ANTI-TUMOUR TREATMENT

Evaluation of international treatment guidelines and prognostic tests for the treatment of early breast cancer

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Summary The clinical decision to treat early-stage breast cancer with adjuvant chemotherapy is sometimes a difficult one because 70–80% of patients who receive chemotherapy would probably have survived without it. To help clinicians in this decision-making process, different tools or ‘decision aids’ have been developed for the treatment of early breast cancer over the years. Some of these tools include clinical treatment guidelines and computer-based programs as well as different prognostic and/or predictive tests such as those based on gene expression profiles or the presence minimum invasive disease. All of these tools try to individualize as much as possible the estimation of the risk of breast cancer relapse and death and to facilitate the clinical decision about giving additional treatment, and ultimately the most appropriate treatment to be given.

Thus, it is important for clinicians to be aware of not only the existence of these tools or ‘decision aids’, but also to know how they have been developed, how frequently they are revised and if they have been validated. In order to address all these concerns, we have carried out a critical review of the most important prognostic tests and clinical guidelines for the treatment of early breast cancer. Information regarding their development process as well as frequency of
Introduction

In 2007, the American Cancer Society estimated that in the next years 180,000 women will be diagnosed annually with invasive breast cancer in the United States and of these 40,000 will die.\(^1\) Nearly half of these women will present with a lymph node-negative, hormonal receptor-positive tumor. Nevertheless, 30% of patients with early disease will suffer disease recurrence, while 40% of patients with node-positive disease will survive without disease recurrence for at least 10 years.\(^2\)

It is well known that both adjuvant hormonal therapy and chemotherapy improve both disease-free survival and overall survival in premenopausal and postmenopausal women up to the age of 70 years.\(^2\) However, the decision to treat early-stage breast cancer with adjuvant chemotherapy is sometimes a difficult one because 70–80% of patients who receive chemotherapy would probably have survived without it, while chemotherapy itself is associated with considerable morbidity and cost, and moreover some patients will suffer disease recurrence in spite of having received chemotherapy.\(^2\)

One of the most important challenges that clinicians have had to face in the treatment of early breast cancer is how to distinguish those patients who will need additional systemic therapy from those patients who will not. This is not only to avoid disease recurrence and death but also to optimize a patient’s well-being and the use of medical resources. To help clinicians in this decision-making process, different tools or ‘decision aids’ have been developed for the treatment of early breast cancer over the years. Some of these tools include clinical treatment guidelines and computer-based programs as well as different prognostic and/or predictive tests such as those based on gene expression profiles or the presence minimum invasive disease. All of these tools try to individualize as much as possible the estimation of the risk of breast cancer relapse and death and to facilitate the clinical decision about giving additional treatment, and ultimately the most appropriate treatment to be given.

Thus, it is important for clinicians to be aware of not only the existence of these tools or ‘decision aids’, but also to know how they have been developed, how frequently they are used and if they have been validated. In order to address all these concerns, we have searched PubMed to find out all the ‘decision aids’ tools that try to facilitate the decision-making process in early breast cancer. These tools were basically international treatment guidelines, computer-based calculators, gene-expression profiles and indicators of minimum invasive disease. Information regarding their development process as well as frequency of revision, validations that have been performed and main limitations of each tool were gathered and critically analyzed.

International treatment guidelines

The objective of international treatment guidelines is to assist oncologists in making the best decision for each individual patient. These guidelines are prepared by experts whose task it is to digest the evidence provided by clinical trials and to translate this evidence into implications for individual patient care.

St Gallen international expert consensus

Since 1978, a panel of experts from St Gallen have met every three years to review and interpret the available evidence on adjuvant systemic treatments in early breast cancer.\(^3\) Subsequently, a Consensus Panel of experts develops a series of guidelines and recommendations to select the best adjuvant systemic treatments for each specific group of patients. A declaration of consensus is reflected by the votes recorded at the Panel session. Later on, a draft manuscript that includes the consensus achieved is written and subsequently reviewed and approved by all members of the Panel, and by other invited opinion leaders.

