Non-endocrine systemic therapies in advanced breast cancer

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Introduction

The management of metastatic breast cancer (MBC) is a major clinical challenge for medical oncologists. Despite all available systemic therapy, MBC remains essentially incurable with a median survival time, after documentation of metastasis, ranging from 18 to 24 months. Chemotherapy (CT) and trastuzumab are the two main modalities of effective systemic anticancer therapy for breast cancer, besides endocrine therapy. Given that the latter has consolidated its prominent role for all women whose tumours express hormone receptors (HR), the other two become important "actors" for women whose tumours have developed endocrine resistance or are expected to be hormone-resistant from the start. Of note, recommendations for systemic therapy for MBC also apply to patients with locally advanced and locally recurrent breast cancer not amenable to locoregional treatment modalities.

The goals of treatment must always be kept in mind. For the majority of patients with MBC, the disease is a chronic illness, with periods of reactivation and remission and a course of multiple therapeutic manoeuvres. In this setting, optimal palliation becomes paramount, combining treatment and prevention of complications with appropriate attempts to prolong survival maximally without adversely affecting quality of life. There might be a very small subset of MBC patients, however, which can enjoy very prolonged survival and possibly cure, with aggressive multidisciplinary treatment. This subgroup must be accurately and timely identified so that the appropriate therapeutic approach is initiated.

Pre-treatment assessment (Fig. 1)

Prior to treatment decision, MBC patients must be carefully evaluated. The first and crucial question to be answered concerns the extent of the disease and whether there are life-threatening lesions and/or imminent catastrophic complications that require urgent and rapid tumour control, which will greatly influence the choice between combination and monotherapy.

An accurate assessment of both risk of rapid disease progression and probability of response to therapy is of utmost importance. Fig. 1 outlines the most relevant clinical parameters that help predict the risk of relatively rapid disease progression, such as the disease-free interval (DFI), the location and the extent of the metastatic sites. The relevant factors to be taken into consideration when determining the likelihood of a response to CT include the above-mentioned parameters, the performance status and the type of prior treatment received. Hortobagyi and colleagues performed a multivariate analysis in 619 women receiving 5-fluorouracil, doxorubicin, cyclophosphamide (FAC) as CT for MBC, and found that the following characteristics were correlated with a low probability of response to CT: weight loss, performance status 2 or 3, prior radiotherapy, prior CT, high alkaline phosphatase, low platelet count, low haemoglobin, low absolute lymphocyte count and, particularly, the extent of the disease.

Since trastuzumab is one of the few agents that may lead to an improvement of overall survival (OS) in MBC, HER-2 status evaluation is indispensable for optimal treatment decision-making.

Lastly, but by no means least, issues of tolerability and quality of life are also crucial, particularly in the virtually incurable, palliative metastatic setting. According to the American Society of Clinical Oncology (ASCO) recommendations, when choosing the optimal treatment approach for MBC, the "quality-adjusted survival" rather than survival alone should be considered. The process of treatment decision-making in MBC is a delicate and challenging one, and patients must always be encouraged to participate. Their preferences and expectations should be taken into consideration, and one should keep in mind that women may have markedly different perceptions of what constitutes an "acceptable treatment" in terms of benefit

LOW		MODERATE, HIGH
Yes	Hormone receptors present	No
No	HER-2 receptor overexpressed	Yes
> 2 years	Disease-free interval	< 2 years
limited	No. of metastases	extensive
soft tissue, bone	Sites of metastases	viscera
No	Vital organ involvement	Yes

Fig. 1. Metastatic breast cancer: factors predictive of low and moderate/high risk of rapid progression.

versus toxicity ratio, and that for some, gains in survival as minimal as 1% are reason enough to undergo treatment, regardless of the anticipated side effects.

A word of caution regarding clinical trials' results

Randomised clinical trials and meta-analyses have been so far our best tools for understanding which therapies provide a sustained survival benefit. However, randomised clinical trials are conducted in a selected patient population and can only indicate the superiority of one treatment over the other *on average* and for the *entire population*. Since breast cancer is a very heterogeneous disease, the extrapolation of this global treatment effect to the individual patient may not always be accurate. The identification of the subset(s) of patients most likely to benefit from a particular drug or regimen, also known as "treatment tailoring" is therefore crucial and has become one of the main tasks of the medical oncology community nowadays. This identification is best done through the conduct of prospective trials asking biologically relevant questions. Because these trials are still a minority, an alternative can be the careful conduct of subset analyses in adequately powered trials, in order to better understand how to maximise the clinical utility of certain drugs or regimens. It is interesting to mention that there is an ongoing controversy regarding the most relevant endpoints of MBC trials. Clinical trials in the metastatic setting seldom use OS as the primary endpoint due to practical limitations particularly related to sample size. Time to progression (TTP) and response rate (RR) are the most commonly used primary endpoints and serve as surrogate markers for OS. However, higher RR and longer TTP do not always translate into detectable survival advantages. This may partially be explained by the fact that the extent to which these surrogate endpoints correlate with OS is influenced by the stage of disease, trial design (e.g. crossover encouraged or prohibited), and number of events at the time of analysis. The majority of MBC trials published so far are underpowered to detect small survival gains, particularly for second and subsequent lines of CT (studies reviewed in Ref. [1]). Another possible explanation is related to the pattern of breast cancer growth, with a typical Gompertzian curve, showing that when the rate of cancer cell killing reaches a certain point, the rate of re-growth of the residual cancer cells starts to rise.

