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Chemo-hormonal therapy for metastatic breast cancer patients: Treatment strategy

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ABSTRACT

In spite of major advances in screening, surgery, radiation therapy, endocrine and chemotherapy (CT) for patients with early-stage breast cancer (BC), there has been only a modest progress in improving survival for women with metastases. Almost all MBC patients are ultimately candidates for systemic therapy, either hormonal or CT. The choice of therapy depends on the disease free interval from the end of adjuvant therapy, whether or not the patient is symptomatic and, if so, the severity these symptoms; and whether the tumour is hormone receptor positive or negative. Standard first-line chemotherapy consists of anthracyclines plus or minus a taxane depending on the end point of treatment. A recently published individual patient's data metanalysis confirms this concept. Taxane-based combinations were significantly better than A-based combinations in terms of response rate (RR) and progression free survival, but not in terms of survival. Polichemotherapy remain indicated if the end point is citoreduction of high tumour burden. Single agent taxane and single agent A are equivalent in term of RR and overall survival (OS) and are prescribed if the end point is the control of disease and prolongation of survival. First line aromatase inhibitors (steroidal or non-steroidal) and subsequent fulvestrant or an AI of the opposite class is an appropriate sequence for the treatment of advanced endocrine responsive disease. The benefit of an angiogenetic therapy with the scope of blocking certain critical pathways for tumoural cells (for example angiogenesis), has recently been confirmed in at least 2 phase III trials comparing CT with or without bevacizumab. The near future will tell us if a new scenario will become standard in clinical practice.

1. Introduction

In spite of major advances in screening, surgery, radiation therapy, endocrine therapy and chemotherapy (CT) for patients with early-stage breast cancer (BC), there has been only a modest progress in improving survival for women with metastases. The median survival for metastatic breast cancer (MBC) patients remains 18–24 months. Almost all MBC patients are ultimately candidates for systemic therapy, either hormonal or CT. The choice of therapy depends on the disease-free interval from the end of adjuvant therapy, whether or not the patient is symptomatic and, if so, the severity these symptoms; and whether the tumour is hormone receptor positive or negative. Despite treatment approaches such as target and hormone therapy for BC, CT remains an important component for the treatment of most BCs. Target agents and/or hormone agents are often combined with CT to improve the results, whilst CT as a single agent or in combination with other agents remains the cornerstone of therapy for HER2-neu negative, hormone receptor-negative patients.

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Patients with oestrogen receptor (ER)- or progesterone receptor (PR)-positive tumours are more likely to develop bone metastases, those with ER- and PR-negative tumours are more likely to develop liver and other visceral metastasis, whereas in the so-called triple negative phenotype there is a higher incidence of developing brain metastases rather than bone or lung metastases. In spite of these biologic differences, all sites of metastatic disease in patients with ER- or PR-positive tumours are potentially responsive to endocrine therapy. For patients with ER- and PR-negative disease who have slowly progressive metastases, minimal symptoms, single site of recurrence or advanced age, a single agent CT could be offered. Conversely, because the overall response rate (RR) to CT is higher than that to endocrine therapy, patients with rapidly progressive tumours, younger age or important tumour-related symptoms should be considered for combination CT. A common concern is whether patients with hormone receptor-positive tumours and symptomatic, rapidly progressing metastatic disease should be considered for a combined modality treatment with CT and subsequently maintenance endocrine therapy. Clinical trials comparing CT alone with CT plus endocrine therapy have occasionally shown a higher RR but no survival advantage for combined treatment.[1] Moreover, there is a theoretical concern that combined modality treatment might be antagonistic.

The goals of systemic therapy in the metastatic setting are prolongation of disease control, maintenance or improvement in the quality of life and above all to prolong survival. Although achieving an objective response is highly gratifying for both patients and physicians, stabilising metastases is also a desirable treatment goal, especially for patients who are minimally symptomatic. Patients with stable metastases for 24 weeks or longer have survival similar to that of patients with complete and partial responses[2]; indeed, it is now common in clinical trials to report the so-called 'clinical benefit response', which includes the percentage of patients with stable disease for 24 weeks or more in addition to the percentage with complete and partial responses.

