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Review

Progress and new standards of care in the management of HER-2 positive breast cancer

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ABSTRACT

The aim of this review article is to examine the available evidence regarding diagnosis and treatment of HER-2 positive breast cancer. This group of breast tumours (up to 30% of the total number of breast cancers) is known for having a more aggressive behaviour. The current recommendations for HER-2 positive tumour diagnosis are discussed since accurate identification of HER-2 amplification or overexpression is key for allowing a correct risk assessment and treatment. HER-2 positive tumours can be treated with trastuzumab (Herceptin, Hoffmann-La Roche, Basel, Switzerland), a monoclonal antibody targeted against the HER-2 receptor. The role of this drug in the metastatic, adjuvant and neoadjuvant setting is reviewed. The results of the recently reported adjuvant trials are commented, as the positive results of these trials changed the standard of care for patients with this particular type of breast cancer.

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1. Introduction

Breast cancer (BC) is one of the most prevalent cancers in the world. Despite progress made in the last 30 years in BC screening and treatment, this disease is still responsible for almost half a million deaths per year worldwide. Approximately half of diagnosed patients will eventually develop metastatic disease. Treatment for metastatic breast cancer (MBC) is palliative, and median life expectancy after recurrence is between 24 and 30 months or less.[1,2]

It is well known that BC is a heterogeneous disease: the difference between hormone receptor (HR) positive and HR negative tumours has an impact on clinical outcome and on treatment.

More recently, it has been determined that up to 30% of BC tumours overexpress the HER-2 receptor. This characteristic is related with more aggressive tumour behaviour than is the case with non-HER-2 overexpressing counterparts. The HER-2 or c-erbB-2 proto-oncogene, located in chromosome 17q, encodes a transmembrane tyrosine kinase receptor that belongs to the EGFR family. This family includes four receptors (HER-1, 2, 3 and 4) that are active in a dimeric form, in either homo or heterodimers.[3]

A recombinant humanised monoclonal antibody directed against the HER-2 receptor, trastuzumab, was developed in the early 1990s. Since the first report of its activity on MBC, this drug has earned an important place in the management of HER-2 positive disease.

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2. HER-2 positive tumours as a distinct biological entity

The evaluation of the prognosis of a tumour based only on its clinical and histopathological characteristics has limitations. Although our molecular knowledge of BC tumours is far from complete, recent progress with microarray technology has led to a deeper understanding of cancer biology through the simultaneous evaluation of the expression of tens of thousands of genes.[4] The challenge is ultimately to get to the point of tailoring treatments for individual patients based on such genomic information.

The gene expression profiling of breast tumours using microarrays allows for a new classification of breast tumours in 4 or 5 different subgroups: basal-like, erb-B2 and luminal subtypes (A/B/C). The genomic profile of HER-2 positive tumours has some particular characteristics: it expresses a specific subset of genes and lacks many genes usually expressed in ER positive tumours.[5] The basal-like and HER-2 groups have been shown to be associated with shorter relapse free survival (RFS) and overall survival (OS). The expression of these sets of genes might represent a distinct group of tumours with a more aggressive natural history and a poorer outcome.[6–8]

3. HER-2 overexpression and amplification detection

Because HER-2 overexpression and amplification have important consequences on the prognosis and treatment of breast cancer, their presence must be accurately determined. Currently, two different methods are being used worldwide, immunohistochemistry (IHC) and fluorescence *in situ* hybridisation (FISH). These two techniques identify different targets and both have advantages and disadvantages.

IHC is a semiquantitative method that identifies HER-2 receptor expression on the cell surface using a grading system (0, 1+, 2+ and 3+). This receptor can be present in all breast cells, and only its overexpression at a level of 3+ is considered to be clinically relevant, while 2+ is doubtful.

FISH is a quantitative method measuring the number of copies of the HER-2 gene present in each tumour cell. Its result is positive or negative, meaning amplification and non-amplification respectively.

IHC is the most widely used technique. It is performed on paraffin tumour blocks, is not time consuming and is relatively low in cost. This is an operator dependant method, and results can be influenced by factors such as the use of different fixation protocols, assay methods, selected antibodies and scoring systems.

