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First-Line Herceptin® Monotherapy in Metastatic Breast Cancer

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Key Words

First-line therapy · FISH · HER2 positive · Herceptin® · IHC 3+ · Metastatic breast cancer · Monotherapy

Abstract

The pivotal phase II and III Herceptin® trials proved the efficacy and safety of second- or third-line single-agent Herceptin and first-line Herceptin in combination with chemotherapy, respectively. In the current trial, 114 patients were randomized to one of two dose groups of first-line Herceptin monotherapy: standard dose of 4 mg/kg initial dose followed by 2 mg/kg intravenous (i.v.) weekly; or high dose of 8 mg/kg initial dose followed by 4 mg/kg i.v. weekly. The regimen was generally well tolerated. A similar incidence of adverse events was demonstrated in the two dose groups with the possible exception of acute infusion-related events such as fever and chills as well as rash and dyspnea, which appear to be more prevalent in the higher dose group. The overall response rate was 26% and response rates were similar between the two dose groups (24% for the standard Herceptin dose group and 28% for the high Herceptin dose group). Subgroup analysis determined a higher response rate in IHC 3+ patients (35%) and FISH-positive patients (41%). When women with stable disease for ≥6 months were included with responders, the clinical benefit rate in IHC 3+ patients was 47%. Median survival was 24.4 months, which is comparable with the survival rate seen in the pivotal phase III combination trial (25 months). Therefore, single-agent Herceptin is an important new option for the first-line treatment of HER2-positive metastatic breast cancer patients.

Introduction

Despite recent advances in therapy for breast cancer, more than 43,000 women in the USA die of metastatic breast cancer each year [Hortobagyi 1998; Landis et al. 1999]. Recently, investigators have evaluated the role of several molecular factors thought to be involved in tumor cell proliferation in order to identify potential targets for novel therapies. The human epidermal growth factor-2 (HER2) is one such factor that has been shown to be

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involved in tumorigenicity [Benz et al. 1992; Di Fiore et al. 1987a, b; Hudziak et al. 1987]. As a consequence, a humanized anti-HER2 monoclonal antibody, Herceptin®, was rationally developed to target HER2-overexpressing breast tumors [Carter et al. 1992].

Preclinical data have demonstrated that Herceptin exerts potent antiproliferative/antitumor activity in ovarian and breast cancer cell lines and in human breast cancer xenograft models [Baselga et al. 1998; Carter et al. 1992; Lewis et al. 1993; Pegram et al. 1992, 1997, 1999]. Based on these data and preclinical pharamacokinetic and favorable toxicology studies, a clinical trial program of Herceptin in small numbers of patients was initiated. Two open-label, phase I dose escalation trials (H0407g and H0452g) of single and weekly-repeated doses of Herceptin monotherapy were conducted in patients with advanced refractory HER2-positive metastatic breast cancer [Shak 1999]. In addition, two phase II trials of Herceptin monotherapy [Baselga et al. 1996] and Herceptin in combination with cisplatin [Pegram et al. 1998] were undertaken. As in the phase I trials, the patient population consisted of heavily pretreated HER2-positive metastatic breast cancer patients. These studies confirmed appropriate dosage, safety and potential efficacy of Herceptin as a single agent and in combination with concomitant chemotherapy in humans. Based on these data, progression to pivotal clinical trials was justified.

Two pivotal trials were conducted in large numbers of HER2-positive metastatic breast cancer patients: a phase II trial of second-/third-line Herceptin monotherapy (H0649g) [Cobleigh et al. 1999]; and a phase III first-line Herceptin combination trial (H0648g) [Mass et al. 2000; Norton et al. 1999; Slamon et al. 1998, 2001]. Details of these trials are described elsewhere [Baselga 2001; Mass et al. 2000; Shak 1999; Slamon et al. 2001]. In brief, Herceptin was administered as a 4-mg/kg initial dose followed by a 2-mg/kg i.v. weekly maintenance dose. In the combination trial, patients were randomized to receive Herceptin plus anthracycline/cyclophosphamide (AC) versus AC alone or, if they had previously received adjuvant anthracyclines, Herceptin plus paclitaxel versus paclitaxel alone.

