The role of chemotherapy and targeted agents in patients with metastatic breast cancer

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Abstract

Metastatic breast cancer has always been a challenging disease to treat, with cytotoxic chemotherapy often being deemed a merely palliative treatment that is given to relieve cancer-related symptoms. However with the introduction of more effective systemic therapies over the last two decades, recently we have witnessed substantial improvements in clinical outcomes such that many patients now live with metastatic secondary breast cancer for many years. Various different cytotoxics are used in clinical practice, and targeted biological therapeutics have an increasing role to play in the management of different breast cancer subtypes. The appropriate use of these different systemic therapeutics has been one of the principal reasons for the continued improvement in clinical outcomes for women with advanced breast cancer, including a probable substantial impact on overall survival.

Introduction

When treating metastatic breast cancer, the primary aim of any systemic therapy is to palliate disease-related symptoms. This is achieved by utilising anti-cancer therapies such as chemotherapy that can impact on tumour growth. It has been shown that quality of life in advanced breast cancer is clearly linked to treatment response [1–3], and that chemotherapy can have a significant benefit for patients due to anti-cancer effects that reduce or prevent tumour-related symptoms. While metastatic breast cancer cannot be cured, modern drug treatment can be very effective in maximising a patient's duration of quality time without disease-related symptoms. In this setting it is always important that this is achieved without any significant treatment-related toxicities.

Historically, cytotoxic chemotherapies were said to have little impact on overall survival, with metastatic disease being deemed incurable. However with the introduction of more effective systemic therapies over the last decade, we have witnessed substantial improvements in clinical outcomes compared to 30 years ago, and many patients now live with metastatic secondary breast cancer for several years. Historical comparisons have shown that the introduction of combination cytotoxic chemotherapy since the late 1970s has produced a modest 9–12 month gain in survival compared with untreated patients [4,5]. Furthermore, any patient with life-threatening visceral disease (i.e. extensive liver metastases) who has a good clinical response to chemotherapy, will clearly have a survival benefit compared to the outcome by not having therapy. Nowadays with more effective cytotoxic drugs, including combinations with targeted biological agents, significant impacts on overall survival have been observed in patients with metastatic disease as discussed below.

This paper will review the role of cytotoxic drugs in the treatment of metastatic disease, and highlight some of the recent developments in schedules and combination approaches with new agents. There are four different systemic therapies used in current clinical practice for the treatment of metastatic breast cancer; endocrine therapies for oestrogen receptor positive (ER+) disease, cytotoxic chemotherapy, supportive therapies including bisphosphonates for bone disease, and more recently targeted therapies including monoclonal antibodies such as trastuzumab for human epidermal growth factor receptor 2 positive (HER2+) disease. In this paper, the role of cytotoxic and targeted therapies will be discussed, with evidence provided for any impact that these therapies have on overall survival.

Indicators for chemotherapy

There are a number of patient- and disease-related factors that are taken into account when deciding whether to start chemotherapy in a patient with advanced disease. Chemotherapy is usually reserved for patients with disease unresponsive to endocrine agents or patients with rapidly progressive visceral

disease. Factors such as treatment-free period, patient age and performance status, volume and site of metastatic disease, together with receptor status are all equally important to consider – for example, patients who have relapsed with ER+ disease with a long treatment-free interval, soft tissue or bone as the dominant site of metastasis with good performance status are usually treated with endocrine therapy in the first instance. In contrast, a young patient with triple receptor negative breast cancer who relapses within a year of adjuvant therapy with symptomatic liver and lung disease requires chemotherapy to palliate and control her disease [6].

Exposure to prior chemotherapy in the adjuvant setting is not an impediment to the benefit of chemotherapy when administered for metastatic breast cancer [7]. However, a disease-free interval of less than 12 months since the end of adjuvant chemotherapy and the presentation of metastatic disease implies a degree of resistance to the previous regimen that will influence the choice of 1st-line chemotherapy for metastatic breast cancer. Following use of first-line chemotherapy, at subsequent disease progression different cytotoxic drugs may be used, albeit careful consideration is needed in relation to likelihood of benefit versus risk of toxicity. Tumour response rates are greatest if patients have previously received one or no prior therapy (40–60%), but decline as treatment progresses (30% in the 3rd-line setting). A prior lack of response to first-line chemotherapy, or a short progression-free period, is associated with a much lower likelihood of subsequent response to second- or third-line chemotherapy [8]. Progression-free intervals in the 3rd-line setting are often only a few months at most in those that benefit from further chemotherapy, and as such a careful discussion with patients should be had regarding the risk–benefit of further lines of therapy, knowing that it might have little impact on overall survival.

