Symposium article

Ongoing trials with trastuzumab in metastatic breast cancer

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Summary
Following the pivotal clinical trials of trastuzumab (Herceptin), further phase II and III studies have been initiated. Preliminary results from a phase II, dose-response study of single-agent trastuzumab in 113 HER2-positive metastatic breast cancer patients without prior chemotherapy for stage IV disease have shown that the overall response rate was 23% (six complete responses and 20 partial responses), with similar results using both standard- and high-dose regimens of trastuzumab. Another phase II study of trastuzumab plus paclitaxel, both given weekly, in 63 HER2-positive and -negative patients with metastatic breast cancer produced an overall response rate of 62% in HER2-positive and 44% in HER2-negative patients. A further phase II study is underway to investigate the combination of trastuzumab plus docetaxel in 30 HER2-positive patients with metastatic breast cancer. Finally, a number of European studies are at an advanced stage of planning or are about to start patient recruitment. These include docetaxel ± trastuzumab, aromatase inhibitor ± trastuzumab, CMF (cyclophosphamide, methotrexate, 5-fluorouracil) ± trastuzumab, vinorelbine + trastuzumab, all in HER2-positive patients, and epirubicin–cyclophosphamide (EC) + trastuzumab in HER2-positive patients vs. EC alone in HER2-negative patients. The results from these trials should be available over the next one to two years.

Key words: docetaxel, epirubicin, Herceptin, metastatic breast cancer, paclitaxel, trastuzumab

Introduction
Data on the response to single-agent trastuzumab (Herceptin) in heavily pretreated, HER2-positive metastatic breast cancer patients have been published previously [1]. In this trial, single-agent trastuzumab resulted in an overall response rate of 15%, although the question remains of what response rate would be expected following trastuzumab administration in patients who were not heavily pretreated. This setting would also be ideal for looking at any dose-response relationship that might exist. When looking at the response to trastuzumab plus chemotherapy, data from the pivotal, first-line study indicate that there is a distinct clinical benefit from adding trastuzumab to chemotherapy. Compared with chemotherapy alone, the addition of trastuzumab increased the response rate from 32% to 50% and time to progression from 4.6 to 7.4 months. More importantly, addition of trastuzumab to standard chemotherapy resulted in an increase in overall survival from 20.3 to 25.4 months [2, 3]. This improvement in survival of about 25% is striking in the metastatic breast cancer setting.

Many studies have examined the use of hormonal therapy in breast cancer patients. The results of those where tumor HER2 status was determined suggest a reduction in response in HER2-positive patients compared with those who are HER2 negative. Similarly, results from other studies taking HER2 status into account indicate that widely used CMF (cyclophosphamide, methotrexate, 5-fluorouracil (5-FU)) regimens may be less effective in HER2-positive tumors. It is reasonable, therefore, to ask whether the addition of trastuzumab in these settings may increase response rates and duration of response. This paper reviews some of the key trials in progress to determine the role of trastuzumab either as a single agent or in combination with a range of chemotherapy agents in patients with HER2-positive metastatic breast cancer.

Trastuzumab as a single agent given first line
The demonstration of efficacy, both as a single agent when given second line and in combination with chemotherapy first line, provides a strong rationale for studying trastuzumab as a single agent as first-line treatment. A randomized, phase II study performed in the USA enrolled 113 women who had not received chemotherapy for their metastatic disease. Patients were randomized to two trastuzumab dose groups: 2 mg/kg or 4 mg/kg i.v. weekly after an initial loading dose of 4 or 8 mg/kg, respectively. One hundred twelve cases were evaluable and the mean age was fifty-four years. More than 50% of the patients were estrogen-receptor (ER) negative, 76% had a high degree of HER2 overexpression (3+), 27% had a disease-free interval of less than 12 months, and 66% had visceral disease, all indicators of a poor prognosis. Approximately two-thirds of the patients had received...
Each patient was allowed to have received a maximum of three prior chemotherapy regimens. Treatment comprised weekly dose-dense paclitaxel (90 mg/m² per week given over one hour until progression) and trastuzumab (initial dose of 4 mg/kg followed by the standard dose of 2 mg/kg). Both agents were continued until disease progression.