The latest St Gallen International Expert Consensus at the time of writing took place in February 2007.\(^4\) In January 2005,\(^4\) a total of 4166 participants from 78 countries directly involved in the treatment of breast cancer were convened, and they represented different medical specialties such as oncology, surgery and gynecology, but also represented were pathologists, epidemiologists and statisticians. Due to the large quantity of new evidence that became available during 2005, a midway update was considered to be necessary and appropriate.\(^5\)

One of the main contributions of the 9th meeting was the recommendation for physicians to give priority to endocrine responsiveness.\(^6\) Thus, three main categories were established: endocrine responsive, with tumors that are highly positive for estrogen receptors (ERs) for which the main (and possibly the only necessary) adjuvant treatment should be endocrine therapy; endocrine non-responsive, with tumors that are negative for ERs for which endocrine therapies would not be of use but for which chemotherapy is effective irrespective of menopausal status; and an intermediate group for which both endocrine therapy and chemotherapy would be required.

The second important contribution was the proposal for a newly modified system for classifying the risk of relapse, which was divided into three different categories: low, intermediate and high risk of relapse. Node-negative status was made an absolute requirement for belonging to the low-risk category. Node-negative patients with a tumor size greater than 2 cm, tumor grade 2 or 3, presence of peritumoral vascular invasion, HER2/neu overexpression or age less than 35 years old were included in the intermediate risk category, along with patients with 1–3 positive lymph
nodes. Lastly, the category of high risk of relapse included patients with 4 or more positive lymph nodes, or 1–3 along with overexpression of the HER2/neu.

Despite the importance and value of the St Gallen International Expert Consensus, there are several concerns regarding the methodology for arriving at consensus. First of all, the Panel of experts reviews new evidence and interprets its significance for the treatment of individual patients, from studies in which the results may be controversial. According to evidence-based medicine criteria, the strongest evidence for therapeutic interventions is provided by systematic review of randomized, double-blind, placebo-controlled trials involving a homogeneous patient population and medical conditions, such as may be seen in the formal meta-analysis undertaken by the Early Breast Cancer Trialists’ Collaborative Group. Although the best available evidence is presented and reviewed at the St Gallen meetings, final recommendations are reached by votes from panelists from the viewpoint of their particular specialty, with no predefined boundaries of their representativeness. Other concerns include the lack of evidence to support the risk classification based on the number of positive lymph nodes, in particular the absolute requirement for node-negative status to be classified in the low-risk category, or the controversy surrounding the risk afforded by peritumoral vascular invasion which is nonetheless clearly accepted by the panelists. Also, risk groups are very heterogeneous and include the intermediate group ‘endocrine response uncertain’ in which the exact boundary between ‘endocrine responsive’ and ‘endocrine non-responsive’ is undecided, and may well be different depending on the clinical settings (i.e. menopausal status). Finally, the fact that the St Gallen consensus is only applicable to those patients in which the primary treatment is always surgery, is an important limiting factor for its widespread use.

**NCCN breast cancer treatment guidelines**

In 1995, the National Comprehensive Cancer Network (NCCN) began a program to develop a comprehensive set of diagnostic, treatment, and supportive care guidelines for most tumors encountered in clinical practice. NCCN Clinical Practice in Oncology is defined as ‘systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances’. Its main purpose is to enhance the clinical decision-making process and is developed from a systematic method.

The NCCN Clinical Practice Guidelines in Oncology consist of an algorithm which outlines care management, a manuscript in which the algorithm is further discussed and all references on which recommendations are based. The purpose of the algorithm is to define recommendations in an orderly way at each step of the disease. Each recommendation has a ‘Category of Evidence and Consensus’ in which both the strength of the evidence behind the recommendation and the degree of consensus about its inclusion is taken into account. Thus, category 1 means high quality evidence supporting the recommendation along with a uniform level of consensus; category 2A means lower quality evidence but still with a uniform level of consensus; category 2B includes lower quality evidence and a non-uniform level of consensus; and category 3 means no evidence and a high level of controversy.