It has become increasingly important to consider a biopsy of metastatic disease (if clinically feasible) at the time of recurrence to establish whether the receptor status of the recurrent disease has changed, and in particular whether this might influence the likelihood of benefit from targeted therapies such as endocrine therapy and/or HER2 antagonists. Reported rates of receptor (ER, PgR, HER2) discordance between the primary tumour and the site of metastases range from 10% to 40%. It has been debated whether this reflects a true change in tumour biology at the time of recurrence, sampling error, or an assay error [9]. However, gain of HER2 expression can occur in 12–15% of ER+ve metastatic breast cancers, and in these cases HER2-directed targeted therapies can then have a major impact in the treatment of the disease.

Chemotherapy

Chemotherapy is used to treat metastatic advanced disease when symptoms develop that require palliation, and/or disease has progressed within visceral organs that threatens quality of life. The choice of drug and/or regimen is determined by a number of patient factors including whether chemotherapy had been used in the adjuvant setting, the treatment-free period (indicator of drug resistance), age and performance status of the patient, and organ function (especially hepatic renal and bone marrow function). Agents used include anthracyclines (epirubicin, doxorubicin) and the taxanes (paclitaxel, docetaxel) if these have not been used in the adjuvant setting, followed by other active therapeutics such as capecitabine, vinorelbine, platinum drugs (cisplatin, carboplatin), gemcitabine.

In addition to balancing the toxicities versus the clinical efficacy for each cytotoxic drug, clinicians must decide whether to use combination regimens versus sequential single agent therapies. In general, response rates tend to be higher with combination regimens when used as first-line therapy, but often at the expense of greater toxicity and short-term deterioration in quality of life. Furthermore, the majority of clinical trials assessing new combination strategies have not been adequately structured to address whether long-term outcomes such as overall survival are equivalent or superior to using the same agents administered sequentially. For example, the E1193 trial showed that the combination of doxorubicin (A) and paclitaxel (T) therapy resulted in improved response rates with no survival benefit over sequential treatment [10]. Likewise, equivalent survival and response rates were observed in a trial comparing single agent mitoxantrone with combination 5-fluorouracil, epirubicin and cyclophosphamide (FEC), with less toxicity and improved quality of life in the monotherapy arm [11]. Indeed, an overview of 106 randomised trials in metastatic breast cancer involving over 17,000 patients suggested only a small, but significant benefit for combination chemotherapy versus single-agent chemotherapy [12].

Thus, many clinicians feel that in the absence of rapid clinical progression or life-threatening visceral metastases, the most effective strategy is to use sequential monotherapy regimens [13]. Combination strategies may still be advisable for some patients of good performance status with rapidly progressing visceral disease and evidence of organ dysfunction,

particularly in the first-line setting. Although some of the more recent combinations have shown an impact on survival, in general single-agent treatment is still considered best for 2nd- or 3rd-line chemotherapy options when toxicity considerations are very relevant in the face of worsening performance status or symptoms in relation to progressive disease. Likewise, single-agent treatment is also preferable for women with extensive life-threatening visceral involvement of the liver or bone marrow where dose-reductions of a single agent are more readily controllable and weekly schedules are often utilised. If organ function improves following successful reduction in tumour burden, then chemotherapy dose can be increased, or combinations utilised.

