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Bevacizumab: the first anti-angiogenic agent approved for the treatment of metastatic breast cancer

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ABSTRACT

The complexity of options available for breast cancer treatment dictates that therapeutic decisions are made on an individualised basis. Subsets of tumours defined in part by steroid hormone receptor and human epidermal growth factor receptor 2 (HER2) status have been identified. Endocrine therapy and the HER2-targeted antibody, trastuzumab, have improved the prognosis for those patients whose tumours express the respective targets. Similar therapeutic advances for patients whose tumours lack these markers have not occurred in the metastatic setting. Tumour growth and proliferation is known to be reliant on angiogenesis, and vascular endothelial growth factor (VEGF) is a key pro-angiogenic mediator. Bevacizumab, a humanised anti-VEGF monoclonal antibody, is the first anti-angiogenic agent to demonstrate clinical benefit when combined with chemotherapy in metastatic breast cancer, providing a doubling of progression-free survival with a manageable safety profile. This supplement considers the development, mode of action, clinical data and future therapeutic use of this agent in breast cancer.

1. Introduction

Breast cancer is the most common malignancy in women with in excess of 1,100,000 cases diagnosed worldwide in 2002.[1] Over 400,000 deaths from breast cancer were reported that year, so despite a relatively good prognosis, breast cancer remains the leading cause of cancer mortality in women.[1] Many women still develop recurrent or metastatic breast cancer, although progress has been made in screening, diagnosis and treatment of early disease. These improvements have led to mortality rates from breast cancer falling steadily in many countries since the early 1990s (Figure 1).[2] Once metastasis has occurred, the disease is considered incurable and treatment is aimed at delaying disease progression, lengthening survival, relieving symptoms and maintaining or improving quality of life. Treatment of advanced breast cancer is complex, with an array of endocrine, chemotherapy and targeted therapy (currently only trastuzumab, bevacizumab and lapatinib) agents available for use in a variety of sequences and combinations. Treatment decisions are made on an individualised basis and are guided by a number of factors, including:[3]

- duration of relapse-free interval since primary diagnosis of breast cancer
- extent and distribution of metastases

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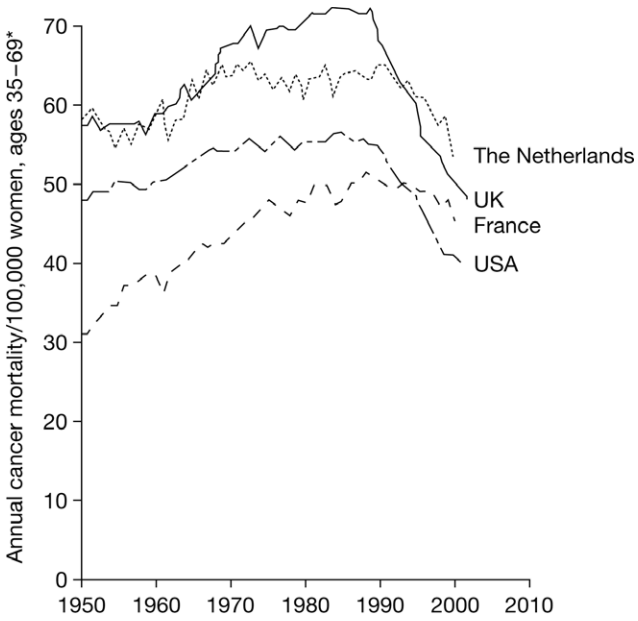
- previous treatments (their effects and tolerance)
- patient symptoms and preference
- anticipated side effects of treatment
- availability and access to treatment.

In addition to these factors, two of the most important considerations in therapy choice relate to the identification of subsets of tumours based on hormone receptor status and human epidermal growth factor receptor 2 (HER2) status.



*Mean of annual rates in the component 5-year age groups

Fig. 1 – Trends since 1950 in age-standardised (35–69) breast cancer mortality rates in four countries.[2] Reprinted from: Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1742, with permission from Elsevier; © 2005.