Treatment decision strategy for MBC in clinical practice

As mentioned before, since trastuzumab has proven added benefit to CT and this benefit is limited to patients with HER-2 overexpressed/amplified tumours, treatment tailoring in 2003 requires HER-2 status determination. After the separation between endocrine-responsive and endocrine-non-responsive disease, the second major division in the treatment decision algorithm for MBC must be, in our opinion, between HER-2-positive and HER-2-negative disease. Accordingly, treatment options will be discussed separately for each subgroup.

Management of HER-2-negative MBC

For women with endocrine-resistant and HER-2-negative MBC, CT is currently the only therapeutic option. Many cytotoxic agents have been available for more than four decades for the management of MBC. Additionally, in the 1980s, combination CT has been shown to be more effective than monotherapy, in terms of RR, response duration, and survival. The development of more powerful agents — namely the taxanes — has challenged this concept, with data suggesting similar efficacy for appropriate sequencing of active drugs in comparison with more toxic combinations.

The most active cytotoxic agents for MBC are the anthracyclines, and the taxanes, followed by alkylating agents, antimetabolites and vinca alkaloids. Used

as single agents, they produce objective responses in 20–80% of patients with MBC. However, complete responses (CR) are rare and short-lived, and less than 20% of patients who achieve a CR maintain that status beyond 5 years. Additionally, initial responses to CT last a median of 8 and 14 months, and progression of disease is almost inevitable.

While the benefit of first-line CT for MBC is unanimously accepted, the value of second- and subsequent lines of CT is more controversial, particularly in terms of survival benefit. The existence of some studies that show a survival advantage of a second-line CT regimen over another is an indirect suggestion that CT may indeed prolong survival over no therapy in MBC, after failure of first-line treatment. However these studies are few and in some the control arm is either a substandard or an "old fashioned" CT regimen. With the exception of the use of taxanes in anthracycline-failing patients, where level 2 evidence supports the use of docetaxel, there is no current universally accepted standard of care for MBC. The true impact of CT on survival and quality of life of MBC patients is still debated and further research is clearly needed. A particularly difficult group of patients is those who failed both anthracyclines and taxanes; currently the two main drug options for these patients are capecitabine and vinorelbine.

Anthracyclines

The CT regimens most commonly used in the late 1960s consisted of cyclophosphamide, methotrexate, 5-fluorouracil (5-FU), prednisone, and vincristine combinations (CMF, CMFP, CMFVP). Since its introduction in the early 1970s, doxorubicin has been considered one of the most active cytotoxic agents in the treatment of breast cancer. Anthracycline-combining regimens were proven at least superior to regimens that did not include anthracyclines in randomised trials, while no randomised study has shown superior results with CMF over FAC. Epirubicin, a doxorubicin analogue, has shown similar efficacy and less toxicity than doxorubicin. In Canada, the initiative was taken to review 13 randomised controlled trials that compared epirubicin and doxorubicin in women with MBC [3]. Three conclusions were drawn: (1) no significant differences in RR or median survival were seen when comparing the two agents using equimolar doses or standard doxorubicin doses versus higher epirubicin doses; (2) a dose-response was observed in studies that evaluated escalating doses of epirubicin; (3) epirubicin at equimolar and equi-myelosuppressive doses induced less nausea and vomiting and less cardiotoxicity.

A randomised clinical trial compared FAC with FEC at equimolar doses of doxorubicin and epirubicin in 263 MBC patients, and equivalent RR, TTP and survival were seen. The FEC regimen was associated with less gastrointestinal, haematologic and cardiac toxicity. Another randomised trial compared single-agent epirubicin and FEC with epirubicin at two different doses, 75 mg/m^2 (FEC-75) and 50 mg/m^2 (FEC-50), in 412 MBC patients. The combination regimes were superior to the single-agent ($P = 0.0006$ and $P = 0.04$, respectively) and FEC-75 produced higher RR and longer survival than FEC-50 ($P = 0.006$).

The optimal duration of anthracycline-based CT is still controversial. A French study evaluated the optimal duration of FEC in the metastatic setting through a phase III trial, in which 392 patients were randomised between 11 cycles of FEC-75; four cycles of FEC-100 followed by eight cycles of FEC-50; and four cycles of FEC-100. Patients randomised to the latter group were treated with the same regimen (FEC-100) at the time of progression. While the RR was higher using the FEC-100 regimen, the OS rate was similar for the three groups. Another phase III study, from the Danish group, compared 18 months and 6 months of treatment with CEF in 359 patients. Both TTP and OS were significantly superior with longer duration of therapy.

Although more efficacious than CMF-type regimens, anthracycline-containing regimens are also more toxic, and the decision to use them must balance the expected benefits with the potential risks. Issues related to the use of combination regimens containing anthracyclines are also still controversial and are discussed in the next two sections. In general, the anthracycline-combination regimens provide higher RR, but similar TTP and OS; a few studies have shown a slight improvement in survival with combinations, such as doxorubicin–vinorelbine or doxorubicin–docetaxel, but at the expense of increased toxicity.

Taxanes

The introduction of paclitaxel and docetaxel in the 1990s has led to additional improvement in the management of MBC. Since currently anthracyclines are commonly used in the early stages of breast cancer (i.e. adjuvant setting, first-line MBC after CMF failure) the incidence of anthracycline-pretreated MBC has increased. In this situation the taxanes became the current standard of care. More recently, the taxanes started to be used earlier in MBC management, in patients with no or minimal prior anthracycline exposure and/or in combination with anthracyclines.

