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Current and future directions in early breast cancer therapy

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Abstract

A growing proportion of women diagnosed with breast cancer present with earlier disease stages, and many will relapse and die from their disease. While survival rates are improving with the development of new systemic therapies, there is an urgency to improve treatment outcomes further in early breast cancer. Gene expression profiling is fundamentally changing our understanding of breast cancer biology at the molecular level. It is providing a refined classification of breast cancer and has reinforced the notion that breast cancer is a heterogeneous disease. This knowledge has great potential for a better selection of patients in need of adjuvant therapy, as well as for tailored treatment approaches. The use of new compounds, such as trastuzumab (Herceptin®) and capecitabine, used in combination with established agents, also represent important advances. The development of both new technologies and novel agents will optimise systemic therapy for early stage breast cancer in the future.

Keywords: Adjuvant therapy; Capecitabine; Early breast cancer; Gene expression profiling; Prognosis; Taxanes; Trastuzumab

1. Introduction

With screening mammography becoming more widely used in the developed world, a growing proportion of women diagnosed with breast cancer present with earlier disease stages. However, many of these women will relapse and die from their disease. Even in patients who have node-negative breast cancer and are considered to be at low risk, the 10-year recurrence rate following exclusive local therapy is 15–47%, while in patients with node-positive disease, the rate reaches levels as high as 25–91% [1,2]. The aim of systemic therapy in early breast cancer is to eradicate micrometastases and, therefore, to reduce the risk of recurrence and death. The oncologist's expertise lies in understanding both the patient and tumour characteristics to optimise the benefits of therapy. Over the past three decades, several tools have been developed to select the best therapies for patients with early breast cancer. The application of known prognostic factors as clinical indices is very useful in this setting. Patient-related factors that affect prognosis include age, menopausal status co-morbidities and race. Tumour-related prognostic factors include the extent of lymph node involvement, tumour size and grade, oestrogen receptor (ER)/progesterone (PgR) receptor status, presence of vascular invasion and HER-2/neu overexpression. Many oncologists rely on guidelines issued by experts following consensus conferences to treat their patients with early breast cancer.

2. Benefits of systemic therapies

Chemotherapy has proven to be beneficial as adjuvant therapy in early breast cancer, with node-positive and high-risk node-negative disease benefiting from anthracycline-based regimens, while the outcome of node-positive disease is further improved by the use of taxane-based regimens. Endocrine therapy using aromatase inhibitors is superior to tamoxifen in postmenopausal patients with ER/PgR-positive breast cancer, and the addition of chemotherapy is effective in a proportion of these patients. In recent years, the molecular agent, trastuzumab (Herceptin®), combined with chemotherapy, has been shown to have a positive impact on survival and disease-free survival in patients with HER-2-positive breast cancer, and has become an important therapeutic option in these patients. In node-positive breast cancer, each subsequent generation of chemotherapy that has been introduced, starting with cyclophosphamide/methotrexate/5-fluorouracil in the 1980s and moving to anthracyclines in the 1990s and more recently to the taxanes, has provided incremental gains in disease-free survival (Table 1). The benefits of taxane-based therapy in the treatment of node-positive breast cancer have now been demonstrated in several clinical trials (Table 2).

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Table 1
Impact of subsequent generations of chemotherapy on reducing recurrence rates of disease in patients with node-positive breast cancer [3].

Treatment	Annual odds of recurrence (%)	Relative risk reduction (%)
No treatment	9	
CMF vs. no treatment	6.8	24
Anthracycline vs. CMF [a]	6.0	12
Anthracycline + taxane vs. anthracycline	5.0	17–23

[a] CMF: cyclophosphamide, methotrexate, and fluorouracil.

Table 2
Contribution of taxanes in node-positive breast cancer from trials with a median follow-up in excess of 4 years [4–8]

Study	Regimen	No. of patients	Hazard ratio	
			Disease-free survival	Overall survival
NSABP B28	AC × 4			
	AC × 4 – P × 4	3060	0.83*	0.94
CALGB 9344	AC × 4			
	AC × 4 – P × 4	3121	0.83*	0.82*
BCIRG 001	FAC × 6			
	TAC × 6	1491	0.72*	0.70*
GEICAM 9906	FEC 90 × 6			
	FEC 90 × 4 – P 100 × 8 wks	1248	0.64*	0.74
PACS 01	FEC 100 × 6			
	FEC 100 × 3 T × 3	1999	0.83*	0.77*

*$P < 0.05$; A, doxorubicin; C, cyclophosphamide; E, epirubicin; F, 5-fluorouracil; P, paclitaxel; T, docetaxel.