Anthracyclines

These are amongst the most active cytotoxic drugs for the treatment of breast cancer. In women with metastatic breast cancer who have not received prior adjuvant anthracycline-based chemotherapy, meta-analyses support the view that anthracycline chemotherapy regimens improve response rates, time to disease progression and indeed overall survival over non-anthracycline containing regimens [12,14]. In patients who have relapsed with no prior anthracycline exposure, first-line treatment options include doxorubicin or epirubicin given either as single agents, or combined with cyclophosphamide (AC or EC) or with cyclophosphamide and 5-FU (FAC or FEC). The anthracenediones such as mitoxantrone are less toxic than anthracyclines, but have been deemed less effective.

However, most patients who relapse with metastatic breast cancer have already received anthracycline chemotherapy as part of their adjuvant treatment protocol. As such either cumulative exposure to anthracyclines, or cardiac risk factors such as age (>70 years) or co-morbidity (ie. diabetes, hypertension, ischaemic heart disease) can make re-treatment with anthracycline difficult. The choice of whether to use an anthracycline or to utilise a taxane has been tested in a randomised trial. Women with metastatic disease exposed to alkylators in the adjuvant setting and/or at most one line of therapy in the advanced setting were randomised to doxorubicin 75 mg/m^2 versus docetaxel 100 mg/m^2 every three weeks [15]. Although docetaxel resulted in a higher objective response rate in this population (48% vs 33%), there was no statistically significant difference in median time to progression (26 vs 21 weeks) or overall survival (15 vs 14 months). Neutropenic fever, infection, cardiac toxicity, nausea & vomiting were more likely with anthracycline therapy whereas the primary toxicities caused by docetaxel consisted of diarrhoea, neuropathy, fluid retention, skin and nail changes. In general, depending on toxicities and performance status if anthracyclines have not been used before in the adjuvant setting, these are given first in advanced disease leaving open the option for subsequent taxane use at progression.

Anthracyclines are considered unsafe in combination with trastuzumab due to the higher risk of cardiotoxicity [16]. The pegylated liposomal formulation of doxorubicin (Caelyx/Doxil) has been shown to have comparable efficacy (progression-free survival 7.8 vs 6.9 months, overall survival 21 vs 22 months) with reduced cardiotoxicity, myelosuppression, vomiting and alopecia in comparison to standard doxorubicin in the first-line treatment of metastatic breast cancer [17]. Recent evidence also supports the utility of re-challenging patients with liposomal doxorubicin plus cyclophosphamide if more than 12 months have passed since completion of an adjuvant anthracycline regimen. In a phase II multicentre trial, this regimen was associated with an overall response rate of 38% and a median time to progression of 12.2 months [18]. Thus, anthracyclines can remain effective therapies in the advanced disease setting, even if they have been utilised before.

Taxanes

Taxanes are now considered one of the most active compounds in clinical use for metastatic breast cancer; they work by stabilising the cell's microtubules through interaction with beta tubulin and preventing depolymerisation, thereby preventing normal chromosomal segregation at mitosis and inducing cell cycle arrest followed by activation of a cell death pathway (apoptosis). The two most commonly used taxanes in clinical practice are paclitaxel and docetaxel, and these drugs are an effective option for those patients previously exposed to an anthracycline. Indeed, a recent Cochrane meta-analysis confirmed a statistically significant overall survival benefit in favour of taxane-containing regimens compared to use of other types of chemotherapy (hazard ratio for survival 0.90) [19].

Subsequently several studies have examined the optimal dosing regimens for the taxanes – for example, weekly paclitaxel is a more effective method of delivering this drug than 3-weekly dosing, and as such is often the treatment of choice for elderly patients or those with poor performance status owing to the

reduced myelo-suppression associated with this schedule, although cumulative neuro-toxicity can be an issue for some patients [20]. Docetaxel administered every 3 weeks has better efficacy compared to 3-weekly paclitaxel, with superior response rates (32% vs 25%), prolonged time to progression (5.7 vs 3.6 months) and overall survival (15.4 vs 12.7 months, hazard ratio 1.41) [21], although at the expense of more haematological toxicity. When docetaxel was tested on a weekly rather than 3-weekly schedule, this gave more toxicities with fluid retention and excess lacrimation [22]. As a consequence, in clinical practice the two most commonly used regimens are weekly paclitaxel 80 mg/m^2 or 3-weekly docetaxel 75–100 mg/m^2.