The development process of the NCCN guidelines includes annual meetings for individual panelists who are chosen from a list of 750 institutional nominees. Specialties that must be included are defined beforehand, and usually include gynecology, medical oncology, neuro-oncology, radiation oncology and surgery. The NCCN process relies on evaluation of scientific data along with expert judgment following a formal procedure for guideline development. In 1996, the NCCN published the first NCCN Breast Cancer Treatment Guidelines, which have been updated periodically. The guidelines address the treatment of all stages of breast cancer, methods of risk-stratification for recurrence and the role of biologic markers, such as HER2 status, ER levels, or genetic markers, as prognostic or predictive factors. Additionally, the effect of age, menopausal status, and ER levels on the benefits achieved by chemotherapy and/or endocrine therapy are also analyzed.

From our point of view, the NCCN Breast Cancer Treatment Guidelines are useful tools for clinicians. They are practical, but also complete and frequently revised. Finally, it is important these guidelines are systematically developed.

**Computer-based risk calculators**

**Adjuvant! online**

Adjuvant! Online is a computer-based tool (www.adjuvantonline.com) that helps health professionals to estimate quantitatively the benefit of adjuvant systemic therapy for women with early-stage breast cancer. Also, it gives the opportunity to share and discuss the information obtained with the patient or her family.

The tool is based on a life Table 1 that predicts outcomes after entry patient age, co-morbidity and tumor characteristics such as histologic grade, tumor size, number of positive lymph nodes and ER status have been taken into account. The program gives a baseline prognostic estimation along with an estimation for the additional improvement expected with endocrine therapy and/or polychemotherapy, both in numerical and graphical formats which may be printed to

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<thead>
<tr>
<th>Table 1</th>
<th>Tools or ‘decisions aids’ for the treatment of early breast cancer</th>
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</thead>
<tbody>
<tr>
<td><strong>International treatment guidelines</strong></td>
<td>• Sant Gallen expert consensus</td>
</tr>
<tr>
<td>• NCCN Breast cancer treatment guidelines</td>
<td></td>
</tr>
<tr>
<td><strong>Computer-based risk calculators</strong></td>
<td>• Adjuvant! Online</td>
</tr>
<tr>
<td>• Neoadjuvant</td>
<td></td>
</tr>
<tr>
<td><strong>Gene expression profiles</strong></td>
<td>• Molecular classification of breast cancer</td>
</tr>
<tr>
<td>• Oncotype DX®</td>
<td></td>
</tr>
<tr>
<td>• MammaPrint®</td>
<td></td>
</tr>
<tr>
<td><strong>Minimal invasive disease</strong></td>
<td>• Bone marrow micrometastasis</td>
</tr>
<tr>
<td>• Circulating tumor cells in peripheral blood</td>
<td></td>
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</tbody>
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be used in consultations. Additional estimates of years of life expectancy and long-term survival curves may also be produced.12

The estimates given in Adjuvant! Online are mainly based on the Surveillance Epidemiology and End Results (SEER) database and on the Early Breast Cancer Trialists’ Collaborative Group meta-analysis,2,13,14 and they have been further validated in a population-based study.15 To perform this validation, demographic, pathologic, staging, and treatment data of 4803 patients with stage I or II breast cancer from a Canadian database were entered into Adjuvant! Online program and 10-year overall survival (OS), breast cancer specific survival (BCSS) and event-free survival (EFS) for each patient were calculated and compared with observed outcomes. For the entire cohort, the predicted and observed 10-year OS, BCSS and EFS were within 1% and were not significantly different (p > 0.05 for each). Also, for more subgroups the differences between the predicted and observed outcomes were within 2% or were not significantly different (p > 0.05), except in women between 20 and 35 years old, older than 75, with lymphatic or vascular invasion or for those patients who received both adjuvant hormonal therapy and chemotherapy. The Adjuvant! program may be used by clinicians to derive an objective estimate of the baseline risks of breast cancer recurrence and mortality in the absence of adjuvant systemic therapy. An optional manual adjustment using the ‘Prognostic Factor Impact Calculator’ (PFIC) can be used to adjust estimations in women ≤ 35 years old, with lymphatic/vascular involvement or other prognostic factors such as HER2 overexpression.

