Advances in Breast Cancer Treatment

a report by

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Breast cancer is the most common malignancy in women living in industrialised countries. Worldwide, it is still the most common cause of cancer death and the most common cause of death in women between 35 and 55 years of age. However, breast cancer mortality has been decreasing in recent years in many industrialised countries such as the UK and the US. Two main explanations have been given for this decline: effective early detection due to more widespread screening efforts and advances in breast cancer systemic therapy. While cure rates as high as 70% seem to be possible in early-stage breast cancer without distant metastases, metastatic breast cancer is still considered incurable using currently available therapies.

In early-stage breast cancer, the 2000 Oxford overview[1] demonstrated a 50% reduction in mortality by a standard anthracycline adjuvant therapy as well as five years of adjuvant endocrine therapy using tamoxifen. With regard to conventional therapies, the addition of taxanes to adjuvant anthracycline-based chemotherapy in node-positive disease and the use of aromatase inhibitors in post-menopausal patients make further mortality reductions likely.

Two major advances in breast cancer treatment have recently changed therapy concepts dramatically. First, accurate risk assessment in early-stage node-negative disease using molecular profiling may avoid overtreatment. Second, the availability of effective targeted therapies has added promising choices to the conventional breast cancer armamentarium. With regard to risk group assessment, urokinase-like plasminogen activator (uPA) and plasminogen activator inhibitor-1 (PAI-1) are the only biomarkers whose clinical efficacy has been proved at the highest level of evidence by a prospective clinical trial.[2] A second confirmatory node-negative breast cancer trial (NNBC)-3 evaluating optimised chemotherapy in high-risk node-negative patients is planned, with more than 2,100 patients recruited at present (for more information see www.germanbreastgroup.de; see also *Figure 1*). Node-negative patients with low levels of uPA and PAI-1 in their primary tumour tissue have an excellent chance of surviving breast cancer, with about a 95% five-year survival rate without any adjuvant systemic therapy. Patients with high levels of either or both factors are at increased risk of relapse compared with patients who have auxiliary lymph node involvement.

Widespread international use of these markers is hampered by the demand for fresh frozen tissue for enzyme-linked immunosorbent assay (ELISA) testing.[3] However, in their annually updated evidence-based guidelines the German Working Group for Gynaecological Oncology (AGO) accepted both factors from 2002 onwards as risk-group classification markers for routine clinical decision-making in node-negative breast cancer, complementing established clinical–pathological factors (for more information see www.ago-online.org). Recently, uPA and PAI-1 have also been recommended for routine clinical use by the American Society of Clinical Oncology (ASCO) tumour marker panel based on the high level of evidence for these markers.[4] Moreover, the predictive impact of high uPA/PAI-1 for enhanced benefit from adjuvant chemotherapy may be considered in individual patients.[5]

For other promising molecular tests, the first clinical trials have just been started, such as The Trial Assigning Individualized Options for Treatment Rx (TAILORx) in the US, using the recurrence score,[6] and Microarray In Node-negative Disease may Avoid Chemotherapy (MINDACT), run by TransBIG using the Amsterdam 70-gene signature[7] for risk assessment. Other gene signatures, such as the 76-gene signature, have also been thoroughly validated for clinically relevant risk group stratification,[8] although not in a prospective clinical trial. The ASCO tumour marker panel also accepted the 21-gene recurrence score (oncotype DX) for routine clinical use.[4]

While endocrine therapy directed against steroid hormone receptors is certainly the oldest form of targeted therapy, novel tumour biological targets have become decisive for therapy decision-making in recent years. To date, the most important novel target is human epidermal growth factor receptor 2 (HER2), a tyrosine kinase growth factor receptor that is overexpressed in about 20–25% of all breast cancers.