Several attempts have been made to find better ways of administering taxanes. Albumin-bound paclitaxel (Nab-paclitaxel) appears to offer the benefit of taxane therapy without the steroid pre-medication, utilising a shorter infusion schedule. In a phase III trial, compared to 3-weekly paclitaxel Nab-paclitaxel gave a significantly improved response rate (33% vs 19%) and time to progression (23 vs 17 weeks), but no difference in overall survival (60 vs 56 weeks) [23]. In a randomised phase II trial comparing Nab-paclitaxel with docetaxel, there was a similar significant improvement in both response rate (49% vs 35%) and progression-free survival (13 vs 7.5 months), but again no improvement in survival [24].

Other microtubule inhibitors

Vinorelbine is a vinca alkaloid that interferes with microtubule assembly and induces a cell cycle arrest at mitosis due to its microtubule targeting activity. It may induce neutropenia as its dose-limiting side effect, and constipation and paralytic ileus are also recognised gastrointestinal effects. Although vinorelbine is active in patients with previously untreated metastatic breast cancer [25], in clinical practice its use tends to be reserved for anthracycline-resistant disease in the second- or third-line setting. Response rates from phase II trials average about 19% (range 14–24%), and indeed one study demonstrated a survival benefit for vinorelbine over melphalan in patients who had failed to respond to an anthracycline regimen [26]. Vinorelbine has also been combined with other active drugs in metastatic breast cancer, in particular 5-fluorouracil or anthracyclines. A phase III randomised study demonstrated similar efficacy of the combination of 5-fluorouracil and vinorelbine compared to docetaxel monotherapy in patients who had received prior anthracycline therapy, but no overall survival benefit [27]. Likewise in a phase III study the combination of doxorubicin and vinorelbine failed to offer any survival benefit over doxorubicin alone [28]. However, oral derivatives of vinorelbine are in development which may be attractive in combination with other active oral agents such as capecitabine.

Two chemotherapy agents that also target microtubules have created interest in terms of whether novel cytotoxic drugs can be active in metastatic breast cancer after prior exposure to anthracycline- and taxane-based chemotherapy. Ixabepilone is a semi-synthetic analogue of epothilone B that may overcome taxane-drug resistance associated with p-glycoprotein expression and tubulin mutations. In a phase II study of ixabepilone in patients previously treated with a taxane in either the adjuvant or metastatic setting, stable disease was observed in over 50% of patients treated, while in a separate study in patients who had progressed on prior taxane therapy the objective response rate was only 12% [29,30]. However, in a large phase III trial of 1221 patients, there was no overall survival benefit with the combination of ixabepilone with capecitabine compared to capecitabine alone [31]. Toxicities experienced with epothilones are neurotoxicity, diarrhoea and febrile neutropenia.

Eribulin mesylate is a microtubule inhibitor and a synthetic analog of halichondrin B derived from the marine sponge *Halichondria okadai*. Pre-clinical work had established that this drug binds to an unique site on tubulin with efficacy in taxane-resistant cell lines, while a phase II trial in patients pre-treated with both anthracycline/taxanes and a median of four prior chemotherapy regimens resulted in a response rate of 11.5% [32]. Subsequently, a randomised phase III trial was performed in 762 patients who had received a median of 4 prior chemotherapies, including at least two regimens for advanced disease together with prior exposure to both an anthracycline and taxane. In these heavily pre-treated patients, eribulin significantly improved the overall survival compared with the treatment of physicians' choice (eg. vinorelbine, capecitabine or gemcitabine), which increased from a median of 10.6 to 13.1 months (hazard ratio 0.81, $P = 0.041$) [33]. Of note, while the objective tumour response rate by independent review was significantly higher for eribulin (12% vs 5%, $P = 0.002$), the improvement in progression-free survival was not significant (2.2 months for control arm, 3.7 months for eribulin, hazard ratio 0.87). However, this was a randomised trial in late-stage disease of a novel agent against real world options that clinicians currently utilise for patients, and the demonstration of a clear 3 month survival benefit recently led to the drug being approved in both the USA and Europe.

