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State of the art therapy for HER2-negative metastatic breast cancer

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ABSTRACT

Metastatic breast cancer (MBC) remains a challenging disease to treat with only a small minority of patients achieving long-term survival. Although great strides have been made in the fight against breast cancer, international consensus to the approach to treat the disease is lacking. Over the past few decades, the introduction of several new agents, including biologically-targeted agents, have impacted disease control as well as survival, albeit modestly. Despite these advances, treatment for the majority of breast cancer remains empirically based, especially in the approach to HER2-negative, endocrine non-sensitive disease. Taxane- and anthracycline-containing regimens continue to be a mainstay of MBC therapy; however, increasing use of these agents in the adjuvant and neoadjuvant settings provides a challenge for the treating oncologist. As such, this review will focus on state of the art therapy for patients with endocrine non-sensitive, HER2-negative MBC, highlighting recent advances offering new treatment paradigms.

1. Introduction

Breast cancer is a diverse disease comprising many biological subtypes. Gene expression studies using DNA microarrays have identified five main subtypes: luminal A, luminal B, HER-2 positive, basal-like and normal breast-like. These subtypes differ markedly in prognosis and in the repertoire of therapeutic target they express. Disease characteristics, such as hormone receptor status, human epidermal growth factor receptor-2 (HER2) status, site and extent of metastatic spread, disease-free interval and type of prior adjuvant therapy, as well as patient characteristics including age, performance status, co-morbidities and patient preferences all play key roles in determining how best to treat an individual patient with metastatic breast cancer (MBC) (Fig. 1). Unfortunately, there are only a few accepted predictive factors associated with treatment benefit, i.e., hormone receptor status and HER2 status. Consequently, for patients with HER2-negative and hormone receptor-negative disease (basal-like subtype), treatment decision-making can be complicated and requires careful consideration of the reported literature. Choosing the appropriate regimen for this group of advanced breast cancer patients can be challenging, but important distinctions in patient and tumour characteristics can help guide treatment decisions (Table 1).

1.1. *Choosing the right chemotherapy regimen*

As treatment in the metastatic setting is palliative, tolerability and patients' quality-of-life are major factors guiding treatment decisions. Chemotherapy is currently the standard of care for women with HER2-negative, endocrine non-sensitive disease or for women with extensive visceral or life-threatening disease regardless of hormone receptor status. The question of how to best administer chemotherapy, in combination or as sequential single-agents, remains unanswered. Almost assuredly, no single strategy is appropriate for all patients. In general, however, administering agents simultaneously tends to yield higher overall response rates (ORR), higher complete

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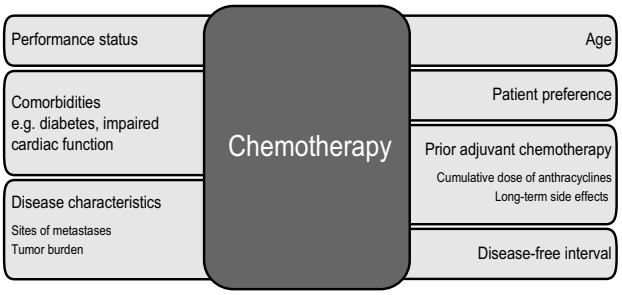

Fig. 1 – Factors to be considered in decision-making.

Table 1 – Choosing the right regimen for advanced breast cancer

'Friendly' agent/regimen	'Aggressive' regimen
Slowly-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
±Biological agents	

response rates (CRR), longer time-to-disease progression (TTP) and in some trials, a modest improvement in overall survival (OS); although, with the cost of increased toxicity. Sequential delivery yields lower response rates and a shorter TTP but avoids additive or overlapping toxicity, and may provide comparable OS relative to combination treatment.[1–3]

1.2. *Taxane- and anthracycline-containing regimens*

In addition to being a mainstay of therapy in the adjuvant and neoadjuvant settings, anthracyclines are standards in chemotherapy regimens for MBC. In the pre-taxane era, randomised trials in MBC demonstrated that anthracycline-containing combination regimens reduced the risk of death when compared with monotherapy and were superior to non-anthracycline-containing combination regimens.[4,5] Since their initial clinical development in the treatment of breast cancer, the taxanes, docetaxel and paclitaxel, have joined the anthracyclines as preferred cytotoxic agents for the treatment of metastatic breast cancer, either as single agents or in combination.