Patients with HER2-positive tumours (either overexpression by immunohistochemistry or gene amplification by fluorescence *in situ* hybridisation [FISH]) derive significant benefit from trastuzumab antibody therapy in the advanced setting as well as in early stages of the disease. In adjuvant therapy, one year of trastuzumab therapy given concomitantly

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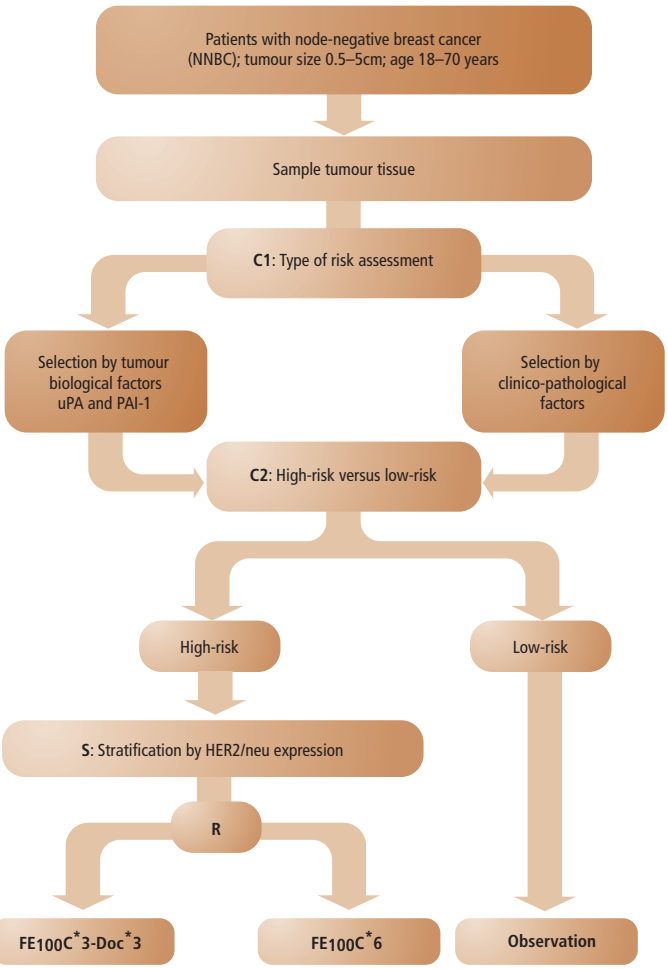
with[9,10] or subsequent to[11] adjuvant chemotherapy cuts the risk of relapse by almost half. Such a dramatic risk reduction in adjuvant therapy is unprecedented. On the basis of the available data from four large phase III adjuvant trials, trastuzumab was approved for adjuvant therapy in Europe in May 2006. In metastatic breast cancer, trastuzumab has been approved for combination with taxane chemotherapy or as monotherapy for more than five years. However, so far treatment strategies after trastuzumab failure have not been supported by data from randomised clinical trials. At the ASCO 2006 meeting, lapatinib, a small orally available tyrosine kinase inhibitor (TKI), was shown for the first time to be more effective in combination with capecitabine chemotherapy than the same monochemotherapy alone in patients after anthracycline, taxane and trastuzumab failure.[12] Moreover, there are now preliminary data suggesting that this orally available TKI may be able to cross the blood–brain barrier and thus be effective against brain metastases in HER2-positive disease, which, so far, pose a significant therapeutic problem. Based on the pivotal trial data,[12] lapatinib has since been approved for metastatic breast cancer (MBC) in the US, although European Medicines Agency (EMEA) approval is still pending.