Breast cancer overview – GLOBOCAN 2002[1]

Number of female cases worldwide: 1,151,298
  Developed countries: 636,000
  Developing countries: 514,000

Proportion of all female cancers: 23%

Number of deaths: 410,712

Proportion of all female cancer deaths: 14%

Age-adjusted survival
  Developed countries: 73%
  Developing countries: 57%

2. Hormonal therapy

While it has been apparent for over a century that steroid sex hormones such as oestrogen play a role in breast cancer, it was not until the early 1970s that the oestrogen receptor (ER) was characterised and an assay developed for its identification. Approximately two-thirds of breast cancers express significant levels of this receptor, with a smaller number expressing the progesterone receptor. The testing of the tumour hormone receptor status of each patient's tumour has now become a key component of care due to its importance as a predictor of response to endocrine therapies.[4,5]

Having generally more acceptable tolerability profiles than chemotherapy, hormonal agents are currently recommended as first-line treatment in most patients with hormone-sensitive metastatic disease.[3,6] Currently available endocrine therapies include selective ER modulators (e.g. tamoxifen) and aromatase inhibitors (e.g. anastrozole, letrozole and exemestane). Tamoxifen was first approved for metastatic breast cancer 30 years ago and has long been considered the gold standard of therapy for hormone-sensitive disease. However, in postmenopausal women with advanced disease, the aromatase inhibitors have been shown to be as or more effective than tamoxifen with reduced toxicity in terms of lower incidences of vaginal bleeding, endometrial hyperplasia and malignancy, and thromboembolic events.[7] Other toxicities, including the depletion of bone mineral density that is associated with increased risk of fractures, are higher with the aromatase inhibitors.[8] Some current guidelines, including those produced by ESMO,[9] recommend consideration of the use of a third-generation aromatase inhibitor as first-line endocrine therapy for postmenopausal women with metastatic breast cancer,[3] although other guidelines, for example those from ASCO,[10] are less certain. Decisions here also need to consider the adjuvant use of these agents preceding relapse.

3. HER2-targeted therapy

More recently, a further marker of prognostic and predictive significance has been identified, HER2 overexpression. HER2 is amplified and/or overexpressed in approximately 20% of breast cancers[11] and this is associated with clinically aggressive disease, poorer prognosis and shorter time to relapse,[12–14] thus testing for HER2 status is recommended in each breast cancer patient.

3.1. *Trastuzumab (Herceptin®)*

Trastuzumab, a humanised monoclonal antibody, was the first agent developed to target the HER2 pathway and is now recommended for the first-line treatment of patients with HER2-positive metastatic disease.[3] While trastuzumab monotherapy is active and well tolerated in

the first- and at least second-line settings for metastatic breast cancer,[15–17] combining the antibody with certain chemotherapeutic agents leads to increased benefits in this patient population.[18,19] In a randomised phase III trial, the addition of trastuzumab to chemotherapy (either an anthracycline plus cyclophosphamide or paclitaxel) significantly increased median time to disease progression (7.4 vs. 4.6 months, $p < 0.001$) and median overall survival (25.1 vs. 20.3 months, $p = 0.046$).[18] Similar benefit was produced in a large, randomised phase II trial when trastuzumab was added to docetaxel (median time to progression 11.7 vs. 6.1 months, $p = 0.0001$; median overall survival 31.2 vs. 22.7 months, $p = 0.0325$).[19] The combination of trastuzumab with anastrozole in postmenopausal patients with HER2-positive, hormone receptor-positive metastatic breast cancer significantly improved time to disease progression (4.8 vs. 2.4 months, $p = 0.0007$), but not median overall survival (28.5 vs. 23.9 months, $p = 0.325$) compared with anastrozole alone.[20] Four large trials including >13,000 women with early breast cancer have since demonstrated the remarkable benefit of using trastuzumab with different chemotherapy combinations in the adjuvant setting. Overall, trastuzumab reduced the 3-year risk of recurrence by about 40–50%. This finding was similar across the trials regardless of patient population, chemotherapy regimen or treatment sequence.[21] The use of trastuzumab has dramatically changed the outlook for patients with HER2-positive disease, resulting in a marked improvement in prognosis.

3.2. *Lapatinib (Tyverb®/Tykerb®)*

Lapatinib is an oral small molecule dual-action tyrosine kinase inhibitor of both HER2 and epidermal growth factor receptor 1. It is currently under evaluation for the treatment of various solid tumours, and has recently been approved by the FDA for the treatment of HER2-positive breast cancer that has progressed following treatment with trastuzumab. In a phase III open-label trial, the addition of lapatinib to capecitabine led to a significant improvement in time to progression (8.4 vs. 4.4 months, hazard ratio = 0.49, $p < 0.001$) in patients who had progressed following prior treatment with an anthracycline, a taxane and trastuzumab, but overall survival was not significantly increased ($p = 0.72$).[22] When an updated efficacy analysis was published, the time to progression improvement with lapatinib, as assessed by an independent review panel, was still significant, but the hazard ratio had increased to 0.57.[23] Further trials of lapatinib in both refractory patients and in the first-line setting are now in progress.

