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First-line, single-agent Herceptin® (trastuzumab) in metastatic breast cancer: a preliminary report

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Abstract

Following confirmation of the appropriate dosage, safety and potential efficacy of Herceptin® (trastuzumab) in small-scale phase I and II trials involving patients with refractory disease, a large trial was conducted in 222 patients with breast cancer who had relapsed after one or two chemotherapy regimens for their metastatic disease. The results showed a positive and durable overall response rate (15% according to a response evaluation committee (REC) assessment) using trastuzumab monotherapy (initial dose 4 mg/kg intravenously (i.v.) followed by 2 mg/kg i.v. weekly). In another recently completed phase II trial, 113 patients were randomised to two dose levels (initial dose of 4 mg/kg i.v. dose followed by 2 mg/kg i.v. weekly, or initial dose of 8 mg/kg followed by 4 mg/kg i.v. weekly) of single-agent trastuzumab as first-line therapy for metastatic disease. The preliminary overall response rate was 23% based on investigator assessment, and tolerability was excellent as in previous trials; efficacy was similar in both dose groups, but the side-effects tended to be more frequent in the higher dose group. The preferred dosage is therefore the same as that currently recommended, i.e. an initial dose of 4 mg/kg i.v. followed by 2 mg/kg weekly i.v. until disease progression.

Keywords: Herceptin® (trastuzumab); Metastatic breast cancer; First-line; Clinical trial; Efficacy

1. Introduction

The human epidermal growth factor receptor-2 (HER2), which is overexpressed on the surface of 20–30% of breast cancer cells, is an accessible target for novel and specific anticancer treatment, e.g. monoclonal antibody (MAb) therapy. Highly specific murine MAbs have been generated to the extracellular domain of the HER2 receptor, of which the most potent is murine MAb 4D5 [1]. The 4D5 murine MAb was humanised using genetic engineering techniques by inserting the epitope recognition regions of 4D5 into a consensus human IgG framework to produce Herceptin® (trastuzumab) [2]. This humanisation circumvents the immunological response, which would otherwise generate neutralising antibodies to murine MAbs during long-term administration in humans. Preclinical animal studies using HER2-positive human breast tumour xenograft models have revealed that trastuzumab exerts potent antitumour activity when used as a single agent and exhibits additive or synergistic antitumour effects when administered in combination with a wide range of cytotoxic chemotherapeutic agents [3–5]. The antitumour

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effects of trastuzumab probably occur via several hypothetical mechanisms [1,3,6–9]. For example, the binding of trastuzumab to overexpressed HER2 receptors on the surface of cancer cells appears to induce antibody-dependent cellular cytotoxicity. Furthermore, HER2 receptor endocytosis and internalisation into cells appears to lead to decreased receptor numbers and signalling, and results in the decreased proliferation.

The present report summarises the clinical development programme of trials in which trastuzumab was administered as a single agent to women with HER2-positive metastatic breast cancer. Particular attention is paid to the preliminary results of the recent trial where trastuzumab was administered as first-line therapy, i.e. trastuzumab was given as monotherapy to patients who had not previously received cytotoxic chemotherapy for their metastatic disease.

2. Early studies of single-agent trastuzumab

Two open-label, phase I clinical trials (H0407g and H0452g) and an open-label phase II trial (H0551g) were performed primarily to evaluate the safety of single and repeated weekly doses of single-agent trastuzumab in patients with advanced refractory HER2-positive metastatic breast cancer [10,11]. These studies showed trastuzumab to be well tolerated over the full dose range studied: grade 3 and 4 adverse events were few and mainly included those that would be expected in patients with advanced refractory disease. These trials allowed progression to a pivotal phase II, single-agent trial (H0649g).

Trastuzumab dose selection for the pivotal trial was based on data from the earlier clinical trials and preclinical studies [2,10–12]. A weekly trastuzumab dose of 100 mg was shown to produce the therapeutic serum drug concentrations defined in preclinical studies [2] in the majority of patients enrolled in the early clinical trials [11,12]. An initial dose of 250 mg allowed these levels to be achieved as rapidly as possible, and the regimen was shown to be well tolerated and effective [11,12]. However, prior to the pivotal trial, the concept that dose adjustment by body weight might more accurately provide therapeutic trastuzumab doses was investigated. This led to the selection of a regimen comprising an initial trastuzumab dose of 4 mg/kg i.v. followed by 2 mg/kg i.v. weekly.