In this review we shall summarise the treatment strategy of endocrine responsive and hormonal receptor-negative advanced disease. The paradigm of HER2-neu positive MBC will be the object of a specific article.

2. CT for HER-2 negative advanced BC

CT is considered for the majority of MBC patients. The median survival of patients with metastases whose disease has become refractory to endocrine therapy or who have receptor-negative tumours is 18–24 months. A major issue in treatment selection is whether to use sequential single-agent therapy or a combination regimen of two or more agents. Response rates to initial therapy with anthracyclines (A), taxanes, capecitabine, vinorelbine, gemcitabine and platinum salts range on average from 25% to 60%, with the median time to progression averaging approximately 6 months. In general, RRs diminish by half when the agents are used as second- and third-line treatment, although there is a great variability amongst trials. Although multidrug regimens of active agents consistently show improved RRs that average approximately 20% higher than those for single agents, single-agent sequential therapy is generally associated with less treatment-related toxicity, and numerous trials have shown no survival advantage for combination therapy compared to single-agent therapy. A Cochrane review and metanalysis published in 2005 comparing single versus combination CT in MBC showed a statistically significant advantage for tumour response and time to progression (TTP), but a modest improvement in overall survival (OS) and increased toxicities for multiagent treatment. At the same time, another Cochrane paper showed that taxane-containing regimens appear to increase OS, TTP and overall response rate (ORR) with respect to non-taxane containing ones.[3,4] Fossati and colleagues in a metanalysis of single-agent versus once used combinations CT found a significant survival benefit for combination therapy that translated into an absolute benefit in survival of 9% at 1 year, 5% at 2 years and 3% at 3 years.[1] No individual trial included in the analysis showed a significant survival benefit for combination therapy, and no recent trials comparing single-agent taxane regimens with multidrug regimens were included. It is unclear whether patients in these trials had access to all the agents used in the multidrug regimens. Most patients with metastases are still best treated using a single-agent, sequential approach. There is no evidence that any specific sequence of active agents is superior to another.

One clinical trial illustrates this principle.[5] Sledge and colleagues randomly assigned 739 patients to either doxorubicin alone, paclitaxel (P) alone or the combination of both agents. The RR and TTP for the combination regimen (47% and 8.0 months, respectively) were significantly higher than those for single-agent doxorubicin (36% and 5.8 months, respectively) or P (34% and 6.0 months, respectively). However, secondary responses after changing over from P to doxorubicin (22%) or from doxorubicin to P (20%) compensated for the higher initial RRs and TTP for the combination regimen. Quality of life and survival time (median of 18.9 months for initial doxorubicin treatment, 22.2 months for initial P and 22.0 months for P) were similar for all groups. A similar trial was performed by Joensuu and colleagues, who compared weekly epirubicin with cyclophosphamide, epirubicin and fluorouracil; RRs, TTP and survival were similar in both groups, whereas quality of life favoured the less toxic, weekly epirubicin regimen.[6] Moreover, unlike combination CT, treatment with a single agent also allows the clinician to assess the benefit of the specific agent being administered.

It appears that effective therapies, given either in combination or sequentially, can be valuable for treating advanced BC. Single-agent, sequential CT treatment has the advantage of isolating which of the agents is proving effective and of simplifying decisions on CT dose optimisation for treatment-related toxicity. For these reasons, this type of CT treatment is preferable for most women receiving treatment for advanced BC.

Choice of first-line CT depends on several considerations: end-point of treatment (symptom palliation versus survival prolongation), age, the wishes and comorbidities of the patient, treatment administered in adjuvant phase (A or not, combination of A and taxanes), extent and symptom associated tumour burden, endocrine responsiveness and disease-free interval from last administered CT.

