FOCUS ON: NEW APPROACHES IN BREAST CANCER

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New approaches to the management of early breast cancer

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Abstract
Major changes are occurring in the approach to the management of early breast cancer. Although the incidence is rising steadily, nevertheless mortality is falling significantly in the United Kingdom and throughout the Western world. To a considerable extent this is because of the use of adjuvant medical therapies along with local treatments for early breast cancer. These include the traditional approaches of endocrine therapy and chemotherapy along with newer approaches including so-called targeted biological therapies including trastuzumab (Herceptin). The challenge now is to select which patients benefit best from each of these treatments. It is clear that breast cancer is no longer one disease but a heterogeneous group of subtypes, each with their own biology and pattern of clinical behaviour.

Keywords: Early breast cancer; medical therapy; local treatment.

Does chemotherapy add to the benefit of endocrine therapy?

This has become one of the key issues for the treatment of early oestrogen receptor (ER)-positive breast cancer. Historically, chemotherapy plus tamoxifen has shown additional benefit in terms of reduced recurrence, and the National Comprehensive Cancer Network and St Gallen guidelines for chemotherapy recommend that chemotherapy should be given for node-positive patients and for node-negative patients if adverse grade or size.

However it is becoming clear that this benefit is mainly in patients with ER-negative cancers, and declines with increasing age. A recent study showed increased disease-free survival with chemotherapy plus tamoxifen, compared with tamoxifen alone but subsequent subgroup analysis has not revealed benefit in significant subsets of patients including those with ER-rich or human epidermal growth factor 2 (HER2)-negative tumours, even with nodal involvement.

Overall, it is likely that only a minority of patients with ER-positive breast cancer benefit from chemotherapy in addition to hormone therapy, but traditional parameters, such as node positivity and size do not accurately predict chemotherapy benefit and newer approaches are needed.

Oncotyping and immunohistochemistry

The Oncotype DX assay involves reverse transcription polymerase chain reaction analysis of 16 tumour-related genes plus 5 reference genes to produce a recurrence score (RS). It has shown significant prognostic value beyond that provided by computer-based programmes such as Adjuvant! Online, but correlation between the two was poor.

A meta-analysis integrating Oncotype DX RS data with pathological and clinical (PC) data has produced a risk classification that can be compared with RS alone. Differences in classification of intermediate risk (26.7% and 17.8% for RS and RSPC, respectively) may be significant, given the lack of clear treatment guidance for this group. Further work is being undertaken on RSPC, which will be made available as a free online tool after acceptance for publication.
On the immunological front, an immunohistochemical score (IHC4), based on data from 4 standard markers (ER, progesterone receptor (PR), Ki67 and HER2), may provide similar amounts of prognostic information to Oncotype DX. However, there is a need for IHC4 standardisation across laboratories to reduce variability. Once validated, a key advantage of the IHC4 score over Oncotype DX will be cost.

**Biological therapies including trastuzumab**

Around 20% of early breast cancers amplify and over-express the HER2 cell surface receptor, and in the past this was associated with an adverse prognosis. The development of the monoclonal antibody trastuzumab (Herceptin) was a major milestone in the treatment of breast cancer and several large adjuvant trials have shown a very significant survival improvement when this is given in combination with or sequentially after chemotherapy. Today trastuzumab is a cornerstone in the management of patients with HER2-positive breast cancer but important challenges remain. One is the optimal duration of treatment: the current standard is 1 year but trials are addressing much shorter (as little as 9 weeks) and much longer (up to 2 years) treatment duration. Likewise there is a question mark over the management of very small (<1 cm) HER2-positive cancers whose prognosis may be worse than originally thought and who may also benefit from adjuvant chemotherapy and trastuzumab.

Recently, further anti-HER2 agents have become available for clinical trials including the small molecule oral signal transduction inhibitor, lapatinib, and the monoclonal antibody, pertuzumab. Trials are underway to see if these have superiority to trastuzumab alone or in combination.

The anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab (Avastin) was also studied in phase III trials in metastatic breast cancer but so far with generally disappointing results. A meta-analysis of 3 phase III trials of chemotherapy with or without bevacizumab revealed no significant increase in overall survival compared with chemotherapy alone. Trials of adjuvant bevacizumab in early breast cancer are underway in the hope that this agent will prove more effective against early disease.

**Triple negative breast cancer**

Breast cancer is a heterogeneous disease, and the subtype triple negative (TN) consisting of ER-negative, PR-negative and HER2-negative disease has recently gained prominence as occurring in around 15% of all breast cancers and carrying an adverse prognosis. Distant recurrence in TN breast cancer tends (TNBC) to be earlier than for breast cancers generally, with a shorter median time from distant relapse to death. TNBC is more prevalent in:

- Women younger than 50 years of age
- Women of African or Hispanic origin
- *BRCA1* mutation carriers

Currently, the only treatment is chemotherapy. There are currently no specific treatment guidelines for TNBC, and little trial evidence on which to base therapy decisions. However, experience shows when chemotherapy is used, TNBC has a better partial cytogenetic response rate than all other breast cancer subgroups. In addition, chemosensitive TNBC is associated with improved outcomes.

Several trials have suggested the sensitivity of TNBC disease to platinum-based therapy. Higher efficacy was particularly associated with young age and low *BRCA1* expression. A trial of cisplatin in combination with gemcitabine in TNBC demonstrated a response rate of 62%. However, response rates in other trials of cisplatin in this setting have been disappointing. Although there is no biological rationale for use of anti-VEGF therapies, 3 randomised trials have demonstrated varying degrees of benefit with first-line bevacizumab, and data are due to be presented at the SABCS 2010. However, the NSABP C-08 trial of bevacizumab in TNBC demonstrated no increase in 3-year disease-free survival. A further 3 phase III trials of first-line bevacizumab in TNBC are underway.

**Poly(ADP-ribose) polymerase inhibitors and other targeted therapies in TNBC**

Among other targeted therapies under investigation for use in TNBC, the poly(ADP-ribose) polymerase (PARP) inhibitors show particular promise. PARP has a key role in DNA repair and its inhibition leads to specific tumour cell death. The PARP inhibitor olaparib has demonstrated pathological response in breast cancer patients carrying *BRCA1/2* mutations, and it is reasonable to ask whether it might have an effect in sporadic TN disease, much of which has downregulated *BRCA1* expression. An update of a study of gemcitabine plus carboplatin, with or without the novel PARP inhibitor, iniparib, in TNBC has shown increased overall survival in the iniparib-containing arm. Given the promise shown by PARP inhibitors for the treatment of TNBC, the next steps will be to better identify patients with TNBC who might benefit from such agents and to understand resistance mechanisms to synthetic cytotoxic treatments, such as cisplatin, which are often used in combination with PARP inhibitors because of their cumulative DNA-damaging effect.
Bisphosphonates as adjuvant therapy

Tumour cells destroy bone by interfering with the dynamic balance between osteoclasts and osteoblasts, and recruiting normal cells into a vicious cycle of bone degradation and tumour growth. Bisphosphonates have an antitumour activity that may involve this cycle, or else as a direct effect on all metastatic processes. Bisphosphonates also appear to have a synergistic activity with chemotherapy. Furthermore, in vitro studies suggest doxorubicin followed by zoledronic acid causes a larger decrease in vascularisation of breast tumour cells than either drug alone, both drugs together or zoledronic acid before doxorubicin. There is currently great interest in the use of bisphosphonates for adjuvant treatment of breast cancer, with several studies underway worldwide.

As yet, the mechanisms by which bisphosphonates act on tumours are unknown. One hypothesis is that there are metastatic niches in bone marrow, which act as a sanctuary for stem cells that may prepare the ground for metastases in liver and lung, and which are vulnerable to zoledronic acid. Further work is required. Early results from 3 trials of zoledronic acid in postmenopausal women with early breast cancer are conflicting, but the AZURE trial of zoledronic acid in primary breast cancer suggests an antitumour effect on the primary tumour. Zoledronic acid was well tolerated in this study with osteonecrosis of the jaw reported in 0.6% of recipients.