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A Population-based Study on the First Forty-Eight Breast Cancer Patients Receiving Trastuzumab (Herceptin®) on a Named Patient Basis in Sweden

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Several studies have presented data on the efficacy and tolerability of trastuzumab within clinical trials. As a minority of patients is included in these trials, we undertook this retrospective study to describe trastuzumab therapy in clinical routine and its tolerability. We reviewed the medical records of the first 48 patients in Sweden who received treatment with trastuzumab on a named patient basis with (n = 29) and without (n = 19) chemotherapy. Forty-six patients had metastatic disease and had failed to respond to several prior regimens before starting antibody treatment. Two patients had locally advanced breast cancer failing on given neoadjuvant therapy. Patients with breast cancers with strong (3 +) c-erbB-2 overexpression tended to have an improved survival from start of trastuzumab treatment versus those with a moderate (2 +) overexpression (p = 0.09). Adverse events were registered in 22 patients (46%). The most common and acute side effects were fever and chills (7 patients, 15%). The toxicity seemed reasonable but two patients (4%) suffered serious cardiac events, both of them having received previous treatment with antracyclines.

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The oncogene c-erbB-2 (also known as HER-2/neu) belongs to the epidermal growth factor receptor (EGFR) family and is located on chromosome 17q12-q21 (1, 2). c-erbB-2 is a 185 kDa transmembrane tyrosine kinase receptor. In addition to human breast cancer, where amplification and overexpression of c-erbB-2 was first found, overexpression has also been found in ovarian-, lung-, gastric-, oral-, prostate-, and bladder cancers (3–11). In breast cancer, overexpression of c-erbB-2 is found in 20–30% of patients and is correlated with a poor prognosis including shorter disease-free and overall survival times (12–14). c-erbB-2 may also be a potential predictive factor for response to anthracycline-based therapies and an inferior outcome of hormonal therapies (14–18). The signalling pathway of c-erbB-2 is complex and studies indicate that the receptor interacts directly or indirectly with many cellular proteins, and potentially the best and easiest way to block the effect of activated c-erbB-2 may be 'upstream', which is on the receptor level (19). Trastuzumab (Herceptin®) is a humanized antibody that targets an epitope on the extracellular domain of c-erbB-2 and thereby specifically inhibits the growth of c-erbB-2 positive tumours (20). Chemotherapy is a cornerstone for the management of receptor negative breast cancers, in both the adjuvant and metastatic setting but the addition of tumour-specific monoclonal antibody therapy offers a new strategy for breast cancer therapy (21). Clinical trials of trastuzumab as second- or third-line treatment with and without chemotherapy have shown results with overall response rates of 24% for combination therapy (22) and 11–15% for trastuzumab alone (20, 23). c-erbB-2 and steroid receptor expressions are inversely related (24). With trastuzumab as first-line monotherapy, a response of 26% has been reported (25). Similarly, a response in 62% of the

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patients has been reported for first-line combination therapy. The median overall survival was statistically significantly improved from 20 to 25 months by adding trastuzumab to chemotherapy compared with chemotherapy alone (median follow-up of 25 months) (26). Synergistic effects with other antitumoural cancer drugs such as cisplatin and vinorelbine have also been reported (27). The main disadvantage with trastuzumab is its cardiac side effects, which are more common when the antibody is combined with chemotherapy, especially antracyclines (28). The studies presenting efficacy with treatment of trastuzumab have so far been randomized trials with, to some extent, narrow inclusion. We therefore undertook this study aiming to investigate the efficacy and possible side effects of trastuzumab therapy in a population-based cohort of patients, which included the majority of patients subjected to this treatment.