Table 1 summarises the results of published randomised phase III trials which evaluated the role of taxanes, given as single agent or in combination, in the two main patient populations: anthracycline-resistant and anthracycline-naïve. Individual studies are reviewed in detail elsewhere [7]. The most relevant "take-home messages" are:

For the patient population previously failing anthracycline-based CT, there are no published trials evaluating the role of paclitaxel as opposed to docetaxel, which was used in four trials: three as monotherapy and in one in association with capecitabine. Despite important design limitations (all studies but one are underpowered and in none of them is crossover part of the study design), these four trials yielded highly consistent results, with the use of docetaxel, in monotherapy or in combination with capecitabine resulting in improved RR, and, most importantly, OS in two of the trials. Taken together, these data provide level 2 evidence that supports the use of docetaxel for MBC after anthracycline failure.

So far, only one phase III trial compared docetaxel as monotherapy versus docetaxel in combination with capecitabine and the combination resulted in a statistical significant survival advantage (14.5 months vs. 11.5 months, $P = 0.0126$) [11]. However, the systematic use of this combination is controversial, given the substantial toxicity of the combination and the lack of a proper comparison with the sequential use of the two agents. Therefore, this regimen can be considered most attractive in "emergency" situations in which a rapid response is needed.

For the patient population with no or minimal anthracycline exposure, no new standard of care exists at the present time. The most important contributing factor is the lack of large and accurately powered trials in this area. Ten trials enrolling a total of 4325 women (!!) evaluated the role of both docetaxel, in monotherapy and in combination, and of paclitaxel, in monotherapy and in combination, as first-line treatment for MBC. All these trials were underpowered to detect small but real differences between the treatment arms. Moreover, in many of these trials, crossover was neither built-in nor allowed, which would more accurately reflect routine clinical practice where MBC patients are treated sequentially with different CT regimens, at disease progression. The use of docetaxel resulted in an improved RR in all of the trials and improved TTP in most of them. However, these advantages did not translate in any survival benefit. For paclitaxel, the randomised trials generated conflicting results in terms of RR and TTP, which nevertheless translated into a survival benefit in two of the studies.

Unsettled issues include the choice between the two taxanes and the best schedule of administration (weekly vs. 3-weekly). No direct comparison between docetaxel and paclitaxel was ever published and, therefore, the choice between the two drugs must rely on indirect comparisons, existing data for each drug in each setting and differences in toxicity profiles, which may be of great importance for certain patients. A relatively large US study ($n = 580$ patients), coordinated by A. Seidman, has compared weekly paclitaxel to 3-weekly paclitaxel: results should be available soon. In the meantime, data from several phase II trials suggest some important advantages regarding toxicity, namely that myelosuppression is substantially reduced for both agents; weekly paclitaxel (80 mg/m^2/week) is a particularly well tolerated regimen, with manageable neurotoxicity and rare febrile neutropenia, which renders it a popular regimen in the metastatic setting.

Importantly, preclinical and clinical data have shown that the cross-resistance between the two taxanes is only partial; consequently their sequential use a few months apart is possible, in particular for patients who are initially taxane-sensitive.

Combination versus sequential CT

The optimal schedule of administration of combination CT in MBC, i.e. concurrent vs. sequential use, remains controversial and the decision must be individualised for each patient. Ideally, a combination regimen should meet three criteria: preclinical evidence of synergy, no cross-resistance between the components, and non-overlapping toxicity profiles.

Data concerning CMF and anthracycline-containing regimens (FAC, FEC) indicate that polychemotherapy produces higher RR than single agents. What is not yet completely clear is if the same agents administered sequentially would have yielded similar results. An important trial addressing the issue of combination versus use of sequential agents has been performed in the taxane era and has been recently published: Sledge and co-authors [17] randomised 739 women with MBC to receive either doxorubicin (60 mg/m^2), paclitaxel (175 mg/m^2/24h) or their combination (doxorubicin 50 mg/m^2 + paclitaxel 150 mg/m^2/24h + granulocyte colony stimulating factor support). Although tumour response and time to treatment failure were improved by the combination, OS and palliative effects were comparable. Of note was that in the single agent arms, a crossover to the alternative agent at the time of progression occurred in 57% of the patients. This trial does not stand on its own: at least five other