The H0649g trial was designed as a large, multinational, multicentre study of single-agent trastuzumab in 222 women with HER2-positive metastatic breast cancer [13]. HER2 positivity was defined as positive when weak (2+) or complete (3+) membrane staining of >10% of tumour cells on immunohistochemistry using antibodies CB11 or 4D5 was observed (clinical trials assay). The overall response rate, as determined by an independent Response Evaluation Committee (REC) in an intent-to-treat analysis, was 15% (95% confidence interval (CI) 11–21%) (8 complete responders (CR) plus 26 partial responders (PR)). In addition, 6% ($n=12$) of the patients had minor responses (MR) and 29% ($n=62$) had stable disease (SD). Overall 22% ($n=49$) of patients were free of disease progression at 6 months. Median response duration for objective responders was 9.1 months (range 1.6–26+ months), median survival was 13 months (range 0.5–30+ months), and median time to disease progression (TTP) was 3.1 months (range 0–28+ months).

An important finding from this trial was confirmation of the tolerability of trastuzumab, which is distinct from the nature and severity of adverse events typically associated with standard cytotoxic chemotherapy agents. This major study supported the use of trastuzumab for women with HER2-positive metastatic breast cancer. The benefit from trastuzumab in this clinical setting combined with the durable objective responses and favourable toxicity profile assisted in the rapid approval of the drug in the USA by the Food and Drug Administration (FDA).

3. First-line, single-agent trastuzumab

Following the previously described pivotal study by Cobleigh and colleagues [13], which showed that single-agent trastuzumab was effective and well tolerated as second- or third-line therapy in HER2-positive metastatic breast cancer, it was decided to determine the efficacy and safety of first-line, single-agent trastuzumab therapy in HER2-positive metastatic breast cancer [14]. The trial had a randomised, single-blind, multicentre design and enrolled a total of 113 patients with HER2-positive metastatic breast cancer. Patients were recruited at 19 North American centres, with the last patient being enrolled on 13 May 1998. Randomisation was into two dose groups: 4 mg/kg initial dose followed by 2 mg/kg i.v. weekly (2 mg/kg group) or 8 mg/kg initial dose followed by 4 mg/kg i.v. weekly (4 mg/kg group). Treatment with trastuzumab was continued until disease progression.

3.1. Study rationale

The primary objectives of the trial were to assess the overall response rate and safety associated with trastuzumab in this patient population. Tumour response was assessed at weeks 8, 16 and 24, and every 12 weeks thereafter. Antitumour response was evaluated by the investigators; this differed from the study by Cobleigh and colleagues [13] where antitumour response was additionally evaluated by an independent REC. Safety was evaluated on a weekly basis by the

Table 1
Overall response rate of trastuzumab as first-line, single-agent therapy in metastatic breast cancer

	2 mg/kg group ($n=58$)	4 mg/kg group ($n=54$)
Overall response	14 (24%) (95% CI, 13–35%)	12 (22%) (95% CI, 11–33%)
No. of complete responses (CR)	2	4
No. of partial responses (PR)	12	8
No. of stable disease (SD) >6 months	4	5
Clinical benefit (CR + PR + SD ⩾6 months)	18 (31%)	17 (31%)

95% CI, 95% confidence interval.

investigators. Any potential cardiac events were evaluated by an independent Cardiac Review and Evaluation Committee (CREC). Secondary trial endpoints were duration of response, TTP, survival and quality of life.

3.2. Demographics

A total of 113 patients with progressive metastatic breast cancer were treated. None had received previous chemotherapy for metastases. HER2 overexpression was confirmed by immunohistochemical (IHC) testing using the chemical trials assay and defined as 2+ or 3+. All patients had measurable disease, while those with bone-only disease were excluded. Karnofsky Performance Status (KPS) had to be ⩾70%.

Data are currently available for 112 evaluable patients with a median follow-up of 11 months (range 1.2–35 months). There were 58 patients in the 2 mg/kg group and 54 in the 4 mg/kg group. The mean age of the patients was 54 years (range 28–86 years). Over half of the patients (55%; $n=62$) had oestrogen receptor (ER)-negative disease and 3+ HER2 overexpression was observed in 76% ($n=85$). Just over one-quarter of the patients (27%; $n=30$) had a disease-free interval of <12 months. Thirty per cent of the patients ($n=34$) had ⩾3 metastatic sites and 66% ($n=74$) had metastatic involvement of the liver or lung. The majority of patients (76%; $n=85$) had KPS ⩾90%. Previous therapy was as follows: adjuvant chemotherapy (68%; $n=76$), anthracycline use (55%; $n=62$), radiotherapy (48%; $n=54$), hormonal therapy (37%; $n=41$) and high-dose chemotherapy plus stem-cell transplantation (12%; $n=13$). The two dose groups were generally comparable in terms of patient demographics and baseline characteristics.