4. The current picture

Although treatment options and outlook have improved over the years for patients with HER2-positive disease, challenges still remain for the majority of patients who have HER2-negative cancer. These patients are a heterogeneous group, some of whom have a better initial prognosis (e.g. hormone-receptor positive – more indolent disease but a continuous and persistent risk of relapse) and some that have a worse prognosis (e.g. hormone receptor- and HER2-negative) with a high initial event rate. In the long term, however, patients have a similar prognosis irrespective of whether their disease is hormone responsive.[24] Systemic treatment options for patients with tumours negative for both hormone receptor and HER2 overexpression, so-called 'triple-negative' phenotypes, were until recently limited in their systemic treatment options to chemotherapy alone. Recently, a basal phenotype, characterised by the expression of basal cytokeratin and other myoepithelial markers, has been identified as a prognostic marker in patients with triple-negative disease.[25] This subset of patients may require a more aggressive treatment approach than those with non-basal phenotype.

At present, the hormone receptor and HER2 status of breast cancer metastases are rarely tested when the status of the primary tumour is known. Studies comparing HER2 status in primary breast tumours and their metastases found an 86–94% concordance between the two suggesting that, although rare, alterations in HER2 status do occur.[26,27] This is unlikely to explain acquired resistance to trastuzumab therapy, however, as the vast majority of cases involved the gain rather than loss of HER2 positivity, including one study in which nine of 24 (37.5%) HER2-negative primary tumours acquired positivity in circulating tumour cells during progression.[28] Alterations in hormone receptor status between primary and secondary breast cancers occur more frequently, with one study reporting an overall discordance rate of 36% in patients who had not received adjuvant systemic therapy.[29] In contrast to the findings with HER2, all reported changes in this study were due to loss of receptor-positive status and were found to correlate with poor response to subsequent endocrine therapy.[29] A second, larger study, however, found both gain and loss of ER positivity.[29,30] Rates of loss of ER-positive status have been reported as 22–24%,[29,30] and may be increased slightly by the use of adjuvant endocrine therapy, but not chemotherapy.[30] These findings suggest that routine testing of hormone receptor, and possibly HER2, status in secondary breast cancer may be advisable in order to optimise therapeutic decisions.

Cytotoxic treatment for breast cancer continues to evolve and advances have been made over the years, with active chemotherapy agents such as the anthracyclines and taxanes becoming available. Use of cytotoxic chemotherapies and hormonal agents in the adjuvant setting have substantially reduced the likelihood of recurrence and increased 15-year survival

rates.[2] The extent of the improvement achieved depends on factors such as patient age, receptor status and the therapeutic regimen chosen. However, despite extensive research assessing new single agents, sequential and combination therapy as well as new approaches to dosing, improvements in the treatment of metastatic breast cancer have been largely disappointing.

4.1. *Bevacizumab (Avastin®)*

Over the past 4 decades, our understanding of tumour biology and molecular pathways has highlighted the importance of angiogenesis to tumour growth and metastasis.[31] Targeted agents are in development to disrupt this process and have potential broad utility for all patients regardless of HER2 or hormone receptor status. To date, no predictive marker has been identified for response to such agents, but as all tumours rely on a blood supply, such a marker may not be necessary.

Angiogenesis is essential for tumour growth and proliferation, and vascular endothelial growth factor (VEGF) is a key mediator of this process.[32] An overview of the role of VEGF and angiogenesis in tumour growth is provided in the next article of this supplement by Dr Joachim Drevs.

Bevacizumab is a monoclonal antibody against VEGF and the first anti-angiogenic agent to be approved for the treatment of metastatic breast cancer. This agent is the humanised form of a murine anti-human VEGF monoclonal antibody, A4.6.1.[33] Preclinical studies have demonstrated the anti-angiogenic and antitumour effects of A4.6.1 in various cell lines in nude mice,[34–36] including the breast cancer cell line MDA-MB 435.[33] Via the inhibition of VEGF, bevacizumab causes the regression, normalisation and inhibition of tumour vasculature,[37,38] reducing the nutrient supply of the growing tumour and allowing more efficient delivery of chemotherapy agents. Clinical trials across a variety of tumour types have led to its current approval for the treatment of metastatic colorectal cancer, non-small cell lung cancer, renal cell cancer and now metastatic breast cancer.