2.1. Taxanes in node-positive breast cancer patients

Information regarding the use of taxanes in node-positive breast cancer patients has been obtained from five key trials. Trial B-28 from the National Surgical Adjuvant Breast and Bowel Project (NSABP) [4] compared four cycles of standard AC chemotherapy (doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2 every 3 weeks) used either alone or followed by four cycles of paclitaxel (225 mg/m^2 over 3 hours). The Cancer and Leukemia Group B (CALGB) 9344 trial also added paclitaxel sequentially after AC [5]. In the Breast Cancer International Research Group (BCIRG) 001 trial, docetaxel/doxorubicin/5-fluorouracil was compared with cyclophosphamide/doxorubicin/5-fluorouracil) [6]. The GEICAM 9906 trial compared six cycles of 5-fluorouracil/epirubicin/cyclophosphamide (FEC) with four cycles of FEC followed by eight weekly paclitaxel administrations [7], while the PACS 01 trial compared six cycles of FEC with three cycles of FEC followed by three cycles of docetaxel [8]. All these trials showed improved disease-free survival with taxanes, while three of them also demonstrated an improvement in overall survival. These results confirm the important role of taxanes as a component of adjuvant therapy for the management of patients with node-positive disease.

Little progress has been made in treatment decisions for patients with node-negative breast cancer, as insufficient data exist. Three trials on taxanes in early stage (E-2197, NSABP B-27 and ECTO-01) [9–11] that have included patients with node-negative tumours among other patients are inconclusive. Ongoing specific chemotherapy trials will clarify the effectiveness of taxanes in this population.

3. Basis for future research

The 10-year survival gain achieved with a taxane-containing regimen in node-positive patients reaches 13% to 21%, compared with no treatment [1]. Although this represents a dramatic improvement in the treatment of breast cancer, it is important to recognize that a great majority of patients do not benefit from such therapies. So, tools commonly used today to select patients who should receive chemotherapy suffer severe limitations.

Human breast tumours are diverse in their natural history as well as in their responsiveness to treatment. After surgery, in any given population of patients with early breast cancer, a proportion of patients will not present with micrometastatic extent and further treatment will therefore not be required; however, a proportion of patients will have resistant disease irrespective of the type of treatment received. Therefore, a large and important subgroup of patients who can benefit from adjuvant chemotherapy remains. In the future, two main lines of research for improving the outcome of treatment are open to investigators. The first is to increase the efficiency of existing therapies by selecting the subgroup of patients who would be sensitive to therapy. Identifying such patients might be achieved in the future by the use of high-throughput technologies, which include genomics and proteomics, since they are likely to help clarify the role that molecular mechanisms play in the response to therapy and in the prognosis of disease. The second line of research would be to increase efficacy of treatment by developing new agents to which breast tumours are sensitive.

4. Increasing efficiency: potential of genomics

Genomics is the study of gene expression within cells for the purpose of understanding disease variation. The phenotypic diversity of breast cancers is accompanied by a corresponding diversity in gene expression patterns, and systematic investigation of these patterns provides the basis for an improved molecular taxonomy based on subtypes of breast cancers. Furthermore, gene expression markers could be identified as clinically useful predictors of response to drug therapy.

Four major molecular subgroups of breast cancer, normal-like, luminal (divided into A and B; and being