3. CT-naive patients

For A-naive patients, single agent (epi)doxorubicin or a combination of these agents with a taxane are appropriate choices. Sequential pre-planned approaches with A and taxane[7,8] appear less toxic and as active as combination schemes. Conversely combination of A and taxanes has not always been shown to be superior to taxane-free schemes. In Bontenbal and colleagues phases II–III trial, 216 patients were randomised to doxorubicin and docetaxel (AD) or 5-fluorouracil-doxorubicin and cyclophosphamide (FAC) combination.[9] In this study, combination with a taxane resulted in a significantly longer TTP and OS and a higher ORR than a taxane-free one. In the same manner, in Jassem et al.'s study[11] which compared FAC and AP in first-line setting, median TTP and OS were significantly longer for AP compared with FAC (TTP 8.3 months versus 6.2 months (P 0.034); OS 23.3 months versus 18.3 months (P 0.013)). Conversely at least four studies comparing A and taxane combination did not demonstrate a benefit in OS compared with A alone.[10,12–14] Probably the differences noted in these trials (other than population sample) are related to the different activity of P and D schedules as reported later in this paper.

In conclusion preferred first-line chemotherapies include sequential single agents (A, taxanes, pegylated lyposomial doxorubicin, capecitabine, gemcitabine, vinorelbine, cisplatinum or carboplatin) with combination CT (AD, AP, FAC, FEC, AC, EC and CMF) preferred for rapidly evolving (visceral and symptomatic) disease in patients with a good performance status.

4. A-pretreated patients

In this population various options exist for the medical oncologist treating advanced BC. Rechallenge with an anthracycline, taxanes alone or in combination with other agents (biological or not) or a non-taxane/non-anthracycline containing CT. Initial studies incorporating taxanes showed that D was superior in RR, TTP and OS to mitomycin and vinblastine combination, offering an increased RR and TTP only compared with methotrexate and 5-FU but showed comparable efficacy to 5-FU + vinorelbine, even if less toxic.[15–17]

For A-pretreated, a well conducted, randomised trial comparing D and capecitabine with D alone in 511 patients would appear to refute mono-CT strategy, because patients treated with the combination regimen have statistically superior RRs and disease-free survival and OS (14.5 months for the combination and 11.5 months for single-agent D).[18,19] However, in this trial only 17% patients were treated with capecitabine after tumour progression on D, and this group had a superior OS compared to patients treated with the combination regimen. Randomised clinical trials in MBC that show improved survival for a specific therapy should be reviewed critically to ascertain that all patients had access to, or treatment with, all active agents, whether as part of protocol therapy or after the protocol therapy had been completed; otherwise patients without access to other effective agents are likely to have poorer survival.

Numerous clinical trials have investigated the activity and efficacy of gemcitabine in association with taxanes. These studies are of great importance, especially in view of the fact that about two-thirds of patients with MBC have already received adjuvant treatment with A and that, in these patients, taxanes are used as standard therapeutics. To compare the efficacy and tolerability of the combination gemcitabine (1250 mg/m^2 days 1 and 8)–P (175 mg/m^2 day 1) with that of P (175 mg/m^2 day 1 q21) alone as first-line therapy in patients treated with A in an adjuvant setting, an international multicentre study has been carried out. The interim analysis of the trial, presented at the 2004 ASCO Annual Meeting, showed a statistically significant increase in RRs, TTP, and in particular, overall response when gemcitabine was added to the taxane. The gemcitabine–P association represents a new therapeutic option as first-line treatment of MBC patients pretreated with A.[20]

