Anti-Cancer Drugs 2001, 12 (suppl 4):S3–S10

Efficacy and safety of Herceptin® in women with metastatic breast cancer: results from pivotal clinical studies

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Amplification of the human epidermal growth factor receptor-2 (HER2) gene and overexpression of the encoded protein are seen in 20–30% of breast cancers, and are associated with aggressive disease and relatively poor prognosis. Thus, HER2 represents an appropriate target for anticancer treatment and the humanized anti-HER2 monoclonal antibody Herceptin® has been developed for this purpose. The efficacy of Herceptin® has been confirmed in two pivotal trials—a monotherapy study in 222 women with HER2-positive metastatic breast cancer who had already received one or two chemotherapy regimens for metastatic disease and a study comparing Herceptin® plus chemotherapy with chemotherapy alone in 469 patients previously untreated for metastatic disease. Herceptin® monotherapy was associated with longer median response duration and survival than previous chemotherapy. Addition of Herceptin® to chemotherapy increased response rates, time to disease progression and survival duration. Benefit was greatest in patients with high-level HER2 overexpression. Herceptin® was well tolerated, with mild to moderate infusion-related reactions, usually seen with the first infusion only, being the most common event. Most patients respond to conventional supportive treatment. Cardiotoxicity, the most serious adverse event observed, occurred mainly in patients exposed to anthracyclines and was generally manageable. Thus, Herceptin® represents a significant development in the management of HER2-positive breast cancer. [© 2001 Lippincott Williams & Wilkins.]

Key words: Breast cancer, clinical efficacy, HER2, Herceptin®, safety.

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Introduction

Metastatic breast cancer is generally an incurable condition[1] and remains a challenge for oncologists. In the US alone, over 80 000 women develop metastatic or refractory breast cancer annually, with rates essentially remaining unchanged in Caucasian women over the 20-year period from 1973 to 1993.[2,3] The mean survival duration after diagnosis of metastatic breast cancer is 18–24 months, although this varies widely according to metastatic site and is considerably lower in patients without visceral involvement.[3]

Treatment objectives in metastatic breast cancer are to maintain the best possible quality of life for patients and improve survival. The past three decades have seen a number of notable developments that have aided clinicians in the realization of these aims; among the most significant outcomes of these research efforts has been the identification and utilization of specific cellular targets for directed therapy.

It is now known that growth factors and their receptors play pivotal roles in the regulation of cell growth and differentiation, and that breast tumors may express high levels of some of these cellular mediators. Malignancy arises when genetic events lead to unregulated expression of growth factor receptors or their signaling pathways; proto-oncogenes that encode these proteins can therefore contribute to the pathogenesis of malignant disease.[4] The human epidermal growth factor receptor-2 (HER2) gene (also known as *neu* and c-*erbB*-2) encodes a 185-kDa transmembrane glycoprotein receptor ($p185^{HER2}$).[5–7] HER2 is one of a family of four closely-related growth factor receptors, designated HER1–HER4, all of which are transmembrane tyrosine kinase receptors with growth-stimulating activity that interact extensively and participate in the control of cell growth, survival and differentiation. HER2 expression varies between different tissues,[8] but normal epithelial cells possess two copies of the gene encoding this receptor. HER2 protein overexpression, which is almost invariably caused by amplification of the HER2 gene,[9] is

ISSN 0959-4973

seen in 20–30% of breast cancers.[10,11] Such tumors are termed HER2 positive. HER2 positivity in breast cancer is associated with more aggressive disease and poorer clinical outcome.[9–13]

