Pharmacotherapeutic report trastuzumab (Herceptin®) used as adjuvant

1. Summary

Using Trastuzumab for one year – as adjuvant to sequential chemotherapy with the combination doxorubicin/cyclophosphamide and paclitaxel or other suitable schedules (see 3.b) to treat women with HER2-positive primary breast cancer who have previously undergone surgery – can lead to a 50% reduction in the risk of the disease and the assumption is that general long-term survival increases. Side effects due to the use of trastuzumab are limited. An exception to this is the damage to the heart function which mainly takes the form of an asymptomatic drop in the left ventricle ejection fraction observed in a considerable number of patients (10-15%). 1-3% of the patients subsequently treated with doxorubicin and trastuzumab develop heart failure that can be severe (NYHA class III and IV). Patients older than 50 years of age seem to be more sensitive to this than younger patients. There is no clarity about the degree to which the drop in the left ventricle ejection fraction is reversible and what the long-term consequences are. No data have yet been published over quality of life.

Conclusion on therapeutic value

In breast cancer patients who are HER2-positive and post-primary surgery, the addition of trastuzumab to chemotherapeutic treatment with doxorubicin/cyclophosphamide, followed by paclitaxel, reduced the risk of disease relapse by approximately 50%. A similar effect was found when trastuzumab was added to a chemotherapeutic treatment based predominantly on doxorubicin or epirubicin. The effect of trastuzumab seems to occur independently: it is not related to the severity of the disease, the hormone receptor status, the use of tamoxifen or an aromatase inhibitor, or the use of radiotherapy. The use of trastuzumab for one year in combination with doxorubicin/cyclophosphamide treatment followed by paclitaxel is also likely to improve overall survival. This is less obvious when prior treatment was based primarily on an antracyclin. Furthermore, there is a lack of clarity about the optimum duration of the adjuvant treatment with trastuzumab. The risk of cardiac side effects is quite substantial. Trastuzumab causes a largely asymptomatic – though possibly long-term – reduction in the heart function in 10-20% of patients, which can lead to congestive heart failure in some patients (1-3%). Therefore, apart from prior screening and monitoring the heart function during sequential courses of treatment with doxorubicin and trastuzumab, continued monitoring of the heart function is required after the treatment has ceased. Depending on the result of future safety assessments, the exact role of trastuzumab in the adjuvant treatment of HER2-positive breast cancer will be further defined. The potential advantages of the use of this drug for this indication, as well as the potential disadvantages, need to be considered. Within this framework, the combination of chemotherapy and trastuzumab has a therapeutic added value for women with HER2-positive primary breast cancer who have undergone surgery.

2. Introduction

Drug	Trastuzumab.
Composition	Trastuzumab 150 mg, flacon with concentrate for solution for intravenous infusion.
Registered indication	The treatment of patients with metastised breast cancer with

	tumours demonstrating an over-expression of HER2. - as monotherapy for the treatment of those patients who have been treated for their metastised disease with at least two chemotherapy schedules. Prior therapy must include at least one antracyclin derivative and a taxan unless the patients are unsuited to these treatments. Hormone receptor-positive patients must also not – or no longer – respond to hormone therapy unless they are not eligible for this therapy (2000*). - in combination with paclitaxel for the treatment of patients whose metastised disease has not been treated with chemotherapy (2000*). - in combination docetaxel for the treatment of patients whose metastised disease has not been treated with chemotherapy (2004*). *year of registration.
Indication to be evaluated	Adjuvant treatment of HER2-positive primary breast cancer (invasive, not metastasized), that have HER2-overexpression, after surgery, chemotherapy (neo-adjuvant or adjuvant) and radiotherapy (if applicable)..
Dose	Metastasized breast cancer: initial dose for one week: 4 mg/kg. Subsequently: 2 mg/kg/week. Treatment is continued until progression occurs. Adjuvant treatment of breast cancer: - initial dose: 4 mg/kg, followed by 2 mg/kg/week - initial dose: 8 mg/kg, followed by 6 mg/kg once per three weeks. Treatment with trastuzumab is to be continued for one year or terminated earlier if progression occurs.
Mode of action	Trastuzumab is a recombinant DNA-derived humanised IgG1 monoclonal antibody that is prepared from the CHO (Chinese hamster ovary) mammalian cell line. The HER2-protein stands for the human epidermal growth factor receptor-2 protein. Overexpression of the HER2 receptor is found in approximately 25% of mammalian tumours. Binding of trastuzumab to HER2 inhibits the growth of tumour cells and mediates antibody-dependent cellular cytotoxicity in the cancer cells with HER2-protein overexpression.
Other	On the 28th April 2006, the CHMP expressed a positive opinion regarding this indication

3. Criteria for the evaluation

In the Netherlands breast cancer is the most frequently occurring malignant disease in women. Breast cancer is confirmed in about 12,000 patients annually and more than 3,000 women die due to the consequences of the disease. The annual incidence of breast cancer has been increasing for quite some time (CBO Breast Cancer Guideline 2005[1]; web-site VIKC, data 1989-2003[2]).