In a study that evaluated the effect of the Adjuvant! program on patients, 95% of physicians reported that the Adjuvant! Decision Guide was easy to understand and 75% reported that it helped them to understand patient’s treatment preferences.16 Also, treatment decisions were more individualized when numerical information from the Adjuvant! program was provided in comparison with a standard pamphlet.

Nevertheless, this tool has several limitations that have to be taken into account. The first one is the lack of validation with more intensive chemotherapy such as taxane-based regimens or newer hormonal treatments such as aromatase inhibitors. Also, it does not take into account the ER status, HER2 overexpression or the genetic profile of the tumor. Other limitations include the fact that it cannot be used in patients with inflammatory, multicentric or late-stage breast tumors as well as after neoadjuvant systemic treatment. Finally, it does not take into account the administration of radiotherapy or how nodal status is assessed.

Neoadjuvant

Neoadjuvant is a series of prediction nomograms based on clinical and pathologic characteristics of the primary tumor that predicts the probability of obtaining pathologic complete response (pCR),17 residual tumor less than 3 cm and breast conserving surgery18 for patients treated with anthracyclines or paclitaxel plus paclitaxel before surgery. These nomograms were developed and validated using 1147 patients treated at the Gustave Roussy Institute and at the University of Texas M.D. Anderson Cancer Center with anthracycline-based or paclitaxel plus anthracycline-based preoperative chemotherapy.17 The clinical and pathologic characteristics of all patients were prospectively entered into a clinical database. A multivariate logistic regression analysis was used to test the association between response to chemotherapy and patient age, tumor size, initial diameter, multicentricity, histologic grade of tumor and ER status. The administration of paclitaxel became important only for those patients who had an intermediate probability of achieving a pCR with anthracyclines alone, but was no better to those patients with chemotherapy-resistant cancers. Additionally, the accuracy of the nomogram that predicts 5-year metastasis free-survival after preoperative chemotherapy was superior to that performed by Adjuvant! Online in terms of calibration and discrimination.17 This is understandable as Adjuvant! Online was not optimized to predict outcomes in the neoadjuvant setting.12 These nomograms were able to predict the probability of achieving pCR and breast conserving surgery as well as the risk of disease recurrence.17,18

Neoadjuvant may be useful for clinicians for discussing different treatment options with patients and for making more informed decisions about primary chemotherapy in the treatment of breast cancer. Patients with a high or an intermediate chemotherapy sensitivity will benefit the most from this alternative, whereas those patients with chemotherapy-resistant cancers probably will not. The fact that this tool is also available as a web-based interface (www.mdanderson.org) may facilitate its counseling role.

On the other hand, there are several concerns regarding its use. The most important one is the lack of a prospective validation of Neoadjuvant. Other concerns are the lack of use of other important pathologic characteristics such as the histologic type of tumor, the initial lymph node status or HER2 overexpression. Also, molecular markers or genetic signatures are not included. Lastly, this tool should be validated with other chemotherapy schedules, different from those used at the sites it was developed.

Gene expression profiles

Much interest has recently been focused on the role of gene expression profiles and other molecular techniques to obtain a more quantitative and rationalized approach for individualized breast cancer treatment.

Molecular classification of breast cancer

The first serious attempt to develop a classification system for human breast tumors on the basis of their gene expression patterns was performed by Perou et al.19 A set of 65 surgical specimens of human breast tumors from 42 women were analysed using complementary DNA (cDNA) microarrays that represented 8102 human genes, and 496 genes were pulled out based on variation in expression between different tumors. They were named ‘the intrinsic gene subset’ and were used to order the tissue samples into four different subtypes (i.e. ‘ER+/luminal epithelial-like’, ‘basal epithelial-like’, ‘erb-B2 overexpressing’ and ‘normal breast-like’). Thus, ER-breast tumors could belong to either the ‘basal epithelial-like’ or the ‘erb-B2 overexpressing’ group, influencing significantly the prognosis of the disease. These
molecular patterns were stable and homogeneous because they could recognize the same tumor by its expression pattern in samples taken from the primary tumor or from metastasis.