HER2 as a target for therapy: pivotal clinical studies

Conventional cytotoxic chemotherapy is undirected, and its use relies on a delicate balance between efficacy and toxicity. Thus, over recent decades, investigation has started to focus on anticancer agents that more specifically recognize cancer cells and target these cells while not affecting healthy cells, thus improving the balance between efficacy and toxicity. The recombinant humanized anti-HER2 monoclonal antibody Herceptin® (trastuzumab) was rationally developed to target breast cancers that are HER2 positive. Herceptin® was shown to be safe and clinically active in early phase I and II clinical studies in women with HER2-positive metastatic breast cancer.[14–16] These encouraging early findings with Herceptin®, the first oncogene-targeted treatment to become available for HER2-positive patients, prompted the setting up of two pivotal clinical trials. One was carried out across 54 centers in seven countries in 222 women with HER2-positive breast cancer who had already received one or two chemotherapy regimens for metastatic disease.[17] These women received Herceptin® monotherapy. The other trial compared Herceptin® plus chemotherapy to chemotherapy alone across 150 centers in 12 countries in 469 women not previously treated for metastatic breast cancer.[18,19,24] All patients enrolled were classified by immunohistochemistry (IHC) as having HER2 2+ or 3+ overexpression (weak to strong complete membrane staining observed in more than 10% of tumor cells). In both studies, an initial dose of Herceptin® 4 mg/kg as a 90-min i.v. infusion followed by 2 mg/kg weekly as a 30- to 90-min i.v. infusion was administered to ensure that adequate serum trough levels were attained and maintained [14,20].

Efficacy of Herceptin® as a single agent

The first study was a single-arm phase II trial in which all patients received Herceptin® monotherapy.[17] As is common for initial trials with investigational anticancer agents, the participants constituted a group with poor prognosis on the basis of incidence of visceral disease and extent of prior treatment. Of the evaluable patients, 32% had received one prior course of chemotherapy and 68% had received two courses. Most had received both anthracycline and taxane treatment, and 26% had undergone high-dose chemotherapy with bone marrow or stem cell rescue before enrolment. Furthermore, 36% of patients had metastases at three or more sites and 70% had liver or lung metastases.

The primary endpoint, as determined by a blinded independent Response Evaluation Committee (REC), was objective tumor response, and was evaluated in all enrolled patients (intention-to-treat analysis) and in all patients who received at least one dose of Herceptin®. Secondary endpoints included duration of response, time to disease progression (TTP), time to treatment failure (TTF) and survival. Adverse events and health-related quality of life (QoL) were also measured. Complete response was defined as the disappearance of a radiographically, palpably and/or visually apparent tumor, whereas partial response was defined as a decrease of at least 50% in the sum of the products of the perpendicular diameters of all measurable lesions. Disease progression was defined as an increase of at least 25% in the size of any measurable lesion, or as the appearance of a new lesion.

Response

The overall response rate was 15% in the intention-to-treat population of 222 patients receiving single-agent Herceptin®. The independent REC identified eight complete (4%) and 26 partial (11%) responses. Notably, there was a tendency towards a higher response rate in patients with higher levels of HER2 protein overexpression: those whose tumors were HER2 3+ ($n = 172$) showed an overall response rate of 18%, as compared to 6% in those whose tumors were HER2 2+.

Improved QoL was also noted in responders. The European Organization for Research and Treatment of Cancer (EORTC) C30 questionnaire[21] was completed by 154 patients at baseline and at week 12 and showed that before disease progression, treatment with Herceptin® was associated with maintenance of health-related quality of life as measured by physical function, role function, social function, global QoL and fatigue scales.[17] Specifically, significant improvements in global QoL ($p = 0.0003$) and social function ($p = 0.002$) were observed, and no change occurred in other parameters.[22] Standard chemotherapy for metastatic breast cancer typically results in decreases in QoL.

Duration of response and survival

The median response duration with Herceptin® therapy was 9.1 months. This compared favorably with the 5.2-month median response duration seen with prior chemotherapy in responders. The overall median survival duration (all patients) was 13 months, with median TTP and TTF of 3.1 and 2.4 months, respectively, in the intent-to-treat population. The benefit associated with Herceptin® is underlined by comparing the median TTF of 11 months in responders with the median of 5.4 months reported for the prior chemotherapy regimen. Of particular interest in this study was the survival of patients with

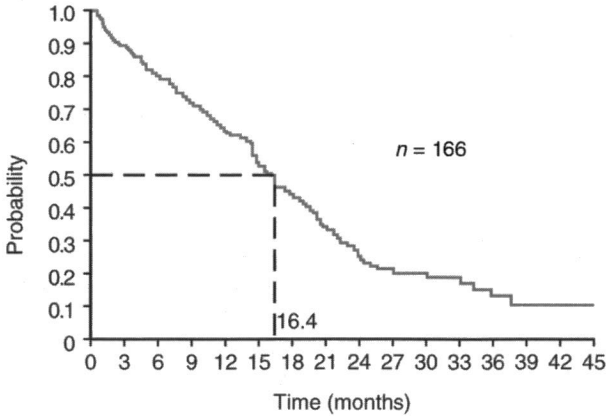

Figure 1. Kaplan-Meier plot showing survival in women receiving Herceptin® monotherapy who expressed the HER2 receptor at the 3+ level by IHC.

