Management of advanced breast cancer

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Metastatic breast cancer (MBC) is usually considered an incurable situation, for which treatments chosen to control the disease, should take into account the maintenance of a good quality of life. The end points of treatment of patients with MBC are influenced by consideration about efficacy and toxicity of the different therapeutic options. The availability of markers predicting response to treatment as well as the discovery of new agents have led to the identification of patients likely to obtain significant advantage from different treatment options. Due to the chronic nature of the MBC, the clinical benefit which encompasses objective response and long stabilization of disease has often become a goal in the metastasing setting.

Key words: metastatic breast cancer, predictive factors

introduction

Metastatic breast cancer (MBC) is a chronic disease requiring specific strategies to control disease progression and related symptoms. Treatment can assure a significant prolongation of survival, symptomatic control and maintenance of quality of life [1, 2]. The decision-making strategy in choosing therapies for patients with MBC depends on different factors involving tumor features, host factors, physician and patient preferences. MBC is considered not curable, with a median survival of 2–4 years for women with MBC at diagnosis [3]. Despite the introduction of new therapeutic options, the impact of therapies on survival is usually very small. Improvement in time to progression (TTP) and in duration of response, however, has been achieved with newer combination or new agent.

The course of MBC is heterogeneous and treatment options should be chosen to increase total duration of the time with no or few disease-related symptoms, with the lowest costs in terms of side-effects of treatment.

treatment options

It is generally accepted that treatment should be offered immediately after diagnosis of metastases, attempting to defer the appearance of symptoms. The decision-making process is complex and requires tailored therapies on the basis of extension of disease, tumor-related symptoms, comorbidities, initial estimation of survival, time to expected response to treatment, patient preference and quality of life. The appropriate therapy is based on predictive factors able to guide the therapeutic decision. In the presence of estrogen receptor (ER)-positive disease, usually endocrine therapy can achieve an overall response rate ranging from 30% to 60%, while similar results are obtained with the use of chemotherapy in case of ER-negative disease. Between these scenarios there is a range of different diseases defined by the grade of endocrine responsiveness or by the lack of information about hormonal receptors for which clinical information assume great relevance. The presence of a long disease-free interval (DFI) from the first diagnosis of breast cancer and the onset of metastasis, bone and/or soft tissue involvement, response to previous endocrine manipulations, and absence of HER2/neu overexpression define a subpopulation more likely to benefit from endocrine therapy.

endocrine therapy

Endocrine therapies are usually well tolerated, enhancing their acceptability as a therapeutic option for patients with MBC. Endocrine therapy should generally be considered as initial treatment of patients with newly diagnosed metastatic disease if the patient’s tumor is ER positive, progesterone receptor (PR) positive, or ER/PR unknown, about one third of patients respond to endocrine therapy with median duration of response of 8–14 months. Chances of response are higher if ER positive (50%–60% response rate) and/or prolonged DFI, with metastatic presentation of soft tissue or bone alone. Moreover, response to one endocrine therapy predicts a higher chance of effectiveness with subsequent hormonal manipulations. The chance of subsequent response, however, decreases after the first line of endocrine therapy [4].

The third-generation aromatase inhibitors have provided new approaches to the endocrine treatment of MBC. Letrozole and anastrozole have been shown to be superior to tamoxifen as first-line treatment of advanced disease. Letrozole resulted in more tumor regression and was associated with longer time to
been tested, in order to optimize the antiangiogenic effects, to minimize toxicity and overcome the repair of endothelial cells. The availability of low toxic and easily delivered regimens that may be administered for a long duration without significant toxicity could provide an effective therapy and a good quality of life. Recently, two trials have shown a response rate of 19% and 20.9% and a clinical benefit (partial remission plus complete remission plus stable disease ≥24 weeks) of about 40% with the use of low-dose cyclophosphamide (50 mg daily) plus methotrexate (5 mg daily twice a week) in patients with MBC [12, 13].

**biologic therapy**

The overexpression of Her2/neu (human epidermal growth factor receptor 2) represents the only reliable predictive factor other than hormone receptors of response to treatments. Her2/neu is overexpressed in 20%–25% of breast cancer, indicating a role for its overexpression in tumorigenesis. Breast cancer that overexpresses Her2 has a more aggressive course and higher relapse and mortality. Trastuzumab is a humanized mAb directed against the extracellular domain of Her2. Trastuzumab alone or in combination with chemotherapy has led to an increase in overall response rate and survival for cancers overexpressing Her2/neu.

Trastuzumab as a single agent resulted in a response rate of 21% in patients pretreated with chemotherapy. Patients treated with chemotherapy plus trastuzumab had an OS advantage as compared with those receiving chemotherapy alone (25.1 versus 20.3 months, \( P = 0.05 \)) [14].

Vascular endothelial growth factor (VEGF) is the most potent and specific antigenic factor and has been identified as a crucial regulator of both normal and pathological angiogenesis. The recombinant humanized anti-human VEGF mAb (bevacizumab) inhibits several activities of VEGF, including endothelial cell growth, vascular permeability and angiogenesis.

Synergy with many cancer chemotherapeutic agents was observed in preclinical studies and in phase I and phase II trials and confirmed in phase III trials. Bevacizumab both alone and in combination with chemotherapy was well tolerated, with hypertension, proteinuria, thrombosis and bleeding being the most commonly reported toxic effects.

A phase II, open-label clinical trial of bevacizumab monotherapy produced encouraging results in patients with breast cancer [15]. This study treated 75 patients with MBC with bevacizumab at escalating doses of \( 3 (n = 18) \), \( 10 (n = 41) \), and \( 20 \text{ mg/kg (} n = 16 \text{) administered intravenously every other week. Objective responses were documented in seven of 75 (9.3%, 6.7% confirmed) patients. The median duration of confirmed response was 5.5 months (range 2.3–13.7 months), with one ongoing partial response at 10 months. The optimal dosage of bevacizumab in that trial was found to be 10 mg/kg every other week, and toxicity was deemed to be acceptable, as only four patients (5.3%) stopped bevacizumab because of adverse events. In another phase II trial, patients received bevacizumab (at a dose of 10 mg/kg every 2 weeks) and vinorelbine at a dose of 25 mg/m\(^2\)/week until progression. This trial has observed 17 responses (one complete and 16 partial) among 55 patients (31% objective response rate) [16]. Bevacizumab was also studied in a phase III clinical trial in...
which previously treated patients with MBC were randomized to treatment with capecitabine alone or capecitabine plus bevacizumab. Although adding bevacizumab to capecitabine produced a highly statistically significant greater objective response rate (19.8% versus 9.1%), in the primary end point of the study, there was no effect on progression-free survival (PFS). Responses to bevacizumab tended to be short and were, therefore, not translated into improved PFS times, which were equivalent at 4.9 months in the combination arm and 4.2 months in the capecitabine-alone arm. Recently, a phase III randomized trial which compared paclitaxel with a combination of bevacizumab plus paclitaxel as first-line treatment of MBC reported an increased objective response rate (28.2% versus 14.2%) and improved PFS with bevacizumab and paclitaxel.

conclusions
Metastatic disease is a chronic disease and the impact of therapy on improvement in quality of life and palliation of symptoms is an important goal of treatment of patients with MBC. All the treatment options should be discussed with the individual patient with clear explanation of the risk-to-benefit ratio. The subjective attitude of the patient is one of the major factors which influence the choice and acceptance of a therapeutic program.

references