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Anthracyclines in the management of metastatic breast cancer: state of the art

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ABSTRACT

Metastatic breast cancer is a heterogeneous disease and hence it is desirable to have a variety of treatment options to meet different treatment aims in individual patients. Anthracyclines are extremely effective single agents in the treatment of metastatic breast cancer, and combination therapy with anthracycline-containing regimens significantly improves response rates and progression-free survival, compared with non-anthracycline regimens. The addition of taxanes further increases the efficacy of anthracyclines as first-line therapy. Combination therapy with trastuzumab, taxanes and anthracyclines has been shown to produce significant improvements in survival, compared with taxanes and anthracyclines alone; however, trastuzumab is associated with significant cardiotoxicity, and augments the cardiotoxicity associated with anthracycline-based regimens. New anthracycline formulations such as non-pegylated liposomal doxorubicin (NPLD) have an important role in the treatment of metastatic breast cancer. NPLD is as effective as conventional doxorubicin formulations, and can be combined with trastuzumab with acceptable toxicity. However, a number of questions remain as to how anthracycline therapy can be optimised. Ultimately, the choice of regimen will require a balance between efficacy and the impact of treatment on the patient's quality of life.

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1. Introduction

Anthracyclines are extremely effective single agents in the treatment of metastatic breast cancer, producing response rates of between 30% and 50%.[1] Combination therapy with anthracycline-containing regimens results in significant improvements in response rates and progression-free survival, compared with non-anthracycline regimens,[2] and combinations of anthracyclines and taxanes are more effective than either agent alone when used as first-line therapy.[3] However, it is important to recognise that patients with metastatic breast cancer are a heterogeneous group, and thus the aims of treatment will differ depending on the circumstances of the individual patient. For example, patients with symptomatic disease and poor performance status will benefit mainly from palliative treatment, while in many elderly patients with indolent disease the aim is to delay progression and improve quality of life. By contrast, in younger patients and those with good performance status, treatment should aim to prolong survival, whereas in patients whose disease is amenable to locoregional control the aim should be to increase response rates.

Recent years have seen the introduction of a number of novel therapies for patients with metastatic breast cancer, and these have resulted in marked improvements

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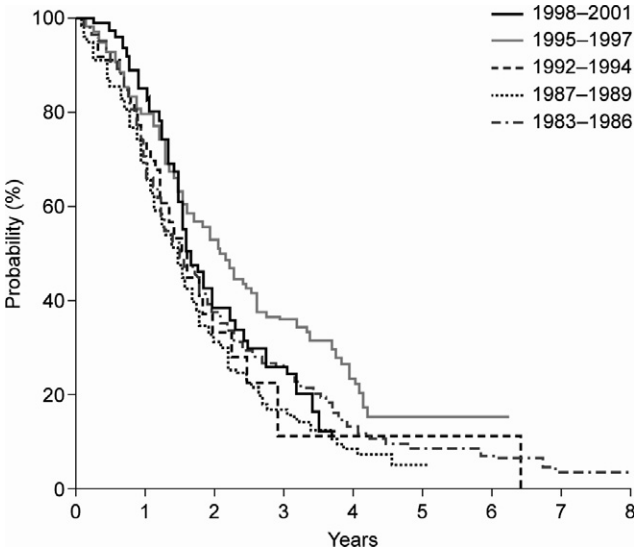

Fig. 1 – Kaplan–Meier plot showing overall survival in patients with metastatic breast cancer recruited into six clinical trials between 1983 and 2001.[4] Reprinted with permission from Gennari A, et al. Survival of metastatic breast carcinoma patients over a 20-year period: a retrospective analysis based on individual patient data from six consecutive studies. *Cancer* 2005;104:1742–50, published by John Wiley & Sons.

in survival.[4,5] For example, in a review of six clinical trials conducted between 1983 and 2001, overall mortality in patients recruited between 1995 and 2001 decreased by 20–30%, compared with patients recruited into earlier trials (Fig. 1);[4] this period coincided with the introduction of the taxanes into clinical practice, and much of the improvement in survival can be attributed to the addition of these agents to anthracycline-based therapy. However, despite the impact of these new treatments, the treatment of metastatic breast cancer is still a major challenge for the clinical oncologist in terms of optimising treatment and minimising toxicity.

2. Challenges in the management of metastatic breast cancer

2.1. Combination versus sequential therapy

Chemotherapy regimens for metastatic breast cancer may involve either combination therapy or sequential use of single agents. Each of these approaches has its own merits and disadvantages. Combination therapy results in higher response rates and faster disease control than single-agent therapy, but is associated with greater toxicity and impairment of quality of life.[6–11] Furthermore, it produces little or no gain in survival, compared with single-agent therapy, and further options after treatment failure are limited. Sequential single-agent therapy is less effective than combination therapy in terms of response rates, but is associated with less toxicity and better quality of life.[6–8]

2.2. Duration of chemotherapy

Numerous trials have investigated the optimal duration of chemotherapy for metastatic breast cancer, with inconsistent results. In a meta-analysis published in 1997, which included data from four studies involving 666 patients, median survival was increased by 23% (95% confidence interval [CI] 9–38%, P = 0.01) in women receiving longer durations of chemotherapy.[12]

Current guidelines state that there is limited evidence to suggest that progression-free survival can be prolonged by the use of continuous chemotherapy, rather than shorter courses,[13,14] but due to the lack of effect on overall survival the detrimental impact of continuous treatment on quality of life should also be considered.[6] Thus, the duration of chemotherapy in an individual patient will depend on efficacy and tolerability in that patient, and on the physician's and patient's preferences.