FISH is a more reproducible technique. However, it is also much more time consuming and more expensive than IHC, multiplying its costs by more than ten (see Table 1).[9]

Which method should be viewed as the gold standard for HER-2 determination remains a debate. IHC/FISH concordance has been explored using FISH as the standard method in almost 3000 samples. A negative IHC result (0 or 1+) correlated with a negative FISH in 97.2% of the cases. Positive 3+ IHC status had a FISH positive correlation of 98.8%. When considering IHC 2+ and 3+, however, specificity dropped to 58.5%, with a sensitivity of 92.6%.[9]

Table 1 – Differences between FISH and IHC[11]

	IHC	FISH
Failure rate	0.08%	5%
Time consumed	4 h	36 h
Pathologist time per case	45 s	7 min
Reagent cost	10 US$	140 US$

FISH has been considered to be more useful than IHC for predicting response to trastuzumab.[10–12] However, in these reports, tumours were classified as HER 2 positive, when they showed IHC 2+ or 3+ results. If only 3+ tumours are viewed as HER-2 positive, both methods are equivalent for predicting response to trastuzumab.[13–16]

It has been shown that HER-2 determination needs to be performed in experienced laboratories with quality control programmes. A central pathology review of the N9831 trial was performed on HER-2 positive tumours according to the results of local laboratories. A total of 26% of the 110 tumour blocks analysed were in fact false positives, and 33% of the 9 FISH + tumours were negative according to the central lab. This unacceptable ratio of false positives led to changes in the inclusion criteria of the protocol, making central confirmation of local positive results mandatory for inclusion of patients in the trial.[17]

Tumour samples of the first 104 patients included in the NSABP B-31 trial were also retested centrally. Eighteen percent (22 cases) of tumours locally classified as HER-2 positive (in almost all cases by using IHC) were in fact false positives when assessed centrally. Interestingly, false positive rates were worse in small labs than in large ones (only one false positive in 22 came from a large laboratory).[18] It is now recommended that laboratories assay at least 250 cases per year to ensure expertise in performing IHC determinations. If this is not the case, a central laboratory should be used as a reference.[19] As FISH is viewed as a more reproducible technique, a minimum of 100 assays/year is considered to provide an acceptable degree of certitude.

Considering the parameters of IHC 0 and 1+ as negative and 3+ as positive, IHC is an acceptable screening method. For IHC 2+ tumours, the results should be confirmed by FISH. This testing algorithm is viewed by many as an acceptable, cost effective approach.[9,13,19,20]

Recently, other methods have been described as options for HER-2 testing. Real time polymerase chain reaction (RT-PCR)[21–23] and chromogen *in situ* hybridisation (CISH)[24–26] have been proposed as cheaper and easier alternatives to FISH. Acceptable correlations between both methods and FISH have been reported. Results are encouraging and warrant further evaluation.

4. Management of advanced disease

4.1. *Trastuzumab single agent*

Intense research has focused on trastuzumab since the first reports of its activity in advanced BC, either as a single agent or in combination with chemotherapy (CT).[27,28]

In a study by Vogel *et al.*, trastuzumab was used as a single agent in first line therapy for 111 patients with HER-2 overexpressing MBC.[27] This trial included patients with both IHC 2+ and 3+ tumours. Responses were observed only in the 3+ subgroup (RR of 35%), and median time to progression (TTP) was 4.9 months. Use of trastuzumab as a single agent in heavily pretreated patients showed a lower RR (15%).[29] This result is consistent with another study of trastuzumab in pretreated patients, which showed a RR of 11%.[30]

4.2. *Trastuzumab in combination with chemotherapy*

A pivotal phase III study randomised 469 patients to receive CT (either paclitaxel or anthracycline based chemotherapy) or CT plus trastuzumab as first line treatment for MBC.[28] Patients in the combination arm had a significantly better TTP than patients on the chemotherapy arm. While the anthracycline-based combination resulted in an unacceptable rate of cardiac heart failure, the taxane-based combination was well tolerated. TTP was significantly higher in the taxane + trastuzumab arm (TTP 6.9 months versus 3 months in the taxane arm) (Table 2).

The other taxane (docetaxel) was tested in a randomised phase II trial as either a single agent or in combination with trastuzumab as first line therapy with 188 patients.[31] The combination arm outscored the chemotherapy arm with respect to both TTP and OS (see Table 2), but formal comparisons between the arms should not be considered valid since this trial was designed as a randomised phase II study.

Table 2 – Taxanes +/– Trastuzumab trials in MBC[28,31]

	Median TTP (m)	ORR (%)	Median OS (m)
Paclitaxel	3	16	18.4
Paclitaxel + T	6.9	38	22.1
p value	<0.001	<0.001	0.17
Docetaxel	NR	34	22.7
Docetaxel + T	NR	61	31.2

Table 3 – Chemotherapy plus trastuzumab trials in MBC

Drug	RR range (%)	Reference
Trastuzumab + single agent CT		
Paclitaxel + T	27–81	[15,28,33–42]
Docetaxel + T	44–83	[31,33,43–55]
Capecitabine + T	45–47	[56,57]
Vinorelbine + T	38–86	[58–69]
Gemcitabine + T	27–44	[70–72]
Cisplatin + T	48	[44]
Trastuzumab + combination CT		
Docetaxel + Cisplatin + T	79	[74]
Docetaxel + Carboplatin + T	56	[74]
Docetaxel + Gemcitabine + T	56	[75]
Paclitaxel + Gemcitabine + T	53–62	[76,77]
Epirubicin + Docetaxel + T	67	[78]

4.3. *Phase II trials of trastuzumab plus single agent chemotherapy*

There is preclinical evidence that trastuzumab has synergistic properties when combined with various cytotoxic drugs.[32] During the last 3 years an important number of phase II studies investigating the efficacy of different CT in combination with trastuzumab for MBC have been published (Table 3).