Other cytotoxic drugs, either as monotherapy or in combinations

Inevitably patients with metastatic breast cancer will develop resistance to both anthracyclines and taxanes. Common therapeutic options in the 3rd-line setting other than vinorelbine include capecitabine, gemcitabine or platinum agents. The relative efficacies of these agents when used alone or in combination, together with any impact on survival, are discussed below. Of note, especially in this 2nd- or 3rd-line setting, any gains in survival that are seen with combination therapy in this setting may be offset by greater toxicity, making combinations less attractive both to clinicians and patients.

1. Capecitabine

Capecitabine is an oral fluoropyrimidine that is converted to 5-fluorouracil by the enzyme thymidine phosphorylase that is overexpressed in tumour tissue. Capecitabine is effective in taxane- and anthracycline-refractory patients, and is generally well tolerated with the benefits of causing minimal hair loss and limited bone marrow suppression. Several phase II studies all confirmed that capecitabine is active and well tolerated in patients who have disease resistant to anthracycline or taxane therapy, with response rates of 20–28% reported [34–36].

The excellent tolerability, in particular the low myelotoxicity associated with the drug, made it an attractive agent to consider in combination with other cytotoxics, especially as preclinical work had showed potential for synergy with taxanes. In a randomised phase III study, over 500 patients (who had been pre-treated with anthracycline) were randomised to capecitabine/docetaxel or docetaxel monotherapy. The combination resulted in an increased response rate (42% vs 30%), time to progression (6.1 vs 4.2 months), and also a significant improvement in overall survival (14.5 vs 11.5 months) [37]. However, these improved efficacy endpoints for the combination including an impact on survival were at the cost of more grade 3 adverse events (71% vs. 49%) that resulted in significantly greater interruption of treatment. Unfortunately, this trial did not address whether sequential administration would have had equivalent benefit with less toxicity, and as such in clinical practice the combination of capecitabine with docetaxel is rarely used, despite the impact on survival.

Another combination regimen that has shown synergy is ixabepilone plus capecitabine in women previously treated but not necessarily resistant to anthracycline and taxane therapy [38]. Although the combination had a better progression-free survival (6.2 vs 4.2 months) compared with capecitabine alone, there was no significant difference in overall survival (16.4 vs 15.6 months) between the two arms. Toxicity was a concern, as nearly a quarter of those in the ixabepilone plus capecitabine arm experienced reversible grade 3–4 neuropathy.

2. Gemcitabine

Gemcitabine is a nucleoside analogue that targets DNA synthesis. The most frequent adverse events are bone marrow suppression with neutropenia. Gemcitabine is active as a single agent in metastatic breast cancer with response rates of 14–37%. Phase II studies in anthracycline- and taxane-refractory patients have documented response rates of 22–30%. Several trials have studied the combination of taxane with gemcitabine, with a phase III trial showing a significantly improved response rate compared with single agent paclitaxel (41% vs 22%), time to progression (5.2 vs 2.9 months) and a significantly superior overall survival (18.6 vs 15.8 months, $P = 0.048$) [39]. Again, whether combination therapy is superior to the same drugs given sequentially (i.e. paclitaxel, then gemcitabine treatment) remains unclear, and this regimen is not widely used despite the benefits including survival observed in the phase III trial.

3. Platinum agents

There is an increasing interest in the activity of platinum agents in metastatic breast cancer, in particular certain subtypes such as triple negative or BRCA tumours. Combinations such as mitomycin C, vinblastine and cisplatin (MVP) are active combination regimens in pre-treated patients with metastatic breast cancer. In a recently reported phase II study, the response rates associated with the MVP regimen were approximately 30% [40]. The toxicity profile is also mild with this regimen with minimal hair loss. Likewise, the combination of cisplatin or carboplatin with 5FU may be well suited to the treatment of patients with significant liver dysfunction.

Disease subtype and impact of chemotherapy on survival

Increasingly it is not unusual for patients to receive different chemotherapies beyond the second-line and third-line settings in advanced disease, yet it has been hard to quantify the actual benefit to patients, and in particular any impact on survival. There are very few

well-conducted randomised trials in this setting that show any meaningful benefit to patients, yet clinicians know that for individual patients if the disease has been chemo-sensitive and responds to each successive therapy, then prolonged remissions with further lines of therapy can contribute to significant periods of good-quality life. This can have a big impact for the survival of an individual patient, although the impact of treatment on a population of women with apparently similar metastatic breast cancer (ie. by age, stage of disease, line of therapy, receptor status, etc) may be minimal overall.

