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Trials of new combinations of Herceptin® in metastatic breast cancer

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Herceptin® extends survival in human epidermal growth factor receptor-2 (HER2)-positive metastatic breast cancer patients when administered with paclitaxel or anthracycline/cyclophosphamide (AC), and the combination with 3-weekly paclitaxel is the current standard first-line therapy. However, other combinations may be equally effective. This review provides information on recent and ongoing trials of new Herceptin® combinations. Preliminary results indicate that Herceptin® plus epirubicin/cyclophosphamide may be effective without the cardiotoxicity of the AC combination. Weekly paclitaxel plus Herceptin® has produced responses in 83% of HER2-positive patients treated. Co-administering Herceptin® with other cytotoxic agents has also been investigated, with combination partners being chosen based on *in vitro* synergy with Herceptin®, known efficacy as monotherapy and convenience of weekly administration (e.g. docetaxel, vinorelbine). High response rates have been observed in these clinical trials, e.g. up to 80% in combination with vinorelbine. Furthermore, Herceptin® in combination with weekly paclitaxel, docetaxel or vinorelbine was well tolerated: there was no significant cardiotoxicity or unexpected toxicity and the combination showed an adverse event profile similar to that seen with monotherapy with the cytotoxic agent. Thus, Herceptin® produces additional clinical benefit when added to all the cytotoxic agents with which it has been examined, further demonstrating its potential for use in HER2-positive breast cancer patients. [© 2001 Lippincott Williams & Wilkins.]

Key words: Clinical trials, docetaxel, epirubicin, Herceptin®, paclitaxel, vinorelbine.

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Introduction

As described elsewhere, the human epidermal growth factor receptor-2 (HER2) gene is a rational target for tailored therapy in breast cancer because HER2 gene amplification is involved in oncogenesis, and HER2 positivity correlates with poor clinical outcome and altered response to therapy.[1,2] The ability to rationally develop and customize monoclonal antibodies to target specific cellular factors has been exploited to produce the anti-HER2 therapy Herceptin®.[3]

Initial phase I and II clinical trials using single and multiple doses of Herceptin® in patients with refractory HER2-positive metastatic breast cancer found that, with repeated weekly administration of Herceptin®, this agent has substantial antitumor efficacy and minimal toxicity compared to cytotoxic chemotherapy.[4–6] These studies were the basis for two pivotal clinical trials which investigated Herceptin® as monotherapy[7] and in combination with paclitaxel or anthracycline/cyclophosphamide (AC).[8–10] In the combination trial, only two combination regimens (paclitaxel or AC) and only certain dose regimens of these agents were examined.[2] However, *in vitro* studies[11,12] of activity against HER2-positive breast cancer cell lines have indicated that combining Herceptin® with other cytotoxic agents may produce antitumor activity similar to or greater than that of the combinations examined in the pivotal clinical trials (Table 1). Among these agents, vinorelbine and docetaxel would appear to offer a particularly high degree of synergistic activity with Herceptin®. Furthermore, different dose regimens of the cytotoxic agents used concomitantly may improve efficacy, tolerability and patient convenience.

Recently reported clinical trials using the standard Herceptin® regimen have begun to provide information regarding some of these new combinations and dose regimens. The aim of this report is to provide information about some of the studies of combination therapy with Herceptin® that have been recently completed or are ongoing. It is stressed that the standard Herceptin® weekly regimen

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(4 mg/kg initial dose followed by 2 mg/kg weekly until disease progression) was used in all of the trials described.

Studies investigating the combination of Herceptin® with anthracyclines

In the pivotal combination trial of Herceptin® plus paclitaxel or AC,[10] the combination of Herceptin® with AC produced the highest response rates and the longest response duration. However, this combination was also associated with an incidence of cardiotoxicity greater than that in any of the other treatment subgroups in this trial (range 26–28%, NYHA grade I–IV cardiac dysfunction). Analysis of cardiac safety in this trial and the Herceptin® monotherapy trials[7,13] demonstrated that cardiotoxicity occurs mainly in women treated with Herceptin® who have received prior or concomitant anthracycline therapy, most notably with doxorubicin.[14] The cardiotoxicity of doxorubicin is well known[15,16] and of the 84 women in Herceptin® trials to date who have not received anthracyclines, only three, all of whom had pre-existing heart disease and were elderly, developed heart failure. It should also be noted that the analyses of cardiac safety in these trials were retrospective and that many cases of cardiotoxicity were asymptomatic, making it difficult to assess the true effect of therapy. However, although it has not been shown that Herceptin® has intrinsic effects on cardiac tissue,[17] the use of Herceptin® in combination with doxorubicin/cyclophosphamide is not indicated outside clinical trials. Trials prospectively examining cardiac safety in patients treated with Herceptin® and doxorubicin are being conducted, including one examining the pharmacokinetics and cardiac safety of Herceptin® in combination with doxorubicin plus paclitaxel, and preliminary results are expected in the near future.