A total of 63 patients, with a median age of 50 years, entered the study. The majority of patients (80%) had visceral disease and nearly all had a good performance status. Of these, 76% had received prior adjuvant chemotherapy and 28% had received chemotherapy for their metastatic disease. Prior anthracyclines were used in 73%, and 21% were considered to be refractory to this agent. Study patients were permitted to have prior taxane treatment provided this had been given more than one year prior to study entry; 13% of the patients had received a prior taxane treatment. Only a very small group (3%) had received high-dose chemotherapy. The median number of infusions received by the patients was 21 (range 1–44). It was possible in this study to deliver close to the scheduled dose intensity of paclitaxel with a median delivered dose of 82 mg/m²/week. Furthermore, the number of missed weeks of paclitaxel infusions was low (4%) and these delays were due to paclitaxel-related toxicity.

Adverse events reported in the trial were similar to those expected from dose-dense weekly paclitaxel. Grade 2 or 3 neuropathy occurred in 34% and 17% of patients, respectively (unpublished data; reported at European Conference on Clinical Oncology, Vienna, 12 September 1999). Neutropenia (grade 3–4) was an infrequent event with only two episodes of febrile neutropenic sepsis. Diarrhea was reported in 7% of patients and cardiac events were rare. Serial ventriculography showed no significant decline in left ventricular ejection fraction at weeks 8, 16, 28 and 40. One patient who had received 615 mg/m² prior doxorubicin developed transient congestive heart failure [unpublished data; reported at European Conference on Clinical Oncology, Vienna, 12 September 1999]. These data indicate that, over the 40 weeks of the study, there was no global trend to deterioration of patients' cardiac function using the combination of trastuzumab and paclitaxel. The overall response rate for all patients in the study (HER2-positive and -negative combined) was 52%. Examining the HER2-positive and -negative subgroups within the trial showed response rates of 62% and 44%, respectively.

Overall, the results from this trial indicate that the tolerability profile of trastuzumab plus paclitaxel was similar to that of weekly paclitaxel when given alone. Of particular importance is the observation that cardiac function was preserved over the study period. Efficacy data indicate that the combination of trastuzumab and paclitaxel is active in HER2-positive patients, although it is not possible to make this same conclusion in HER2-negative patients because of the lack of a taxane only group in this study.

These provocative data have led to the modification of the Cancer and Leukemia Group B (CALGB) study.

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**Trastuzumab plus taxanes**

Following the demonstration that trastuzumab is active both as a single agent and in combination with chemotherapy, further exploration of the taxane combination, either with novel schedules or using taxanes other than paclitaxel, has been undertaken. Trials have either been performed or are underway to determine the most clinically effective and well-tolerated combinations for consideration in both the metastatic and adjuvant breast cancer settings.

**Trastuzumab plus weekly paclitaxel**

This study was conducted to evaluate the safety of trastuzumab plus weekly paclitaxel, with a secondary objective being the evaluation of the therapeutic efficacy of the combination [5]. Patients had histologically confirmed metastatic breast cancer, with HER2 status being confirmed by immunohistochemical assessment. Each patient was allowed to have received a maximum...
9840 comparing a dose-dense vs. standard paclitaxel regimen in combination with trastuzumab (Figure 1). In this trial, HER2-positive patients will be randomized to receive either weekly dose-dense paclitaxel plus trastuzumab (4 mg/kg initial dose followed by 2 mg/kg weekly) or three-weekly paclitaxel plus weekly trastuzumab until disease progression. HER2-negative patients in this study will be randomized to receive chemotherapy followed by a second randomization for chemotherapy ± trastuzumab. It is hoped that this study will reveal whether trastuzumab has clinical benefit in both HER2-positive and -negative patients.