In both trials Herceptin was well tolerated. Adverse events were generally mild to moderate and mainly associated with the first infusion. Cardiotoxicity was the most significant serious adverse event, particularly in patients receiving concomitant anthracyclines. However, in most cases this serious adverse event was manageable with standard medical treatment.

An independent Response Evaluation Committee (REC) determined tumor responses in the intent-to-treat-population (n = 222) of the pivotal phase II trial. They found an overall response rate of 15%, duration of response of 9.1 months and a median survival of 13 months. The median time to treatment failure (TTF) was 11 months which compared favorably with that for the prior regimen of chemotherapy (5.4 months).

Results for the pivotal combination trial were assessed at median 35 months follow-up. The primary endpoint of the trial, time to disease progression (TTP), was significantly improved in the Herceptin plus chemotherapy group compared with the chemotherapy alone group (7.4 versus 4.6 months). In addition, response rates, median duration of response and TTF were all significantly higher in the Herceptin plus chemotherapy group compared with the chemotherapy alone group. Of particular note, median survival duration was significantly increased from 20 months to 25 months by the addition of Herceptin to chemotherapy.

Following on from the pivotal trials, a phase II trial of Herceptin monotherapy was initiated in HER2-positive breast cancer patients who had not received prior chemotherapy for metastatic disease.

First-line Herceptin Monotherapy Trial

Study Design

In total, 114 women with HER2-positive metastatic breast cancer were enrolled into the multicenter, randomized trial [Vogel et al. 2000]. Enrollment closed May 1998. Patients were randomly assigned to one of two Herceptin dosing schedules, either: standard dose of 4 mg/kg initial dose followed by 2 mg/kg i.v. weekly, or high dose of 8 mg/kg initial dose followed by 4 mg/kg i.v. weekly. Treatment continued until disease progression.

Study Rationale

The primary objectives of the trial were to evaluate overall response rates and safety of first-line Herceptin monotherapy in each dose group. Tumor responses were assessed by the investigators at weeks 8, 16, 24 and every 12 weeks thereafter. Unlike the pivotal phase II monotherapy trial, an independent Response Evaluation Committee (REC) was not additionally employed to assess tumor responses in this study. An independent Cardiac Review Evaluation Committee (CREC) evaluated potential cases of cardiac dysfunction and safety was assessed by the investigators on a weekly basis. Secondary end-

points of the trial were duration of response, TTP, duration of survival and quality of life (QoL).

Patient Demographics/Eligibility

The patients enrolled in this trial were women with progressive breast cancer who did not wish to receive cytotoxic chemotherapy for metastatic disease. Eligible patients had not received prior chemotherapy for stage IV disease. In addition, patients had to have measurable disease; patients with bone-only lesions were excluded. HER2 status was determined by immunohistochemistry (IHC) and only IHC 2+ or 3+ patients were included in the study. The study protocol stipulated that Karnofsky Performance Status (KPS) had to be ≥ 70%, although 75% of patients enrolled in the study had a KPS of >80%.

At a median follow-up of 19 months (range 1.2 to 45.9 months) 3 of 114 patients were inevaluable: 1 patient received only one dose of Herceptin; 1 patient received four doses of Herceptin but did not have a post-baseline evaluation; the third patient did not have evidence of metastatic disease. Of the 111 evaluable patients, 58 were randomized to the standard Herceptin dose group and 53 were randomized to the high Herceptin dose group. Generally, patient demographics were comparable between the two dose groups. The mean age of patients was 54 years (range 28 to 86 years). Approximately half (52%) of the patients were estrogen receptor (ER) negative and approximately three-quarters (76%) were IHC 3+ HER2 overexpressors. Of those patients for whom fluorescence in situ hybridization (FISH) results were available (n = 62), more than half (41 of 62 patients) were FISH positive for HER2 overexpression. Twenty-eight percent of patients had a disease-free interval of ≤ 12 months. Approximately one third (31%) of patients had ≥ 3 metastatic sites and 67% had metastases of the liver and lung; 10% of patients demonstrated superficial metastases only. Patients had received prior adjuvant therapy for breast cancer including: chemotherapy (68%), anthracyclines (51%), and transplants (13%). In addition, 46% had received prior radiotherapy and 37% hormonal therapy.