4.4. *Phase II trials of trastuzumab in addition to combination chemotherapies*

Trastuzumab has also been added to combination chemotherapy for MBC. All of these trials have shown RR higher than 50% (Table 3).

One trial of a combination of trastuzumab, paclitaxel and carboplatin after eight cycles of weekly trastuzumab single agent as first line treatment for MBC reported a RR of 84% for the combination.[73] These results should be interpreted cautiously: of the 61 enrolled patients, a response to single agent trastuzumab was documented in 14% of them. The authors excluded nine patients from their RR analysis (almost 15% of the sample) for 'lack of measurable disease'. Finally, only 31 patients received the combination of all three drugs, since those patients progressing on single agent trastuzumab received only carboplatin and paclitaxel. The reported 84% RR was found in this latter subgroup. This type of selection bias must be taken into consideration when analysing the antitumour activity of this regimen.

4.5. *Randomised phase II and phase III trials of trastuzumab plus combination chemotherapy*

The efficacy of trastuzumab in combination with CT has been evaluated in randomised trials. In one randomised phase II trial, patients received carboplatin and paclitaxel on either a

Table 4 – Paclitaxel, carboplatin and trastuzumab in two different schedules in MBC[79]

	n	RR	PFS	OS (2 years)	Grade 4 neutropenia	Febrile neutropenia
Paclitaxel 200 mg/m^2 3-weekly Carboplatin (AUC 6) 3-weekly Weekly trastuzumab during CT (six cycles max) (then 3-weekly)	43	65%	9.9	54%	67%	16%
Paclitaxel 80 mg/m^2 weekly Carboplatin (AUC 2) weekly Weekly trastuzumab during CT (six cycles max) (then 3-weekly)	48	77%	13.8	73%	12%	2%

Table 5 – Paclitaxel and trastuzumab +/– carboplatin in MBC[80]

	n	RR	TTP (m)	OS (m)
Paclitaxel 175 mg/m^2 3-weekly C (AUC 6) 3-weekly Weekly trastuzumab	93	52%	11.9	42.1
Paclitaxel 175 mg/m^2 3-weekly Weekly trastuzumab	95	36%	6.8	33.3
		$p = 0.04$	$p = 0.02$	$p = 0.27$

weekly or in a 3-weekly schedule, in both cases with trastuzumab (weekly during CT, and later on 3-weekly). At the first interim analysis, the weekly arm was as least as effective and less toxic than the 3-weekly one (even taking into account that the trial was not designed for comparisons between arms) and recruitment was stopped in the 3 weekly arm (Table 4).[79]

A phase III trial compared paclitaxel, trastuzumab and carboplatin with paclitaxel plus trastuzumab.[80] A significant benefit with respect to RR and TTP was achieved on the 3-drug arm, without any impact on OS (Table 5) (the primary end point was not identified in the abstract).

An ongoing phase III trial is comparing docetaxel 100 mg/m^2 plus trastuzumab (weekly during CT, then 3-weekly) with docetaxel 75 mg/m^2 plus trastuzumab (weekly during CT, then 3-weekly) plus a platinum salt 3-weekly (either carboplatin AUC 6 or cisplatin 75 mg/m^2). This BCIRG trial may confirm the hypothesis that platinum salts further enhance the activity of trastuzumab + taxane combinations.

In summary, combining trastuzumab with cytotoxics can result in high RR. However we have to bear in mind that the vast majority of the reported trials are only single arm phase II studies, and consequently there are limitations to the utility of the available evidence.