Later on, this classification was further refined by analyzing a larger number of tumors and dividing the previous ‘ER+/luminal epithelial-like’ group into two or three new subgroups called ‘luminal subtype A’ with the highest expression of ER+, ‘luminal subtype B’ and ‘luminal subtype C’ (sometimes considered as ‘luminal subtype B+C’ and with a low to moderate expression of ER). Also, they observed that this classification of tumors could be used as a prognostic marker with respect to overall and relapse-free survival. In fact, both the ‘basal epithelial-like’ and the ‘erb-B2 overexpressing’ subtypes were associated with the shortest survival and relapse-free survival times. This fact is clinically reasonable if we take into account that both subtypes express with high frequency either the Erb-B2 oncoprotein or TP53 mutations, which are well-known markers of poor prognosis in breast cancer. Lastly, a difference was observed in outcome for tumors classified as luminal A versus luminal B+C, with the latter having a worse disease course. These different molecular subtypes of breast cancer may respond differently to neoadjuvant chemotherapy. The ‘basal-like’ and ‘erb-B2’ subtypes were associated with high rates of pCR (45% in each subgroup), whereas the luminal tumors had a poor pCR rate of 6%, after an anthracycline/taxane-containing neoadjuvant chemotherapy. This molecular classification for breast cancer was not only able to predict disease course, but also distinct sensitivities to preoperative chemotherapy.

Based on these five gene expression patterns, immunohistochemical profiles for the breast cancer subtypes were developed and validated in a large population-based epidemiological study to facilitate their clinical use. The ‘basal epithelial-like’ subtype was equivalent to the ER-/PR-/HER2-/cytokeratin 5&6+/HER1+ profile; the ‘erb-B2 overexpressing’ subtype was equivalent to the ER-/PR-/HER2+ profile; the ‘luminal A’ was equivalent to the ER+/PR+/HER2-profile; and the ‘luminal B’ to the ER+/PR+/HER2+ profile. Those tumors which were negative for the five immunohistochemical markers (ER, PR, HER2, HER1 and cytokeratin 5&6) were considered unclassified. The prognostic value of this new immunohistochemical-based tumor classification was demonstrated.

In summary, the molecular classification of breast cancer in five different subtypes is a useful tool that shows not only different prognoses for the disease, but also distinct sensitivities to preoperative chemotherapy. The possibility of developing immunohistochemical profiles based on these molecular subtypes may facilitate their use in routine clinical practice. However, it would be desirable to confirm the equivalence between both types of tumor classification. If this equivalence is demonstrated, the use of treatment guidelines like NCCN or St Gallen that currently take into account ER, PR and HER2 as prognostic and predictive markers would be also supported.

**Oncotype DX®**

Oncotype DX® is a clinically validated 21-gene assay that quantifies through a recurrence score (RS) of 0–100 and a recurrence risk group (low, intermediate, or high) the likelihood of breast cancer recurrence in women with node-negative, ER-positive early breast cancer; but it is also able to predict the magnitude of the chemotherapy benefit.

The methodology of the assay includes RNA extraction from formalin-fixed, paraffin-embedded (FFPE) tumor specimens, followed by purification and analysis by reverse transcription-polymerase chain reaction (RT-PCR). RS is calculated from the gene expression results.

The clinical validation of the 21-gene panel and RS calculation has been performed retrospectively in a large multicenter clinical trial using a prospectively collected data set and in a large population-based case-control study. From 675 tumor blocks obtained from patients included in the National Surgical Adjuvant Breast and Bowel Project clinical trial B-14, 668 adequate RT-PCR profiles were obtained and used to test whether the RS calculated could predict the rate of distant recurrence at 10 years. In a multivariate Cox model, the RS provided significant predictive power independently of age and tumor size (p < 0.001), and also it had predictive power of overall survival (p < 0.001). To confirm and extend these findings, the performance of this 21-gene assay was evaluated in a case-control study among 4,964 node-negative breast cancer patients from a community hospital. Cases and controls were matched with respect to age, race, adjuvant tamoxifen, medical facility and year of diagnosis. The RS was calculated for each patient, and a logistic regression analysis found a positive relationship between the risk of breast cancer death and RS in ER-positive, tamoxifen treated and untreated patients (p = 0.003 and p = 0.03, respectively).