As the taxanes and the anthracyclines are two of the most active classes of agents in breast cancer, several trials have compared standard anthracycline-based combinations with taxane–anthracycline combinations in the first-line treatment of MBC. Early trials evaluating paclitaxel in combination with doxorubicin demonstrated high response rates of over 80%, but with unexpectedly high rates of congestive heart failure (CHF), approximating 18–20%.[6,7] These cardiac effects have been attributed to pharmacokinetic interactions between paclitaxel and both doxorubicin and its metabolite, doxorubicinol. Several strategies to maintain efficacy and minimise cardiotoxicity of the doxorubicin–paclitaxel combination have been investigated, including extending the interval of time between doxorubicin and paclitaxel administration, prolonging the infusion duration of paclitaxel to 24 hours, limiting the cumulative doxorubicin dose to 360 mg/m^2, substituting docetaxel for paclitaxel, and substituting epirubicin or novel forms of doxorubicin, such as pegylated liposomal doxorubicin, for standard doxorubicin.

Unlike paclitaxel, early trials of docetaxel have not shown significant pharmacokinetic interactions with either doxorubicin or epirubicin.[8,9] Results of phase III trials investigating the combination of docetaxel-based anthracycline combinations as first-line therapy for MBC have been encouraging in terms of ORR and TTP but have also been associated with an increased toxicity. In addition, there has been a lack of consistent survival benefit when compared with standard anthracycline-based combination regimens.[10–12]

Based on inconsistent results from clinical trials utilising single-agent and combination taxane therapy, including the lack of a predictable survival benefit in most of these trials, guidelines for the optimal use of taxanes in the first-line MBC setting are lacking. A recently reported meta-analysis evaluated individual patient data from relevant trials of taxanes, either alone or combined with anthracyclines, in the first-line treatment of MBC. The goal of this meta-analysis was to determine if a survival benefit could be shown in the overall population or in a subset of patients with visceral metastases.[13] Data were collected for all of the 3953 patients randomised in the 11 trials included in this analysis; 3034 patients contributed to the comparison of taxane–anthracycline combinations versus non-taxane-containing anthracycline combination regimens and 919 from trials comparing single-agent taxanes with single-agent anthracyclines. The analysis demonstrated that whilst progression-free survival (PFS) was significantly better with single-agent anthracycline therapy when compared to single-agent taxane therapy for the first-line treatment of MBC, OS was similar in both groups. Taxane–anthracycline combinations resulted in significantly better ORR but offered only a marginal benefit in PFS and no benefit in OS when compared with anthracycline combinations that did not contain a taxane. In the visceral versus non-visceral disease analysis, there was a slightly more pronounced effect favouring the incorporation of taxanes. This meta-analysis failed to demonstrate a gain in survival associated with the introduction of the taxanes in the first-line treatment of MBC. However, it did establish their contribution to provide an improved chance of response, which may be important in subsets of patients. The relationship of RR as a surrogate endpoint for survival prolongation has not been firmly established.[14–16]

1.3. *Incorporating targeted therapies in HER2-negative disease*

Recent strides in the clinical development of targeted biological therapies offer new hope and an entirely new treatment paradigm for patients with MBC as evidenced by the pivotal practise changing anti-HER2 therapeutic, trastuzumab. Recently, much excitement and research has been focused on the development of agents that inhibit tumour angiogenesis. Vascular endothelial growth factor (VEGF) and its receptors are key regulators of the process of angiogenesis, which

makes them desirable therapeutic targets. Bevacizumab, a humanised monoclonal antibody directed against all isoforms of VEGF-A, is first in its class to be investigated in MBC. Both preclinical and early clinical trials suggest bevacizumab has anti tumour activity as well as a favourable toxicity profile, with hypertension, proteinuria, thrombosis and bleeding being the most commonly reported toxicities. These toxicities are rarely therapy-limiting.[17,18]