Bevacizumab (Avastin, Genentech) is a humanised monoclonal antibody directed against all isoforms of VEGF-A. Trial E2100 compared P alone with P plus bevacizumab as initial therapy for patients with MBC (40% and 17% of patients pretreated with an anthracycline and taxane in adjuvant phase). From December 2001 to May 2004, a total of 722 patients were enrolled. P plus bevacizumab significantly prolonged progression-free survival as compared with P alone (median, 11.8 versus 5.9 months; hazard ratio for progression, 0.60; $P < 0.001$) and increased the objective RR (36.9% versus 21.2%, $P < 0.001$). The overall survival rate, however, was similar in the two groups (median, 26.7 versus 25.2 months; hazard ratio, 0.88; $P = 0.16$).[21]

Another debate is which taxane is useful in first-line setting. A phase III trial of one taxane compared to another was published in 2005 by Jones and colleagues. D 100 mg/m^2 and P 175 mg/m^2 both day 1 every 21 d were compared in patients with advanced BC who had progressed after an A-containing CT regimen. D was superior to P in terms of OS (15,4 vs 12, 7 months) TTP (5,7 vs 3,6 months). ORR was higher for D. This study used a suboptimal P schedule. Infact weekly administration seems superior to three-weekly P. In a recent study including both Her-2 neu positive and negative advanced BC, weekly P was superior to a three-weekly administration: RR (42% versus 29%, unadjusted odds ratio (OR) = 1.75; $P = .0004$), TTP (median, 9 versus 5 months; adjusted HR = 1.43; $P < .0001$), and survival (median, 24 versus 12 months; adjusted HR = 1.28; $P = .0092$). Neurotoxicity is a treatment-limiting toxicity for weekly paclitaxel.[22,23]

To summarise a taxane (weekly P or three-weekly D) alone or in combination with other cytotoxic or biological agents represents a sound option for MBC (A-pretreated).

5. A- and taxane refractory BC

For A and taxane pretreated patients the prognosis remains poor even though other active agents (capecitabine, gemcitabine, platinum compounds, vinorelbine and lapatinib) can be proposed. Capecitabine is an orally administered fluoropyrimidine that is metabolised to 5-fluorouracil by a series of enzymatic steps. The efficacy of capecitabine in MBC has been well documented in clinical trials that included patients refractory to taxane therapy. Overall response rates have ranged from 15% to 26%, with the median response duration and survival ranging from 5.0 to 8.3 months and 10.1 to 15.2

months, respectively. Gemcitabine is a nucleoside analogue of deoxycitidine that is enzymatically activated within cells to inhibit DNA synthesis. Following A-based or taxane-based CT, gemcitabine in doses of 800–1000 mg/m^2 was well tolerated, and produced RRs ranging from 17% to 23%.

The vinca alkaloid, vinorelbine, is a fairly commonly used treatment for BC that has shown promising results in the setting of refractory advanced disease. Vinorelbine has been evaluated in multiple phase II trials, with RR ranging from 16% to 34%. No phase III comparative information exists for vinorelbine versus other single agents in the management of patients with BC.[24–32] Oral formulation of vinorelbine appears active in MBC, either in first-line or subsequent-line therapy, alone or in combination with capecitabine, for example.[33–39]

Carboplatin and cisplatin have also demonstrated good activity in combination with other agents (especially taxanes and gemcitabine) in pretreated patients (RR range 29–62%).[40–45]

In a large randomised trial of BC patients who had been previously treated with A and taxanes, Miller and colleagues.[46] reported a better RR with bevacizumab plus capecitabine compared with capecitabine monotherapy; but survival rates did not differ in the two treatment groups.

Advancements in cell biology have expanded our understanding of fundamental molecular pathways, opening the way for new and innovative treatments in MBC patients already treated with hormone, A and taxane therapies. In the near future ixabepilone, nanoparticle P, vinflunine and novel biological agents will expand treatment option in this setting. Both patients and clinicians have every reason to be optimistic.