higher levels of expression of the HER2 receptor (Figure 1).[23] The median duration of survival was extended from 13 to 16.4 months in women with HER2 3+ expression, with a number of patients (about 10%) surviving for at least 45 months. Together with the tumor response results reported earlier, these findings suggest that Herceptin® monotherapy has enhanced clinical benefit in patients with high levels of HER2 overexpression.

Herceptin® in combination with chemotherapy

In the pivotal phase III study, a total of 469 patients with HER2-positive metastatic breast cancer who had not received previous chemotherapy for metastatic disease were randomized to receive either chemotherapy alone or chemotherapy plus Herceptin®.[18,19,24] Patients who had no history of adjuvant treatment with anthracyclines were randomized to receive either anthracycline therapy (doxorubicin 60 mg/m^2 or epirubicin 75 mg/m^2) plus cyclophosphamide (AC) 600 mg/m^2 alone (n = 138) or in combination with Herceptin® (n = 143). Patients with a history of adjuvant treatment with an anthracycline received paclitaxel 175 mg/m^2 alone (n = 96) or in combination with Herceptin® (n = 92). Demographics for the various subgroups were broadly similar, with approximately one-third of patients having three or more metastatic sites, approximately 70% having lung or liver metastases and 70–80% being HER2 3+. However, performance status was lower ($p < 0.05$) and adjuvant anthracycline therapy more common in the paclitaxel subgroups. The dosage of Herceptin® was the same standard dose that was used in the monotherapy trial (4 mg/kg i.v. initial dose followed by 2 mg/kg i.v. weekly). Chemotherapy was given every 3 weeks for 6 cycles, with additional cycles at the discretion of the investigator. Data are now available for 96% (451 of 469) of participating patients,[19] with a median follow-up of 35 months.

Table 1. Efficacy of Herceptin® (H) in combination with chemotherapy (CT) in the pivotal phase III study: overall results for all patients (n = 469) and those with HER2 3+ status (n = 349)

	H + CT	CT alone
Median TTP(months)		
all patients	7.4[a]	4.6
HER2 3+ patients	7.8[a]	4.6
Response rate (%)		
all patients	50[a]	32
HER2 3+ patients	56	31
Survival (months)		
all patients	25[a]	20
HER2 3+ patients	29[a]	20

[a]$p < 0.05$.

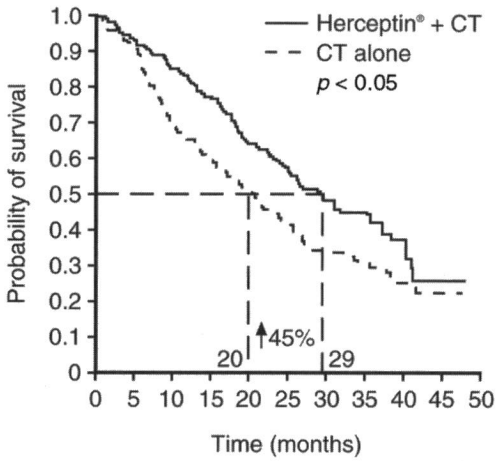

Figure 2. The addition of Herceptin® to chemotherapy (anthracycline or paclitaxel) increases the survival of strongly HER2-positive women with metastatic breast cancer by 45%.

Benefit of adding Herceptin® to chemotherapy

Addition of Herceptin® to chemotherapy significantly increased the median TTP from 4.6 to 7.4 months. The increase was greater in HER2 3+ patients (Table 1). Survival duration was prolonged by 5 months overall by adding Herceptin® to chemotherapy, and by 9 months (45%) in HER2 3+ patients (Table 1 and Figure 2).[19,23] Such increases in survival have not been observed with any other drug introduced for the treatment of metastatic breast cancer.