Table 1

Randomised phase III trials of taxanes in metastatic breast cancer

Study, year [Ref.]	No. of patients	Treatment	RR (*P* value)	TTP (*P* value)	OS (*P* value)	Crossover	Conclusion
Minimal or no previous anthracycline exposure							
Single-agent							
Chan, 1999 [12]	Total: 326	D	47.8%	26 w	15 m	Allowed.	D > A
	2nd-line: 174	A	33.3% (0.008)	21 w	14 m	28% and 26%, respectively.	(RR)
Bishop, 1999 [15]	209	P	29%	5.3 m	17.3 m	No. At progression,	P ≫ CMFp
		CMFp	35% (0.37)	6.4 m (0.25)	13.9 m (0.068)	epirubicin recommended	(OS)
Paridaens, 2000 [16]	331	P	25%	4.2 m	15.6 m	Early (76 vs. 75%) or delayed	A < P
		A	41% (0.003)	7.5 m (<0.001)	18.3 m (0.38)	(46 vs. 65%) as study design	(RR, TTP)
Sledge, 2003 [17]	739	P	34%	6.0 m	22.2 m	Allowed	A = P < AP
		A	36%	5.8 m	18.9m	Part of study design	
		AP	47% (<0.007)	8.0 m (<0.009)	22.0 m		
Combination							
Nabholtz, 1999 [8]	429	AD	60%	37.1 w	NA	NA	AD > AC
		AC	47% (0.012)	31.9 w (0.015)			(RR, TTP)
Mackey, 2002 [14]	484	DAC	55%	31 w	21 m	D post-study given to 11% of	DAC > FAC
		FAC	44% (0.023)	29 w (0.51)	22 m (0.93)	DAC and 38% of FAC	(RR)
Jassem, 2001 [18]	267	AP	68%	8.3 m	23.3 m	Not part of the design but P	AP ≫ AC
		FAC	55% (0.032)	6.2 m (0.034)	18.3 m (0.013)	post-study given to 10% of FAC	(OS)
Biganzoli, 2002 [19]	275	AP	58%	5.9 m	20.6 m	Allowed, but not part of	AP = AC
		AC	54% (0.51)	6.0 m (0.69)	20.5	study design	
Luck, 2000 [20]	560	EP	46%	39 w	NA	NA	EP = EC
		EC	41%	33 w (0.089)			
Carmichael, 2001 [21]	705	EP	67% 56%	6.5 m	13.7 m	NA	EP = EC
		EC	6.7 m (0.72)	13.8 m (0.92)			
After anthracycline failure							
Single-agent							
Nabholtz, 1999 [13]	392	D	30%	19 w	11.4 m	Allowed.	D ≫ Mito+VBL
		Mito+VBL	11% (<0.0001)	11 w (0.001)	8.7 m (0.0097)	12% and 24%	(OS)
Sjöström 1999 [9]	283	D	42%	6.3 m	10.4 m	Recommended.	D > M→F
		M→F	21% (<0.001)	3.0 m (<0.001)	11.1 m (0.79)	18% and 28%	(RR, TTP)
Bonneterre, 2002 [10]	176	D	43%	6.5 m	16 m	NA	D = FUN
		FUN	38.8%	5.1 m	15 m		
Combination							
O'Shaugnessy, 2002 [11]	511	D+Cape	41.6%	6.1 m	14.5 m	Not part of study design, but	D+Cape ≫ D
	≥2nd-line: 340	D	29.7% (0.006)	4.2 m (0.0001)	11.5 m (0.0126)	Cape post-study to 15% of D	(OS)

D = docetaxel; P = paclitaxel; A = doxorubicin; C = cyclophosphamide; M = methotrexate; F = 5-fluorouracil; E = epirubicin; Mito = mitomycin; VBL = vinblastine; N = vinorelbine; Cape = capecitabine; NA = not available; w = weeks; m = months.

reports have come to similar conclusions regarding the value of adequately selected single agents in the last 5 years. One recent randomised phase III trial, however, is often quoted by oncologists who remain convinced that combination CT is the standard of care. O'Shaughnessy et al. [11] reported a higher RR, a longer TTP, and improved OS for the combination of docetaxel and capecitabine when compared to single agent docetaxel. However, the lack of crossover, which resulted in only 17% of patients initially treated with docetaxel subsequently receiving capecitabine at progression, makes the survival superiority of the combination uncertain, since it does not allow an accurate comparison between the concurrent and sequential administration of both drugs.

In view of the high toxicity of this combination (docetaxel/capecitabine), as well as of anthracycline/taxane combination regimens, it is our view that in the palliative metastatic setting, these regimens should be reserved for symptomatic patients, and for those with significant visceral involvement, for whom a rapid and effective tumour responsive is crucial.

The proper evaluation of these regimens in the adjuvant setting would be of great interest.

Other cytotoxic agents

As discussed above, no standard of care exists for subsequent lines of CT, particularly after failure of both anthracyclines and taxanes, and treatment options for these patients are limited. Among the several agents used in this setting are continuous 5-fluorouracil (5-FU) and its derivatives (such as oral capecitabine), vinorelbine and docetaxel (in patients who have already received paclitaxel). The first two agents are the most commonly used in view of their manageable toxicity profile and reasonable efficacy. A direct comparison between capecitabine and vinorelbine is currently being done in a randomised phase III trial, coordinated by the European Organisation for Research and Treatment of Cancer (EORTC).

Capecitabine

The first oral fluoropyrimidine approved by the Food and Drug Administration (FDA) for the treatment of patients with MBC who failed prior anthracycline- and taxane-based CT is a prodrug that undergoes a three-step conversion process to active 5-FU, the last one at the tumour site, and that clinically mimics the activity of continuous infusional 5-FU. Additionally, capecitabine has the great advantage of being orally administered, which is especially important in the metastatic setting. Provided that an equivalent level of efficacy is maintained, a drug with a convenient method of administration and reduced need for hospitalisation represents an important contribution to improvement of care.

Phase II studies demonstrated that capecitabine is an active agent in the treatment of MBC, and that significant responses can be achieved in women already treated with anthracyclines and taxanes. The FDA-approved dose and schedule are 2,500 mg/m^2/day given orally for 14 days followed by one week of rest. However, retrospective studies suggest that a slightly lower starting dose (2,000 mg/m^2/day) is better tolerated with preserved efficacy. Based on the results of a randomised phase II trial, which compared capecitabine and CMF as first-line treatment for MBC, an ongoing randomised phase III trial is evaluating the efficacy of capecitabine in this setting. With the primary endpoint being quality of life-adjusted TTP, MBC patients are being randomised between the classical Bonadonna CMF regimen every 28 days and one of two capecitabine regimens with identical planned dose intensities: either 1,000 mg/m^2 twice daily on days 1–14 in a 21-day cycle or 666 mg/m^2 twice daily every day.