In the first phase III trial of bevacizumab in MBC patients who had received prior chemotherapy for metastatic disease, the addition of bevacizumab to capecitabine demonstrated better ORR compared with capecitabine alone, but no benefit in PFS or OS.[19] Although disappointing, the lack of benefit in survival endpoints in this highly refractory population was not surprising, as it has been shown that angiogenic pathways become more numerous and redundant as breast cancer progresses. To test the hypothesis that anti-angiogenic agents would prove superior in a less refractory patient population, the Eastern Cooperative Oncology Group, led by Kathy Miller and colleagues, evaluated the role of bevacizumab in combination with chemotherapy in chemo-naïve MBC.[20] In this trial (ECOG2100), patients were randomised to paclitaxel (90 mg/m^2) on days 1, 8, and 15 every 4 weeks alone or in combination with bevacizumab (10 mg/kg) on days 1 and 8. Patients with HER2-positive disease were excluded unless they had received prior trastuzumab or had a contraindication to trastuzumab use. Previous treatment with a taxane in the adjuvant setting was permitted if the disease-free interval was greater than 12 months. The primary end-point of the trial was PFS. The findings from the most recently reported interim analysis demonstrated a doubling of the ORR (29.9% versus 13.8%; $p < 0.0001$) and a significantly prolonged PFS (11.4 months versus 6.11 months; HR 0.51, $p < 0.0001$) favouring the bevacizumab-containing arm; OS data are premature and remain unreported. Toxicity was manageable with small increases in grade 3 peripheral neuropathy and fatigue reported for the combination treatment. Approximately 15% of patients in the combination arm developed hypertension requiring medication; no effect on cardiac function was noted. Thromboembolic events, serious bleeding and grade 3 or 4 proteinuria were rarely reported. In addition, there were no significant differences in symptom burden or health-related quality-of-life (HRQL) scores between the 2 treatment arms.[21] Obtaining these results from the patients' perspective provides reassurance that the increase in PFS is not at the cost of impairments in HRQL.

Recently, investigators studied the combination of capecitabine (1000 mg/m^2 twice daily on days 1–15; 28 doses) and bevacizumab (15 mg/kg on day 1; repeated every 21 days until progression) in a single-arm, 2-phase study, for the first-line treatment of HER2-negative MBC.[22] The trial met the primary endpoint of TTP (90% power to test an improvement in the TTP from 4 months, as reported previously for single-agent capecitabine, to 5.6 months), reporting 5.7 months in the intention-to-treat population. The combination produced an ORR of 38% and median OS has not been reached but is in excess of 16 months. Of note, patients with ER-positive disease did better than patients with ER-negative tumours (median TTP 8.9 versus 4 months for patients with ER-positive and ER-negative disease, respectively) (Table 2). These data are provocative, and even with the limitation of the small number of patients entered in the subgroup analysis, clearly ask for a better definition of the patients most likely to benefit from VEGF-directed therapies.

Lapatinib, an oral tyrosine kinase inhibitor with dual activity against both epidermal growth factor (EGFR) and HER2, has demonstrated clinical activity for HER2-overexpressing advanced breast cancer.[23] The role of this small molecule was recently studied in women with either HER2-negative or unknown MBC.[24] Patients were randomly assigned to receive either lapatinib (1500 mg once daily) and paclitaxel (175 mg/m^2) every 3 weeks or the same paclitaxel regimen and placebo. Although the ORR was significantly higher in the paclitaxel/lapatinib group compared with the paclitaxel/placebo group (35.1% versus 25.3%, $p = 0.008$, respectively), there was no difference in median duration of response (6.5 versus 6.2 months), median TTP (6.7 versus 5.3 months), event-free survival (5.8 versus 5.2 months) or OS (22.8 versus 22.0 months). Approximately 15% of study participants on blinded central review of archival tumour tissue had tumours that overexpressed HER2. Retrospective analyses demonstrated that combination therapy in these HER2-positive women produced a significantly better ORR, TTP, event-free survival and a similar but non-significant trend for OS.

1.4. *Maintenance therapy*

In addition to lingering questions on how best to give chemotherapy as well as the optimal agent(s) to utilise, questions also remain on the optimal duration of treatment. Most trials that have attempted to answer this question have demonstrated a benefit for TTP in continuing chemotherapy, although not for survival. A meta-analysis of four of these trials showed a modest survival advantage for women randomised to more cycles of chemotherapy.[25] Two recently reported trials, the MANTA and GEICAM 2001-01, have attempted to address the role of maintenance therapy in MBC. In the MANTA trial, no improvement in PFS was demonstrated from an interim futility analysis in patients who were randomised