Efficacy

The overall response rate (ORR) for first-line Herceptin monotherapy (ITT analysis) was 26% (95% CI: 18 to 34%) including 7 complete responses (CR) and 23 partial responses (PR). A further 13 patients had stable disease (SD) lasting >6 months for an overall clinical benefit (CR plus PR plus SD) of 38% (95% CI: 29 to 47%). Response rates were similar in the two dose groups for evaluable patients (table 1). The overall response rate was 24% (95% CI: 13 to 35%) [3 CR and 11 PR] in the standard-dose group compared with 28% (95% CI: 16 to 40% [4 CR and 11 PR] in the high-dose group.

Table 1. Response rate by dose in evaluable patients following first-line single-agent Herceptin

	Number of patients	
	2 mg/kg	4 mg/kg
Treated	58	53
Complete response (CR)	3	4
Partial response (PR)	11	11
CR + PR	14 (24%) (95% CI 13–35%)	15 (28%) (95% CI 16–40%)

Table 2. Response according to HER2 status following first-line single-agent Herceptin

	Number of patients*	
	FISH+	FISH–
Response	17/41 (41%)	1/21 (5%)
Response rates, % (95% CI)		
FISH+	41 (26–56%)	
IHC 3+	35 (24–44%)	
IHC 2+ or 3+	26 (18–34%)	

* FISH results were available for 62 of 114 patients.

Subset analysis demonstrated that, as expected, the response rate was quantitatively higher in patients with superficial metastases only. However, responses were also demonstrated in patients with liver or lung metastases. These response rates were particularly impressive if the definition of response included those patients with SD >6 months. Approximately one-third of patients demonstrated a response regardless of whether prior adjuvant therapy consisted of doxorubicin chemotherapy or stem cell transplantation.

Of particular note, the ORR was higher in the IHC 3+ subgroup (35%) compared with the overall (IHC 2+ and 3+) group (table 2). Interestingly, all responses (CR plus PR) were demonstrated in the IHC 3+ group, although 7% of IHC 2+ patients achieved SD >6 months.

Recent data have demonstrated that IHC and FISH are 82% concordant overall [Mass et al. 2000]. While IHC 3+ and FISH are highly concordant (89%), only 24% of

Table 3. Adverse events by dose group following first-line single-agent Herceptin

	Incidence, % patients			
	2 mg/kg (n = 59)		4 mg/kg (n = 55)	
	all	severe	all	severe
Pain	59	8	58	9
Asthenia	53	7	58	7
Fever	36	2	45	0
Nausea	37	3	47	2
Diarrhea	36	2	24	5
Headache	29	3	38	2
Chills	22	0	40	2
Rash	20	0	38	0
Rhinitis (epistaxis)	20 (12)	0	18 (7)	0
Dyspnea	15	0	25	2

IHC 2+ tumors are FISH positive. Analysis of response rates in patients for whom FISH results were available (n = 62) in the first-line Herceptin monotherapy trial, demonstrated that all but one objective response occurred in FISH-positive patients. The exception was a patient who was 3+ by IHC (a single-copy overexpressor). Response rates were 41% in FISH-positive patients compared with 5% in FISH-negative patients (table 2). Although not statistically significant, these data suggest a greater clinical benefit for FISH-positive compared with IHC 2+ and 3+ patients combined. When patients achieving stable disease for ≥ 6 months are added to the responders, the clinical benefit rate in IHC 3+ patients was 47%.