Analysis of treatment subgroups showed TTP to be more than doubled (from 3 to 7.1 months) when Herceptin® was added to paclitaxel therapy (Table 2). In addition, survival duration was increased by 40% relative

Table 2. Efficacy of Herceptin® (H) in combination with chemotherapy (CT) in the pivotal phase III study: results by treatment subgroup [anthracycline (AC) or paclitaxel (P)] for all patients ($n = 469$) and those with HER2 3+ status ($n = 349$)

	H + AC ($n = 143$)	AC alone ($n = 138$)	H + P ($n = 92$)	P alone ($n = 96$)
Median TTP (months)				
all patients	7.8[a]	6.1	6.9[a]	2.7
HER2 3+ patients	8.1[a]	6.0	7.1[a]	3.0
Response rate (%)				
all patients	56	42	41	17
HER2 3+ patients	60	42	49	17
Survival (months)				
all patients	27	21	22	18
HER2 3+ patients	31[a]	21	25	18

[a]$p < 0.05$.

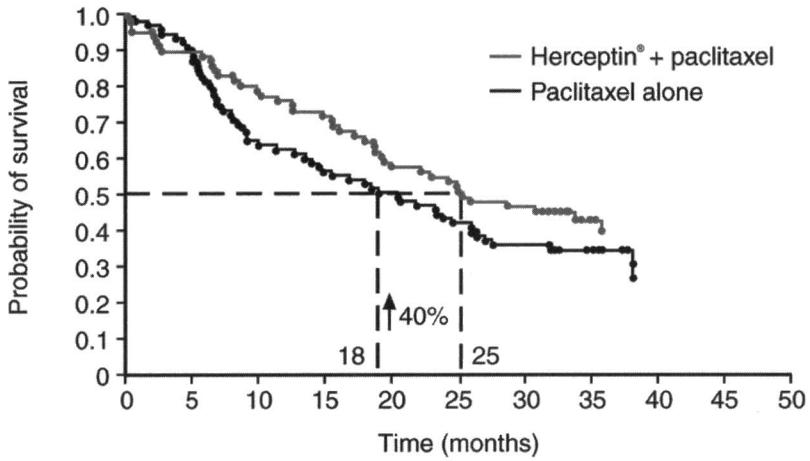

Figure 3. Survival in strongly HER2-positive patients treated with paclitaxel with or without Herceptin®. The addition of Herceptin® increased survival by approximately 40% in this population. Note that 65% of patients who initially received paclitaxel alone received Herceptin® following disease progression.

to paclitaxel alone in HER2 3+ patients who received Herceptin® in addition to paclitaxel (Figure 3).[19,23] This is particularly noteworthy because patients receiving paclitaxel had a history of prior anthracycline treatment and a shorter disease-free interval, and were thus likely to have a particularly poor prognosis.

Addition of Herceptin® to chemotherapy increased overall response rates (Table 1), particularly in patients treated with paclitaxel (Table 2): the response rate was increased from 17 to 41% overall and to 49% in HER2 3+ patients relative to paclitaxel alone (17%).[19,23]

Thus, the addition of Herceptin® to chemotherapy is associated with significant improvements in TTP and overall survival, particularly in patients who are strongly HER2-positive. It is important to note that the majority of patients initially randomized to chemotherapy alone subsequently received Herceptin® after disease progression (65% of paclitaxel-treated patients).[19] This type of crossover design, in which patients who received Herceptin® after disease progression are included in the chemotherapy-alone groups for analysis, would normally be expected to bias the study against the demonstration of a survival advantage.

QoL

QoL analysis using the EORTC QLQ-C30 questionnaire was also performed in this trial.[24] This demonstrated that patients treated with Herceptin® plus chemotherapy experienced an initial decline in QoL as measured using all five primary domains, but this was followed by a return to baseline or improvements beyond baseline (global QoL and social function). In contrast, patients treated with chemotherapy alone experienced worsening in all five primary domains that did not recover. Baselga *et al.*[26] considered some of the secondary domains included in the EORTC QLQ-C30 questionnaire and the specific breast cancer module (BR-23), and observed significant improvements in the pain domain and dyspnea question of QLQ-C30, and in the systemic treatment side effects domain of BR-23 in patients treated with Herceptin® plus

chemotherapy. Thus, overall it appears that the addition of Herceptin® to chemotherapy results in at least maintained QoL in contrast to the worsening QoL observed in patients treated with chemotherapy alone.

