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Treatment of advanced breast cancer: current status

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Metastatic breast cancer is a major and increasing public health problem. The 5-year survival for this disease is only 15%, and while hormonal and chemotherapeutic options have had a significant impact on long-term survival for patients with localized disease, treatment for disseminated disease remains essentially palliative. New treatment options are urgently needed to improve the prospects for patients with metastatic breast cancer, particularly for those with disease characteristics indicating a particularly poor prognosis. Docetaxel (Taxotere®) is a promising new drug and has shown encouraging activity in patients with disease resistant to anthracyclines and in patients with visceral metastases, both of which indicate a poor prognosis. Although docetaxel is, at present, only licensed for use in patients with anthracycline-resistant disease, this highly active drug should now be developed for first-line treatment, and eventually for adjuvant use.

Keywords: Metastatic breast cancer, docetaxel (Taxotere®), anthracyclines, drug resistance.

Metastatic breast cancer is an almost uniformly fatal disease. It is the leading cause of death in women aged 40–55 [1] and must be considered a major public health problem. The median survival for patients diagnosed with metastatic breast cancer is in the range of 17–20 months, and the 5-year survival rate is only 15%. Only patients with disease confined to the bones may experience a more indolent course of the disease and have a greater chance of survival over 5 years, the 5-year survival rate for these patients being 30–40%. Patients with visceral disease, particularly liver metastases, have a particularly poor prognosis, with a median survival of only 8 months [2]. These dismal statistics confirm that there is a crucial need for new active agents and novel treatment strategies for breast cancer patients.

Adjuvant hormonal and chemotherapeutic treatments are increasingly given to patients with early disease in the hope of enhancing their probability of cure. Unfortunately, when the disease recurs at distant sites, the available treatments are essentially palliative. First-line treatments for metastatic disease involve endocrine therapy, whenever appropriate, and chemotherapy, in hormone-resistant or unresponsive disease. Patients who have been exposed to adjuvant chemotherapy will generally be less responsive to first-line chemotherapy for advanced disease, and disease responsiveness to chemotherapy continues to decline in second-line and further treatments, both in terms of response rate and time to disease progression (Table 1) [3–6]. Patients whose disease has become resistant to first-line hormonal therapy may experience some benefit from alternative, second-line hormonal therapy, or from chemotherapy, but responsiveness to therapy also decreases in this group (Table 1) [4]. This fall in responsiveness from adjuvant through first-line to second-line therapies, reflects the development of drug resistance, which presents a major challenge to medical oncology today. It is only through the introduction of new drugs and novel treatment strategies that we can hope to improve the quality, and length of life for patients with advanced breast cancer.

Results of phase II trials have confirmed the early reports that docetaxel (Taxotere®) is one such new drug with remarkable activity against breast cancer. Not only is docetaxel proving to be a very active drug, but it also shows an unusual pattern of responsiveness, with activity that does not markedly decrease from the first to the second or third line of treatment [10].

In spite of the considerable problems posed by the treatment of advanced disease, improvements in outcome have been obtained by the introduction of new agents, such as the anthracyclines [11,4,12]. The

Table 1. Advanced disease treatment results (data from [7–9])

Therapeutic intervention	Response rate (%)	Median time to progression
Endocrine therapy		
First-line	30–60	~ 10 months
Second-line	15–25	~ 6 months
Chemotherapy		
First-line	40–60	~ 8 months
Second-line	20–40	~ 4 months

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Table 2. Outcome of complete responders in randomized clinical trials of chemotherapy + hormonal therapy for metastatic breast cancer run by the European Organization for Research and Treatment of Cancer (EORTC) Breast Cancer Cooperative Group

Outcome	Relative risk (95% CI)	p
Death		
Anthracyclines used		
No	1	
Yes	0.39 (0.22–0.67)	0.0008
WHO performance status		
0	1	
1–2	2.07 (1.17–3.66)	0.012
Disease progression		
Anthracyclines used		
No	1	
Yes	0.28 (0.16–0.47)	0.0001

CI, Confidence Interval; WHO, World Health Organization. Multivariate analysis was used to assess the statistical significance of variables.