The impact of extending the duration of chemotherapy beyond the standard number of cycles has recently been investigated in a systematic review of 11 randomised trials evaluating first-line chemotherapy in patients with metastatic breast cancer.[13–23] Longer durations of chemotherapy were associated with a marginal increase in overall survival, equivalent to approximately 3 months (hazard ratio [HR] 0.91, 95% CI 0.84–0.99) and a significant prolongation of progression-free survival (HR 0.66, 95% CI 0.6–0.72), compared with shorter durations. Only one of these trials evaluated the impact of different durations of treatment on health-related quality of life.[15] In this study, continuous chemotherapy was associated with better quality of life, compared with intermittent therapy; patients receiving continuous treatment showed significantly better scores for physical wellbeing, mood, appetite and general quality of life compared with those receiving intermittent treatment. Changes in quality of life were found to be independent predictors of subsequent survival.

These findings support the use of prolonged chemotherapy in patients with metastatic breast cancer, provided that significant toxicity is avoided and progressive disease is not present. However, a number of questions remain to be answered, including whether the same drugs should be repeated or different drugs used in a planned sequence (see above), the role of low-dose maintenance therapy, and the optimal combination of conventional chemotherapy and targeted therapies such as trastuzumab.

It is, however, worthwhile noting that of the 11 trials included in the meta-analysis only in the one comparing two different durations of a 5-fluorouracil–epirubicin–cyclophosphamide regimen was a significant

improvement in overall survival detected, favouring longer anthracycline administration. While today the hypothesis of prolonging an anthracycline regimen until disease progression might not be considered feasible due to possible cardiac safety issues, an alternative strategy could include the use of anthracyclines for a preplanned number of cycles, followed by a less cardiotoxic drug such as a taxane.

2.3. Rechallenge after adjuvant chemotherapy with anthracyclines

The impact of anthracycline therapy on long-term survival in patients with metastatic breast cancer is highlighted by the finding that approximately 20% of patients in whom a complete response is achieved remain in remission after 10 years.[24] Such findings raise the possibility that survival could be further prolonged by rechallenge after an initial response with agents with proven efficacy. This approach has been shown to be effective in a number of cancers, including ovarian and colon cancer, but its use may be limited by cumulative toxicity.

A number of retrospective studies have investigated the use of anthracyclines as first-line treatment in patients who have previously received adjuvant chemotherapy.[25–29] All studies included a group of patients who had not received adjuvant therapy and groups who had received adjuvant therapy with either anthracyclines or cyclophosphamide, methotrexate and fluorouracil (CMF)-based regimens. These studies showed that previous adjuvant anthracyclines had no significant effect on overall or progression-free survival, as compared with non-anthracycline-containing adjuvant chemotherapy, provided that disease-free survival was at least 1 year following completion of adjuvant anthracycline. These findings suggest that rechallenge with anthracyclines should not be excluded in patients who have previously received adjuvant therapy, even if this included anthracyclines.[25]

The use of non-pegylated liposomal doxorubicin (NPLD), a novel formulation designed to reduce the risk of anthracycline-related cardiotoxicity while maintaining antitumour efficacy, has been evaluated in patients with metastatic breast cancer who had previously received adjuvant therapy with anthracyclines.[30] This study was a retrospective analysis of two trials[31,32] comparing NPLD with conventional doxorubicin, either alone or in combination with cyclophosphamide. The overall response rate was significantly higher with the liposomal formulation than with conventional doxorubicin (31% vs 11%, $P = 0.04$), and this formulation was also associated with a significant increase in time to treatment failure and similar overall and progression-free survival, compared with conventional doxorubicin (Fig. 2).