As such, both patient and tumour heterogeneity can minimise the impact that chemotherapy may have on survival within large clinical trials. Recent research has suggested that different molecular subtypes of breast cancer have distinct patterns of metastatic spread which are associated with very different median durations of survival. A study from Canada in a well-defined population of over 3,700 patients first diagnosed 20–25 years ago mapped the site of metastatic relapse to one of 6 breast cancer subtypes as determined by a gene expression profile-validated immuno-histochemical surrogate panel (ER+ luminal A, ER+ luminal B, luminal ER+ HER2+, ER–HER2+ enriched, basal-like, and triple negative non-basal like) [41]. Median durations of survival were 2.2 years for luminal A, 1.6 years for luminal B, 0.7 years for HER2 enriched, and 0.5 years for basal-like. Many of these patients had not received modern types of systemic therapy, so these data represent a rare opportunity to characterise the natural history (including survival) of the various subtypes of metastatic disease.

In addition to their natural history, it is increasingly clear that different subtypes of breast cancer respond differently to different drugs; for example triple negative breast cancer may respond well to platinum drugs and vinca-alkaloids and less well to other drugs, while ER+ disease can be less chemo-sensitive in general, and HER2+ disease will respond best to combinations of certain chemotherapies with HER2-targeted agents. Thus, it is not surprising that previous studies of an individual chemotherapy drug given to an unselected group of patients with different molecular subtypes of metastatic breast cancer consistently failed to show a significant impact on overall survival due to heterogeneity of different subtypes of breast cancer. In future it will be becoming increasingly important to target the benefit of specific therapies to certain groups of the disease, in order to maximise the clinical benefit. Attempts have also been made to see whether gene profiling assays can identify subgroups of breast cancer that respond to individual chemotherapies such as taxanes – while promising results have been suggested for some of these assays, they have not yet been validated for routine clinical practice.

Targeted agents

HER2 targeted therapies

Substantial progress with systemic therapies for metastatic breast cancer has been made within the last decade following the development of biological agents that target key oncogenic pathways within breast cancer cells. At least 20–25% of breast cancers over-express the type 1 peptide growth factor receptor HER2 due to amplification within the cancer cell of the *HER2/neu* oncogene on chromosome 17. Rational drug design led to the development of recombinant monoclonal antibodies that target the extra-cellular domain of the HER2 trans-membrane receptor, and thus inhibit the growth of tumour cells. Furthermore, pre-clinical work demonstrated clear synergy when such therapies were combined with chemotherapy agents, in particular the taxanes. The approved HER2 targeted drugs in clinical practice include the monoclonal antibody trastuzumab, and the small molecule tyrosine kinase inhibitor lapatinib.

The early phase II studies with trastuzumab in women with HER2+ metastatic disease that was resistant to chemotherapy showed remarkable efficacy when given as monotherapy, with response rates of 11–15%, response duration of 9.1 months and a median survival of 13 months in patients otherwise refractory to existing therapies with only a few months to live [42,43]. When trastuzumab was used as a first-line therapy in those with the strongest expression for the HER2 receptor (3+ on immuno-histochemical assay, or with gene amplification by fluorescent in-situ hybridisation), then a response rate of 35–61% was observed, something unheard of before for a biological agent given on its own [44].

The subsequent pivotal clinical trials confirmed that these agents synergise with cytotoxic chemotherapy drugs, enhancing clinical response rates and prolonging progression-free survival [16]. The combination of trastuzumab with either paclitaxel or docetaxel resulted in response rates ranging from 41% to 61%, in some cases doubling the response rate seen with the single agent cytotoxic alone [16,45,46]. The significant clinical efficacy that was observed with these drugs also impacted on overall survival when given in the first-line setting. Two pivotal trials changed clinical practice for HER2-positive metastatic

breast cancer, with significant gains being observed in overall survival (an additional 5–9 months) in the first-line metastatic setting by the addition of the biological agent, even despite subsequent cross-over to the addition of the biological agent in the control arm [16,46]. This substantial impact on survival in metastatic disease demonstrated the powerful effect of targeted agents, and that appropriately used systemic therapies can have substantial effects that significantly alter clinical outcome.