MATERIAL AND METHODS

The present analysis is based on the retrospective review of the medical records from the first 48 patients in Sweden with metastatic breast cancer who have received treatment with the monoclonal antibody trastuzumab. As the drug trastuzumab at the time of treatment was not a registered drug in Sweden, all patients were treated on a named patient basis, approved by the Swedish Medical Products Agency. The criterion for approval was that the patients should have breast cancer with a moderate (2+) or strong (3+) c-erbB-2 overexpression that failed on conventional therapies. Initially, only single-agent treatment with trastuzumab was approved. After some months, combination therapy (trastuzumab and chemotherapy) also was accepted and became the most common choice of treatment. All patients, with the exception of two, had metastatic disease and had failed several hormonal and/or chemotherapy regimens before starting treatment with trastuzumab. Two patients had a primary, locally advanced breast cancer that did not respond to the initial neoadjuvant chemotherapy. The patients were treated at 12 different clinics. All patients but four had received previous adjuvant treatment (chemotherapy and/or radiotherapy and/or hormonal therapy). Thirty-one of 48 patients (65%) had received adjuvant chemotherapy, 31/48 (65%) had received adjuvant radiotherapy and 13/48 (27%) had received adjuvant hormonal therapy (9/13 had received tamoxifen). Before treatment with trastuzumab, with or without chemotherapy, 56% (27/48) had already received three or more combinations of chemotherapy and/or hormonal therapy for metastatic disease. The first patient started treatment in December 1998 and the 48th patient started treatment in April 2000. Follow-up time was 6–24 months. Patient characteristics are listed in Table 1. Time to first recurrence was longer for the patients who later received single therapy compared with those who received combination therapy, 29 months and 21 months, respectively ($p = 0.02$). Median time from primary diagnosis, and diagnosis of metastatic disease to the start of treatment with trastuzumab also showed statistically significantly differences between the two treatment groups. Median time from primary diagnosis to relapse was 72 compared with 42 months for patients who received single-agent versus combination therapy, ($p = 0.001$). Similarly, time from metastatic disease to start of trastuzumab therapy was 32 and 12 months, respectively ($p = 0.03$). Nineteen out of 48 (40%) patients had three or more metastatic sites at the start of treatment with trastuzumab. Fifty-two percent (25/48) had skeletal metastases, 40% (19/48) lung metastases, and 38% (18/48) had liver metastases. In the group that later received single monoclonal antibody therapy, we found that 12/19 patients (63%) had received three or more previous chemotherapy regimens compared with 8/29 (28%) in the group who later received combination therapy. Patients underwent echocardiography, to investigate cardiac function with the focus on ejection fraction, before the start of treatment with trastuzumab. Analysis of time to progression, survival from start of trastuzumab therapy and overall survival related to differences in the degree of c-erbB-2 protein expression were based on 38 patients (10 tumours were not separated into strong or moderate expressers). Eleven of the tumours had a moderate (2+) c-erbB-2 overexpression compared with 27 with a strong (3+) overexpression. The patient follow-up during therapy was not standardized in an objective manner in all patients, which is why the response to treatment cannot be correctly defined with the help of medical records. Sometimes only a patient's symptoms were monitored. In most cases, treatment continued until the patients presented progressive symptoms or new metastases, either on clinical examination or with relevant radiological techniques.

Antibody administration

A loading dose of 4 mg/kg was administered intravenously over 90 min, followed by weekly administrations of 2 mg/kg over 30 min. Before trastuzumab infusions, the patients received oral doses of 2 mg clemastin and 1 g paracetamol to reduce the risk of acute side effects. The cytostatics used in combination with trastuzumab varied because of differences in therapeutic principles and previously delivered drugs. The different combinations of chemotherapy and trastuzumab are summarized in Table 2. Nineteen patients (40%) received single-agent therapy with trastuzumab, while 29/48 (60%) received trastuzumab in combination with chemotherapy.

