

## Triple-negative Phenotype in Metastatic Breast Cancer – Where Do We Stand in Terms of Treatment?

a report by

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Treatment of breast cancer has come a long way. The recent elucidation of distinctive molecular breast cancer subtypes through gene expression profiling has shed light on the heterogeneous clinical behaviour and outcomes of seemingly alike morphological breast cancers.<sup>1</sup> This information could be translated in the scenario of clinical trials and clinical practice as a streamlined approach for targeting specific molecular defects on cancer cells that are thought to drive tumour cell progression. A subpopulation emerging as having particularly poor prognosis is those patients who have disease that is receptor-negative for oestrogen, progesterin and human epidermal growth factor receptor 2 (HER2 or HER2neu – triple-negative disease). The lack of these targets obviates any consideration regarding use of hormone therapies or HER2- targeted agents.

So, how should we approach this orphan disease? The awareness that these patients benefit less from current treatments than other populations is increasing among researchers, and new clinical trials are being designed to investigate responsiveness to treatment in this patient population. Chemotherapy represents the gold standard treatment for these patients. In this article, we will provide some

guidelines on how to properly use chemotherapy in the metastatic setting and evaluate whether there is room for combining chemotherapy with biological agents in an HER2-negative population in clinical practice.

The decision as to which type of chemotherapy/regimen should be given to patients with metastatic breast cancer as first-line chemotherapy should be based on the individual (i.e. performance status, biological age and co-morbidities) and their specific disease characteristics (i.e. tumour burden and disease-free interval) and take into account prior treatments received in the adjuvant setting, as well as patient preference. Attaining longer survival is certainly a primary aim when treating metastatic patients. However, physicians should not overlook treatment-related toxicity as it can have a detrimental impact on quality of life.<sup>2</sup> For this reason an aggressive polychemotherapy regimen should be proposed only for a specific subgroup of patients, namely symptomatic patients with rapidly progressive disease in whom a prompt response is necessary (see *Table 1*).<sup>3</sup>

In the last few years, data from two phase III trials comparing single-agent chemotherapy with polychemotherapy have been published. O'Shaughnessy et al. randomised a total of 511 anthracycline pre-treated patients with advanced breast cancer to receive docetaxel 100mg/m<sup>2</sup> or docetaxel 75mg/m<sup>2</sup> on day one, plus capecitabine 1,250mg/m<sup>2</sup> on days one to 14 every three weeks.<sup>4</sup> The primary end-point of the study was time to disease progression (TTP). The addition of capecitabine to docetaxel resulted in increased response rate (RR) (42 versus 30%), prolongation of TTP (6.1 versus 4.2 months) and longer survival (median survival 14.5 versus 11.5 months). This improvement in efficacy was counterbalanced by an increase in the incidence of side effects such as hand-foot syndrome, stomatitis and diarrhoea in the combination arm. Overall, grade 3 adverse events were reported in 49 and 71% of patients in the single-agent and combination arms, respectively. An analysis of post-study therapy showed that only 17% of patients treated with single-agent docetaxel received capecitabine at progression.

Albain et al. randomised a total of 529 patients with advanced breast cancer to receive paclitaxel 175mg/m<sup>2</sup> or gemcitabine 1,250mg/m<sup>2</sup> on days one and eight, plus paclitaxel 175mg/m<sup>2</sup> on day one every three weeks.<sup>5</sup> The primary end-point of the study was overall survival. The addition of gemcitabine to paclitaxel resulted in increased RR (40.8 versus 22.1%), prolongation of TTP (5.2 versus 2.9 months) and longer survival (median survival 18.5 versus 15.8 months). This improvement in efficacy was counterbalanced by an increase in the incidence of side effects in the combination arm, which mainly consisted of haematological toxicity and grade 3 fatigue. An analysis of post-study



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therapy showed that only 14% of patients treated with single-agent paclitaxel received gemcitabine at progression.

