expression according to immunohistochemistry, are associated with greater chances of complete pathological response to chemotherapy, while those tumours that overexpress hormone receptors or lobular histologies are less likely to achieve complete pathological response with chemotherapy[60,61].

Alternatively, Her-2/neu overexpression is a clear predictive factor of response to trastuzumab, although we also know that it increases the chances of response to inhibitors of aromatase compared to tamoxifen, when endocrine treatment is chosen[62].

The genetic profile can predict pathological results, so that it is more likely for pathological response to occur in triple negative tumours or in those who have a luminal B profile[63-65].

A recent meta-analysis concluded that complete response with chemotherapy is more likely in patients with triple negative (31.1%) and positive Her-2/neu (38.9%) tumours than in tumours that only overexpress hormone recpetors (8.3%)[66].

However, it is not just biological factors that are related with tumour chemosensitivity. Dynamic analysis, spectroscopic analysis with MRI[67], and positron emission tomography[68] can predict sensitivity to treatment if they are carried out early-on once systemic treatment has been undertaken. The differences regarding the baseline studies of contrast uptake or SUV (in the case of PET) are related with the chances of systemic treatment response.

PET has a high sensitivity for evaluating neoadjuvant treatment response but with a low specificity, so that it cannot be recommended as an isolated technique for taking decisions[69].

FUTURE OF PRIMARY SYSTEMIC THERAPY

Neoadjuvant treatment is undoubtedly a realistic option in many scenarios, but it continues to be a treatment that has potential for development, with the introduction of new treatments or new indications or even as a substitute for surgery in certain patient subgroups.

In spite of the importance of local treatment in breast cancer, over time the aggressiveness of surgery has been diminishing, making procedures more and more conservative, with less aggression against the axillary lymph node, improved cosmetic results and a reduction in secondary effects. This has all been possible thanks to the increase in the anti-tumour efficacy of systemic treatments.

Much research still needs to be done and improve-

ments need to be made to the systemic treatment of localised breast cancer with neoadjuvant intent, but in the near future, the main improvement will be the availability of an individualised treatment, based on the patient's genetic profile and predictive biological response factors, using early response assessment methods that are probably based on sufficiently sensitive image techniques and with few false positives.

An appropriate selection of systemic treatment, with local efficacy, and an adequate response assessment using imaging methods with false negatives could mean that in the future, in some patients, surgery could become unnecessary for treating localized breast cancer.

The current extensive biological knowledge about tumours is making it possible to use highly selective treatment options efficient for certain types of tumour (anti Her-2/neu drugs, for example). However, just as it has been shown in other tumours (melanoma, colon cancer, lung cancer…) shortly we will have very efficient systemic treatments for small groups of patients that could be easily selected for this purpose.

Currently many studies are in progress on a range of agents (PARP inhibitors and other targeted agents) in the neoadjuvant context.

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