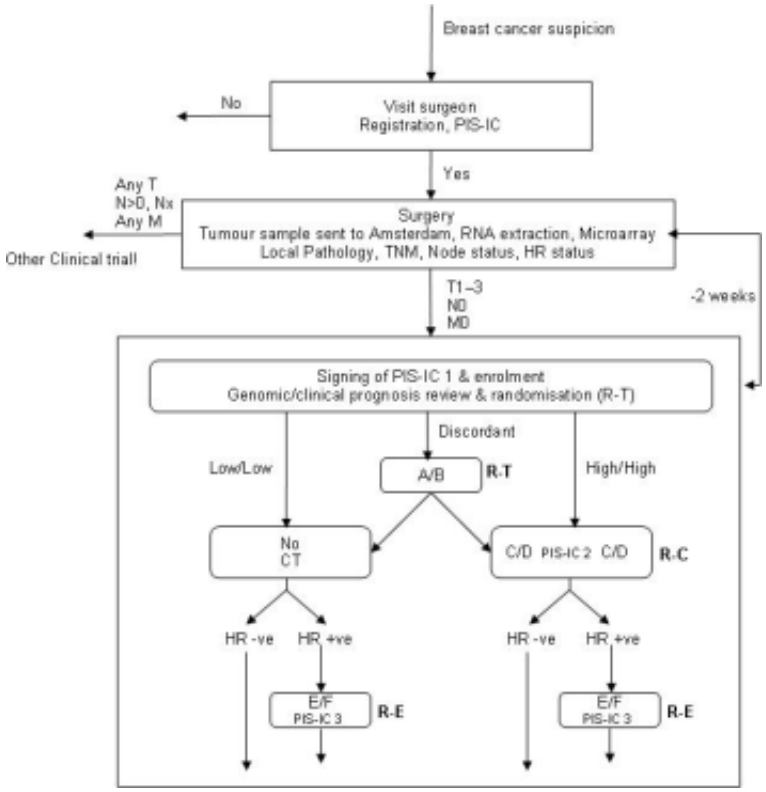

Fig. 1. MINDACT study design. A/B, treatment decision based on genomic or clinical prognosis; C/D, anthracycline-based chemotherapy (CT) versus docetaxel/capecitabine; E/F, letrozole versus tamoxifen followed by letrozole; PIS IC, patient information sheet and informed consent; R-C, chemotherapy randomisation; R-E, endocrine therapy randomisation; R-T, treatment decision randomisation.

ER-positive), basal-like (mostly ER-negative) and erbB2 positive (mostly HER-2 amplified), have been identified using gene expression profiling of breast tumours [12]. These molecular subtypes of breast cancer have been shown to respond differently to chemotherapy. In the neoadjuvant setting, for example, basal-like and erbB2 positive subtypes have higher pathological complete response rates to paclitaxel and doxorubicin-containing preoperative chemotherapy (both 45%) than luminal A and B and normal breast-like cancers (6% and 0%, respectively) [12]. This study is of great interest because the results suggest that different sets of genes that are present in different molecular subgroups may predict the response to a particular chemotherapy regimen.

Landmark studies with potential implications for clinical management of breast cancer include the work of scientists at the Netherlands Cancer Institute who investigated global molecular expression levels in tumour samples using microarray technology [13,14]. They were able to identify a molecular signature that was associated with 'poor' clinical prognosis and a signature linked to 'good' clinical prognosis. From this differentiation between two subpopulations of patients, they were able to accurately predict relapse-free survival in both node-negative and node-positive breast cancers.

Hopefully in the future it will be possible to customise treatment based on both predictive and prognostic signatures derived from gene expression profiling, to distinguish between patients who do or do not require more treatment, patients who should receive standard adjuvant therapy, and those who should receive new experimental therapy.

4.1. MINDACT trial

Given the high potential of gene expression profiling to change clinical practice, it is important to validate this new prognostic tool in a large, independent and prospective trial. The Microarray In Node negative Disease may Avoid ChemoTherapy (MINDACT) trial is a multicentre, prospective phase III, randomised study that is already in advanced stages of preparation (Figure 1) [15]. It will be run through the Breast International Group network and coordinated by the European Organisation for Research and Treatment of Cancer (EORTC). MINDACT will evaluate the role of a 70-gene prognosis signature in the selection of good prognosis versus bad prognosis patients with node-negative breast cancer. Great uncertainty persists in selecting node-negative women who need adjuvant chemotherapy and those who do not. To this end, the MINDACT trial will also aim to identify the subgroup of patients who can be spared this aggressive treatment without affecting distant metastasis-free survival.