3.3. Efficacy

The overall response rate was 23% (95% CI, 15–31%) (6 CR plus 20 PR). A total of 9 patients (8%) had SD lasting >6 months (range 6.3–16.2 months). Thus, 31% of the patients from the two groups were assessed as having derived clinical benefit from the treatment (CR plus PR plus SD lasting ⩾6 months).

The overall response rate was similar in the two dose groups (Table 1), indicating no clinically significant effect of dose on the efficacy of trastuzumab. Subset analyses showed the rates of overall response and clinical benefit to be particularly encouraging for patients who demonstrated 3+ HER2 overexpression on IHC testing and those who had previously undergone stem-cell transplantation (Table 2), although small patient numbers means that these results need further confirmation. The rates for overall response (23% versus 22%) and clinical benefit were surprisingly similar for first-line trastuzumab in the present study and the investigator assessment of efficacy (as opposed to the REC) for second- or third-line trastuzumab in metastatic breast cancer [13].

Table 2
Rates of overall response and clinical benefit from first-line, single-agent trastuzumab in subset analysis

Group (no. of patients)	Overall response rate (CR + PR) *n* (%)	Rate of clinical benefit (CR + PR + SD ⩾6 months) *n* (%)
Overall ($n=112$)	26 (23)	35 (31)
Liver metastases ($n=44$)	11 (25)	12 (27)
3+ HER2 ($n=85$)	26 (31)	35 (41)
Prior adjuvant doxorubicin ($n=59$)	15 (25)	19 (32)
Prior stem-cell transplantation ($n=13$)	5 (38)	6 (46)

CR, complete response; PR, partial response; SD, stable disease; HER2, human epidermal growth factor receptor-2.

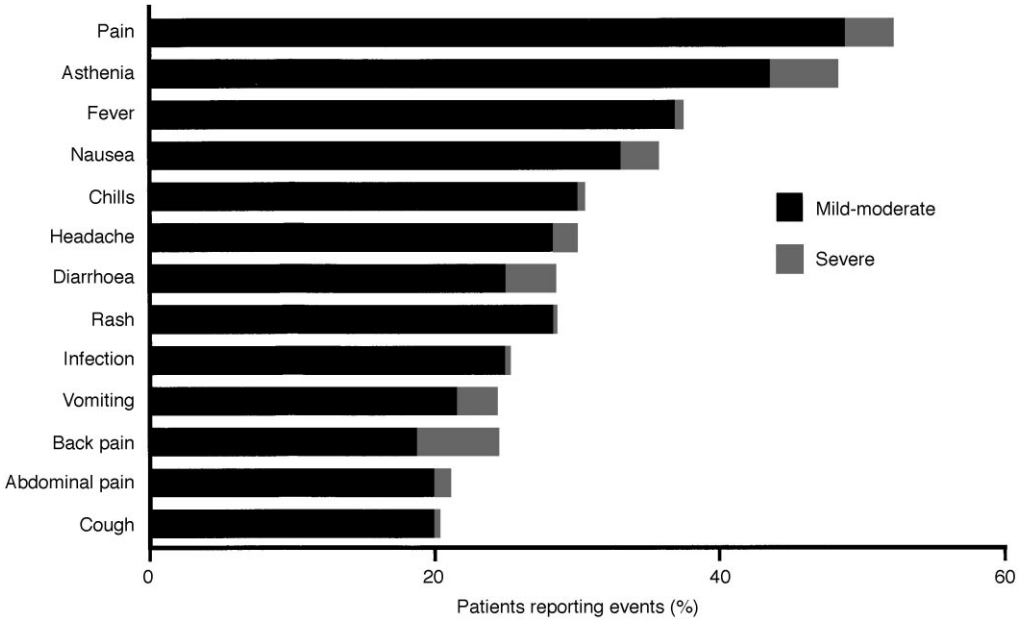

Fig. 1. Adverse events seen in ⩾20% of patients in the trial where trastuzumab was used as single-agent, first-line therapy.

