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Metastatic breast cancer: why are we here and where are we going?

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Abstract

The 1990s might be viewed as a golden age for the therapy of metastatic breast cancer with the introduction of new cytotoxic drugs and regimens to improve quality of life and prolong survival. The taxanes and anthracyclines have emerged as the most active agents, and investigation of these drug classes in combination has been eagerly pursued. Increased understanding of the biology of breast cancer is providing novel treatment approaches. Trastuzumab, a monoclonal antibody directed against the HER-2/neu protein, has become an important therapeutic option for patients with HER-2/neu-positive metastatic breast cancer. Other molecularly targeted therapeutic interventions are being introduced and are under current development. There are many reasons for optimism for the future regarding the treatment of metastatic breast cancer. This devastating disease poses a major challenge, but after decades of clinical trials and many attempts to refine the use of chemotherapy, we are now moving into a more informed era.

Keywords: Chemotherapy; Metastatic breast cancer; Molecularly targeted therapy; Survival; Trastuzumab

1. Introduction

In most developed countries, breast cancer is second only to lung cancer as the most common cause of cancer-related death in women [1], and thus represents a serious healthcare problem. Worldwide, 40–70% of patients ultimately develop metastatic disease [2]. However, the incidence of metastatic breast cancer (MBC) is likely to decline due to earlier diagnosis through mammographic screening and the increased use of adjuvant systemic therapy, and the prevalence may increase because women with MBC are living longer. When breast cancer cells metastasise to distant organs, the disease is typically incurable. Optimal palliation and prolongation of life are, therefore, the main goals of treatment. It is important to use all available treatments to obtain maximal control of symptoms, prevent serious complications, and prolong life with minimal disruption to lifestyle and quality of life.

Perhaps no form of cancer is as susceptible to such a variety of different types of drug therapy as with breast cancer. Over the last 40 years, our knowledge about the clinical behaviours of breast cancer has increased substantially. Our ability to identify several prognostic subgroups and predict hormone-sensitive and hormone-resistant disease has led to more rational utilisation of endocrine and cytotoxic treatments. Supportive therapy to treat the inevitable consequences of MBC, such as pain and bone metastases, has also improved substantially. This review focuses on the developments in chemotherapy and molecularly targeted therapy for the treatment of MBC.

2. Chemotherapy of metastatic breast cancer: a historical perspective

2.1. Early developments

In the late 1950s, the first attempts to combine two or more chemotherapeutic agents to manage MBC had begun. Greenspan et al. treated a group of women with methotrexate and thiotepa with such dramatic results for the time that his paper was initially rejected because it was thought to be incredible [3]. Cytotoxic chemotherapy for breast cancer began to be used on a consistent basis in the 1970s. Single agents used in chemotherapy until the 1990s included alkylating agents (cyclophosphamide) and antimetabolites (5-fluorouracil, methotrexate) and the antitumour antibiotics (doxorubicin, mitomycin). Chemotherapy has now been demonstrated to have an important role in this disease demonstrating clear palliative benefits, a survival prolongation [4,5] and the rescue of patients with impending visceral failure. Breast cancer has been shown to be the most chemotherapy-sensitive of the common adult tumours. However, prolonged chemotherapy-induced complete remission is rare (approximately 1% after 5 years or more).

In addition to the choice of drugs, the treatment regimen can affect the palliative benefits in patients. This has been

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demonstrated in randomised trials comparing continuous with intermittent chemotherapy [6,7]. In one study, each approach was tested using doxorubicin combined with cyclophosphamide or using cyclophosphamide combined with methotrexate, fluorouracil and prednisolone [6]. Unexpectedly, the analysis showed that continuing chemotherapy was associated with a better quality of life than intermittent chemotherapy in virtually all of the variables studied [6]. Disappointingly, the percentage of patients with MBC who achieved prolonged remission with chemotherapy remained low.

Most clinical trials addressing this issue have found no overall survival benefit in continuing chemotherapy indefinitely, although it may delay the time to disease progression [6–8]. The recent phase III MANTA (Maintenance Paclitaxel) study, which addressed the role of taxanes in maintenance therapy for MBC, found no significant improvement in progression-free survival with a contemporary taxane-containing regimen plus an anthracycline, followed by 8 weeks of maintenance paclitaxel when compared with a control arm without maintenance paclitaxel [9].