Statistical analysis

For statistical analysis of disease-free survival and time from primary diagnosis to start of treatment with trastuzumab, the Kaplan–Meier method (log-rank test)

Table 1

Patient characteristics, 48 patients

	No. of patents	% (n = 48)	Single treatment	% (n = 19)	Combination treatment	% (n = 29)
Receptor status, Estrogen (ER) and Progesterone (PR)						
ER and PR positive	13	0.27	7	0.37	6	0.21
ER and PR negative	17	0.35	7	0.37	10	0.34
ER positive and PR negative	4	0.08	0	0.00	4	0.14
ER negative and PR positive	4	0.08	1	0.06	3	0.10
ER and PR unknown	10	0.21	4	0.21	6	0.21
No. of positive lymph nodes at diagnosis						
None	13	0.27	5	0.26	8	0.28
1 to 10	25	0.52	11	0.59	14	0.48
$\geqslant 10$	4	0.08	1	0.05	3	0.10
No axillary dissection	6	0.13	2	0.11	4	0.14
No. of metastatic sites						
1	46	0.96	19	1.00	27	0.93
2	37	0.77	18	0.95	19	0.66
$\geqslant 3$	19	0.40	11	0.58	8	0.28
Dominant metastatic sites						
Skeleton	25	0.52	10	0.53	15	0.52
Lung	19	0.40	8	0.42	11	0.36
Locoregional disease	17	0.36	10	0.53	7	2.24
Liver	18	0.38	5	0.26	13	0.45
Adjuvant treatment						
Chemotherapy	31	0.65	12	0.63	19	0.66
Radiation	31	0.65	13	0.68	18	0.62
Hormonal therapy	13	0.27	2	0.11	11	0.38
Adjuvant chemotherapy	31	0.65	12	0.63	19	0.66
CMF	14	0.29	8	0.42	6	0.21
FEC	6	0.13	1	0.05	5	0.17
Tailored high-dose FEC	3	0.06	1	0.05	5	0.17
CMF and AC	3	0.06	2	0.11	5	0.17
High-dose chemotherapy with bone marrow resque	7	0.15	3	0.16	4	0.14
No. of treatments before treatment with trastuzumab						
$\geqslant 3$	27	0.56	15	0.79	12	0.41
Prior chemotherapy regimens						
$\geqslant 3$	20	0.42	12	0.63	8	0.28
Prior hormonal treatment	22	0.46	11	0.58	11	0.38
c-erbB-2 expression						
3+	27	0.56	10	0.53	17	0.59
2+	11	0.23	4	0.21	7	0.24
Positive (not graded)	10	0.21	5	0.26	5	0.17
Disease-free interval			29 months	p = 0.02	21 months	
Median time from primary diagnosis			72 months	p = 0.001	42 months	
Median time with metastatic disease			32 months	p = 0.03	16 months	

was employed, using the JMP 3.1 software from the SAS Institute Inc. The same method was used for analysis of overall survival and survival from start of treatment with trastuzumab.

RESULTS

Median overall survival for all 48 patients was 58.6 months. The median overall survival from start of trastuzumab therapy was 8.5 months and the median time to progression during trastuzumab therapy was 2.2 months. Patients with a strong (3+) overexpression (n = 27) had a non-significant trend to survival advantage from start of trastuzumab therapy compared with patients with a moderate (2+) c-erbB-2 protein overexpression (n = 11), 9.0 months versus 6.9 months (p = 0.09). Sixteen of 48 patients (33%) did not show any sign of response to therapy, according to the medical records. The majority of these patients discontinued trastuzumab treatment after only six courses (6 weeks) of therapy. There were no differences in c-erbB-2 overexpression (2+ or 3+) in the group of patients that showed no response to therapy with trastuzumab compared with those who at least at the beginning of treatment had some kind of response to the therapy. The number of patients on single and combina-

Table 2

Description of therapy for all 48 patients; trastuzumab only (n = 19) or in combination with different chemotherapy regimens (n=29)

	n = 48	%
Trastuzumab only	19	40
Trastuzumab with chemotherapy	29	60
Taxanes	15	52
Weekly paclitaxel	5	17
Paclitaxel every third week	2	7
Weekly Docetaxel	7	24
Docetaxel every third week	1	3
Vinorelbine	10	34
Vinorelbine days 1 and 8	6	21
Weekly vinorelbine	3	10
Vinorelbine every second week	1	3
Carboplatin every third week	1	3
Miltefosin	2	7

tion therapy, respectively, was also the same in the two groups. Among the patients with no response to trastuzumab therapy, we found all six patients with brain metastases. Two patients had brain metastases at the start of treatment and four were given the diagnosis during the first weeks of therapy with trastuzumab. Attempts to make subanalyses of therapy response in relation to different metastatic sites were neither possible nor relevant owing to the small subgroups and the fact that this was not a randomized trial.