Angiogenesis plays an important role in the growth and spread of all types of solid tumour. Vascular endothelial growth factor (VEGF), a key mediator of angiogenesis, and other angiogenesis markers have been associated with outcome in breast cancer. Several antiangiogenic agents are in development for breast cancer; of these, bevacizumab (a humanised monoclonal antiVEGF antibody) has been the most thoroughly investigated to date. It was the first antiangiogenic agent to demonstrate efficacy benefit in MBC,[13] with two phase III trials showing improved response rate and time to progression for the combination of chemotherapy (capecitabine[13] or paclitaxel[14]) and bevacizumab versus chemotherapy alone. Moreover, in this indication the toxicity profile was quite acceptable, with hypertension being the most frequent toxicity reported. In March 2007, the combination of paclitaxel with bevavizumab was approved by the EMEA for first-line MBC based on the registration trial by Miller et al.[14] Ongoing phase III trials are now investigating the efficacy of bevacizumab and other agents in MBC, including HER2- or hormone-receptor-positive disease, as well as in the adjuvant or neoadjuvant setting. In addition, sunitinib – a multi-TKI that is directed against VEGF receptor, as well as other tumour cell TKIs, and which has recently been approved for both renal cell cancer and gastrointestinal stromal tumour after failure of standard therapy – is currently being investigated in phase III trials in metastatic breast cancer. Many more novel agents targeting signal transduction, tumour angiogenesis or metastasis are currently being evaluated in clinical phase I–III trials.

Conclusions

A more thorough understanding of tumour biology has led to significant advances in breast cancer management today. Molecular markers such as uPA/PAI-1, the recurrence score or messenger RNA (mRNA) profiles, such as the 70 or 76 gene profile, are able to select patients with early-stage disease who can be spared the burden of adjuvant chemotherapy due to their excellent prognosis. Other molecular markers serve as targets for promising targeted therapies that have the potential to enhance the efficacy of conventional therapeutic approaches such as chemotherapy or endocrine therapy. Trastuzumab, an antibody directed against HER2-positive tumours, has become standard in adjuvant as well as palliative breast cancer therapy. After trastuzumab failure, lapatinib, a small orally available TKI, has shown significant efficacy and is now being evaluated in early-stage breast cancer as well. Moreover, bevacizumab and other agents targeting tumour angiogenesis are currently being evaluated in clinical phase II–III trials in HER2-positive and HER2-negative disease. Future therapy concepts in breast cancer will need to incorporate molecular risk assessment as well as novel targeted agents for optimal individualised therapy concepts. ■

Figure 1: Node-negative Breast Cancer-3 Trial Comparing Tumour Biological Factors uPA/PAI-1 with Clinicopathological Criteria for Risk Stratification in Node-negative Breast Cancer



The trial aims at avoiding overtreatment for low-risk node-negative patients as well as optimising therapy for high-risk node-negative patients. It is run by the German Working Group for Gynacological Oncology (AGO) and the German Breast Group (GBG) and as of 21 November 2007 has randomised 2,106 patients.

1. Early Breast Cancer Trialists' Collaborative Group, *Lancet*, 2005;365:1687–1717.
2. Jänicke F, et al., *J Natl Cancer Inst*, 2001;93:913–20.
3. Harbeck N, et al., *J Clin Oncol*, 2002;20:1000–7.
4. Harris L, et al., *J Clin Oncol*, 2007;33:5287–5312.
5. Harbeck N, et al., *Cancer Res*, 2002;62:4617–22.
6. Paik S, et al., *N Engl J Med*, 2004;351:2817–26.
7. van Veer L, et al., *Nature*, 2002;415:530–36.
8. Foekens JA, et al., *J Clin Oncol*, 2006;24:1665–1771.
9. Romond EH, et al., *N Engl J Med*, 2005;353(16):1673–84.
10. Slamon D, et al., Phase III randomised trial comparing doxorubicin and cyclophosphamide followed by docetaxel (ACT) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (ACTH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2-positive early breast cancer patients: BCIRG 006 study, San Antonio Breast Cancer Symposium, 2005;1.
11. Piccart-Gebhart MJ, et al., *N Engl J Med*, 2005;353(16): 1659–72.
12. Geyer CE, et al., *N Engl J Med*, 2006;355:2733–43.
13. Miller KD, et al., *J Clin Oncol*, 2005;23(4):792–9.
14. Miller KD, et al., *Breast Cancer Res Treat*, 2005;94(Suppl. 1): S6, abstract 3.