Exploring the appealing strategy of combining cytotoxic and biological agents, a large randomised phase III trial compared capecitabine alone and capecitabine in combination with the humanised monoclonal antibody bevacizumab (directed against the vascular endothelial growth factor), in 462 patients with anthracycline- and taxane-refractory breast cancer. The first results were recently presented and were, unfortunately, negative regarding TTP, the study's primary endpoint. Final results and survival data are awaited.

Vinorelbine

This cell cycle-specific microtubule inhibitor acts through the destabilisation of the microtubules, in contrast to the taxanes. Vinorelbine delivered intravenously at 25–35 mg/m^2 on days 1 and 8 of a 3-week cycle has been documented to generate a consistent level of activity, with overall RR ranging from 20% to 40% and an acceptable toxicity profile both as a single agent and in combination with other compounds. Objective RRs have also been reported in patients who progressed after anthracyclines and taxanes. The low incidence of alopecia and other non-haematological toxicities makes vinorelbine particularly attractive for the palliative treatment of MBC. Granulocytopenia, the dose-limiting toxicity of this agent, is transient and, at current recommended dose levels, rarely results in life-threatening consequences. Furthermore, this agent is particularly well tolerated in elderly patients. Recently, an oral formulation of vinorelbine

was evaluated as first-line chemotherapy for MBC and results suggest that it is an effective and well-tolerated agent, offering an alternative to the intravenous route.

Metronomic chemotherapy

Metronomic CT consists of the administration of cytotoxic drugs at relatively low doses but according to a frequent "metronomic schedule" that seems to optimise the angiogenic effects of CT in preclinical studies. A low dose cyclophosphamide/methotrexate metronomic regimen was recently shown to have clear-cut anti-tumour efficacy in MBC. It might represent a reasonable treatment option in patients with relatively indolent disease who are not candidates for or who are not willing to receive more toxic regimens.

Management of HER-2-positive MBC

The human epidermal growth factor receptor 2 — HER-2 (also referred to as erbB-2 and HER-2/neu) is a member of the type I growth factor membrane receptor family, which is overexpressed and/or amplified in 20–30% of breast cancers and has been associated with shorter survival. Trastuzumab (Herceptin®) is a humanised monoclonal antibody that selectively binds to the extracellular domain of HER-2 and has multiple mechanisms of action. Although not yet fully understood, these are known to include: (a) G1 arrest via upregulation of the cyclin-dependent kinase inhibitor p27; (b) induction of antibody-dependent cellular cytotoxicity (ADCC), through interaction with CD16 on natural killer cells and complement-mediated tumour cell killing; (c) receptor downregulation from the cell surface; (d) stimulation of HER-2 homodimerisation and partial prevention of heterodimers formation; (e) inhibition of post-receptor downstream signal transduction; (f) inhibition of the production of angiogenic factors such as the vascular endothelial growth factor (VEGF); and (g) inhibition of constitutive HER-2 cleavage/shedding mediated by metalloproteases. HER-2 cleavage results in the release of the soluble extracellular domain (ECD) and constitutive activation of the remaining membrane-associated HER-2 domains, a truncated receptor known as p95, which leads to activation of signal transduction.

In MBC patients whose tumours overexpress HER-2, trastuzumab has proven to be an active drug both as single agent and in combination with CT. As a monotherapy, trastuzumab has shown an overall RR of 35% when given as first-line therapy for MBC with a 3+ HER-2 overexpression, and of 18% in patients previously treated with CT for MBC. Combination treatment with CT resulted in improved OS (25.1 months vs. 20.3 months; $P = 0.046$), longer TTP (7.4 months vs. 4.6 months; $P < 0.001$), higher RR (50% vs. 32%; $P < 0.001$) and a longer duration of response (9.1 months vs. 6.1 months; $P < 0.001$) [2]. Since 1998 in the US and 2000 in Europe, trastuzumab is approved as monotherapy for the treatment of patients with MBC whose tumours are HER-2 overexpressed/amplified and who have received one or more chemotherapy regimens for metastatic disease. It has also been approved, in combination with paclitaxel, as first-line therapy for HER-2 MBC previously treated with anthracyclines in the adjuvant setting.

The activity of trastuzumab is highly dependent on the HER-2 status of the tumour. Patients who are more likely to benefit from treatment with this drug are the ones with HER-2 highly positive tumours, defined as an overexpression of 3+ score by immunohistochemistry (IHC) or gene amplification by fluorescence *in situ* hybridisation (FISH). There is however a high level of laboratory inter-variability, particularly with the IHC technique, due to a lack of procedure standardisation. Controversial issues include the choice of antibody, the use of antigen retrieval (i.e. a technical procedure designed to facilitate the interaction between the antibody and the corresponding antigen), the scoring system used, and the best cut-off value for defining a tumour as HER-2-positive or -negative. The only FDA-approved IHC method for HER-2 detection is the HercepTest (Dako, Glostrup, Denmark); however, this test method has been criticised due to a high rate of false positive cases when compared with FISH results, and it is not widely used in European countries. FISH has been considered as a more standardised and reliable technique, but recent quality control studies with this technique have shown that discordant results for HER-2 gene status can be observed between different centres. In view of these "assay" problems, it might be sometimes indicated to recheck the HER-2 status, particularly if the tumour has poor prognostic features (i.e. hormone receptor-negative, grade 3 and short disease-free interval) and the first laboratory has limited experience with HER-2 testing.