4.6. *Trastuzumab cardiotoxicity*

The risk of developing cardiac heart failure (CHF) with the use of trastuzumab rises with a large cumulative dose of doxorubicin and advanced age. The highest risk was identified to reside in the simultaneous administration of trastuzumab and doxorubicin[81] (Table 6). Patients on trastuzumab usually undergo close monitoring of cardiac function, with left

Table 6 – Cardiac toxicity due to trastuzumab plus chemotherapy[81]

Cardiac dysfunction	Doxorubicin + trastuzumab	Doxorubicin	Paclitaxel + trastuzumab	Paclitaxel
Symptomatic or asymptomatic	27%	8%	13%	1%
NYHA class III or IV	16%	3%	2%	1%

NYHA: New York Heart Association. Class I: patients with no limitation of activities; they suffer no symptoms from ordinary activities. Class II: patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion. Class III: patients with marked limitation of activity; they are comfortable only at rest. Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

Table 7 – Proposed algorithm for managing trastuzumab induced cardiotoxicity[82]

Physical status	LVEF	Action		
		Trastuzumab	LVEF monitoring	Management
Asymptomatic	↓ but normal	Continue	Repeat in 4 weeks	
	↓> 10 points but normal	Continue	Repeat in 4 weeks	Consider blockers
	↓ 10–20 points and LVEF > 40%	Continue	Repeat in 2 to 4 weeks *Improved*: monitor *Not improved*: stop trastuzumab	Treat for CHF
	↓> 20 points to < 40% or LVEF < 30%	Hold	Repeat in 2 weeks *Improved to* > 45%: restart trastuzumab *Not improved*: stop trastuzumab	Treat for CHF
Symptomatic	↓< 10 points	Continue		Search for non cardiac pathology (e.g. anaemia)
	↓> 10 points and LVEF > 50%	Continue	Repeat in 2 to 4 weeks *Stable or improved*: continue trastuzumab *Worsened*: stop trastuzumab	Treat for CHF
	↓> 30 points	Stop		Treat for CHF

Table 8 – Trastuzumab plus liposomal doxorubicin trials in MBC

Author	Regimen	Patients characteristics	*n*	RR	LVEF drop	CHF
Wolff[84]	Docetaxel 60 mg/m^2 PLD 30 mg/m^2 (Caelyx) Trastuzumab	First line, no prior anthracyclines	40	45%	10%	0%
Theodolou[83]	LD 60 mg/m^2 (Myocet) Trastuzumab	Previous treatments for MBC accepted	39	59%	2.60%	2.60%
Cortes[85]	Paclitaxel 80 mg/m^2 weekly LD 50 mg/m^2 (Myocet) Trastuzumab	LABC or previously untreated metastatic	54	92.6%	15%	0%
Chia[86]	PLD 50 mg/m^2 (Caelyx) Trastuzumab	First line	30	52%	10%	0%

ventricular ejection fraction (LVEF) measurements taken at baseline and regularly thereafter. Unlike with doxorubicin, trastuzumab related heart disease is not dose dependant. Symptomatic cardiac failure developing under trastuzumab usually responds favourably to standard medical treatment. Patients with asymptomatic LVEF drops can recover their cardiac function just by withdrawing from trastuzumab treatment. Some of them may even be able to resume trastuzumab treatment when monitored closely. A treatment algorithm for controlling the cardiac function in patients on trastuzumab has been proposed by Keefe *et al.* (Table 7).[82]

4.7. *Trastuzumab plus anthracyclines*

Doxorubicin is among the most active drugs in BC treatment but, as indicated, its combination with trastuzumab causes an unacceptable rate of cardiac toxicity. Because the doxorubicin liposomal formulations (LD) have virtually no cardiotoxic properties -unless given at very high cumulative doses-, different trials of LD plus trastuzumab have been performed.[83–86] It is difficult to perform a cardiac safety joint analysis of these trials since cardiac safety endpoints were not similar. Nevertheless, the overall conclusion is that this combination is safe, with usually only mild or asymptomatic cardiac toxicity and acceptable antitumoural activity (Table 8).

Epirubicin, reported to be as effective as doxorubicin and less cardiotoxic,[87] has been used in combination with trastuzumab in a phase I study: two different doses in combination with cyclophosphamide (60/600 mg/m^2 and 90/600 mg/m^2) and trastuzumab were tested as first line treatment for MBC on 51 patients who did not previously receive an anthracycline.[88] The protocol cardiac endpoint was defined as an LVEF decrease of 10 points or more from screening, LVEF decrease to less than 50%, symptomatic heart failure, severe arrhythmia, acute coronary syndrome or the need for cardiopulmonary resuscitation. This trial reported acceptable cardiac safety profiles, with only two patients in the high dose epirubicin arm and one in the low dose epirubicine group meeting any of the predefined cardiac endpoint among a total of 25 and 26 recruited patients respectively. After this first analysis, the trial continued to recruit patients in a randomised phase II design. The interim RR is 62% for the 60 mg/m^2 epirubicin arm and 64% for the 90 mg/m^2 epirubicin one.[88] This trial is ongoing.