**Trastuzumab plus docetaxel**

A phase II, multicenter study of trastuzumab plus docetaxel is underway in the USA [6]. Taxane-naive, HER2-positive metastatic breast cancer patients receive the combination as first- or second-line treatment for their metastatic disease. The dose of docetaxel is 75 mg/m² every three weeks for six cycles with trastuzumab at the usual dose of 4 mg/kg loading followed by 2 mg/kg weekly continued until disease progression. At the time of reporting, 17 patients had received one and 10 infusions of docetaxel. These preliminary data show that there were two partial responses from 14 evaluable patients, and no major toxicity issues. Further results from this trial are awaited.

An additional study is underway to compare trastuzumab plus docetaxel vs. docetaxel alone as first-line treatment for metastatic breast cancer. This multinational, randomized, phase II study includes HER2-positive patients who have received prior anthracyclines in the adjuvant setting. A total of 156 patients across 50 centers is planned to be enrolled. The objective is to establish the response rate and the safety of this combination when given first line. Patients are randomized to receive docetaxel 100 mg/m² every three weeks for six to nine cycles ± trastuzumab 4 mg/kg initial dose followed by 2 mg/kg weekly continued until disease progression.

**Trastuzumab plus anthracyclines**

In addition to examining the combination of trastuzumab and the taxanes paclitaxel and docetaxel, further exploration of the anthracycline interaction has been undertaken. Trials have either been performed or are underway to develop appropriate monitoring so that trastuzumab and anthracyclines can be combined in both the metastatic and adjuvant breast cancer settings.

A phase I–II, comparative, open-label study is in progress to determine the cardiac safety of trastuzumab in combination with epirubicin plus cyclophosphamide (EC) when used as first-line treatment for metastatic breast cancer. Anthracycline-naive, HER2-positive patients receive trastuzumab plus EC with HER2-negative patients receiving EC alone. The HER2-negative patients serve as a comparator group for the baseline incidence of cardiotoxicity. Epirubicin is administered at two dose levels in this study. An initial 25 patients received 60 mg/m² with subsequent patients, up to a total of 225 across 35 centers, receiving 90 mg/m², provided toxicity at 60 mg/m² is acceptable. All patients undergo extensive cardiac monitoring, particularly the first 25 who were studied in Germany, involving the measurement of every cardiac function and aspect of cardiac performance.

**Trastuzumab plus other anti-cancer agents**

Trastuzumab is also being investigated in combination with a range of other widely used cytotoxic and endocrine therapies, including CMF, vinorelbine, capecitabine and aromatase inhibitors.

**CMF ± trastuzumab**

The European Organization for Research and Treatment of Cancer (EORTC) is currently evaluating a combination of CMF with and without trastuzumab. The aim of this trial is to establish the safety and efficacy of trastuzumab plus CMF in patients with HER2-positive metastatic breast cancer. Patients are permitted to have received adjuvant chemotherapy, and up to one regimen of chemotherapy, including anthracyclines or taxanes, for metastatic disease. CMF is administered for eight cycles, preferably using an oral schedule although an i.v. schedule is acceptable if the oral schedule is not tolerated, ± trastuzumab at the usual 4 mg/kg initial dose followed by 2 mg/kg weekly until disease progression (Table 2).

The endpoints of this study are objective response rate, progression-free survival, overall survival and toxicity, particularly the incidence of clinical cardiac tox-

### Table 2. Design of CMF ± trastuzumab trial.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>CMF (cyclophosphamide, methotrexate, 5-fluorouracil)</td>
<td>For eight cycles</td>
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<tr>
<td>± Trastuzumab</td>
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<tr>
<td>Cyclophosphamide</td>
<td>Until disease progression</td>
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<tr>
<td>Methotrexate</td>
<td>100 mg/m² days 1–14 p.o. or</td>
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<td>5-FU</td>
<td>600 mg i.v. days 1 and 8</td>
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<tr>
<td>± Trastuzumab</td>
<td>40 mg/m² i.v. days 1 and 8</td>
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<tr>
<td>± Trastuzumab</td>
<td>600 mg/m² i.v. days 1 and 8</td>
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icinity. This study has clear importance because of the widespread global use of CMF as a treatment for metastatic breast cancer. In addition, the results would have clear significance for future adjuvant studies.