In the following article, 'Clinical data for anti-angiogenic agents in previously treated advanced breast cancer', Professor Nadia Harbeck reviews the early clinical data for bevacizumab and other agents that inhibit the VEGF pathway. Bevacizumab has been investigated in advanced or metastatic breast cancer in combination with a number of commonly used chemotherapy regimens, including capecitabine,[39] vinorelbine,[40] docetaxel,[41] and metronomic cyclophosphamide plus methotrexate.[42] All combinations demonstrated activity, suggesting a role for bevacizumab as a backbone of first-line therapy for advanced breast cancer. These trials led to the design of the E2100 study, in which bevacizumab was combined with paclitaxel in the first-line treatment of patients with metastatic breast cancer. An overview of this pivotal trial is provided by Professor David Cameron and includes coverage of the significant benefits achieved in the first-line setting (a doubling of progression-free survival) for all patient subgroups with the addition of bevacizumab to paclitaxel[43] (see 'Bevacizumab in the first-line treatment of metastatic breast cancer').

Bevacizumab is generally well tolerated, with an adverse event profile that differs from those of chemotherapy agents. The most common adverse events observed in trials of breast cancer and other malignancies include hypertension, proteinuria, wound-healing complications and minor mucocutaneous bleeding events. The effects of blocking VEGF action are thought to underlie the observed adverse events. Dr David Miles describes the safety profile of bevacizumab across indications, outlining how common adverse events can be managed (see 'Management of toxicity in patients receiving therapy with bevacizumab').

To date, agents providing clinical benefit in advanced disease have also proven efficacious in earlier settings. This has been the case for the aromatase inhibitors, taxanes and trastuzumab and, based on its mechanism of action, would appear likely for bevacizumab. Investigations of bevacizumab in breast cancer have now progressed from advanced to early disease and the exploration of the role for this agent in the adjuvant and neoadjuvant settings. In the adjuvant setting, inhibition of angiogenesis may prove to be highly effective, as the very early stages of tumour development are dependent upon VEGF for malignant growth and proliferation. Thus, bevacizumab may help to prevent the growth and spread of existing micrometastases. In the neoadjuvant setting, regression and normalisation of existing tumour vasculature may be more important, causing the tumour to shrink, thus allowing resection. A description of ongoing trials of bevacizumab in these settings can be found in the final paper of the supplement, together with a discussion of rational future development opportunities for this VEGF inhibitor based on its mode of action. Although bevacizumab functions by inhibiting a specific molecular target, no test is available to select patients for bevacizumab therapy. Several of the ongoing trials described in this supplement incorporate molecular studies in an attempt to identify predictive markers for benefit from this agent. To date, however, attempts to correlate potential markers, including baseline tumour and/or plasma VEGF levels, with benefit from bevacizumab in large clinical trials in several tumour types have proved unsuccessful.[44–47] In order to better understand the biology of metastatic breast lesions, biopsy and functional imaging studies will be needed, aimed at finding therapy-predictive gene- or protein-based signatures and to detect early responses.

Recent improvements in breast cancer therapy

Third-generation aromatase inhibitors: anastrozole, letrozole, exemestane

HER2-targeted agents: trastuzumab, lapatinib

Angiogenesis inhibitors: bevacizumab

5. Conclusions

Notable advances have been made in the treatment of patients with hormone receptor-positive and HER2-positive breast cancer. However, an improved understanding of the critical role of angiogenesis in tumour viability and progression has led to a novel therapeutic approach for those with triple-negative disease. While bevacizumab may potentially benefit patients with triple-negative disease, results of trials testing this hypothesis are not currently available, other than in the subgroup of such patients in the E2100 study, where a similar benefit was seen for all patients in the trial (see 'Bevacizumab in the first-line treatment of metastatic breast cancer').

As the first anti-angiogenic agent to demonstrate significant clinical benefit by improving progression-free survival when combined with paclitaxel for first-line breast cancer therapy, bevacizumab is now being investigated in a variety of treatment combinations and disease settings. Clinical trial results across indications suggest that bevacizumab is well tolerated by most patients, with long-term safety studies in progress. This supplement provides an overview of the history and development of anti-angiogenic therapy, a review of the most current efficacy and safety data for bevacizumab within the metastatic breast cancer setting, and a snapshot of what lies ahead for this important and unique molecule.

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Conflict of interest statement

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