Currently, follow-up is too short to enable conclusions regarding the duration of response and survival duration to be drawn. However, at analysis the median TTP was 3.4 months over the whole group and 8 months in those achieving CR or PR. In patients with SD lasting >6 months, median TTP was 10.8 months. At the time of analysis (median follow-up 11 months), 67% of patients were alive with survival duration ranging from 1.2 to 35.3+ months. At least 1 patient has been in continuing remission on trastuzumab therapy for >3.5 years.

3.4. Adverse events

Trastuzumab was generally well tolerated in this study. Adverse events were mainly of a mild-to-moderate nature, with severe adverse events being reported infrequently. Common events most likely caused by treatment were fever, chills, headache, rash and diarrhoea (Fig. 1); most of the other adverse events were probably disease related. Fever and chills caused by trastuzumab most commonly occurred following administration of the first dose of the drug and did not subsequently recur. Adverse events that are commonly associated with cytotoxic chemotherapy were rare with trastuzumab: alopecia ($n=4$), anaemia ($n=3$), mucositis ($n=1$) and leucopenia ($n=1$). The incidence of adverse events tended to be higher in the 4 mg/kg compared with the 2 mg/kg dose group (Table 3).

Only 1 patient had cardiac dysfunction (cardiac symptoms or asymptomatic decrease (>10%) in ejection fraction) according to the CREC. This patient had pericardial tamponade with malignant pleural effusion and pericardial effusion at study entry. Treatment was discontinued because of secondary disease progression. Three cases of potential cardiac dysfunction are currently awaiting review.

There were 37 deaths: 17 in the 2 mg/kg group and 20 in the 4 mg/kg group. None of the deaths occurred during the study and in all cases the patients had secondary metastatic breast cancer. No patients discontinued treatment due to adverse events.

4. Conclusions

Trials of single-agent trastuzumab therapy in women with HER2-positive metastatic breast cancer have progressed from small-scale preliminary studies in patients with refractory disease to large-scale trials. In all previous large-scale trials, trastuzumab has been used at a weekly dose of 2 mg/kg. However, in the most recent

Table 3
Adverse events by dose group

Adverse event	Incidence (no. of patients)			
	2 mg/kg ($n=58$)		4 mg/kg ($n=54$)	
	All n (%)	Severe n (%)	All n (%)	Severe n (%)
Asthenia	27 (47)	2 (3)	28 (52)	4 (7)
Chills	13 (22)	0 (0)	21 (39)	1 (2)
Fever	19 (33)	1 (2)	23 (43)	0 (0)
Flu syndrome	7 (12)	0 (0)	6 (11)	0 (0)
Headache	14 (24)	1 (2)	19 (35)	1 (2)
Diarrhoea	19 (33)	1 (2)	13 (24)	3 (6)
Vomiting	12 (21)	1 (2)	16 (30)	2 (4)
Rash	11 (19)	0 (0)	18 (33)	0 (0)

trial, the preliminary results of which are reported here, patients were randomised to trastuzumab at weekly doses of 2 and 4 mg/kg. This proved to have little impact on outcome because the response rates in the 2 and 4 mg/kg dose groups were similar. However, there was a tendency towards a higher rate of side-effects in the higher dose group. These data support the selection of the currently recommended regimen of a 4 mg/kg initial dose followed by 2 mg/kg weekly because it produces a similar efficacy to higher doses while limiting the number of side-effects. Whether adjusting the dose interval will enable higher trastuzumab doses to be used while maintaining its tolerability remains to be determined.

In conclusion, trastuzumab has been shown to be active as a single agent in HER2-positive patients who had received no previous chemotherapy for metastatic breast cancer. Trastuzumab was well tolerated and common chemotherapy-associated adverse events, such as myelosuppression and mucositis, were rare. Confirmed cardiac toxicity has not been encountered in this clinical trial to date (median follow-up 11 months). The preliminary data reported here indicate that trastuzumab monotherapy may be an effective therapeutic option for first-line therapy of metastatic breast cancer, particularly in women who do not want to undergo chemotherapy. However, confirmation of this role awaits the final results of this study and confirmatory studies. Based on the similarity in outcomes between the two dose groups studied, the currently recommended regimen, i.e. an initial dose of 4 mg/kg i.v. followed by 2 mg/kg i.v. weekly, should be used and continued until disease progression.

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