Venturini *et al.* reported the results of a study combining epirubicin, docetaxel (both drugs at 75 mg/m^2 every 3 weeks) and weekly trastuzumab as first line treatment for 45 patients with MBC. The cardiac endpoints were symptomatic congestive heart failure, a drop in the LVEF of > 20 points from baseline or a drop of the LVEF below 45%. Twenty-two percent of the patients experienced such cardiac events, but all of them responded satisfactorily to medical treatment. The reported RR was 67%.[78]

In another anthracycline, taxane and trastuzumab study, Bianchi *et al.* studied two cohorts of 16 patients each with MBC not previously treated with chemotherapy. The first cohort received a combination of doxorubicin and paclitaxel (60/150 mg/m^2) for three cycles followed by weekly paclitaxel (80 mg/m^2), with weekly trastuzumab started simultaneously with the AT combination. In the second cohort, trastuzumab was administered with paclitaxel as a single agent. No cases of clinical cardiac heart failure were reported, and those asymptomatic patients whose LVEF dropped below 50% later recovered appropriate cardiac function. The overall RR for the 32 patients was 87%.[89]

Table 9 – Neoadjuvant trials of trastuzumab in combination with CT

Author	Drugs	RR (%)	pCR (%)
Burstein[115]	Trastuzumab qw × 12 Paclitaxel q3w (175 mg/m^2)	75	18
Bines[116]	Trastuzumab qw × 14 Docetaxel qw (36 mg/m^2)	70	12
Moluçon[117]	Trastuzumab qw × 18 Docetaxel q3w (100 mg/m^2)	95	28
Schiffhauer[118]	Trastuzumab qw × 12 Docetaxel q3w (100 mg/m^2)	NR	25
Harris[119]	Trastuzumab qw × 12 Vinorelbine qw (25 mg/m^2)	88	19
Hurley[120]	Trastuzumab qw × 12 Docetaxel q3w (70 mg/m^2) Cisplatin q3w (70 mg/m^2)	NR	26
Steger[121]	Trastuzumab qw × 12 Docetaxel qw (30 mg/m^2) Epirubicin qw (35 mg/m^2)	100	22
Griggs[122]	Trastuzumab qw × 12 Docetaxel q3w × 4 (100 mg/m^2)	77	18
Jahanzeb[123]	Trastuzumab qw × 12 Docetaxel q2w (60 mg/m^2) Vinorelbine q2w (45 mg/m^2) (Dose dense)	88	39

Table 10 – Trastuzumab adjuvant trials designs

Trial (accrual)	Patients characteristics	Treatment regimens	Trastuzumab schedule	Duration of therapy	Trastuzumab and radiotherapy
NSABP B-31 (2700)	Node positive	AC × 4 → *P* × 4 AC × 4 → *P* × 4 + Trastuzumab	Weekly	1 year	Concurrent
NCCTG N9831 (3000)	Node positive	AC × 4 → *P* × 4 AC × 4 → *P* × 4 + Trastuzumabstartingconcurrently with*P* AC × 4 → *P* × 4 + Trastuzumabstartingafter*P*	Weekly	1 year	Concurrent or sequential
BCIRG 006 (3150)	Node positive or high risk node negative	AC × 4 → *D* × 4 AC × 4 → *D* × 4 + Trastuzumabstartingconcurrently with*P* *D* + CDDPorCBDP × 4 + Trastuzumab	Weekly with chemo, then every 3 weeks	1 year	Concurrent
BIG 01-01/ HERA (5100)	Any small (< 1cm) node negative tumours not eligible	Any accepted chemotherapy alone Trastuzumab 1 year after chemotherapy Trastuzumab 2 years after chemotherapy	Every 3 weeks	1 or 2 years	Sequential

In summary, combining trastuzumab with cytotoxics can cause high RR but we have to bear in mind that the vast majority of the reported trials are single arm phase II studies. Consequently, there are again limitations with respect to the utility of the available evidence. Ongoing studies of trastuzumab in combination with less toxic anthracyclines will provide us with more information about cardiac safety.

4.8. *Trastuzumab schedule*

Almost all published trials of trastuzumab have used a weekly schedule, starting with a loading dose of 4 mg/kg followed by 2 mg/kg. New evidence suggesting that this drug may have a longer half life than originally supposed[90] led to the question of whether a more convenient 3-weekly schedule was as effective as the weekly one.

The combination of trastuzumab and paclitaxel, with both drugs administered to 32 patients according to a 3-weekly schedule was published in 2003.[91] Trastuzumab was administered with a loading dose of 8 mg/kg followed by maintenance doses of 6 mg/kg. No unexpected toxicities were noted, there was no worsening of the cardiac toxicity rate, the combination was well tolerated, and the RR was 59% with a median time to progression of 12 months. A pharmacokinetics (PK) sub-study showed that there were no major differences between the data obtained from trials with either weekly or 3-weekly schedules.