Therapy with trastuzumab is usually well tolerated, with the most common side effects (in about 40% of patients) being infusion-associated symptoms, a symptom complex most commonly consisting of chills and/or fever that usually occurs during or immediately following the first injection. The symptoms are usually mild to moderate in severity, effec-

tively treated with acetaminophen, diphenhydramine, and meperidine, and rarely need drug discontinuation. The incidence and reoccurrence of such symptoms is substantially lower with subsequent infusions. The most worrisome side effect of trastuzumab is the risk of cardiotoxicity, which is higher in patients previously treated with anthracyclines and/or with advanced age. This risk is around 4% with monotherapy, 13% when trastuzumab is given in combination with paclitaxel, and 27% when combined with anthracyclines. The mechanism of cardiotoxicity is still under investigation but may be related to the fact that the HER-2 receptor has a critical role in cardiac development: it is thought to participate in an important pathway for growth, repair, and survival of adult cardiomyocytes, and can be detected in the adult heart, although at low levels. Unlike anthracycline-induced cardiotoxicity, trastuzumab-induced congestive heart failure is usually successfully treated with standard treatment and it is not dose-dependent. Of note, recovery of symptoms occurs both if trastuzumab is withdrawn and if it is continued.

Trastuzumab is generally administered on a weekly schedule. However, the recent estimation that the half-life of trastuzumab is in the range of 28 days has led to the development of a 3-weekly regimen. This 3-weekly dosing is pharmacokinetically sound, logistically more convenient for patients, has similar anti-tumour activity to that of the weekly schedule, and is therefore becoming more commonly used both in current clinical practice and in adjuvant clinical trials (HERA trial).

Several questions remain unanswered regarding the optimal use of trastuzumab in the treatment of breast cancer (Table 2). These include: (a) is single agent trastuzumab followed by chemotherapy as effective as the combination trastuzumab + chemotherapy? (upfront monotherapy use versus combination); (b) what is the optimal trastuzumab–chemotherapy combination?; (c) is there an indication to pursue trastuzumab after disease progression? (duration of treatment); (d) why do nearly 60% of HER-2-positive tumours not respond to trastuzumab therapy and what are the potential mechanisms of resistance to this drug?

The upfront use of trastuzumab in monotherapy with adding of CT at disease progression, if proven as efficacious as the initial combination regimen, will have obvious advantages in terms of quality of life and cost effectiveness.

Preclinical data has shown that trastuzumab is capable of enhancing, either in an additive or a synergistic way, the activity of several cytotoxic agents, besides anthracyclines and paclitaxel, and more recently several other combination regimens have been tested in the clinical setting, including platinum compounds, docetaxel, vinorelbine, gemcitabine and capecitabine. The RRs are high, ranging from 45% to 84%. Of note, the triplet combination of trastuzumab–carboplatin–taxane has proven superior in terms of RR and TTP to the trastuzumab–paclitaxel doublet, and therefore, is an attractive regimen in "emergency" situations.

As with all anticancer drugs, trastuzumab is usually prescribed for as long as clinical benefit is achieved or until important toxicity arises. When used in combination with CT, in the majority of patients the cytotoxic agent(s) is discontinued due to intolerance and trastuzumab alone is pursued, sometimes for several years. Controversy arises when disease progression is seen during trastuzumab monotherapy. Indirect data from retrospective studies of trastuzumab used in first- and second-line seem to suggest a role for the use of a different combination of trastuzumab–CT at disease progression. These data need however confirmation and an ongoing trial is evaluating the role of vinorelbine + trastuzumab after failure of trastuzumab + a taxane, as opposed to vinorelbine alone. A situation where continuation of trastuzumab is justifiable is when CNS involvement occurs while all other systemic metastases are well controlled, providing that

Table 2

Current knowledge and future perspectives in the use of trastuzumab in the treatment of advanced breast cancer

What we know
Combination with paclitaxel improves survival of metastatic breast cancer patients
Patients who benefit have HER-2 3+ or FISH+ tumours
Its half-life is in the range of 28 days, making the 3-weekly schedule an attractive option
Early use of trastuzumab is "key" for obtaining improved survival
First-line single agent trastuzumab has significant activity
Trastuzumab has a cardiotoxic potential, with risk factors being anthracycline exposure and advanced age
What we need to learn
What are the mechanisms of resistance to trastuzumab?
Is single agent trastuzumab followed by chemotherapy as effective as trastuzumab + chemotherapy? (upfront monotherapy use versus combination)
What is the optimal trastuzumab-chemotherapy combination?
Is there an indication to pursue trastuzumab after disease progression? (optimal duration of treatment)
What we need to explore
Blocking several membrane tyrosine-kinase receptors
Blocking the HER-2 receptor and a downstream effector
Combining Herceptin® and endocrine therapy
Combining Herceptin® and a proteasome inhibitor
Combining Herceptin® and a COX-2 inhibitor

appropriate local treatment is done (CNS external radiation, γ-knife, surgery).

The observation that, even in patients with HER-2 overexpressed (3+) and/or amplified, the response rate to trastuzumab is not higher than 40% as single agent in first-line treatment of MBC and that the median duration of response to this agent is 9 to 12 months, has raised the important issue of both *de novo* and acquired resistance to trastuzumab. The mechanisms of resistance to trastuzumab (reviewed in detail in [28]) are a subject of intense research and seem to include the expression pattern of HER-dimers in the tumour, the proportion of phosphorylated HER-2 receptor, the HER-family receptors associated signalling pathways (i.e. IGF-IR, MAP-kinase and the PI3K-AKT pathways), the cyclooxygenase-2 (COX-2) pathway, and some innovative hypotheses such as the possibility for HER-2 and EGFR to directly act as transcription factors.