Table 2 – Capecitabine plus bevacizumab in first-line MBC

	ITT (N = 109)	ER-negative (n = 49)	ER-positive (n = 51)
Median TTP, months (95% CI)	5.7 (4.9–8.4)	4 (3.0–4.9)	8.9 (7.5–13.6)
Median OS, months (95% CI)	16+ (12.9-NR)	7.5 (5.6–16)	16.6+ (15.1-NR)
ORR (CR + PR)	38%	27%	47%

CI, confidence interval; ER, oestrogen receptor; ITT, intent-to-treat; NR, not reached; ORR, overall response rate; OS, overall survival; TTP, time-to-progression.

after a response or stable disease to a contemporary taxane-containing regimen and 8 courses of maintenance paclitaxel versus no maintenance therapy.[26] A number of variables confound these results, including small sample size due to premature closing of trial, the concurrent use of hormonal therapy, the less optimal every-3-week schedule of paclitaxel, as well as the fact that patients undergoing this aggressive combination as upfront therapy are often younger and healthier and have better outcomes than those who are treated with less aggressive treatment. Another reasonable explanation for the lack of benefit seen in this trial is the more effective administration of up-front therapy in this trial compared with previously reported trials; nonetheless, the findings suggest that women with MBC without progression after adequate taxane-containing first-line chemotherapy do not benefit from the administration of additional courses of single-agent paclitaxel.

The GEICAM 2001-01 trial, on the other hand, did demonstrate a statistically significant improvement in PFS for patients receiving pegylated liposomal doxorubicin (PLD) (40 mg/m^2 every 28 days for 6 cycles) as maintenance therapy after the standard first-line MBC GEICAM regimen of three cycles of doxorubicin 75 mg/m^2 followed by three cycles of docetaxel 100 mg/m^2, both given every 21 days (A → T).[27] Maintenance endocrine therapy was not allowed in the GEICAM trial. Despite the lack of strong data clearly suggesting an advantage in introducing an endocrine therapy as maintenance treatment at the completion of chemotherapy in endocrine-sensitive patients, this strategy is of common use in clinical practise and can be considered a limitation of the study. In any case, based on the results of this trial, the GEICAM will consider PLD maintenance as a standard approach to MBC in future clinical trials. Based on the favourable tolerability of targeted agents in MBC, clinical trials of these agents are also underway in the maintenance setting.

1.5. *The role of taxanes and anthracyclines in the rechallenge setting*

Despite adequate treatment for primary breast cancer, many patients with apparently localised disease develop overt metastatic disease later in life. A challenge facing oncologists currently is the increasing number of patients who have been exposed to both anthracyclines and taxanes in the adjuvant setting. For these patients, treatment options include cytotoxic agents not utilised in the adjuvant setting or to rechallenge the patient with an anthracycline and/or taxane; either option with or without the addition of a targeted agent such as bevacizumab or lapatinib.

Rechallenging a patient with a drug with proven efficacy represents an opportunity to extend the role of active agents in a patient with chemo-sensitive disease. Treatment-free interval or time to recurrence is an important consideration in this setting. If time to recurrence is greater than 12 months to several years following adjuvant therapy, re-treatment with prior active agents is worth considering. If progression or disease recurrence takes place in a relatively short time (e.g. <6–12 months), the use of different classes of agents is generally preferable.

An international expert panel published evidenced-based consensus guidelines suggesting that re-introduction of an anthracycline more than 12 months after prior anthracycline adjuvant or neo-adjuvant therapy is considered a viable option for first-line MBC treatment.[28] The efficacy of anthracycline rechallenge has been shown to be independent of prior adjuvant therapy, including anthracyclines or CMF.[29] An analysis of survival by prior adjuvant anthracycline use from a phase III trial of doxorubicin–cyclophosphamide (AC), docetaxel or alternating AC and docetaxel as first-line chemotherapy for patients with MBC, found no difference in OS whether or not patients had received prior anthracyclines.[30] This adds to the body of literature indicating that prior adjuvant use of anthracyclines does not adversely affect outcomes with subsequent anthracycline use after relapse.