Another study published by Baselga *et al.* used trastuzumab as single agent first line therapy in a 3-weekly schedule. There was a RR of 23% in 105 MBC patients, and the median TTP was 3.4 months. Again, a pharmacokinetics analysis did not show significant differences between the 3-weekly and weekly schedule.[92]

Unfortunately, no randomised trials have compared weekly versus 3-weekly schedules directly. Clinical experience with the weekly schedule is larger, but there is increasing evidence that the 3-weekly schedule is equally effective and safe. Importantly, the PK profiles of the two schedules do not differ, and the 3-weekly regimen is more convenient for patients and caregivers. In view of the above, it is reasonable to consider the 3-weekly schedule for most patients, while perhaps reserving the weekly schedule for highly symptomatic patients.

A third scheduling approach is currently being studied by Leyland-Jones: patients receive weekly loading doses of 6 mg/kg during the first 3 weeks and then 3-weekly infusions at the same dose from week 4 onwards. The goal of this schedule is to more quickly reach the steady state concentration of the drug. This pharmacological model is already current practice with other drugs, for example, digoxin. The first results using this schedule were presented at ASCO 2005, and the pharmacokinetics data looked very encouraging.[93]

4.9. *Trastuzumab therapy after progression*

When treating patients with a combination of CT plus trastuzumab, CT is commonly administered until the maximum response is obtained, while trastuzumab is continued until disease progression. Preclinical data and retrospective analysis of clinical trials back the hypothesis that continuing treat-

ment with trastuzumab after disease progression may provide patient benefit.[94,95] While this approach remains non standard, two prospective trials are ongoing to evaluate its merit. One US Intergroup study is randomising patients who progressed on taxanes plus trastuzumab to vinorelbine versus vinorelbine plus trastuzumab, and the BIG 3-05 study is randomising the same patient population to capecitabine versus capecitabine plus trastuzumab. We hope that these two trials will provide us with an answer to this question, which also has economic implications.

4.10. *HER-2 patients and central nervous system metastases*

Higher rates of SNC metastases in patients with HER-2 overexpressing tumours on trastuzumab treatment have been reported. It is still not clear if these observations point to a distinct clinical behaviour, since retrospective studies have well known limitations.[96–104] There is debate about whether this difference (if it actually exists) is due to a higher risk of SNC metastases associated with HER-2 overexpression, or if it is due to a change in the natural history of the disease caused by trastuzumab treatment. There have been reports of patients on trastuzumab who develop CNS metastases while showing a good response in other sites.[101,104,105] An important issue is that, because of its high molecular weight, trastuzumab does not cross the blood-brain barrier (BBB). Recently, a retrospective study by Lai *et al.* with more than 300 patients failed to show a relationship between the risk of CNS metastases occurrence and either HER-2 status or trastuzumab treatment.[98] There is no evidence that screening for CNS metastases in asymptomatic patients of this subgroup would provide an OS benefit.

There has been one case reported of the administration of intrathecal trastuzumab treatment in a patient with meningeal carcinomatosis but showing good clinical response in other disease sites. The treatment did not produce any clinical benefit, but no side effects were noted. A clinical trial would be important in order to evaluate whether this therapy could be useful as a treatment option for these particular patients.[106]

4.11. *Trastuzumab and other targeted therapies*

So far there are no standard combinations of trastuzumab with other biological agents. One trial combining trastuzumab with gefitinib (an agent targeting HER-1, another receptor of the HER family) was stopped prematurely due to unacceptably low efficacy at an interim analysis. A possible explanation for this may be that the HER-3 receptor pathway was not blocked, and that tumour cells, as a result, were may be able to survive.[107] Another phase II study using trastuzumab and celecoxib to treat trastuzumab pretreated patients yielded negative results.[108] A phase I trial of trastuzumab plus lapatinib (a competitive inhibitor of HER-1 and HER-2 tyrosine kinases) showed an adequate tolerability and encouraging response rates.[109] Further evaluation of this association is warranted.

Different trials combining trastuzumab with a variety of targeted therapies are currently underway.

5. HER-2 tumours and endocrine therapy

Patients with HER-2 positive, HR positive tumours can benefit from endocrine therapy, even if they seem less responsive than their HER-2 negative counterparts.[110] There is some weak evidence that tamoxifen should be replaced by aromatase inhibitors in the treatment of HER-2 positive patients. The current view however, is that HER-2 status should not be used to decide which endocrine therapy a patient should receive. The 2005 ASCO recommendations did not support the use of HER-2 in decision-making regarding endocrine treatment.[111] Almost simultaneously, at the 2005 St Gallen consensus panel meeting, it was proposed to create a new risk category named 'endocrine response uncertain'. In this category, HER-2 overexpression is recognised as a marker of relative resistance to endocrine therapy, and as a trigger for aromatase inhibitor prescription.[112] The subject of HER-2, endocrine treatment and resistance has been reviewed in depth by Ring *et al.*[113] The question whether aromatase inhibitors are a better option than tamoxifen for this population still has no definitive answer. To the best of our knowledge, none of the adjuvant trials comparing tamoxifen against any aromatase inhibitor reported a clear benefit for AI versus tamoxifen in HER-2 overexpressing cases.