Furthermore, the value of Oncotype DX® in predicting the benefit of chemotherapy has been shown in a recent study. In this trial, 651 eligible patients were treated with tamoxifen alone or with tamoxifen plus chemotherapy. Results showed that patients with high-RS (>31) tumors had a large absolute benefit from chemotherapy (relative risk: 0.26; 95% CI: 0.13–0.53; mean absolute decrease in 10-year distant recurrence rate: 27.6%; SE: 8.0%), whereas patients with low-RS (<18) tumors derived minimal, or no, benefit from chemotherapy (relative risk: 1.31; 95% CI, 0.46–3.78; mean absolute decrease in distant recurrence rate at 10 years: –1.1%; SE: 2.2%). In between, there were patients with intermediate-RS tumors (≥18 and <31) who did not appear to derive a large benefit from chemotherapy, but in whom it was not possible to exclude it completely. A large phase III trial (TAILORx: Trial Assigning Individualized Options for Treatment) sponsored by the National Cancer Institute, which is currently ongoing, will further elucidate how adjuvant hormonal therapy compares with adjuvant chemo-hormonal therapy in those women whose tumors fall in the ‘uncertain chemotherapy benefit’ category according to Oncotype DX®. This study will enroll over 10,000 breast cancer women in the United States and Canada, and will examine whether genes that are frequently associated with risk of recurrence for women with early-stage breast cancer can be used to assign patients to the most appropriate and effective treatment. Finally, RS has shown to be more accurate than NCCN guidelines as an indicator of prognosis for node-negative, ER-positive, early breast cancer as well as being cost-effective.
Recently, ASCO has recognized the usefulness of Oncotype DX to predict the recurrence risk of ER-positive, node-negative breast cancer patients who are being treated with tamoxifen. Specifically, ASCO said that "Oncotype DX may be used to identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy. In addition, patients with high RS appear to achieve relatively more benefit from adjuvant chemotherapy (CMF) than from tamoxifen." In the future, the results of the TAILORx trial will let us know the benefit of chemotherapy in patients with low Oncotype DX scores, and offer to our patients the best option between hormonal therapy or a combination of both chemotherapy and hormonal therapy.

In summary, Oncotype DX has been shown to predict 10-year distant recurrence in patients with ER-positive, lymph node-negative breast cancer, and also to predict chemotherapy and endocrine therapy response. Another advantage of this technique is that Oncotype DX only requires fixed tissues in paraffin-embedded blocks instead of fresh frozen tissue. However, the prognostic role of Oncotype DX has not yet been established in other groups of breast cancer patients such as patients with ER-negative tumors or with advanced or metastatic disease. Lastly, the high cost of the assay may be an important limitation for its routine clinical use.

**MammaPrint®**

MammaPrint® is a 70-gene expression profiling test that predicts the risk of metastasis in women with node-negative and ER-positive or negative early breast cancer. This test, developed at the Netherlands Cancer Institute and at the Antoni Van Leeuwenhoek Hospital, uses DNA microarrays and has to be performed with fresh tumor samples. To assess the entire gene expression pattern of a tumor sample, messenger RNA (mRNA) is extracted from the sample and labeled with a fluorescent dye. The labeled mRNA, together with the labeled mRNA from a control sample, is hybridized to a DNA microarray.

Clinical validation of the 70-gene prognosis profile has been performed in a cohort of 295 consecutive breast cancer patients on whom a gene-expression signature with low Oncotype DX scores, and offer to our patients the best option between hormonal therapy or a combination of both chemotherapy and hormonal therapy.