The combination of trastuzumab with other microtubule inhibitors like vinorelbine has shown significant clinical efficacy [47], while combining trastuzumab and capecitabine is another appropriate option [48]. A subsequent phase III study demonstrated the utility of maintaining HER/2 targeting even beyond progression on trastuzumab-containing regimens. In the GBG26 study, patients with a median duration of 45 weeks of prior trastuzumab exposure were randomised to receive capecitabine alone, or capecitabine with continuation of trastuzumab. The combination therapy group achieved a greater response rate (48% vs 27%) and time to progression (9.2 vs 5.6 months), although overall survival was not statistically different (25.5 vs 20.4 months) [49].

As such, routine practice has been to continue some form of HER2 targeted therapy in at least the 2nd-line setting, despite the failure to impact on survival. Options include either continued trastuzumab and an alternate cytotoxic (vinorelbine or capecitabine), or switching the HER2-targeted component of the regimen to the small molecule tyrosine kinase inhibitor lapatinib. This oral small molecule inhibitor of HER2 and EGFR1 has shown non-cross resistance in preclinical work and similar synergy when combined with cytotoxics. Lapatinib monotherapy as first-line treatment in trastuzumab-naive metastatic breast cancer has activity similar to that reported for first-line trastuzumab monotherapy [50]. In combination with capecitabine, it also demonstrated an improved response rate (22% vs 14%) and time to progression (8.4 vs 4.4 months) compared to capecitabine monotherapy alone among women who had progressed following prior trastuzumab based regimens, although the final survival analyses did not show a significant different in median overall survival [51]. Likewise in ER+HER2+ metastatic disease, the combination of lapatinib with the aromatase inhibitor letrozole was significantly more effective than letrozole alone in terms of clinical benefit rate (48% vs 29%) and progression-free survival (8.2 vs 3.0 months), but without a significant impact on survival [52]. An additional benefit is that lapatinib penetrates the blood–brain barrier and may impact on CNS metastases, with evidence for both clinical efficacy in tumour shrinkage [53], and in responders control of disease and its symptoms for at least 6 months [54].

Increasing evidence suggests that dual biological combinations of drugs to completely block HER2 (i.e. combination of trastuzumab and lapatinib) could be more effective than single-agent therapy. In a recent randomised phase III trial in advanced disease, patients who had progressed through a median of 3 trastuzumab-based regimens and/or 4 chemotherapy regimens were randomised to combination lapatinib 1000 mg daily plus trastuzumab weekly, or to lapatinib monotherapy 1500 mg daily. Even in this heavily pretreated population, the combination arm had an improved response rate (10.3% vs 6.9%) and significantly prolonged disease progression (12.0 vs 8.1 weeks) [55]. There was a significant improvement in survival (median 14.0 vs 9.5 months), representing a 26% reduction in the risk of death even in these heavily pre-treated patients.

Various novel agents that target HER2 are in development which could be effective when disease becomes resistant to trastuzumab. Strategies that are in clinical development include antibody-cytotoxic conjugates like trastuzumab-DM1, new monoclonal antibodies such as pertuzumab, or dual EGFR-HER2 inhibitors like neratinib [56–58]. It remains to be seen whether these will offer any additional impact on survival compared with the substantial gains that we have witnessed with trastuzumab.

Angiogenesis inhibitors

Other targeted agents that have been used in clinical practice include angiogenesis inhibitors such as the monoclonal antibody bevacuzimab against vascular endothelial growth factor receptor (VEGF). An initial randomised trial indicates that the combination of paclitaxel with bevacizumab significantly improved progression-free survival compared to paclitaxel alone (11.3 vs 5.8 months) with a more than doubling of the response rate. However in this trial, overall survival was the same in both treatment arms [59]. Similarly, the combination of bevacizumab with docetaxel improved progression-free survival when compared to docetaxel alone (10.1 vs 8.2 months), although the overall survival was similar across all three arms of this trial [60]. As such, there has been controversy regarding the true added survival benefit of this drug in combination with chemotherapy, leading the FDA in the USA to withdraw the licence due to limited efficacy and concern re the toxicity profile.