Particular aspects of the "natural history" of HER-2 overexpressing breast cancer must be kept in mind for optimal management of patients with this disease: (1) their great propensity to develop brain metastases calls for close monitoring of any symptoms or signs suggestive of CNS involvement; in our opinion, patients who show dramatic responses to trastuzumab (± CT) outside CNS might benefit from close monitoring of CNS disease occurrence through periodic MRI of the brain; these patients, indeed, might enjoy prolonged survival, unless brain metastases are poorly controlled; (2) the occurrence of some "dramatic" responses in visceral organs, such as the liver, is an impetus for the development and proper investigation of multimodality therapy in selected women (including, for example, radiofrequency ablation of liver metastatic residues in the absence of detectable extrahepatic metastases).

In summary, HER-2-overexpressing breast cancer might be a disease on its own, requiring new thinking in terms of optimal management. This concept is reinforced by recent gene profiling studies, using the DNA microarray technology, and showing that, indeed, this BC subset has a distinct gene expression pattern!

Treatment tailoring

For both HER-2-positive and HER-2-negative breast cancer, the issue of treatment tailoring, e.g. a treatment adapted to each patient with her unique tumour characteristics, is the goal of a growing number of current breast cancer clinical and translational research efforts.

The role of HR as predictors of response to endocrine treatment and of HER-2 overexpression/amplification for trastuzumab therapy is well established. Concerning CT, the situation is unfortunately very confusing, with no predictive marker currently recommended for routine clinical use, despite the substantial amount of markers already investigated. This is mainly due to the small size and retrospective nature of all the studies published so far, making them underpowered to draw definite conclusions. Additionally, there are important issues related to the collection of tumour samples, which are particularly relevant in the metastatic setting where routine biopsy of metastatic sites is not always feasible and where metastases usually occur several years after initial diagnosis, rendering the access to the primary tumour block even more difficult. Studies have shown that the degree of concordance in the expression of biological markers between primary tumours and their correspondent metastases seems to be very high. However, this is still a controversial question and further confirmation is desirable. Lack of reproducibility across different laboratories with respect to the detection methods used is another important problem, as exemplified above for HER-2 status determination.

Nevertheless, the research efforts from the last decade have provided a substantial amount of data and interesting hypotheses: (1) overexpression/amplification of HER-2 seems to be associated with comparatively greater benefit from anthracycline-containing or taxane-containing regimens than from CMF or CMF-like regimens and lower the threshold for prescribing of these drugs by many oncologists; (2) topoisomerase II-α may play a key role for the prediction of response to anthracycline-based CT; (3) *p*53-mutated tumours might be less sensitive to anthracyclines while retaining sensitivity to taxanes; (4) microtubule-associated parameters (MTAP) may be relevant for the prediction of response to taxane-based CT.

Joint meta-analysis and large multicentre prospective trials are already planned/ongoing to test some of these hypotheses. It is hoped that these trials and the clinical application of new techniques such as DNA microarray and proteomics, with their potential ability to define "biological signatures" of both prognostic and predictive value, will make treatment individualisation the routine approach in a not too distant future.

The "special case" of long-term survivors

Long-term follow-up, beyond 3 to 5 years, is exceptional in the MBC literature due to the median survival (range, 2 to 4 years). Only a few reports

have presented 5-, 10-, and even 15-year follow-up data. A small subset of MBC patients can be cured. Long-term survival seems to be associated with: (a) achievement of a complete remission after treatment for MBC; (b) young age and excellent performance status; (c) limited metastatic disease such as disease limited to a single organ site, and particular to a single lesion. Patients with a solitary recurrence or metastatic lesion that can be surgically removed and/or treated with radiotherapy at curative doses can become long-term survivors, a situation also referred to as stage IV NED (no evidence of disease). Aggressive, multidisciplinary therapy is therefore justifiable in this selected group of patients.

A very particular situation is the isolated metastases to the supraclavicular lymph nodes (SCLN). Until December 2002, these patients were classified as stage IV breast cancer. However, studies have shown that, if treated aggressively with combined modality therapy consisting of chemotherapy, surgery, and radiotherapy, disease-free survival (DFS) rates at 5 and 10 years can be as high as 34% and 32%, and OS rates at 5 and 10 years were 41% and 31%, respectively. At a median follow-up of 11.6 years, the median DFS was 1.9 years and the median OS was 3.5 years. These data suggest that patients with ipsilateral supraclavicular metastases and no other evidence of distant metastases should be treated with a curative intent. However, in routine clinical practice, since patients with SCLN-positive disease were considered to be stage IV and therefore incurable, they were commonly treated with palliative measures only, an approach that has recently been questioned. Recognising this fact, the recent revision of the American Joint Committee on Cancer staging system for breast cancer has reclassified patients with isolated ipsilateral supraclavicular nodal metastases as stage IIIC disease [30]. Further supporting this change, a recent publication of a Canadian retrospective study of 574 patients has shown that patients with Nodal–M1 breast cancer (defined as isolated supraclavicular metastases) have significantly better outcomes than patients with M1 disease (other metastases) and their OS is similar to patients with stage IIIB disease.

Locally recurrent breast cancer

Locally recurrent breast cancer, even if amenable to optimal loco-regional treatment modalities, has a dismal prognosis, with a great majority of patients developing distant metastasis in the following months. For this reason, there have been several attempts to conduct randomised clinical trials exploring the benefit, if any, of systemic therapy administration following radical loco-regional treatment and a "NED" status. So far, all these trials have failed since they have faced serious problems of accrual explained by the unwillingness of patients either to receive or not receive CT under these circumstances.