6. Duration of CT

The length of time patients with stable disease should undergo CT remains a major issue, especially for those who have high-quality responses or disease stabilisation but major treatment-related toxicity. Contrary to the perception of many, quality of life is not adversely affected and may even be improved in many patients actively receiving CT. Coates and colleagues compared continuous therapy with AC or CMF with intermittent therapy using three cycles of the same regimen with reinstitution of therapy at the time of disease progression.[47] In this trial, patients receiving continuous therapy had superior RRs, TTP and quality-of-life scores, but no improvement in survival. A similar trial by the Piedmont Oncology Association randomly assigned patients who had responding or stable disease after six cycles of CAF to either CMF or observation, followed by reinstatement of CMF at disease progression.[48] Although TTP was more than twice as long for patients on continuous therapy than for those with interrupted treatment (9.4 versus 3.2 months, respectively), OS was similar. Falkson and colleagues randomly assigned 141 patients whose measurable disease showed a complete response after six cycles of CAF to receive either chemo-hormonal therapy or undergo observation.[49] Time to disease progression was 19 months for patients given chemo-hormonal therapy and 8 months for patients under observation; OS was similar. These data suggest that a 'drug holiday' is associated with a shorter TTP but no adverse effect on survival. Recently, new drugs have entered clinical trials to compare different durations of treatments. Gennari and colleagues treated patients with A and P combination followed by P or no therapy in responding or in stable disease patients. Median survival and TTP did not differ in the two groups.[50] Oncologists should share these data with patients, as some patients may wish a 'drug holiday' whereas others, especially those with substantial tumour-related symptoms before treatment, may wish to continue their therapy. In addition, these data support newer randomised trial designs that, after remission induction with standard treatment, compare new agents with observation, or new agents with established agents. Such designs use TTP as the major treatment end-point, and are especially suitable for the investigation of biologic agents.

7. Hormonal therapy for endocrine responsive (HER-2 negative) advanced BC

Women with recurrent or metastatic disease characterised by tumours that are ER and/or PgR positive are appropriate candidates for initial endocrine therapy, especially if the disease is confined to bone and or lymphnodes. Choice of first-line hormonal therapy depends on the initial adjuvant treatment, tamoxifen or aromatase inhibitor (AI) based. If the patient had been pretreated with adjuvant antioestrogen therapy or relapses during the same treatment (for example tamoxifen), first-line therapy with an AI (anastrozole or letrozole) is superior to megestrole acetate.[51,52]

For postmenopausal women who are antioestrogen naive or have relapsed more than 1 year from previous antioestrogen therapy, the AI therapy appears to have a minimal but superior outcome compared with tamoxifen. So appropriate first-line therapies in this setting are antioestrogens and AIs.[53–56]

Fulvestrant is a pure ER antagonist or down-regulator without agonist properties that has been approved as a second-line therapy following tamoxifen in postmenopausal women with advanced BC. In a randomised, double-blind, parallel-group, multinational study comparing 250 mg fulvestrant given as an intramuscular monthly injection or daily tamoxifen (n = 587) as a first-line therapy for advanced BC in postmenopausal women, no significant differences were seen between groups for TTP or RR at a median follow-up of 14.5 months.[57] Treatment with fulvestrant in patients whose disease progressed after treatment with tamoxifen resulted in similar TTP and RR compared with anastrozole,[58] providing another treatment option for postmenopausal women with hormonal receptor positive advanced BC. For premenopausal women standard first-line endocrine therapy (if antioestrogen naive) is a course of an antioestrogen with or without chemical or radio/surgical ovarian ablation. In the setting of antioestrogen pretreatment, after inducing ovarian ablation, the patient can be treated with endocrine therapy as for postmenopausal women.