Despite the antitumour efficacy demonstrated by the anthracyclines, particularly doxorubicin, their use is often limited by the development of significant toxicity, mainly irreversible cardiotoxic effects that occur at increasing rates with increasing cumulative doses of anthracyclines. It is also important to note that the use of anthracyclines is generally not recommended in settings where patients are at a greater risk for the development of cardiac toxicity, i.e. older patients. As such, novel dosage forms such as PLD have been developed in an attempt to modify the toxicity profile of conventional doxorubicin whilst maintaining its efficacy. In a randomised phase III trial in the first-line treatment of MBC, PLD (50 mg/m^2 every 4 weeks) and conventional doxorubicin (60 mg/m^2 every 3 weeks) had comparable efficacy in RR, TTP and OS. PLD was associated with significantly less cardiotoxicity, but mild to moderate hand–foot syndrome was observed in the PLD group.[31] In all subgroups analysed, including patients at high risk for developing CHF and those that received prior adjuvant anthracycline therapy, there was a significantly decreased risk of developing cardiotoxicity with PLD versus doxorubicin (Table 3). In fact, in a subgroup of patients who received prior adjuvant anthracyclines, the risk of cardiotoxicity was sevenfold higher with conventional doxorubicin compared with the pegylated liposomal form.

Table 3 – Pegylated liposomal doxorubicin vs conventional doxorubicin in high-risk MBC

	N	Cardiotoxicity events	HR	95% CI
⩾65 years of age				
PLD	78	0	N/A[a]	N/A[a]
Doxorubicin	66	9		
Prior adjuvant chemotherapy				
PLD	38	1	7.27	0.93–56.80
Doxorubicin	40	11		
Cardiac risk factor				
PLD	122	5	2.7	1.01–7.18
Doxorubicin	121	21		

CI, confidence interval; HR, hazard ratio; PLD, pegylated liposomal doxorubicin.
a HR cannot be determined as there are no events in the PLD group.

PLD has been evaluated in combination with other active agents in the treatment of MBC, including paclitaxel, docetaxel, cyclophosphamide, gemcitabine, vinorelbine and trastuzumab. These trials demonstrated considerable activity and tolerability of PLD in both the metastatic and locally advanced settings, with a number of these trials including patients who had received prior anthracyclines and/or taxanes. In a phase II trial, PLD was evaluated in 79 women with MBC who had been previously treated with conventional anthracyclines; 23% received prior adjuvant anthracyclines, 68% received anthracyclines for metastatic disease, and 9% had received anthracyclines in both the adjuvant and metastatic settings.[32] Patients were considered anthracycline-resistant if they had disease progression on prior anthracyclines or within 6 months of adjuvant therapy. Not only did these patients fare well overall, even with 30% having received $\geqslant 3$ previous regimens for MBC, no difference in clinical benefit rate (ORR + SD $\geqslant$ 24 weeks) was observed between patients who had received PLD > 12 months and those who received it within 12 months of their last anthracycline therapy. Importantly, no patients developed CHF or had a decrease in LVEF of greater than 15%, highlighting the safety as well as the clinical activity of PLD in patients with previous anthracycline exposure.

2. Conclusions

Despite advances in the treatment of MBC, only approximately 10% of patients are long-term survivors. Randomised trials have been fundamental in helping to select treatment strategies but the aim of MBC therapy is still primarily palliative and focused on prolonging survival and improving QoL versus cure. Chemotherapy remains the gold standard for patients with HER2-negative, ER- and PgR-negative breast cancer. Extremely important would be the identification of potential targets to customising treatment, looking not only at the development of biological agents but also at a tailored approach to chemotherapy. Ongoing studies are evaluating the role of platinum compounds. The rationale is based on the fact that roughly 80% of basal-like tumours present BRCA-1 loss-of-function. The BRCA-associated genome surveillance complex plays a key role in DNA repair. Therefore patients whose tumours have DNA repair defective pathways should be particularly sensitive to DNA-damaging agents such as platinum compounds.

Poly (ADP-ribose) polymerase (PARP) is a DNA sensor that signals the presence of DNA damage and facilitates DNA repair. There are 17 PARP isoenzymes although PARP-1 seems to play a critical role in signalling DNA damage and facilitating DNA repair. There are six different compounds inhibiting PARP that are currently under evaluation in phase I–II clinical trials. Interestingly enough, BRCA-1 protein deficient cells seem to be highly sensitive to PARP inhibition compared to wild-type cells. These pre-clinical data support the concept that the combined use of DNA-damaging agents and PARP inhibitors might be highly effective in triple-negative breast cancer patients carrying BRCA-1 dysfunction. With a deeper knowledge of the biology of basal-like tumours their approach will progress from an era of empirically based treatment to an era of tailored therapies.

Conflict of interest statement

The author indicates no potential conflict of interest

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