At a median follow-up of 9 months, 21 patients had not reached disease progression at the time of analysis. In responding patients (CR plus PR) median TTP was 18.8 months. For those patients not achieving a clinical benefit, median TTP was 1.8 months. Median duration of survival was 24.4 months (range 1.2 to 45.8+ months).

Safety

Herceptin was generally well tolerated as first-line monotherapy. As found in the pivotal Herceptin trials, most adverse events were mild to moderate and typically associated with the first infusion, rarely occurring with subsequent infusions. The most common adverse events were pain, asthenia, fever and chills. Overall, the incidence of adverse events was similar between the two Herceptin dose groups. However, acute infusion-related events such as fever and chills, as well as rash and dyspnea tended to occur more frequently with the higher dose schedule (table 3). Statistical analysis is required to determine whether this difference is significant. Adverse events typically associated with cytotoxic agents were rare in this study: alopecia 7%, leukopenia 4%, thrombocytopenia 1%, anemia 3%, and stomatitis 2%. In addition, assessment using the EORTC QLQ-C30 questionnaire demonstrated that most patients had either clinically meaningful improvements or no change in health-related QoL after beginning Herceptin monotherapy [Osoba et al. 2000].

Reports of serious cardiac events in the pivotal phase II and III Herceptin trials [Cobleigh et al. 1999; Cook-Bruns 2001; Ewer et al. 1999] prompted a retrospective analysis of cardiac events in this trial by an independent, blinded CREC. Cardiac dysfunction was defined by the CREC as symptomatic heart failure or an asymptomatic decrease ($<10\%$) in left ventricular ejection fraction (LVEF). According to these criteria, three patients (2.6%) were identified as experiencing cardiac dysfunction, although one of these cases was not related to Herceptin therapy. In the remaining two patients, Herceptin therapy was discontinued after approximately 1 year.

There were 65 deaths, 34 in the standard Herceptin dose group and 31 in the high Herceptin dose group. None of these deaths occurred during the study and all deaths were due to progressive metastatic breast cancer.

Cross-Trial Comparisons

Although it is normally not possible to compare different trials with statistical accuracy, the first-line Herceptin monotherapy trial and the pivotal first-line Herceptin combination trial (H0648g) had the same investigators, similar patient populations and were run in parallel. Therefore, it is possible to compare these two trials in a cross-trial analysis with a view to identifying general trends between them.

In terms of patient demographics such as mean age, KPS, number of metastatic sites and HER2 positivity, there was virtually no difference between patients enrolled into each trial. However, differences were seen between the two trials in terms of the prior adjuvant chemotherapy patients had received. By nature of the trial design, the majority of patients in the Herceptin plus paclitaxel arm of the pivotal combination trial had received prior adjuvant doxorubicin (97%), while only 1% of patients had received prior doxorubicin in the Herceptin plus AC arm of this trial. In contrast, 51% of patients in the first-line monotherapy trial had received prior doxorubicin.