Many women with hormone responsive BC benefit from sequential use of endocrine therapies at the time of disease progression, unless visceral crisis appears. Recent National

Comprehensive Cancer Network (NCCN) BC guidelines advise up to three hormonal therapy lines in the presence of endocrine sensitive disease. The same guidelines recommend the use of an AI in postmenopausal women with recurrent BC who had received antioestrogen treatment within the past 12 months.[59] Another option for second-line endocrine treatment is fulvestrant, which has been shown to be as effective as anastrozole in patients whose disease progressed during tamoxifen treatment (see above). Several studies have evaluated sequential hormone therapy and found small but consistent response regardless of the order in which therapy was administered.[60–62] The recently presented phase III EFECT trial evaluated sequential therapy with an AI compared to fulvestrant.[63] Six hundred and ninety-three postmenopausal women with advanced endocrine responsive BC who had recurrent or progressive disease following treatment with a non-steroidal AI were randomised to receive either exemestane or a modified loading dose of fulvestrant. Median TTP was 3.7 months in both groups; RR and rate of clinical benefit were also identical. The median duration of response was quite long, ranging from 9.8 to 13.5 months and CB was seen in up to 29% patients with visceral dominant disease, regardless of prior response to non-steroidal AI. Again, this indicates that patients with hormone-sensitive BC benefit from sequential administration of available hormone agents. To summarise AI and fulvestrant as first- and second-line treatments (in case of tamoxifen adjuvant treatment) and fulvestrant with subsequent AI (if the patient has been treated with an AI in the adjuvant phase) represent standard options for endocrine responsive, postmenopausal patients. For premenopausal patients, treated with adjuvant tamoxifen (alone or combined with LHRH analogues) options are represented by an AI combined with LHRH analogues and later by medroxy progesterone acetate or megestrole acetate.

8. Conclusion

MBC has to be considered a chronic disease, and the oncologist now has multiple treatment options to prolong disease control. Standard first-line chemotherapy consists of anthracyclines plus or minus a taxane depending on the end-point of treatment. A recently published individual patient's data metanalysis confirms this concept. Taxane-based combinations were significantly better than A-based combinations in terms of RR and progression-free survival, but not in terms of survival. Polychemotherapy remains indicated if the end-point is cytoreduction of high tumour burden. Single agent taxane and single agent A are equivalent in terms of RR and OS and are prescribed if the end-point is the control of disease and prolongation of survival.[64] First-line AI (steroidal or non-steroidal) and subsequent fulvestrant or an AI of the opposite class is an appropriate sequence for the treatment of advanced endocrine responsive disease.

Today systemic therapy is at the cornerstone of treatment in the advanced setting. Prognosis remains severe (from months to a few years) even if some long-term survivors exist, in particular those who achieve long-term (complete) remission with standard chemotherapy regimens.[65,66] Surgical resection of secondary or primary sites in stage IV disease (lung, liver, brain, primary tumours with synchronous indolent metastasis) can be offered in selected cases, obtaining prolongation of survival and/or local control.[67–72]

Concern regarding critical aspects remain. In particular what is the choice of first-line therapy in oligometastatic and paucisymptomatic, endocrine responsive disease? Is a poly-CT better than a mono-CT in a rapidly progressing disease? Is there a role for a maintenance therapy after obtaining a clinical benefit, or after the introduction of a more frequent and convenient schedule of administration (metronomic therapy)? Finally what is the role of biological agents in combination with chemotherapy or hormonal therapy? Interesting areas of research represent the so-called triple negative BC (non-expressing hormonal receptor and Her2-neu). In this setting high dose therapy, platinum salts, ixabepilone (recent interesting data had been presented at 2007 SABCS by Rugo et al.[73]) and target agents are in a phase of intense study.

The benefit of an angiogenetic therapy with the scope of blocking certain critical pathways for tumoural cells (for example angiogenesis) has recently been confirmed in at least two phase III trials comparing CT with or without bevacizumab. Combination of endocrine agents with target therapies with the scope of overcoming primary and secondary resistance is emerging as interesting solution. The inefficacy of A in Her2-neu disease, at least in adjuvant setting, seems to delineate a possible new strategy: from more toxic CT drugs to more specific, target oriented molecules. The near future will tell us if this scenario will become standard in clinical practice.

Conflict of interest statement

All authors disclose no financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work.

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