In both trials, the combination regimens were associated with a longer survival than single-agent chemotherapy. However, it should be noted that the low cross-over rate to the ‘added’ agent in patients who progressed during single-agent chemotherapy may explain the survival advantage.

The combination of an anthracycline with a taxane has been extensively investigated in clinical trials and compared with standard anthracycline-based regimens. Results have been discordant. A meta-analysis of randomised trials comparing either anthracycline–taxane combination regimens versus anthracycline-based regimens, or single-agent anthracycline versus single-agent taxane regimens, for the first-line treatment of metastatic breast cancer has recently been performed.<sup>6</sup>

Focusing on polychemotherapy comparisons, individual patient data were collected for 3,034 patients in eight randomised trials. Response rates were 57% (10% complete) in taxane-based combinations and 46% (6% complete) in control arms ( $p < 0.001$ ). The hazard ratios (HRs) for taxane-based combinations compared with control arms were 0.92 (CI 0.85–0.99;  $p = 0.031$ ) for progression-free survival (PFS) and 0.95 (CI 0.88–1.03;  $p = 0.24$ ) for survival. There was no indication that the benefit of taxanes was more pronounced among patients with visceral disease than among those without or among patients who were oestrogen-receptor-negative.

Based on the results of this meta-analysis we can conclude that the benefit of adding a taxane to an anthracycline is modest. However, due to the greater chance of tumour shrinkage, an anthracycline–

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taxane combination could be considered the treatment of choice when a response is desirable, i.e. in patients with life-threatening, rapidly progressive disease.

Biological agents can play a role in the setting of triple-negative disease. Angiogenesis plays an important role in breast cancer and has been correlated with dismal characteristics in terms of

**Table 1: Choice of Chemotherapy for Metastatic Breast Cancer Based on Patient and Disease Characteristics**

Friendly Agent/Regimen	Aggressive Polychemotherapy
Slow-progressing disease	Rapidly progressing/life-threatening disease
Any site provided limited visceral involvement	Massive visceral involvement
Asymptomatic patient	Symptomatic patient
Indication for polychemotherapy but frail	Fit

disease biology, treatment resistance and clinical outcomes.<sup>7</sup> Vascular endothelial growth factor (VEGF) is a specific and critical mitogen for endothelial cells. Bevacizumab is a humanised monoclonal antibody against VEGF.<sup>8</sup>

Due to the greater chance of tumour shrinkage, an anthracycline–taxane combination could be considered the treatment of choice when a response is desirable, i.e. in patients with life-threatening, rapidly progressive disease.

Randomised clinical trials have recently been reported with the use of this agent in metastatic breast cancer patients. In the Eastern Cooperative Oncology Group (ECOG) E2100 trial, a total of 680 women with advanced breast cancer were randomly assigned to receive paclitaxel 90mg/m<sup>2</sup> on days one, eight and 15 every four weeks with or without bevacizumab 10mg/kg every two weeks as first-line therapy.<sup>9</sup> In this trial the addition of bevacizumab to paclitaxel resulted in an increase in response rate (13.8% with paclitaxel alone versus 29.9% in the combination arm) and an improvement of PFS of approximately five months (median PFS 6.11 months with paclitaxel versus 11.4 months with paclitaxel plus bevacizumab), which was highly statistically significant (HR 0.51).

Recently, investigators studied the combination of capecitabine 1,000mg/m<sup>2</sup> twice daily on days one to 15 and bevacizumab 15mg/kg every 21 days in a single-arm, two-phase study for the first-line treatment of HER2-negative metastatic breast cancer.<sup>10</sup> The trial met the primary end-point of TTP (90% power to test an improvement in the TTP from four months – as reported previously for single-agent capecitabine – to 5.6 months), reporting 5.7 months in the intention-to-treat population. Of note, patients with ER-positive disease did better than patients with ER-negative tumours (median TTP 8.9 and four months for patients with ER-positive and ER-negative disease, respectively). These data are provocative and clearly ask for a better definition of those patients most likely to benefit from VEGF-directed therapies. ■

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