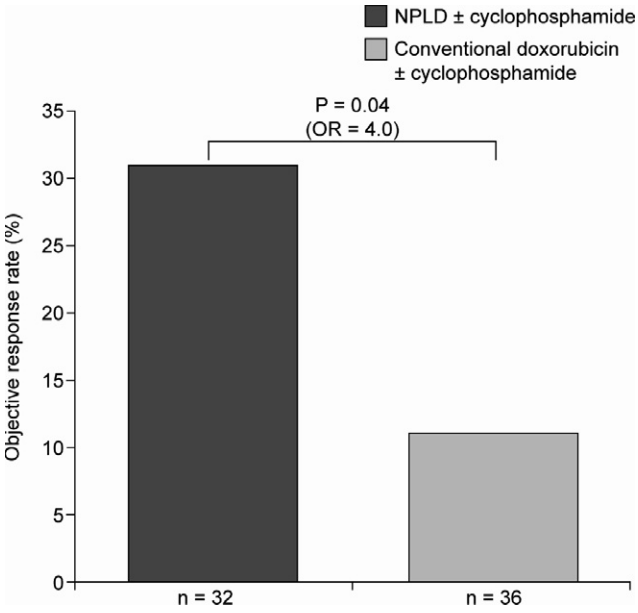

Fig. 2 – Objective response rate (complete plus partial responses) in 68 patients with metastatic breast cancer receiving non-pegylated liposomal doxorubicin (NPLD) or conventional doxorubicin after previous anthracycline therapy.[30] OR, odds ratio.

3. Combination therapy with anthracyclines and trastuzumab

Trastuzumab is a monoclonal antibody directed against the extracellular domain of the human epidermal growth factor receptor-2 (HER2), over-expression of which occurs in 25–30% of breast cancers and is associated with a poor prognosis.[33] The rationale for combination therapy with anthracyclines and trastuzumab derives from the finding that the addition of trastuzumab to a combination of anthracycline and cyclophosphamide resulted in increased response rates and improvements in progression-free and overall survival.[33]

However, trastuzumab is associated with significant cardiotoxicity, and the addition of this agent augments the cardiotoxicity associated with anthracycline-based therapy. For example, in the original clinical trial described above, the incidence of cardiac dysfunction in patients receiving anthracyclines, cyclophosphamide and trastuzumab was 27%, compared with 8% in patients receiving anthracyclines plus cyclophosphamide alone, 13% in those receiving paclitaxel and trastuzumab, and 1% in those receiving paclitaxel alone.[33] This is a cause for concern because registry data suggest that, at least in women with early breast cancer, those with HER2-positive breast cancer tend to be older than the patients enrolled in this trial; these patients might therefore be expected to have a higher prevalence of pre-existing cardiovascular disease. Currently, however, there are few

data on the cardiac safety of elderly patients treated with trastuzumab.

Potential approaches to the problem of cardiotoxicity with anthracycline–trastuzumab combinations include the use of low-dose trastuzumab plus epirubicin, which may offer a lower risk of cardiotoxicity. These approaches have recently been investigated in a phase II trial involving 44 patients who had not previously received chemotherapy for metastatic breast cancer.[34] Patients received six cycles of epirubicin plus low-dose (1 mg/kg/week) trastuzumab, which was continued for 1 year. Overall, 27 patients (61%) showed a complete or partial response, a response rate comparable with that achieved with combinations of anthracyclines and conventional doses of trastuzumab. However, 34% of patients developed cardiovascular adverse events; six patients (13.6%) showed decreases in left ventricular ejection fraction (LVEF) of more than 15%, and two (4.5%) developed congestive heart failure.

As noted above, NPLD has been shown to offer comparable efficacy and a lower risk of cardiotoxicity, compared with conventional doxorubicin.[30–32] This agent might therefore offer a means of decreasing the cardiotoxicity associated with anthracycline–trastuzumab combinations. This approach has been evaluated in a recent phase I study involving 40 patients.[35] Overall, five patients (13%), four of whom had received adjuvant therapy with doxorubicin, showed reductions in LVEF to below 50%. Cardiac events leading to discontinuation of study therapy occurred in only two patients; both had previously received cumulative doxorubicin doses of 240 mg/m^2, and in both cases cardiotoxicity was reversible. The overall response rate was 50%. These findings suggest that the combination of NPLD with trastuzumab is effective in HER2-positive patients with metastatic breast cancer, and is associated with a lower risk of cardiac toxicity than conventional doxorubicin–trastuzumab combinations.

4. Conclusions

Metastatic breast cancer is a heterogeneous condition, the biology of which may differ from that of primary breast cancer and may even differ between cell clones. This heterogeneity means that the aims of chemotherapy will vary depending on the patient's circumstances, and so it is desirable to have a variety of therapeutic options. Anthracyclines may still be considered a cornerstone of chemotherapy for breast cancer patients, and the potential benefits of these regimens are enhanced by the addition of trastuzumab in HER2-positive patients.

New anthracycline formulations such as NPLD have a potentially important role in the chemotherapy of metastatic breast cancer.[31] The available evidence shows that NPLD is as effective as conventional doxorubicin formulations, and can be combined with trastuzumab with acceptable toxicity.[35–38]

A number of outstanding issues remain about how chemotherapy regimens for patients with metastatic breast cancer can be optimised, including the question of whether combination or sequential therapy is most appropriate and the role of low-dose chemotherapy after initial response. Ultimately, the choice of therapy in a given patient will require a balance between efficacy (in terms of response rates and survival) and quality of life.

5. Conflict of interest statement

Dr Gennari has received honoraria from Cephalon. Dr D'Amico disclosed no conflicts of interest.

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