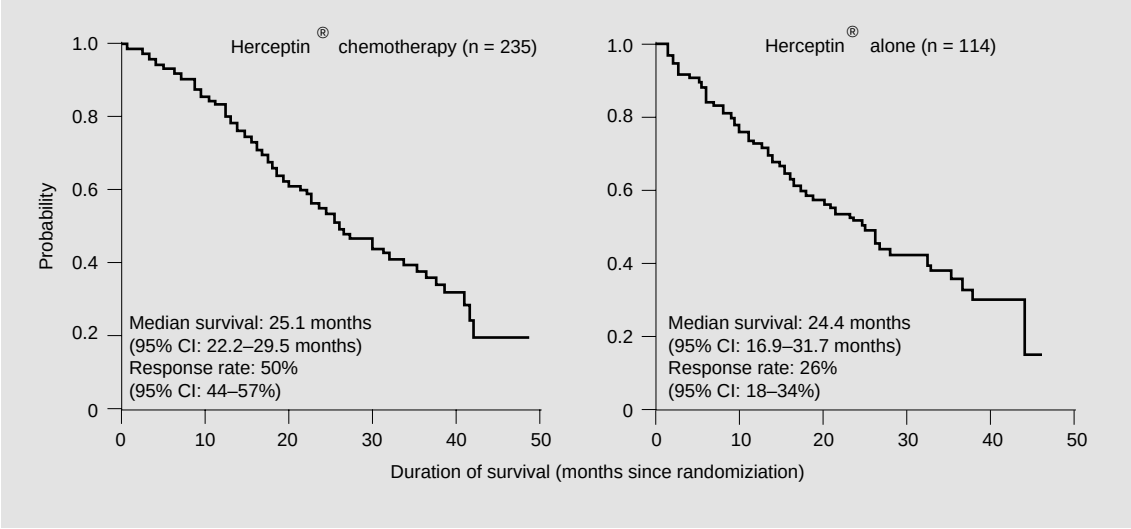

Fig. 1. Duration of survival following Herceptin plus chemotherapy (H0648g) or first-line Herceptin monotherapy.

These differences aside, comparison of Kaplan-Meier estimates of survival demonstrates similar survival duration between the two trials. Median survival for first-line Herceptin monotherapy was 24.4 months compared with 25.1 months for Herceptin plus chemotherapy (fig. 1). Similar survival rates were also seen between first-line Herceptin monotherapy and Herceptin plus paclitaxel (24.4 versus 22.1 months, respectively) and Herceptin plus AC (24.4 versus 26.8 months, respectively). However, response rates for Herceptin monotherapy were approximately half those of the combination therapy.

Analysis of outcomes in the two trials based on FISH data shows that not only is survival rate comparable between the two trials for FISH-positive patients (22.9 versus 26.8 months for first-line Herceptin monotherapy versus Herceptin plus chemotherapy, respectively) but that response rates are also similar (41% for first-line Herceptin monotherapy versus 54% for Herceptin plus chemotherapy).

Conclusions

The results from the first-line monotherapy trial demonstrate that Herceptin is active as a single agent in HER2-positive breast cancer patients who have not received prior therapy for metastatic disease. Importantly, efficacy was not improved by increasing the dose of Herceptin. A greater clinical benefit was observed in IHC 3+ patients than in the overall population, a trend which has also been demonstrated in the pivotal Herceptin trials [Baselga 2000; Mass et al. 2000].

Herceptin was well tolerated as first-line monotherapy and demonstrated a favorable safety profile. The incidence of cardiotoxicity also appeared to be lower in this study than in previously reported Herceptin trials, where the incidence of prior anthracycline exposure was greater. Moreover, based on the similar safety profile seen between the two dose groups in this study, it seems unlikely that Herceptin-associated adverse events are dose related, with a few possible exceptions. Therefore, since both efficacy and safety were similar between the two dose groups, the standard Herceptin dose (4 mg/kg initial dose followed by 2 mg/kg i.v. weekly maintenance dose), which was also the dose used in the pivotal trials, would be the preferred dosing schedule.

The results from this study indicate that FISH may offer a more accurate means of patient selection than IHC. Similar conclusions have also been drawn from the analysis of outcomes based on FISH positivity in the pivotal Herceptin trials [Baselga 2000; Mass et al. 2000]. It is likely that FISH allows the selection of all HER2 high overexpressors (including 24% of IHC 2+ patients) who are most likely to benefit from Herceptin therapy.

It is not possible to directly compare individual trials and deduce statistically significant conclusions about similarities. However, a comparison between the first-line Herceptin monotherapy and first-line Herceptin combination therapy trials does suggest that, although response rates are higher in the combination trial, overall survival

duration is similar for first-line Herceptin monotherapy and first-line Herceptin combination therapy. This begs the question of when and how Herceptin should be used. The survival benefit and superior safety profile of first-line Herceptin monotherapy compared with chemotherapy highlights the potential of this regimen for palliative treatment of women with HER2-positive metastatic breast cancer. Furthermore, the greater level of clinical benefit seen when Herceptin monotherapy is used as first-line rather than second/third-line treatment indicates that patients are more likely to benefit from up-front use of Herceptin therapy.

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