A small randomised trial by the Swiss Group for Clinical Cancer Research (SAKK) strongly suggests benefit in terms of time to distant metastasis of "pseudo-adjuvant" tamoxifen in these patients having HR-positive tumours. A recently opened BIG (Breast International Group) trial, coordinated by the IBCSG (International Breast Cancer Study Group), will try to answer the question of a potential CT benefit in these patients with the much needed cooperation of several other groups.

Conclusions

Figs. 2 and 3 represent our view of a practical algorithm designed to guide treatment decision making in clinical practice and based on current knowledge. It should however be emphasised that treatment algorithms cannot apply to all patients and that management of MBC should be individualised. While the knowledge of which regimen works better in general needs to be evidence-based, there remains difficulties in determining which patients will truly benefit from them.

Two important messages for the clinician are that, at the present time, the selection of optimal sequence of systemic therapies is, at best, level-2 evidence-based and that HR and HER-2 status determination are mandatory for adequate treatment decision and tailoring in MBC.

Future prospects

After the successful development of trastuzumab, several other biological agents have been developed and some are in advanced stages of clinical development.

A promising agent is 2C4, a new monoclonal antibody that binds to a different epitope of the extracellular domain of HER-2. 2C4 has properties significantly different from trastuzumab, the most important of which is perhaps its ability, unlike trastuzumab, to block the association of HER-2 with other HER family members (heterodimers formation) and, therefore, to prevent ligand-dependent HER-2 signalling in both low- and high-HER-2-expressing tumour cell lines.

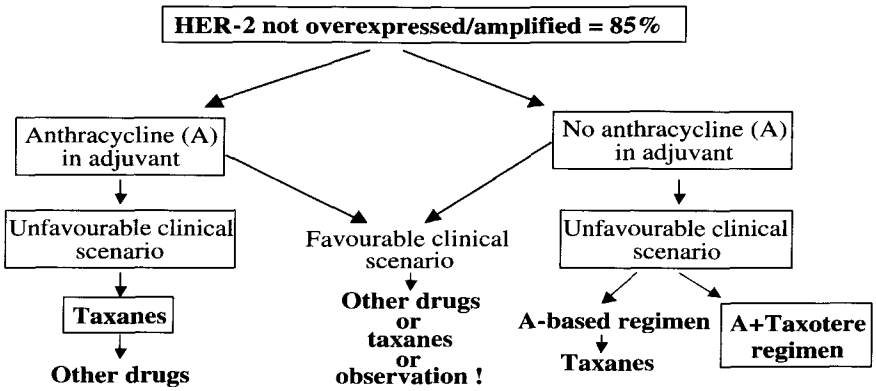

Fig. 2. Treatment decision algorithm for HER-2-negative breast cancer. Favourable clinical scenario: indolent disease, with no life-threatening metastatic lesions. Unfavourable clinical scenario: aggressive disease, with life-threatening metastatic lesions or lesions that require emergent therapy with rapid response.

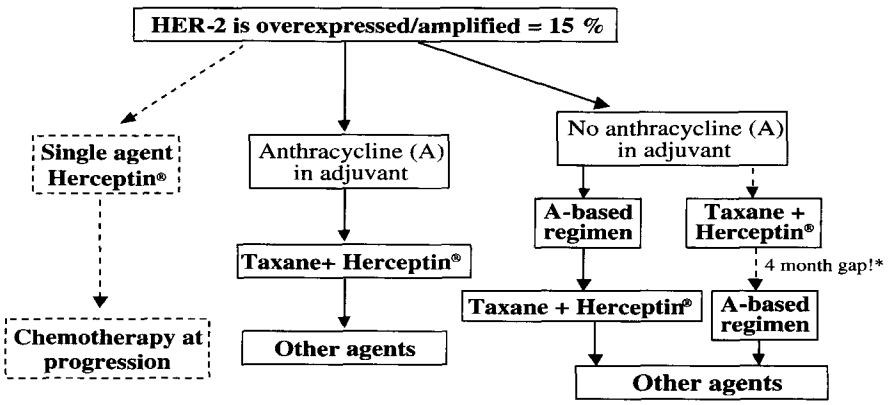

Fig. 3. Treatment decision algorithm for HER-2-positive breast cancer. * Required if one wants to minimise the risk of cardiotoxicity with anthracyclines (in view of the long halflife of Herceptin®in blood).

A phase I study has shown that 2C4 is safe without dose-limiting toxicities, and phase II studies will soon begin.

Several other agents targeting several crucial pathways, such as the MAPK pathway, the PI3K-AkT cell survival pathway or the angiogenesis pathway, are currently under evaluation. CCI-779, an m-TOR inhibitor, Zarnestra® (R-115777), a RAS farnesyltransferase inhibitor, and bevacizumab (an anti-VEGF antibody) are examples of such agents. Another interesting drug in development is PS-341, a proteasome inhibitor, responsible for the degradation of various proteins, including membrane receptors such as HER-2 and a variety of proteins involved in apoptosis. Inhibition of the proteasome leads to activation of the apoptotic pathway and additive or synergistic effects with CT, trastuzumab (or endocrine therapy) are foreseen. Some of these drugs show promising single agent activity in MBC patients and represent new challenges as far as optimal integration into the drug armamentarium for advanced disease is concerned.

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