Given the efficacy of the combination of Herceptin® with doxorubicin/cyclophosphamide, several studies are examining the use of Herceptin® in combination with other, potentially less cardiotoxic anthracyclines. Epirubicin is known to be less cardiotoxic than doxorubicin[18] and may therefore be a useful agent to combine with Herceptin®. A phase I/II clinical trial of Herceptin® plus epirubicin/cyclophosphamide (EC) is currently being conducted in Germany by the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO). The primary objective of the trial is to compare the cardiac safety of Herceptin® plus standard doses of EC with that of EC alone, with efficacy as a secondary objective.

Women with metastatic breast cancer who have not been previously treated for their metastatic disease and have not previously received anthracycline therapy are eligible for the study. Patients with evidence of existing cardiac disease are ineligible for inclusion in this trial. HER2 status is determined with a 3+ score on immunohistochemistry (IHC) or a positive fluorescence *in situ* hybridization (FISH) result being defined as HER2 positive. The study design involves recruitment of an initial group of 25 HER2-positive patients treated with epirubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 every 3 weeks for 6 cycles. Herceptin® was administered concomitantly according to the standard weekly regimen. Cardiac function has been intensively monitored: electrocardiography, exercise stress and resting echocardiography, and angiography were performed at baseline, and electrocardiography and echocardiography and assessment of dose-limiting cardiotoxicity were performed every 3 weeks.

Strict criteria for defining acceptable levels of cardiotoxicity have been established. If these are met in the initial 25 patients, the epirubicin dose will be increased to 90 mg/m^2 for 4–6 cycles and a further 25 patients will be recruited. Cardiac safety in these patients will determine whether further patients are treated at this or the lower epirubicin dose. A total of 100 HER2-positive patients will be treated with the appropriate dose of epirubicin, cyclophosphamide and Herceptin®, and 100 HER2-negative patients with epirubicin plus cyclophosphamide at the same dose. Cardiac safety will be compared in these two treatment groups.

Recruitment into the initial phase has been completed and no clinical cardiotoxicity has been seen in any of the 25 patients enrolled. Therefore, recruitment into the second phase of the trial, in which the epirubicin dose is increased, has commenced.

In addition to epirubicin, there are other anthracycline formulations that have been developed with the aim of reducing cardiotoxicity. Two liposomal doxorubicin formulations, pegylated liposomal doxorubicin (Caelyx®) and liposome-encapsulated doxorubicin (Myocet®), will be examined in combination with Herceptin® in a number of phase II trials.

Herceptin® in combination with weekly paclitaxel

Paclitaxel administered 3-weekly is a well-studied and effective regimen for the treatment of metastatic breast cancer, producing response rates usually in the range of 30–40%,[19–21] although rates as high as 60% have been reported.[22,23] The variable response to 3-weekly paclitaxel would appear to depend on a host of factors, e.g. dose intensity, duration of infusion, limiting toxicity (usually hematologic), disease stage and degree of prior treatment.[24,25] However, the use of dose-intense, dose-dense (weekly) administration of paclitaxel is able to produce response rates as high as 53%, which is at least comparable to that of 3-weekly paclitaxel, without significant hematologic toxicity.[26,27] Response rates as high as 78% have been achieved with more intense weekly doses but this necessitates

Table 1. Combination index (CI) scores for *in vitro* activity of Herceptin® with different chemotherapeutic agents against HER2-positive breast cancer cell line[11,12]

Synergistic (CI < 1)		Additive (CI ~ 1)		Antagonistic (CI > 1)	
Vinorelbine[11]	0.34	Doxorubicin[11,12]	0.82–1.16	Gemcitabine[11]	5.34
Docetaxel/carboplatin[11]	0.34	Paclitaxel[12]	0.91	5-Fluorouracil[12]	2.87
Docetaxel	0.41	Epirubicin[11]	0.99		
Etoposide[12]	0.54	Vinblastine[12]	1.09		
Cisplatin[12]	0.56	Methotrexate[12]	1.15–1.36		
Cyclophosphamide[11]	0.57				
Paclitaxel/carboplatin[11]	0.64				
Thiotepa[12]	0.67				
Liposomal doxorubicin[11]	0.70				

frequent dose reduction because of significant hematologic toxicity and/or requirement for stem-cell support.[28,29]

Herceptin® has already been shown to be effective and well tolerated when used in combination with 3-weekly paclitaxel[9,10,12,30] and this is currently the preferred cytotoxic chemotherapy partner for Herceptin® in clinical practice. The rationale for trials combining Herceptin® and paclitaxel according to a weekly schedule includes the known efficacy and safety of weekly paclitaxel, and the potential convenience of administering both agents concurrently.