One prospective trial compared letrozole to tamoxifen in the neoadjuvant setting.[114] It was evident that letrozole was more active than tamoxifen in terms of response for patients with HER-2 overexpressing tumours. However, no conclusions can be drawn regarding possible differences in OS from this trial, which only investigated a very short (4 months) endocrine therapy.

Currently, two randomised trials are investigating an aromatase inhibitor +/− trastuzumab as first line endocrine treatment for metastatic disease. One phase III study (Mo 16722;eLEcTRA) is comparing letrozole to letrozole + trastuzumab, while the second is a phase II/III trial (BO16216) evaluating anastrozole versus anastrozole plus trastuzumab. The recruitment for this last trial is already closed, and the first results are awaited.

6. Trastuzumab in the neoadjuvant setting

Neoadjuvant therapy is a widely accepted treatment strategy for patients with locally advanced BC. Tumour chemosensitivity can be assessed directly, and tumours can be downstaged, facilitating surgery. Trastuzumab has been combined with both single agent chemotherapy and with chemotherapy combinations in the neoadjuvant setting. All these data derive from phase II trials using weekly trastuzumab (Table 9) and show excellent RR, with pathological complete response (pCR) in more than 10% of patients.

The MD Anderson group has reported the results of a phase III trial comparing paclitaxel followed by FEC with or without simultaneous trastuzumab as neoadjuvant treatment. This trial had a planned accrual of 168 patients, but an unplanned interim analysis, triggered by the high pCR rate reported by pathologists after 34 patients had completed therapy, showed a statistically significant difference of pCR between the study arms favouring trastuzumab treatment (66.7% versus 25%; $p = 0,05$). After evaluating the results of the 42 patients randomised (pCR of 65.2% versus 26.3%;

Table 11 – American trials joint analysis, BCIRG trial and HERA trial results

	N	Median FU	HR for DFS	HR for distant recurrence	HR for distant DFS	HR for OS	Cumulative incidence of severe cardiac events
HERA	3387	1 year	0.54 ($p < 0.0001$)	NA	0.49 ($p < 0.0001$)	0.76 ($p = 0.26$)	
Control	1693						0.10%
1 year trastuzumab	1694						0.50%
Pooled analysis of NSABP B-31 and NCCTG-N9831	3351	2 years	0.48 ($2p = 3 \times 10 - 12$)	0.47 ($2p = 8 \times 10 - 10$)	NA	0.67 ($2p = 0.015$)	
Chemotherapy	1679						0.60%
Chemotherapy + trastuzumab	1672						4%
BCIRG	3222	2 years		Non reported	Non reported	Non reported	
Anthracycline + taxane	1073						0.95%
Anthracycline + taxane + trastuzumab	1074		0.49				2.34% (significant difference)
Carboplatine + taxane + trastuzumab	1075		0.61				1.33%

FU: Follow up, HR: hazard ratio, NA: non available.

$p = 0.016$), the independent data monitoring committee (IDMC) suggested to stop recruitment in the control arm of the study and disclosed the results.[124]

This decision is subjected to criticism. There is no definitive evidence that such a high pCR rate will eventually translate into a benefit in clinical outcome. In terms of safety (trastuzumab was given simultaneously with epirubicin), it would have been useful to compare the cardiac dysfunction rates between the arms.

Neoadjuvant treatment involving trastuzumab has shown encouraging results, but given the lack of solid data regarding its therapeutic index, this approach remains experimental.

7. Trastuzumab in the adjuvant setting

After obtaining evidence of trastuzumab efficacy in MBC, the next logical step was to test this drug in the adjuvant setting. In the last few years four large trials were launched almost simultaneously, with a total planned accrual of more than 13,000 patients. These trials vary with regard to their designs, exploring the role of trastuzumab after or in combination with a variety of different chemotherapies. A description of the four trials can be found in Table 10. All these studies share in their design strict cardiac safety surveillance with early stopping rules for unacceptable cardiac toxicity findings.