contribution of anthracycline and non-anthracycline regimens to long-term survival of patients with metastatic breast cancer was assessed amongst 1054 patients recruited to randomized clinical trials of chemotherapy by the European Organization for Research and Treatment of Cancer (EORTC) Breast Cancer Cooperative Group. Amongst these 1054 patients, only 75 (7%) were confirmed to have clinical complete remissions after external review (Tomiak *et al.*, manuscript in preparation). Approximately one-third of these complete responders lived beyond 8 years. Multivariate analysis of prognostic factors for long-term survival revealed that inclusion of an anthracycline in the chemotherapeutic regimen significantly reduced the risk of progressive disease and the risk of death (Table 2). The only other factor with a significant impact on disease progression and death was the patient's performance status (Table 2). It is too early to assess the impact of docetaxel therapy on long-term survival, but early indicators are encouraging [13–15].

Resistance to anthracyclines, any prior chemotherapy, and the presence of liver metastases are among the factors which are associated with a low probability of response to chemotherapy. The work presented at this symposium will illustrate that docetaxel has shown significant activity in all of these situations, indicating that this drug may have a significant impact on the natural history of breast cancer.

The major patterns of clinical management of breast cancer, in Europe, are summarized in Figure 1, and illustrate the situations in which the taxoid drugs, docetaxel and paclitaxel, can be used at present, in line with current registration restrictions. The first division of patients with metastatic disease in this schema depends on whether or not they have received anthracycline drugs in the adjuvant setting. In patients who have not received adjuvant anthracyclines, first-line treatment for metastatic disease would usually include an anthracycline drug. It is the response to this first-line treatment which allows further subdivision of patients into anthracycline-sensitive and -resistant groups. There is no doubt that the taxoids are the treatment of choice for anthracycline-resistant tumours. In patients with a more favourable disease course, there are alternative treatment options, as de-

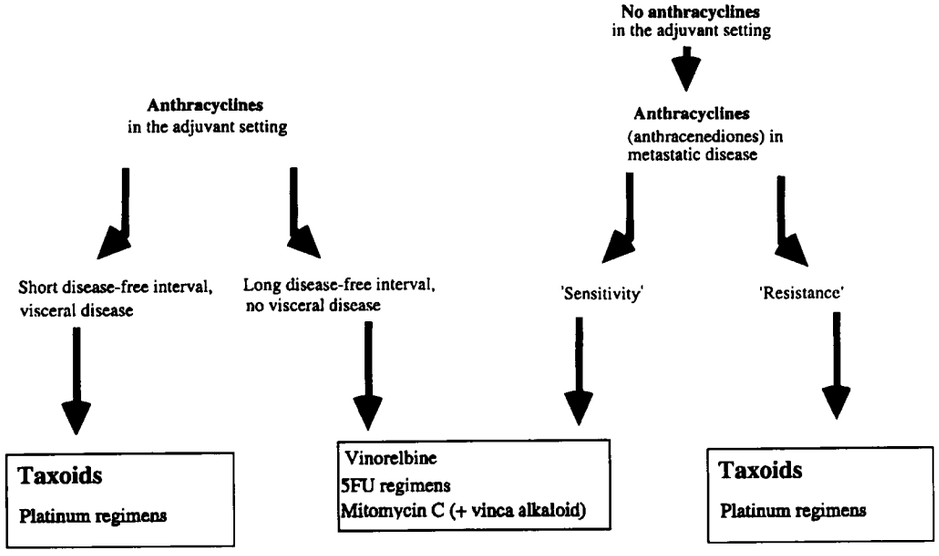

Figure 1. Selection of chemotherapy regimens for metastatic breast cancer.

tailed in Figure 1. In patients who did receive anthracyclines in the adjuvant setting, the major division depends on the disease-free interval, with taxoids as the treatment of choice in patients whose disease progressed soon after adjuvant treatment. If the disease-free interval is longer, indicating less aggressive disease, there are a number of valid treatment options. Although the registration restrictions only allow taxoids to be used when clinical resistance to anthracyclines is evident, there is no good clinical reason for delaying the use of these very active drugs until drug resistance has become a problem. Further clinical research will allow taxoid drugs to progress from the second-line setting for metastatic breast cancer to the first-line setting, and then to the adjuvant setting. It is the responsibility of clinical research scientists to ensure that the use of these active drugs is extended rapidly and safely.

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