Comparison of Herceptin® and paclitaxel monotherapy

Although direct comparisons between Herceptin® monotherapy and conventional chemotherapy have not been carried out to date, it is possible to retrospectively compare data from the Herceptin® monotherapy phase II trial[17] and from the paclitaxel monotherapy arm of the randomized phase III study.[19] This approach is reasonable because patients were recruited on the basis of HER2 status as determined by the same central laboratory and the studies were conducted concurrently by the same group of investigators in patients with similar prognostic characteristics at baseline.

Overall objective tumor response rates were similar between HER2 3+ patients in the two groups: 17% of 77 patients receiving paclitaxel monotherapy responded compared with 18% of 172 patients who received Herceptin® monotherapy. However, the median duration of response with Herceptin® in this subgroup of individuals was twice that with paclitaxel (9 versus 4.6 months). It should be noted here that the comparison of these two drugs may be biased in favor of paclitaxel by prior treatment status: at enrolment, patients receiving Herceptin® had received one or two chemotherapy regimens for metastatic breast cancer whereas those receiving paclitaxel monotherapy had received no prior treatment for metastatic disease.

Clinical safety of Herceptin®

Research into antibody therapy in patients with cancer is driven not only by the potential efficacy of these agents, but also by the potential for achievement of selective therapeutic effects without the often severe toxicity seen with conventional chemotherapy. Safety data for Herceptin®, available from a clinical trials database involving 930 patients and from a postmarketing surveillance program in which over 30 000 patients have been exposed to Herceptin®, show that the drug does indeed possess this advantage.

The most common side effect observed in clinical trials to date is reactions related to Herceptin® infusion, which affect approximately 30–40% of patients. These usually manifest as chills or fever and most often occur with the first infusion, tending to be mild to moderate in intensity (Figure 4).[14,17,27] With subsequent infusions, the risk of such infusion-related reactions is very low, ranging from 3% with Herceptin® monotherapy[17] to 5% when

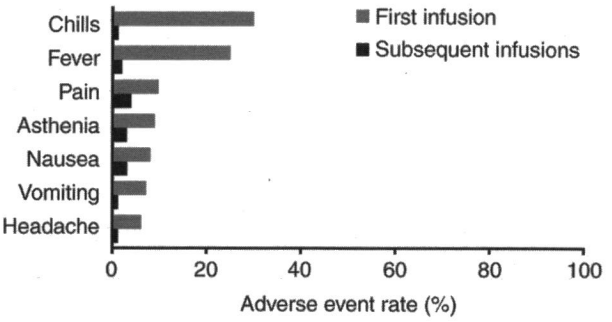

Figure 4. Infusion-related adverse reactions in patients receiving Herceptin® monotherapy in the pivotal phase II study.[17] Chills and fever were reported most commonly. Note the very low incidence of reactions with second and subsequent infusions.

Herceptin® is used in combination with chemotherapy.[18,19] In the pivotal phase II study of Herceptin® monotherapy, infusion-related reactions necessitated only temporary interruption of the Herceptin® infusion, and were treated successfully in the majority of cases with acetaminophen, diphenhydramine and/or meperidine.[17]

A number of other side effects have occurred, including nausea, vomiting, pain, headache and dizziness.[27] These effects are mild to moderate in severity and also tend to occur only with the first infusion of Herceptin.® Thus, the general tolerability profile of Herceptin® is good, as would be expected based on its targeted nature. A key feature is that no severe nausea, vomiting or alopecia has been observed. These events are known to have a significant impact on QoL.[28] Furthermore, another of the major adverse effects of chemotherapy, myelosuppression, is rare with Herceptin® monotherapy.[17] However, two adverse events warrant further consideration: cardiac dysfunction and serious infusion-related reactions.