5. Increasing efficacy: new compounds

5.1. Molecular agents: trastuzumab

Trastuzumab, a monoclonal antibody directed against the HER-2/neu protein, is an important new molecular agent that has a major role in the treatment of patients with HER-2-positive breast cancer. The BCIRG 006 trial compared a docetaxel with carboplatin and trastuzumab regimen (TCH, six cycles, with 1 year of trastuzumab) with AC (four cycles) followed by docetaxel (four cycles) without (AC-D) and with (AC-DT) trastuzumab for 1 year. A total of 3222 patients with early node-positive breast cancer, or high-risk node-negative breast cancer, and HER-2-positive status were enrolled. The projected 4 year disease-free survival for the AC-D arm was 73%, and there were significant improvements over this for both DCT (80%) and AC-DT (84%) (Table 3). These findings confirm the important role of anthracyclines (even in combination with trastuzumab) in treating patients with HER-2-positive breast cancer. A future investigation will be to determine how best to combine anthracyclines with trastuzumab in the adjuvant setting.

Table 3
Improvement in disease-free survival in 3222 patients with HER-2–positive breast cancer treated with a trastuzumab-based regimen in the Breast Cancer International Research Group (BCIRG) 006 trial

Arm		4-year DFS	DFS events
1	AC × 4 cycles → T × 4 cycles + H 1 yr	73%	147*
2	AC × 4 cycles → T × 4 cycles + H 1 yr	84%	77^{+}
3	TC × 6 cycles + H 1 yr	80%	98

DFS, disease-free survival; AC, doxorubicin + cyclophosphamide; T, docetaxel; H, trastuzumab; TC, docetaxel + carboplatin.
* $p = 0.0000005$ between arms 1 and 2; $^{+}$ $p = 0.000153$ between all arms.

5.2. Gemcitabine and capecitabine

Gemcitabine and capecitabine have demonstrated single-agent activity in metastatic breast cancer without severe toxicities in most patients. Both drugs are highly active in combination regimens containing taxanes, and these regimens improve overall survival over single agent taxanes. These data lend support for a synergistic effect and make gemcitabine and capecitabine logical partners to taxanes in the treatment of early breast cancer.

A recent randomised phase III trial has demonstrated high activity with the combination of gemcitabine and paclitaxel in anthracycline-pretreated patients [16]. The combination was associated with significantly improved median overall survival (18.5 versus 15.8 months), response rate (39.3% versus 25.6%), median time to disease progression (5.2 versus 2.9 months) and quality of life compared with paclitaxel alone. Apart from neutropenia, there was no significant increase in toxicity for the combination [16].

Additional trials of gemcitabine in combination with a taxane for the treatment of early breast cancer are ongoing. In a phase III German trial, standard FEC therapy will be followed by taxane with or without gemcitabine. This study is in the process of recruiting a total of 3658 patients. The tAnGo trial is a phase III trial that will investigate the efficacy of epirubicin-based adjuvant chemotherapy followed by paclitaxel or paclitaxel combined with gemcitabine in an every 3-week schedule. The targeted population of 3152 women with early stage breast cancer has been accrued and the first results are awaited in the near future [17]. The NSABP B38 study is a phase III, three-arm trial that will explore the efficacy of three schedules of chemotherapy. The three arms include a combination of docetaxel, doxorubicin and cyclophosphamide (TAC), versus a dose dense (DD) AC followed by paclitaxel (DD AC → P) versus DD AC followed by paclitaxel plus gemcitabine (DD AC → PG). This trial will enrol 3400 patients with node-positive breast cancer and has currently accrued over 2000 patients. Neo-tAnGo is a neoadjuvant study of sequential epirubicin with cyclophosphamide and paclitaxel with or without gemcitabine in the treatment of 800 women with high-risk early breast cancer. A second randomisation will take place in this trial to receive or not to receive bevacizumab [18]. In total, there are in excess of 10,000 patients recruited in adjuvant trials with gemcitabine, 2000 patients recruited in neoadjuvant trials with gemcitabine, and 15,000 patients recruited in trials with capecitabine, all combined with taxanes. We await the results from such large numbers of patients with interest.

6. Conclusions

In the present era where we are rapidly moving from the use of classical prognostic factors towards molecular oncology in breast cancer management, only results from large, well-conducted, prospective trials will shorten the time for the clinical application of new markers and technologies. The evaluation of new biological and cytotoxic drugs in adjuvant therapy remains a high priority. Developing and embracing both new technologies and novel agents will be important in the future to optimise systemic therapy for early stage breast cancer.

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