One of the larger trials of Herceptin® combination therapy for which results have been reported to date investigated the efficacy of Herceptin® in combination with weekly paclitaxel.[31] This phase II trial recruited 95 women with metastatic breast cancer, predominantly with multiple metastatic sites and visceral disease (80%). HER2 status was determined using various IHC tests (HercepTest, PAb1, TAB250 and CB11) and a FISH test. All patients, regardless of HER2 status, were treated with Herceptin® plus paclitaxel (90 mg/m^2 i.v. weekly). The majority of patients (65%) had received previous anthracycline therapy. The overall response rate in all patients was 56.8%. The overall response rates in patients who were HER2 positive as determined using the TAB250, CB11 and HercepTest® IHC assays were 81, 76 and 69%, respectively. The overall response rates were similar when HER2 status was determined using FISH instead of IHC: 75% in HER2-positive patients. Response rates were significantly higher in HER2-positive than HER2-negative patients using each test ($p \leq 0.032$).

The safety profile of the regimen was similar to that of weekly paclitaxel monotherapy, indicating that Herceptin® does not exacerbate the toxicity of paclitaxel.[31] Hematologic and non-hematologic toxicities were manageable, with the main event being grade 3 or 4 neuropathy in 28% of patients, which was related to paclitaxel therapy and managed by paclitaxel dose reduction. Infusion-related reactions were infrequent. Episodes of grade 3 or 4 neutropenia were seen in 6% of patients; febrile neutropenia occurred in a further three patients.

Cardiac function was intensively monitored using serial ventriculography throughout the trial in view of the extensive pretreatment of the patients with anthracyclines. Cardiac function as monitored using left ventricular ejection fraction (LVEF) was generally preserved for at least 1 year of combination treatment, although seven patients experienced a decrease in ejection fraction of more than 20% from baseline and serious cardiac events occurred in three patients (decrease in LVEF to 10%, acute myocardial infarction after 8 months of therapy and anterior wall myocardial infarction).[31]

These results have provided the rationale for further studies of this combination. Such studies are currently being performed, e.g. CALGB 9840 and NCCTG 9831, or are planned, e.g. a phase II trial of weekly paclitaxel alone or in combination with Herceptin®, in the metastatic, adjuvant and neo-adjuvant settings. It should also be noted that an alternative 3-weekly Herceptin® dose regimen is being examined in combination with 3-weekly paclitaxel, with preliminary data indicating good tolerability.[32]

Herceptin® in combination with docetaxel

Based on preclinical data (Table 1),[12] docetaxel may be expected to have better synergy with Herceptin® than paclitaxel. Clinical proof of this would be interesting in Europe, where docetaxel is used more widely than paclitaxel for the treatment of metastatic breast cancer. Docetaxel monotherapy produces favorable response rates when administered according to a dose-dense weekly schedule in patients with metastatic breast cancer.[33,34] Preliminary reports of phase II US trials that have examined the combination of Herceptin® administered according to the standard schedule of 4 mg/kg followed by 2 mg/kg i.v. until disease progression with docetaxel are available and indicate that this regimen is well tolerated and active (Table 2).

Kuzur *et al.*[35] are investigating Herceptin® plus docetaxel 75 mg/m^2 i.v. every 3 weeks for 6 cycles in a multicenter trial. Data for 21 patients with metastatic

Table 2. Phase II trials of Herceptin® in combination with docetaxel

Trial	Design[a]	Response rate (%)
Kuzur *et al.*[35]	Herceptin® plus 3-weekly docetaxel 75 mg/m^2	44
Nicholson *et al.*[36]	Herceptin® plus weekly docetaxel 35 mg/m^2	54
Malik *et al.*[37]	Herceptin® plus weekly docetaxel 33 mg/m^2	83

[a]Herceptin® is administered according to the standard regimen (4 mg/kg i.v. followed by 2 mg/kg i.v. weekly until disease progression) in all of these trials.

breast cancer, all of whom were HER2-positive as determined by IHC (14 patients 3+ and seven patients 2+), have been reported. One complete and six partial responses have been observed in the 16 evaluable patients. Six of these seven major responses occurred in 3+ patients. Median time to disease progression exceeded 6 months. There was no evidence of cardiotoxicity and the adverse effects were typical of those expected for docetaxel alone.

