New developments in the treatment of metastatic breast cancer: from chemotherapy to biological therapy

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Introduction

The management of metastatic breast cancer (MBC) is a major challenge for medical oncologists. MBC is still almost always incurable and the average survival time for patients after diagnosis of metastatic disease is 18–30 months. As a consequence, the current therapeutic goals are palliative, including symptoms control, disease control with prolongation of survival and quality of life improvement. To achieve these goals, the optimal choice of treatment must be driven by disease and patient characteristics. Clinical parameters such as age of patient, performance status, disease-free interval, numbers and sites of lesions (soft tissue, bone, viscera) are routinely integrated with biological factors (estrogen receptor/progesterone receptor status, overexpression of HER2-neu) when deciding treatment. Patient preference is also an important consideration, and treatment decision should always be made after exhaustive discussion of all options with the patient.

Hormonal therapy is effective in 30% of patients, some of whom derive long-term benefit from sequential hormonal manipulations. Most patients have hormone-refractory tumors, and eventually all breast cancers become hormone resistant. Cytotoxic chemotherapy is the treatment of choice for these patients.

The progressive introduction of new agents into clinical practice represents an important development in the treatment of MBC. How do we apply these new drugs in clinical practice? In view of the fact that palliation rather than cure is the most likely result of therapeutic intervention in patients with advanced breast cancer, the safety profile and the possibility of chronic administration at the cost of good tolerability are crucial elements in the evaluation of new drugs.

Chemotherapy

Historically, anthracyclines (doxorubicin and epirubicin) represented a standard of care in MBC. Two meta-analyses and several trials showed that anthracycline-containing regimens produced objective responses in a higher percentage of patients, and that time to progression or response duration was longer than with combinations that did not contain an anthracycline [1–3]. There is also evidence that some patients with complete responses when treated with anthracycline-containing regimes [5-fluorouracil, doxorubicin and cyclophosphamide (FAC)] in the first-line metastatic setting may see a benefit in terms of long-term survival, confirming the use of this chemotherapy for patients with potentially chemo-sensitive breast cancer (M. D. Anderson experience, 36%, 26% and 24% survival evaluated after 5, 10 and 15 years, respectively) [4, 5].

The increasing use of chemotherapy, particularly anthracycline-based regimens, in the adjuvant setting has highlighted the need for new treatment options for metastatic disease. Among the novel chemotherapeutic drugs introduced in the 1990s, taxanes have emerged as the most powerful compounds in breast cancer, and their introduction into the clinic represents an important step in improving the efficacy of cytotoxic therapy.

Paclitaxel was the first taxane to show activity in breast cancer. This drug produces objective responses in 40% to 60% of patients with untreated or minimally treated MBC. The efficacy of this agent persists in patients with chemotherapy-refractory tumors, including those with anthracycline resistance [6, 7]. Docetaxel was subsequently developed, and several phase II and III trials reported high activity in first- and second-line therapy of MBC, as well as in patients previously exposed or resistant to anthracyclines [8–11]. The results of these studies, taken together, indicate that paclitaxel and docetaxel are effective as single agents and as part of combination regimens in the treatment of MBC, and that taxane-containing regimens are generally reported to be superior to non-taxane containing ones [8, 12–14]. Based on this evidence, taxanes are now considered among the most active agents for the management of MBC.

The combined use of taxanes with anthracyclines was the next logical step for the development of highly effective chemotherapy combinations and to test their role in MBC, as well as to proceed to adjuvant strategies. Several phase III randomized trials have compared anthracycline–taxane combinations to standard anthracycline-based regimes [15–19]. These studies showed better response rates in the taxane arm (Nabholtz et al., AD versus AC: 59% versus 47%; Mackey et al., TAC versus FAC: 54% versus 43%) than in the standard arm. No significant improvements in complete responses have been
Combination with hormonal agents and with newer targeted agents represents another interesting approach. Several trials of trastuzumab plus hormonal therapy are now ongoing or are planned to test the association with either tamoxifen or new aromatase inhibitors [31, 32].

In more recent years, much was expected from the use of novel HER-targeted agents. In particular, small-molecule tyrosine kinase inhibitors (TKIs) such as erlotinib (Tarceva®) and gefinitib (Iressa®) are both HER1/EGFR-targeted reversible TKIs, and several phase I/II trials showed encouraging results in a range of tumor types [33, 34]. In breast cancer patients, co-overexpression of HER1 and HER2 gave a poorer prognosis than overexpression of either agent alone [35, 36]. Based on this observation, the combination of these two agents may eventually represent a new and useful treatment for breast cancer patients [37]. Furthermore, agents targeting other pathways, such as the Ras pathway with farnesyl transferase inhibitors (FTIs), and mTOR with rapamycin analogs are currently under investigation. FTIs are a group of agents that target the Ras family and their downstream signaling pathways. Less than 2% of breast cancers have mutations of the Ras gene. However, continuous activation of Ras pathways can occur because of permanent upstream growth factors activation, so that aberrant function of the Ras signal transduction pathway is common in breast cancer [38].

Targeted therapy with anti-HER2 agents is therefore an exciting area of research and represents an important step in the management of MBC. Considering that single-agent therapy will not significantly improve the time to disease progression and overall survival, the investigation of trastuzumab in combination with novel biological agents based on potential synergies could lead to efficacious and well tolerated regimens, specifically tailored to the patient’s particular characteristics. Several trials are ongoing and we have to await their results to clarify the role of these targeted agents in the treatment of breast cancer and, consequently, their applicability into clinical practice.

As mentioned above, patients with metastatic disease are treated with many chemotherapeutic agents and, more recently, with ‘targeted therapy’, generally in sequence, until no further palliative benefit can be expected. There is no ideal approach, since none is curative in this situation, but there may be better and worse choices for particular patients in particular situations. Our historical approach to treatment could be summarized as ‘one fits all’, but we have to consider the extreme heterogeneity of breast cancer and the role of predictive factors in tailoring therapy. The real problem is how to select the patient and consequently the treatment.

Recent advances in molecular techniques hold the potential of revolutionizing clinical practice. In particular, microarray technology hold the promise of further increasing our understanding of the complexity and heterogeneity of breast cancer, providing new information for the prognostication and prediction of breast cancer outcome. The application of gene expression profiling for studying breast cancer will likely become a tool for better characterizing patients, and eventually tailoring treatment to individual needs [39–43].
References


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