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Circulating tumor cells in peripheral blood

The presence of circulating tumor cells (CTC) in the peripheral blood of breast cancer patients is increasingly being used, either for staging or predicting disease progression. In patients with metastatic breast cancer, it was observed that patients with high levels of CTC (>5 per 7.5 ml of whole blood) before treatment had shorter median progression-free survival (2.7 months) and overall survival (10.1 months) than those with fewer than 5 CTC per 7.5 ml (7.0 months, \( p < 0.001 \); >18 months, \( p < 0.001 \), respectively). The prognostic value of CTC levels in metastatic disease was further confirmed in early breast cancer patients using the markers cytokeratin-19 (CK19) or the oncoprotein HER2.\(^{34}\) The presence of CK19 mRNA-positive cells in peripheral blood of node-negative breast cancer patients was associated with early clinical relapse \( (p < 0.00001) \) and disease-related death \( (p = 0.008) \) before receiving any treatment. This association was independent of the chemotherapy regimen later administered and confirmed the independent predictive and prognostic value of CTC in early breast cancer. These findings were further confirmed by a prospective cohort study in which the detection of HER2 mRNA-positive CTC after chemotherapy was associated with a reduced disease-free interval \( (p = 0.006) \), but not with overall survival \( (p = 0.2) \) in node-negative patients.\(^{35}\) In this study, adjuvant chemotherapy could only eliminate HER2 mRNA-positive CTCs in 30% of patients.

Although the detection of occult tumor cells in the bone marrow or peripheral blood of patients with early breast cancer is associated with poor prognosis, several aspects should be further clarified. Firstly, it is not clear whether the detection of CTCs should be performed in all patients at the time of diagnosis, or if the presence of CTCs at diagnosis should modify the adjuvant therapeutic strategy, and secondly whether the detection of CTCs during treatment should suggest the administration of secondary adjuvant treatments. Results from other prospective randomized clinical trials should help to answer these questions.

Discussion

Tailoring systemic treatment based on individual patient and tumor characteristics helps clinicians to develop better therapeutic strategies and to prevent many patients from receiving unnecessary cytotoxic therapy.\(^{36}\) Clinical treatment guidelines, either international or national ones,\(^{37}\) were one of the first tools developed to help clinicians to individualize adjuvant systemic therapies for patients with early breast cancer. Guidelines are thought to enhance the quality of care not only by reducing under-treatment, over-treatment and wrong treatment,\(^{38}\) but also by diminishing treatment variability and medical costs. One study recently examined the effect of following NCCN breast cancer guidelines on survival, quality of life and hospital cost.\(^{39}\) Their findings demonstrated that adherence to NCCN guidelines significantly reduced the cost of breast cancer care without adversely affecting survival and quality of life.

Two important factors have to be taken into account when the quality of a treatment guideline is being evaluated. The first is the frequency of review. If clinical practice guidelines are to remain relevant, they must be continuously updated.\(^{40}\) New studies may have a major impact on practice recommendations, and if the steering committee has not created a mechanism to incorporate this new information, then guidelines will rapidly become outdated. The second factor to be taken into account is the way that the guideline has been developed and whether this development has been through a systematic process. It is considered that there are two main methods of developing clinical practice guidelines.\(^{41}\) One of these methods is through the consensus of experts, while the other is through the more formal way of analyzing literature to create an evidence-based guideline. Using quality assessment instruments, evidence-based guidelines have been demonstrated to be of higher quality than consensus-based guidelines, although no major disagreement over guidelines has actually been noted regardless of the method used for their development.\(^{41}\)

In this review, both St Gallen and NCCN guidelines have been critically reviewed. Both tools seem to be useful for clinicians, but several aspects are open to improvement. First, the frequency of review in St Gallen, which is usually once every three years, seems nowadays to be insufficient due to the high volume of new evidence being acquired on early breast cancer during recent years. In fact, a midway update of the 9th meeting was required for this reason.\(^{4,5}\) Other aspects include the lack of prior definition of the expert participants according to not only their medical specialty, but also their cultural influence, or the lack of evidence to support some of their assumptions. From the clinical point of view, the heterogeneity of patients included in the intermediate risk group is disappointing. In contrast, NCCN Breast Cancer Guidelines are reviewed every six months and differentiate between the ‘Category of Evidence’ and the ‘Category of Consensus’, which may be very helpful for clinicians. Also, NCCN precisely describes the criteria for selecting individual panelists and the development process of the guideline, which is required to be ‘systematic’. The algorithms developed by NCCN are practical and they are discussed in peer-reviewed journals in which all references that support guidelines are included. Finally, NCCN Breast Cancer Guidelines include most of the genetic markers which are currently accepted to have a prognostic or predictive value.