The NSABP has already published the results of the cardiac safety analysis of the B-31 protocol. The protocol pre-specified that the absolute difference of cardiac events (either symptomatic cardiac failure confirmed by MUGA or echocardiogram or cardiac death) between arms should not be greater than 4%. In the trastuzumab arm 4.28% of patients experienced a cardiac event, while this rate was 0.78% in the control arm. Since the difference was 3.5% (confidence interval 1.6% to 5.3%), the trial continued as planned. Asymptomatic drops of the LVEF were seen in 11.3% of patients under trastuzumab therapy. Of these patients, 66% showed a significant improvement of their cardiac function over time.[125]

The efficacy results of three of the large adjuvant trials were presented at the 2005 ASCO meeting. The NSABP and the NCCTG results were presented together after a joint interim analysis had been performed, as decided by the National Cancer Institute. The interim results of the HERA trial were also presented for the first time. Both the combined NSABP/NCCTH and HERA studies showed strikingly positive results, presented in Table 11.

After the release of these results, the control arms in the three studies were closed. While the primary end point of NSABP B-31 was OS, in the HERA and the NCCTG trials it was DFS. Both analyses showed significant improvements in DFS in the trastuzumab arms and in the case of the joint American trials analysis, which has a longer follow up, a significant difference in survival benefit was also found in the pooled data analysis. In HERA, a significant difference in time to distant relapse was reported and suggests that an OS benefit might be seen as the study matures.

Cardiac toxicity seemed somewhat higher in the American trials, where trastuzumab was administered concurrently with CT and/or radiotherapy. Longer follow up is essential to more accurately evaluate the respective cardiac risks of these regimes.

Of note, no results for the 2-year trastuzumab arm of the HERA trial were disclosed by the HERA IDMC: this arm remains open and comparative efficacy results relative to the 1 year treatment are expected in the next 2 years.[126,127]

The results of the fourth trial, BCIRG 006, were presented at the 2005 SABCS meeting. It confirmed the results of the previous trials, showing a significant difference in terms of DFS, without a significant difference in OS so far. This trial showed a significant difference on symptomatic cardiac events in the anthracycline-trastuzumab arm when compared to the control arm, while there was no difference in the taxane-carboplatin-trastuzumab arm compared to the control arm.[128]

Another trial investigated the value of a short trastuzumab adjuvant therapy (9 weeks) on patients receiving either docetaxel followed by FEC or Vinorelbine followed by FEC, with or without trastuzumab for HER-2 positive patients (this population consisted of 231 patients). The DFS was significantly better on the trastuzumab arm after 38 months of median follow up (HR: 0.43, $P = 0.0078$) with a non significant benefit on survival. This shorter trastuzumab therapy was not associated with a drop of the LVEF in the trastuzumab arm.[129] The positive result of this trial using a shorter treatment period may be important due to the problems associated with the cost of trastuzumab.

Similarly to the scenario in the advanced setting, several clinical questions remain open: 1) Which is the optimal use of trastuzumab and chemotherapy, sequential or concurrent? 2) What is the optimal duration of trastuzumab therapy? 3) Which chemotherapy/trastuzumab regimen is the most effective and safe? 4) Should trastuzumab be given to patients with HER-2 positive tumours, but with other favourable prognostic factors (size less than 1 cm, grade 1)?

We hope we will be able to answer these questions in the next few years.

8. Conclusion

Despite the fact that HER-2 overexpressing tumours have received a lot of attention in the last few years, many questions remain unanswered. While trastuzumab treatment is standard in the metastatic setting, there is no consensus regarding optimal schedule (weekly versus 3-weekly), duration of therapy (until progression versus reintroducing trastuzumab in combination with a different cytotoxic drug after progression) or optimal CT combination.

The most solid evidence regarding trastuzumab treatment for MBC derives from phase III trials involving taxanes with or without trastuzumab. Given that taxanes are increasingly being used to treat early BC it is important to identify which other cytotoxic drugs in combination with trastuzumab are active for these patients in case of relapse. The data, so far, show that fortunately, trastuzumab adds little toxicity to that caused by most CT agents, while it does result in high response rates.

Another issue that deserves accelerated investigations is trastuzumab resistance. Not all patients respond to trastuzumab and all responding patients eventually show progressive disease. The possible influences of the HER/ERBB signalling network as well as the role of other molecular suspects have been reviewed elsewhere.[130,131]

Finally, the recent provocative results of the trastuzumab adjuvant trials are rapidly inducing a shift in standard practice, with the real challenge being the high cost of adjuvant trastuzumab.

Other anti HER-2 treatment strategies in development will undoubtedly be evaluated as alternatives to trastuzumab or as complementary approaches. One can start dreaming of converting a highly lethal disease into a largely curable entity.

Conflict of interest statement

Dr Martine Piccart: Consultant / Advisory Role: GlaxoSmith-Kline (less than 10,000$). Honoraria: Roche (Hoffmann La Roche) (less than 10,000$). The rest of the authors do not have any conflicts of interest to declare.

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