2.2. The 1990s: a golden age for MBC therapeutics?

Little further progress in the treatment of MBC was made until the last decade of the 20th century. New cytotoxic drugs with high activity, such as taxanes (paclitaxel and docetaxel), navelbine, gemcitabine and capecitabine, all of which were introduced in the 1990s, raised the hopes of patients with MBC owing to the higher efficacy with tolerable toxicity. Newer targeted therapies, such as trastuzumab, were also introduced, as were the new hormone agents letrozole and exemestane, and the bisphosphonates.

A pivotal study of patients with MBC was the first to demonstrate a superior response rate with docetaxel compared with the standard chemotherapeutic agent of its time, doxorubicin [10], some 15 years after the introduction of the latter agent. In a cohort of 326 patients with MBC who had failed an alkylating-containing regimen, docetaxel demonstrated significantly better objective response rates compared with doxorubicin (48% versus 33%, $P = 0.008$).

The taxanes and anthracyclines have emerged as the most active agents for treating women with breast cancer. As such, investigation of the two drug classes in combination regimens has been eagerly pursued. The rationale for combining docetaxel with an anthracycline includes high clinical activity of each individual agent, lack of complete clinical cross resistance, and non-overlapping toxicity profiles. Phase II and III randomised trials have compared docetaxel–anthracycline-based regimens with older anthracycline-based combinations as first-line therapy for women with MBC [11–14]. In each of these studies, significant improved outcomes were reported in favour of the docetaxel–anthracycline combinations (Table 1). Three of the studies [11–13] demonstrated significantly longer time to disease progression, while just two showed significantly longer survival times [12,13]. The observed survival improvements were modest, demonstrating the limitations of chemotherapy for MBC.

Recent efforts with paclitaxel have focused on optimising efficacy and reducing toxicity. Outcomes from the Cancer and Leukemia Group B (CALGB) 9840 trial showed that weekly administration of paclitaxel resulted in superior response rates and time to disease progression in patients with MBC when compared with administration of the conventional 3-weekly paclitaxel regimen [15]. A total of 735 patients with MBC were randomised 60:40 to receive either 80 mg/m^2 of paclitaxel administered intravenously once a week or the standard regimen of 175 mg/m^2 of paclitaxel given every 3 weeks. The objective tumour response rate was significantly greater among patients receiving weekly paclitaxel compared with those given the every-third-week regimen (40% versus 28%, $P = 0.017$). The time to disease progression was 9 months with weekly paclitaxel versus 5 months with the conventional dosing schedule ($P = 0.0008$). There was also a trend towards longer survival for patients who received the weekly schedule (24 months versus 16 months, $P = 0.17$).

Table 1
Outcome of studies on anthracyclines plus docetaxel versus standard regimens in first-line treatment of metastatic breast cancer [11–14]

Reference	Number of patients	Schedule	Response rate (%)	Time to disease progression (months)	Survival (months)
[11]	429	AT 50/75	59*	8.6*	22.5
		AC 60/600	47*	7.3*	21.7
[12]	142	ET 75/75	63*	7.8*	34*
		FEC 500/75/500	34*	5.9*	28*
[13]	216	AT 50/75	64*	8.8*	22.6*
		FAC 500/50/500	41*	6.6*	16.1*
[14]	484	TAC 75/50/500	55*	7.1	21
		FAC 500/50/500	44*	6.7	22

*Significant, $P < 0.05$; A, doxorubicin; C, cyclophosphamide; E, epirubicin; F, 5-fluorouracil; T, docetaxel

Two other drugs that have been investigated in MBC are the antimetabolites, capecitabine and gemcitabine. Capecitabine plus docetaxel, and gemcitabine and paclitaxel have both been shown to provide a survival advantage over the corresponding single-agent taxane in prospective, randomised trials that were carried out in patients with anthracycline pre-treated disease [16,17]. These trials, however, were criticised for the low rate of cross-over to the antimetabolite in the taxane single-agent arms.