Cardiac safety

Cardiac dysfunction was the most clinically significant adverse event in clinical trials of Herceptin® and was not predictable on the basis of preclinical study results. Retrospective analysis of cardiotoxicity in the pivotal phase II and III trials showed the highest rate of cardiac dysfunction in patients receiving Herceptin® in combination with an anthracycline (27%); this compared with a rate of 7% in patients receiving anthracycline therapy alone (Table 3). In addition, cardiac dysfunction was seen in 12% of patients receiving Herceptin® in combination with paclitaxel and in 1% of recipients of paclitaxel alone. Of patients receiving Herceptin® alone, 4% experienced cardiac dysfunction.[29]

It should be noted that the definition of cardiac dysfunction in this analysis included asymptomatic decrease in

Table 3. Summary of cardiac adverse events in pivotal clinical trials of Herceptin®: retrospective analysis of Herceptin® (H) alone or in combination with anthracycline (AC) or paclitaxel (P) (all values shown as percentages of patients)

	H + AC	AC alone	H + P	P alone	H alone
Cardiac dysfunction (including asymptomatic decrease in LVEF)	27.0	7.0	12.0	1.0	4.0
Symptomatic heart failure (initial)	16.0	3.0	2.0	1.0	3.0
Residual symptomatic heart failure (after treatment)	6.0	0.7	0	0	1.5
Death due to cardiac dysfunction	0.7	0.7	0	0	0.9

left ventricular ejection fraction (LVEF). However, this parameter was not measured before treatment and it is therefore not possible to accurately measure the rate of asymptomatic changes in LVEF associated with any of the regimens used in these studies. Of more clinical relevance is the incidence of symptomatic heart failure (16% with Herceptin® plus AC), which was considerably lower than the incidence of cardiac dysfunction as defined above (Table 3). Moreover, cardiac dysfunction was reversible in the majority of patients: most patients with symptomatic heart failure continued to receive Herceptin® and most of these showed improvement with conservative standard treatment. As shown in Table 3, rates of residual heart failure after treatment were very low, with rates of death due to cardiac dysfunction ranging from 0 to less than 1%. Furthermore, results to date show no apparent difference in cardiac outcome between patients who continue Herceptin® and those who withdraw from treatment, and there appears to be no cumulative effect of the drug in this respect (Figure 5).[29]

Available evidence indicates that cardiotoxicity in patients receiving Herceptin® is likely to be linked to concomitant anthracycline exposure, with age as the only other identified risk factor.[30] Therefore, Herceptin® is not currently indicated for use in combination with anthracyclines. In the pivotal clinical trials and one further study of first-line monotherapy with Herceptin®,[31] most patients who developed cardiac dysfunction had received either prior or concomitant anthracycline treatment. Of the 84 women in these trials who had not been exposed to anthracyclines, only three showed signs of heart failure after treatment with Herceptin®. However, all had pre-existing cardiac disease and were elderly (aged 71–79 years), and all improved with standard treatment.[30]

Patients who are affected by adverse cardiac events while receiving Herceptin® generally show no significant deterioration in cardiac function after standard medical management when the drug is continued. Nevertheless, it is recommended that cardiac function should be monitored regularly (every 3 months) by echocardiography, electrocardiography or multigated radionuclide angiography (MUGA) after baseline assessment, and that standard medication is used in patients in whom cardiac failure develops.

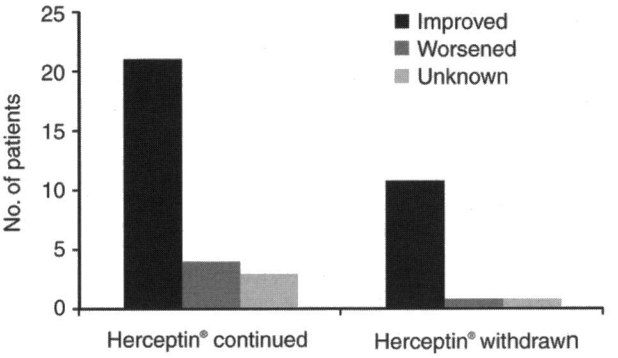

Figure 5. The outcome of patients who developed cardiac dysfunction was similar whether or not Herceptin® was withdrawn.

In patients who experience asymptomatic decreases in LVEF, clinicians should consider discontinuing Herceptin® therapy in those showing no evidence of a tumor response to Herceptin®. Careful risk/benefit assessment is necessary in patients with symptomatic heart failure; this also applies to patients with a history of hypertension or documented coronary artery disease.