Hence, the use of clinical guidelines may enhance the quality of care in early breast cancer patients, but clinicians need to be reminded that a certain degree of subjectivity is inherent in them and that it is almost impossible to eliminate completely biases by the experts to exclude reasonable choices or to incorporate personal opinions. Also, clinical guidelines would improve if they would incorporate new technology tests such as gene expression profiling as soon as these new tests were appropriately validated.

Other tools frequently used by clinicians include computer-based risk calculators such as Adjuvant! Online or NeoAdjuvant. They are mostly founded in the same clinical and histologic markers used by clinical guidelines including factors such as age, tumor size, lymph-node involvement, histologic grade or expression of hormonal receptors. In contrast however, risk calculators are able to give quantitative risk estimations. This provides an opportunity to discuss
with the patient and to better understand a patient’s treatment preferences.16 In spite of these advantages, prospective validations of the prognoses obtained using these programs are needed as well as the necessity of including other markers, histologic or genetic, as soon as they are validated.

More recently, new tools for clinicians have been developed based on gene expression profiles. The molecular classification of breast cancer into different subtypes such as ‘luminal A’, ‘luminal b’, ‘erb-B2’ or ‘basal’ has been demonstrated to have prognostic and predictive value. However, early reports have used unsupervised analysis, which may be unstable when new cases are added. Thus, if this type of molecular classification is shown to be no better than immunohistochemical profiling in predicting outcome, molecular classification may well be of less use due to the complexity of deriving it. Other gene expression profiles like the 21-gene assay (OncoType®) or the 70-gene assay (MammaPrint®) appear to be very useful for clinicians. OncoType® has the advantage over MammaPrint® that it can be performed on fixed paraffin-embedded blocks instead of fresh frozen tissue. Time will tell whether this fixation process affects RNA degradation and therefore risk estimations. Also, ASCO has communicated the advantages of using Oncotype DX RS.28 In spite of that, at this point in time the only breast cancer prognosis test approved by both, the USA Food and Drug Administration (FDA) and its European counterpart (EMEA), is MammaPrint®.

Studies indicate that they are superior to other tools based only on clinical or histologic criteria including Adjuvant! Online, St Gallen or NCCN guidelines,27,29 however these profiles give information about the recurrence risk of each patient but not about how treatment would modify this risk. Recently, a prospective community-based feasibility study (RASTER) showed that the use of a 70-gene prognosis signature was feasible in a Dutch community hospital,37 but future studies demonstrating whether its use actually improves survival, or at least quality of life, are still needed. Main limits of gene profiles include variability in normalization and reproducibility. Also, these assays are more applicable only in certain groups of early breast cancer patients and their high cost may limit their widespread use in clinical practice.

Lastly, two markers which are indicative of the presence of minimal invasive disease are bone marrow micrometastasis and CTCs which have been demonstrated to be of importance in early breast cancer from a prognostic point of view. CTCs in the blood stream are a much easier source for assessing prognosis than bone marrow, but both of them need further validation.

In summary, it is clear that gene expression profiling has superseded current standards such as the St Gallen or NCCN guidelines in accurately estimating the recurrence risk of breast cancer. In the near future, clinical decisions will most likely be dictated by the genetic characteristics of the tumor, and clinical characteristics will become less important. Until the routine use of gene expression profiles is possible, clinicians have available all the tools or ‘decision aids’ mentioned in this review, although their limitations should be taken into account. These tools should always be used as an aid in the decision-making process, and not as a replacement of good clinical judgment.

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