PARP inhibitors

Poly (ADP-ribose) polymerase 1 (PARP) is a nuclear enzyme that is required for the repair of single-strand DNA breaks (SSB) [61,62]. PARP inhibitors were initially developed as potentiators for chemotherapy through inhibition of damage repair, although the subsequent demonstration that cancer cell lines with defects in the *BRCA1* and *BRCA2* genes were highly sensitive to PARP inhibitors *in vitro* suggested that these drugs may have efficacy as monotherapy in women with hereditary breast cancer [62,63]. This preclinical evidence translated into substantial efficacy in early clinical trials of PARP inhibitors, in particular the oral PARP inhibitor olaparib [64]. In the phase II trial which studies two doses of olaparib in women with confirmed *BRCA1/2* mutated advanced breast cancer, the objective response rate with the highest dose was 41% [65].

The shared characteristics of triple negative breast cancer (especially of the basal subtype) with hereditary *BRCA1* related cancers led to the investigation of PARP inhibitors in metastatic TNBC. In an open label phase II study, 123 patients with metastatic triple negative breast cancer (TNBC) were randomised between the chemotherapy doublet gemcitabine/carboplatin given alone, and gemcitabine/carboplatin given in combination with the PARP inhibitor iniparib (BSI-201) [66]. The primary endpoint was clinical benefit rate (CBR), and the addition of iniparib significantly improved CBR from 34% to 56% ($P = 0.01$). In addition, impressive enhanced efficacy was seen in the secondary endpoints, with improved median progression-free survival (3.6 months to 5.9 months, HR 0.59, $P = 0.01$) and improved overall survival (median 7.7 months to 12.3 months, HR 0.57, $P = 0.01$). Despite these promising early results, including an impact on overall survival, a subsequent larger phase III trial in 519 patients with TNBC failed to demonstrate any improved benefit of the addition of PARP inhibition to platinum based chemotherapy [67]. A possible explanation for this negative result in a larger population is that even within TNBC, significant heterogeneity exists, suggesting that not all tumours even within this subgroup will benefit from PARP inhibition. More research is clearly needed to identify who benefits from this type of the specific targeted agent.

Conclusions – impact on survival

The outcomes for women who develop metastatic breast cancer are now substantially improved compared to a decade ago, due in part to the development and introduction into routine clinical practice of numerous different systemic therapies that control advanced disease more effectively and maintain a patient's quality of life. As illustrated above, the impact on quantity of life (i.e. overall survival) of individual therapies in various randomised trials has been mixed, although it is clear that certain new agents such as the taxanes and the HER2-targeted therapies have produced substantial gains in survival due to their much greater efficacy.

Oncologists utilise existing systemic therapies to get maximum benefit for their patients, and novel therapies continue to emerge that may further benefit patients. However, with a plentiful array of effective drugs to use in the advanced disease setting, often successfully given in sequence as multiple subsequent lines of therapy, this gives clinical trials in the first-line setting an increasingly impossible challenge to prove that any new agent alone will impact on overall survival in a statistically significant and meaningful way. As such, registration of effective new therapies based on showing an overall survival benefit is a hurdle that may or may not be appropriate or achievable, and many have argued that significant gains in progression-free survival without adverse toxicities should be sufficient to allow a new therapeutic strategy to be approved by regulatory authorities. For patients, both quality and quantity of life are important, and having numerous effective therapies to use has undoubtedly yielded important gains in long-term survival such that most patients now live with secondary breast cancer for a number of years.

Conflict of interest statement

The author has an interest in relation with one or more organisations that could be perceived as a possible conflict of interest in the context of the subject of this paper. Advisory board: GlaxoSmithKline, Roche; Corporate-sponsored research: AstraZeneca, GlaxoSmithKline.

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