Trastuzumab ± aromatase inhibitor

In terms of combining trastuzumab with endocrine therapies, a further randomized, open-label, phase II–III study is underway to examine an aromatase inhibitor plus trastuzumab vs. an aromatase inhibitor alone. A total of 200 post-menopausal women who are ER and/or progesterone-receptor positive and have HER2-positive metastatic breast cancer will receive the combination as first-line therapy. Prior adjuvant chemotherapy is allowed. Endpoints of the study are response rate, response duration, time to disease progression, survival and safety. The rationale for using an aromatase inhibitor rather than tamoxifen in a trial of this type relates to the difficulty of enrolling tamoxifen-naïve patients.

Trastuzumab plus vinorelbine

Vinorelbine is often used as a single agent for second- or third-line treatment in metastatic breast cancer. It has been proposed to perform a phase II study of a weekly regimen of vinorelbine 30 mg/m² plus trastuzumab 2 mg/kg continued weekly until disease progression. The combination will be given as first-line treatment in 60 HER2-positive metastatic breast cancer patients with the objectives of establishing safety, response rate, time to progression and survival.

Trastuzumab plus capecitabine

A further concept under development is a study of trastuzumab plus the enzymatically activated, orally-administered fluoropyrimidine capecitabine. This combination provides a potentially active and well-tolerated regimen, which may be particularly useful in patients who are unsuitable for hormonal therapy or intensive chemotherapy. Another possibility is to use this regimen following treatment failure, perhaps considering patients who have failed trastuzumab plus a taxane.

Discussion and conclusions

Previously published data indicate that single-agent trastuzumab results in an overall response rate of 15% in heavily pretreated, HER2-positive metastatic breast cancer patients [1]. This response rate is impressive in this setting, however, the observation cannot be used to determine the role of single-agent trastuzumab in first-line therapy. In response to this question, preliminary data from a phase II, dose-response study of single-agent trastuzumab has demonstrated an overall response rate of 23% (6 complete responses and 20 partial responses) [4]. Follow-up results from this trial are expected to confirm the clinical benefit of using trastuzumab as a single agent in first-line therapy.

When looking at the response to trastuzumab plus chemotherapy, data from the first-line pivotal study indicate that there is a distinct clinical benefit from adding trastuzumab to chemotherapy. In particular, addition of trastuzumab to standard chemotherapy resulted in an increase in overall survival from 20.3 to 25.4 months [2, 3]. This kind of survival benefit is unusual in the metastatic breast cancer setting, particularly when one considers that two-thirds of the chemotherapy patients received subsequent trastuzumab therapy at failure. To further determine the clinical benefits of adding trastuzumab to various types of chemotherapy regimens, a range of different studies have been performed or are currently underway. A phase II study of trastuzumab plus paclitaxel, both given weekly, in 63 HER2-positive and -negative patients with metastatic breast cancer produced an overall response rate of 62% in HER2-positive and 44% in HER2-negative patients [5]. These data indicate that the regimen of trastuzumab plus weekly paclitaxel has significant activity in HER2-positive patients. A further phase II study is underway to investigate the combination of trastuzumab plus docetaxel in 30 HER2-positive patients with metastatic breast cancer [6]. Preliminary data indicate that the combination of trastuzumab plus docetaxel is well tolerated. Treatment with trastuzumab in each of these trials was generally well tolerated; adverse events were mainly of a mild-to-moderate nature and no patient had to discontinue therapy because of adverse events.

Ongoing studies of trastuzumab in breast cancer seek to capitalize on the positive outcomes of the pivotal studies of single-agent trastuzumab and trastuzumab’s use in combination with chemotherapy. These studies can be seen as important generators of clinical hypotheses that require further testing to maximize clinical benefits and minimize toxicity.

Note

Dr Bell has reported that he serves on a Roche advisory board for Herceptin.

References


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