Nicholson *et al.*[36] are examining Herceptin® plus docetaxel 35 mg/m^2 i.v. weekly for 6 weeks followed by 2 weeks off-drug in repeated 8-week cycles as first- or second-line therapy in patients with HER2-positive metastatic breast cancer. Data have been reported for 14 patients (10 3+ and four 2+ by IHC), with one complete and six partial responses in 13 patients assessable for response. There was no symptomatic cardiotoxicity, although a single patient developed a transient asymptomatic decline in left ventricular ejection fraction. This trial will eventually accrue 34 patients.

Another ongoing trial is examining Herceptin® in combination with docetaxel 33 mg/m^2 i.v. weekly without any drug holiday in 25 patients with HER2-positive (IHC 2+ or 3+) metastatic breast cancer. Preliminary results have revealed partial responses in five of six assessable patients receiving the Herceptin® plus docetaxel combination.[37]

These data are promising and further results are awaited with interest. However, any data from these trials will require confirmation in larger randomized trials. An ongoing randomized, multicenter European phase III trial that will recruit 156 patients will provide such information on the efficacy and tolerability of this combination. This trial is comparing docetaxel with and without Herceptin® as first-line therapy for HER2-positive (defined as IHC 3+ or IHC 2+ and FISH-positive) metastatic breast cancer. Herceptin® is administered according to the standard dose regimen and docetaxel is administered at a dose of 100 mg/m^2 every 3 weeks for 6 cycles, with an option to continue after this. The primary objective of this trial is to assess overall response rate, with safety, time to progression, time to treatment failure, duration of response and survival as secondary objectives.

In Germany, a randomized phase II study of Herceptin® in combination with either of two regimens of docetaxel as first-line therapy for metastatic breast cancer is being conducted. A total of 100 patients who are HER2 positive (3+ by IHC using the HercepTest® or 2+ and FISH positive) and have previously received anthracycline-containing adjuvant therapy will be enrolled. The docetaxel regimens used are 100 mg/m^2 i.v. every 3 weeks for 6–8 cycles or 35 mg/m^2 i.v. weekly for 6 weeks followed by 2 weeks off-drug in repeated 8-week courses. The aim is to determine which of these regimens is best when used in combination with Herceptin® based on antitumor activity (response rate and duration, time to progression, and survival) and safety.

A number of other, predominantly European trials are also planned or ongoing and will examine various docetaxel-containing regimens. These include: a phase II trial of docetaxel, Herceptin® and capecitabine in metastatic breast cancer due to start in February 2002; an ongoing phase II trial of docetaxel, Herceptin® and epirubicin in metastatic breast cancer; and planned phase II trials of docetaxel plus Herceptin® as neo-adjuvant therapy for breast cancer.

Herceptin® in combination with vinorelbine

The combination of Herceptin® with vinorelbine is attractive based on preclinical data, which indicate that these agents are synergistic (Table 1). In addition, the clinical profiles of these agents indicate that the combination is likely to be well tolerated: vinorelbine does not induce cardiotoxicity, nausea/vomiting or alopecia.[38] In addition, both agents can be conveniently co-administered on a weekly schedule. A phase II trial in 40 women with metastatic breast cancer has provided the first evidence that this rationale translates into clinical benefit.[39]

Patients with HER2-positive (IHC 2+ or 3+) metastatic breast cancer were eligible to receive second- or third-line Herceptin® (4 mg/kg initial dose followed by 2 mg/kg weekly i.v.) plus vinorelbine (25 mg/m^2 weekly i.v.). The study was later extended to allow first-line therapy. HER2 status was 3+ in 30 patients (75%) and 2+ in 10 (25%). Cardiac function was monitored regularly and left ventricular ejection fraction was determined every 8 weeks.

The overall response rate was 75% (Table 3), but higher, at 80%, in patients who were 3+ by IHC. These rates compare favorably with the response rates of 40–50% that are usually seen with vinorelbine alone in similar patients.[40,41] The response rate was particularly high (84%) when the combination was used at first-line therapy.