Serious infusion-related reactions

A small number of serious infusion-related reactions have been reported in patients receiving Herceptin®. Postmarketing surveillance data to March 2000 reveal 74 reports of such reactions in around 25 000 treated patients, which represents a reported incidence of approximately 0.3%.[30] Serious infusion-related reactions were associated predominantly with the first infusion and were usually seen within the first 2 h of treatment. Most patients affected developed respiratory symptoms, including dyspnea, bronchospasm and respiratory distress. Anaphylactoid reactions such as hypotension and rash have also been reported. However, most of these individuals ($n = 65$) responded to supportive treatment with antihistamines, corticosteroids, β-adrenoceptor agonists and/or oxygen therapy. Over one-third of patients were re-challenged successfully and continued to receive Herceptin® with no further reactions. Fatal outcomes were

extremely rare (reported incidence 0.04%) and were all seen in patients with pre-existing severe malignancy-related respiratory distress.

It is therefore recommended that patients with severe dyspnea at rest associated with advanced malignancy, or those requiring supplemental oxygen, should not receive Herceptin®. Patients with disease this advanced are generally not eligible for any form of active anticancer therapy. As a general rule, patients receiving Herceptin® should be monitored for severe infusion-related reactions, particularly during the first infusion. The majority of mild reactions can be managed with analgesics/antipyretics and antihistamines (as in the phase II monotherapy trial); serious reactions can usually be managed by stopping the Herceptin® infusion and with standard supportive therapy such as oxygen, β-adrenoceptor agonists and corticosteroids.

Discussion

The concept of targeting specific abnormalities in tumor cells is a relatively recent development in anticancer therapy and is an approach that is now being widely investigated, with targets ranging from growth factor receptors to angiogenic factors.[32] Biological agents such as monoclonal antibodies are particularly attractive as targeted therapies because they can be rationally designed to target specific factors and mimic naturally occurring molecules.[33] Until recently, the only targeted biological agent available for the treatment of malignancy was the chimeric monoclonal antibody rituximab, which is now a standard therapy for non-Hodgkin's lymphoma.[34] However, the widespread approval of the humanized anti-HER2 monoclonal antibody Herceptin® for the treatment of HER2-positive metastatic breast cancer has demonstrated that the concept of using targeted biological agents to produce antitumor effects in solid tumors is effective.

Data from the pivotal clinical trials show that Herceptin®, when given as second/third-line monotherapy, produces durable tumor responses in patients with metastatic breast cancer, even in heavily pretreated individuals.[17] The clinical benefit of Herceptin® monotherapy in this population is greater in HER2 3+ than 2+ patients. Furthermore, the response of HER2 3+ patients to Herceptin® monotherapy is better than that of a patient group treated with first-line paclitaxel monotherapy, even though the paclitaxel group had a better overall prognosis.

In combination with paclitaxel, Herceptin® is associated with substantially increased response rates and TTP as compared to patients receiving paclitaxel alone.[19] Similarly to patients treated with Herceptin® monotherapy, the response to therapy with Herceptin® plus paclitaxel is greatest in strongly HER2-positive patients (HER2 3+), with a 40% increase in median survival duration relative to paclitaxel alone.[19,23]

Herceptin® is well tolerated by the majority of patients and is not generally associated with increases in the incidence or severity of adverse events seen with chemotherapy alone. Indeed, the favorable tolerability profile of Herceptin® offers the potential for therapeutic benefit without the debilitating adverse effects experienced with conventional chemotherapy. This, together with the significant clinical benefit of Herceptin® therapy, is reflected in the maintenance or improvements in QoL observed in the pivotal trials. The primary adverse event of note is cardiac dysfunction, which is associated mainly with concurrent anthracycline use.[30] For this reason, use of the Herceptin® plus anthracycline combination is not currently approved outside of clinical trials. However, patients who develop cardiac dysfunction can usually be managed with standard medical therapy and in most cases the problem is reversible. Although infusion-related reactions are common, these tend to be mild in most patients and are usually associated with the first infusion only. More serious infusion-related reactions have been noted, but these tend to occur in severely debilitated patients with malignancy-related respiratory compromise.[30]

Based on these results from pivotal clinical trials, Herceptin® is approved for the treatment of HER2-positive metastatic breast cancer as first-line therapy in combination with paclitaxel and as monotherapy for patients who have received prior chemotherapy for metastatic disease. Appropriate patient selection and monitoring generally ensure that the risk/benefit ratio of Herceptin® is very good. This, coupled with the significant increases in survival duration that can be obtained with Herceptin®, means that this novel agent represents a significant advance in the management of metastatic breast cancer patients.

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