2.3. Survival in the 1990s

Population registry databases continue to document increasing overall survival rates at 1 and 2 years in patients diagnosed with MBC, beginning in 1990 and continuing to this day [4]. These demonstrate that chemotherapeutic agents have a positive impact and that some progress is being made in the treatment of MBC. The chemotherapy drugs that have most clearly demonstrated a survival advantage include the taxanes, capecitabine, gemcitabine and the anthracyclines. All patients with MBC should have access to these agents at some stage during the natural history of their disease. In addition, trastuzumab should be mandatory for patients with HER-2-positive breast cancer, as well as one to three lines of hormonal therapy for patients who have oestrogen receptor-positive disease.

3. Molecular era of treatment: trastuzumab

An increased understanding of the molecular biology of breast cancer has led to the identification of novel therapeutic targets. Recently, the transmembrane tyrosine kinase receptor, HER-2/neu, was identified as an oncogene overexpressed by about 30% of breast cancers [18]. These HER-2/neu-overexpressing breast cancers define a subset of tumours that are characteristically more aggressive and somewhat more resistant to chemotherapy than those not overexpressing the oncogene, and women who develop them have a shorter survival. The development of trastuzumab (Herceptin®), a humanised monoclonal antibody specific for HER-2/neu, has revolutionised the management of metastatic HER-2/neu-overexpressing breast cancers [19]. Since its launch in 1998, trastuzumab has become an important therapeutic option for patients with HER-2/neu-positive breast cancer.

A European-based trial called HERA proved to be a pivotal study on the addition of trastuzumab after chemotherapy in patients with HER-2-positive MBC. Preliminary results of this study were presented at the Annual Meeting of the American Society of Clinical Oncology in 2005 [20]. The addition of trastuzumab was shown to significantly improve response, time to disease progression and overall survival. It was concluded that the addition of trastuzumab was associated with greater absolute benefit in the adjuvant treatment of breast cancer than any other single agent in the history of treatment. Moreover, targeting a specific set of patients with breast cancer allowed this smaller group with a previously worse prognosis to markedly improve their outcome. This clear demonstration of trastuzumab efficacy against HER-2/neu-overexpressing MBC has led to a regeneration of adjuvant trials.

A recent study conducted by the Breast Cancer International Research Group (BCIRG) further demonstrated the synergistic antitumour activity of trastuzumab combined with chemotherapy [21]. This study evaluated the benefit of two trastuzumab-based regimens in HER-2-amplified breast cancer. Patients were randomised to receive doxorubicin and cyclophosphamide (AC) followed by docetaxel (T), AC followed by T and trastuzumab (H), or TCH. Treatment with AC-TH and TCH was associated with a significantly improved disease-free survival compared to treatment with AC-T (hazard ratio of 0.49 with AC-TH and 0.61 with TCH). There was a statistically significantly higher incidence of cardiac events in patients receiving AC-TH compared to those receiving AC-T (2.3% versus 1.2%, $P = 0.046$), and no significant difference was observed between the AC-T and TCH arms (both 1.2%, $P = 1.00$) [21].

4. Looking ahead

The development of novel molecularly targeted agents continues. The anti-angiogenic agent bevacizumab, is currently attracting attention and demonstrating promising results in patients with MBC. In the Eastern Cooperative Oncology Group (ECOG) 2100 study, for example, adding bevacizumab to paclitaxel chemotherapy was found to significantly improve response rate (28.2% versus 14.2%, $P < 0.0001$) and increase progression-free survival (10.97 months versus 6.11 months, $P < 0.001$) among women being treated for the first time for recurrent breast cancer or MBC, compared with those who received paclitaxel alone [22]. This was the first study to show a benefit of anti-angiogenic therapy in patients with breast cancer. Further studies on the utility of bevacizumab in the adjuvant setting are clearly warranted.

There are many reasons to be optimistic for the future regarding the treatment of MBC. In most developed countries survival of patients with breast cancer has improved during the 1990s and the early years of this century. This devastating disease poses a major challenge, but after decades of clinical trials and many attempts to refine the use of chemotherapy we are now moving into a more informed era of research.

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