Table 3. Response rates in patients receiving Herceptin® plus vinorelbine for metastatic breast cancer (data from Burstein *et al.*[39])

Response	No. of patients	Response rate (%)
Overall response		
CR	3	8
PR	27	68
CR + PR	30	75
SD >6 months	2	5
PD	8	20
Response according to HER2 status		
3+	30	80
2+ or positive	10	60
Response according to prior regimens for metastatic disease		
0	19	84
1	14	64
2	7	71

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

The combination was well tolerated and no unexpected adverse reactions occurred. As has been observed with other Herceptin® combinations, the toxicity profile was typical of that expected for vinorelbine monotherapy.[38] The major adverse effect was neutropenia, which was manageable with dose adjustment. Non-hematologic side effects were mild to moderate in severity. Importantly, cardiac function was generally maintained for the duration of patient follow-up, although four patients were removed from the study according to protocol (one with NCI grade 1 and three with grade 2 cardiotoxicity).

These data support the synergy between Herceptin® and vinorelbine and have provided the basis for the design of more extensive phase II and III trials of this regimen in both Europe and North America. A confirmatory phase II trial involving 22 centers will be conducted in the US as a prelude to planned phase III trials. A European phase II trial involving 60 patients will also examine this combination and two other US phase III trials have also been designed. The first will determine whether vinorelbine or a taxane is most active in combination with Herceptin®. The other will investigate the timing of the addition of chemotherapy to Herceptin® by randomizing women to receive either Herceptin® monotherapy first line followed by Herceptin® plus vinorelbine at disease progression or Herceptin® plus vinorelbine as first-line therapy.

Discussion

The standard Herceptin® regimen (4 mg/kg initial dose followed by 2 mg/kg weekly until disease progression) has been shown to produce significant clinical benefit in combination with paclitaxel or anthracycline/cyclophosphamide in HER2-positive patients with metastatic breast cancer in a large clinical trial,[8,9] with an improvement in survival of up to 45% being of particular note.[10] Weekly Herceptin® plus 3-weekly paclitaxel has become the standard combination regimen because of potential cardiotoxicity when Herceptin® is used concurrently with doxorubicin. However, the combination of Herceptin® with AC produced the greatest clinical benefit in this trial. Therefore, the cardiac safety profile of combinations of Herceptin® with anthracyclines other than doxorubicin, which are known to be less cardiotoxic, is currently being investigated. The anthracyclines being studied include epirubicin and liposomal forms of doxorubicin, and preliminary results with the combination of Herceptin® with EC are encouraging.

The use of dose-intense, dose-dense weekly paclitaxel monotherapy has produced response rates similar to those observed with 3-weekly paclitaxel regimens but with less hematologic toxicity. Combining weekly Herceptin® with weekly dose-dense paclitaxel has produced a response rate of 81% in HER2-positive patients.[31] Again, the regimen was well tolerated: toxicity reflected that of weekly paclitaxel monotherapy and cardiac function was maintained for at least 1 year. Thus, co-administration of weekly Herceptin® and paclitaxel is a convenient, effective and well-tolerated regimen that warrants further investigation in large clinical trials.

The trials discussed above indicate that there is potential to improve either the safety or efficacy, or both, of Herceptin® used in combination with agents with which it is known to have good clinical efficacy. However, a number of other agents are currently used in the treatment of breast cancer and it would be interesting to study the effects of combining Herceptin® with these. Current clinical trials are assessing a number of different combinations, but the most advanced are examining Herceptin® plus docetaxel or vinorelbine. These trials are attempting to determine whether the observed *in vitro* synergy between these agents and Herceptin® translates into clinical benefit. Preliminary results in HER2-positive patients have shown high response rates, e.g. 80% for the combination of Herceptin® with vinorelbine weekly in IHC 3+ patients and up to 83% for Herceptin® plus docetaxel. Moreover, Herceptin® did not exacerbate the toxicity of these agents and cardiotoxicity did not appear to be a clinically relevant problem. Further phase II/III trials of Herceptin® in combination with docetaxel or vinorelbine in patients with HER2-positive metastatic breast cancer will provide more conclusive data on the clinical efficacy of these combinations.

As well as these studies of combinations for which at least some clinical data are available, a series of planned trials will examine the combination of Herceptin® with other cytotoxic agents. These will include platinum analogs, hormonal therapy, the 5-fluorouracil derivative capecitabine and other agents. Thus, the current

Herceptin® clinical trial program will provide extensive data on the potential to combine Herceptin® with a wide variety of cytotoxic agents in patients with HER2-positive metastatic breast cancer. Based on data obtained to date, it appears likely that the tolerability of Herceptin® combinations will be similar to that of monotherapy using the cytotoxic agent, while efficacy is improved. Thus, the options available for the use of Herceptin® in the management of patients with HER2-positive metastatic breast cancer are likely to increase.

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