All symptoms registered as adverse events during therapy in the medical records are listed in Table 3, including those with an uncertain relationship to the monoclonal antibody treatment. Forty adverse events of some kind were registered for 22 (46%) of the 48 patients. The

Table 3

Adverse events

Fever/Chills at first administration (loading dose)	7 (2)
Pain	5
Fever	4 (1)
Diarrhoea	3
Nausea	3
Fever/chills at subsequent administrations	2
Infection	2 (2)
Oedema	2
Vomiting	2
Pruritus	2
Rash	2 (1)
Reduction of EF but no cardiac symptoms	2
Congestive heart failure (no reduction of EF)	1 (1)
Congestive heart failure with reduction of EF	1 (1)
Dyspnoea	1
Conjunctivitis	1

According to the medical records, a total of 40 adverse events in 22 patients were registered, 8 of which were serious adverse events (requiring overnight hospitalization) and repeated within parentheses. Ten of the patients with adverse events had received trastuzumab alone and 12 had received trastuzumab in combination with chemotherapy.

percentage of adverse events among patients who had received combination therapy was 42% (12/29) compared with 53% (10/19) in the group treated with single-agent trastuzumab. The most common and acute side effects in this study population were fever and chills, which occurred in 7 patients (15%). These acute side effects often occurred only at the first loading dose, but not during subsequent lower-dose infusions. Eight of the patients were hospitalized because of adverse events. Two of these patients (A and B) had serious symptoms of cardiac failure and required intensive care. Both were treated previously with antracycline-containing therapy. The previous treatment with epirubicin was 2024 mg (1124 mg/m^2) for patient A and 2013 mg (1059 mg/m^2) for patient B. Before the onset of cardiac symptoms, patient A had received three courses with trastuzumab alone. A conventional x-ray revealed enlargement of the heart and signs of congestive heart disease. Echocardiography revealed pericardial fluid, of which a total of 1800 ml was extracted. As there were no signs of permanently reduced ejection fraction, the treatment with trastuzumab was resumed two months later, now as combination therapy with paclitaxel, without any cardiac symptoms. Patient B developed symptoms after two courses with trastuzumab and docetaxel. The acute echocardiography showed a markedly reduced ejection fraction of 11%. Two months later, during which treatment was withheld, the ejection fraction improved to 30% and the patient resumed chemotherapy, but no further treatment with trastuzumab was delivered. Two more patients, one with combination therapy (chemotherapy and trastuzumab) and the other with single-agent therapy, had an asymptomatic decreased ejection fraction, but continued treatment. Earlier, these two patients had also been subjected to antracyclines.

DISCUSSION

The majority of patients receiving trastuzumab therapy are unlikely to be included in randomized clinical trials for a variety of reasons, such as non-measurable disease, only skeletal metastases, cerebral metastases, and less optimal clinical condition. Here we present data from trastuzumab therapy in clinical routine. The present group of patients had advanced stage metastatic disease, with a poor prognosis, while they had failed on prior standard regimens. In this material *all* of the first 48 patients in Sweden who received therapy with trastuzumab on a named patient basis were included.

The median overall survival time from start of antibody treatment in the material was a slightly less than median duration of survival in previous reports; 8 months compared with, for example, 13 months (second- or third-line single-agent therapy) and 25 months (first-line combination therapy) (23, 26). This is to be expected, as this patient material is national and population based, and

most likely markedly different from the highly selected patient material in randomized studies aiming at demonstrating positive effects. Thirty-eight patients were divided into strong (3+) or moderate (2+) c-erbB-2 overexpressers. Among these patients, those with a strong overexpression tended to have a better rate of survival from start of treatment with trastuzumab compared with the patients with a moderate (2+) overexpression, which is also reported elsewhere (23, 26). Estimation of the total amount of adverse events as well as the amount of serious adverse events indicated a low degree of toxicity, but was probably underestimated in the medical records. However, our assessments of toxicity in this material confirm results in previous prospective studies (20, 23, 26). The main disadvantage with trastuzumab is its cardiac side effects, which are more common when the antibody is combined with chemotherapy, especially antracyclines. Little is known, however, about the exact mechanisms. Cobleigh et al. (23) reported a reduction in cardiac ejection fraction in 9 out of 222 patients (4%) who received trastuzumab alone, 6 of them being symptomatic. All nine patients had received either prior therapy with antracycline or had a cardiac history before the start of trastuzumab treatment. In previous publications cardiac dysfunction has been estimated as 18–27% in patients given anthracyclines, cyclophosphamide, and trastuzumab compared with 3–8% in patients given anthracycline and cyclophosphamide alone. Similarly, cardiac dysfunction for therapy with paclitaxel and trastuzumab has been reported as 2–13% versus 0–1% in patients given paclitaxel alone (26, 28). With regard to the registered cardiac toxicity, we cannot be sure of how many of the patients in this material underwent echocardiography just for follow-up in clinical routine to compare ejection fraction (EF) before and during therapy with trastuzumab. The number of patients with reduced EF but no cardiac symptoms during therapy may therefore be underestimated in this patient material also.

Important differences in patient characteristics are seen between the two treatment groups concerning time from primary diagnoses to first recurrence, time from primary diagnosis to start of treatment with trastuzumab and time from first recurrence to start of treatment with trastuzumab. Approximately 80% in the group who received single-agent treatment compared with 40% in the group who received combination treatment had received three or more previous chemotherapy and/or hormonal therapies. This is probably explained by the fact that the first patients receiving trastuzumab in Sweden were allowed single therapy only, as there was less experience of the drug, and that the first patients started therapy with trastuzumab at a later, or more advanced stage of disease.

In our patient material 16 patients discontinued therapy owing to disease progression or lack of response. Most of them stopped after only six treatments (6 weeks). This may be too short a treatment period for relevant therapy evaluation, especially when compared with rituximab therapy for malignant lymphomas (29, 30). Response to rituximab therapy improved from 40% to 60% when the patients were treated during eight compared with four consecutive weeks. It is possible that a prolonged course is needed, especially for patients with a large tumour bulk (29, 30). Response evaluation for chemotherapy is normally scheduled after two or three courses given at three-week intervals. It is unlikely that the response to biological treatment should be shorter, rather the contrary.

The method used to determine the protein expression of c-erbB-2 in this material was immunohistochemistry on paraffin-embedded tumour material. For almost all patients the HercepTest (Dako approved by the Food and Drug Administration) was used. In earlier reports, immunohistochemistry was often used probably because it is relatively easy to run. Major disadvantages with the method are problems with grading of the intensity, including inter- but also, intra-observer variability and most likely inter-laboratory variation (31). Standardization of parameters such as method for heat-induced epitope retrieval, automated equipment for immunostaining, and scoring systems are important in order to achieve maximal interlaboratory agreement. Some of the variation between different studies concerning the prognostic and predictive value of c-erbB-2 may be explained by the different methodologies used for detection of c-erbB-2 (31, 32). Gene amplification detected by FISH has become the gold standard, but in clinical routine immunohistochemistry is now often the method of choice. Further investigation is needed concerning which method we should use for c-erbB-2 evaluation in clinical routine.

In conclusion, in this population-derived patient material the recorded toxicity appears to be limited and acceptable, although probably underestimated in the medical records. As in previous reports, the results indicate a better response to trastuzumab therapy in patients with metastatic breast cancer with a strong (3+) compared with a moderate (2+) c-erbB-2 overexpression. Which group of patients would be likely to benefit most from treatment with trastuzumab, and which chemotherapy agents the most optimal to add need to be further studied.

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