Since the beginning of the nineteen-seventies, when systemic adjuvant chemotherapy was introduced for the treatment of operable primary breast cancer, the prognosis of the disease has improved considerably, partly due to the use of tamoxifen, aromatase and taxans. By making optimum use of these and other therapeutic possibilities, the relative risk of metastases and mortality has been reduced by more than 50% in spite of the increasing incidence of breast cancer. The effect of the improved treatment extends over a time period of more than 15 years (EBTCG valuation 2005)[3].

Approximately 25% of breast tumours demonstrate an overexpression of epidermal growth factor receptor-2 (HER2). Metastases of these tumours occur relatively rapidly. The occurrence of HER2 is correlated to a poor prognosis of the disease[1,3]. Because of the positive results of trastuzumab in treating HER2-positive metastasized breast cancer, attempts are currently initiated at an early stage of the disease to eliminate or reduce the influence of HER2-mediated processes on the disease's development. In May 2005 the provisional results of three large phase III studies were announced in which the adjuvant use of trastuzumab was compared with the effect of a current chemotherapeutic treatment. This was followed in the summer of 2005 by a publication in a peer-reviewed journal (Piccart-Gebhart et al. 2005[4]; Romond et al. 2005[5]). The outcomes of the interim analyses resulted in patients from the control groups being switched to treatment with trastuzumab. In addition, the guidelines for adjuvant treatment of primary breast cancer were adjusted in many countries.

3.a Applicability

Trastuzumab was registered in the United States in 1998 and in the EU in 2000 for the treatment of patients with HER2-positive metastised breast cancer (1B text[6]). The use of trastuzumab in the (neo-)adjuvant treatment of patients with primarily operable breast cancer has not yet been registered.

3.b. Choice of comparative treatment

Adjuvant chemotherapeutic treatment that is recommended in the treatment guidelines[1] is eligible as comparative treatment. In general this is comprised of an antracyclin that is administered, in combination with other drugs, during a two- to four-week cycle, four to six times. The combinations that are eligible are cyclophosphamide/methotrexate/5-fluorouracil (CMF: 6 cycles), doxorubicin/cyclophosphamide (AC: 4 cycles), 5-fluorouracil/epirubin or doxorubicin/cyclophosphamide (FEC/FAC: 4-6 cycles), or doxorubicin/docetaxel/cyclophosphamide (TAC: 4-6 cycles). There are indications that TAC is more effective than FEC during overexpression of HER2. Treatment with FEC is preferred (5 cycles), AC/paclitaxel (4 cycles) or TAC (6 cycles)[1]. Apart from the presence or absence of HER2, the choice of treatment also depends on age, the degree of advancement of the disease (in particular the spread into the lymph system), and the hormone receptor status. This last parameter determines whether further use is made of tamoxifen or an aromatase inhibitor[1]. The treatment with which the effect of

trastuzumab was compared in the two studies, doxorubicin/cyclophosphamide (AC) followed by paclitaxel, is in accordance with the advice given in the guideline[1].

3.c. Methods

This evaluation was based on study results published in renowned (peer-reviewed) journals. For the purpose of the evaluation, a literature search was done on 10th February 2006 (Medline via PUB-Med and the Cochrane Library). The search terms used were trastuzumab, with or without "early or operable breast cancer", "anthracyclins", "docetaxel", "epirubicin", "paclitaxel" and "taxans". The search provided a number of additional references[14,15].

Therapeutic evaluation

This evaluation is limited to the four phase III studies in which the effects of trastuzumab as adjuvant to chemotherapeutic treatment after the surgical removal of tumour tissue is evaluated. With regard to side effects, data from the study of patients with metastised breast cancer[6] was used.

4.a. Phase III study of adjuvant use – clinical study set-up

Up till now the provisional results of three large and well-designed phase III studies have been published[4,5] (Table 1). Participants in the studies were women with surgically treated primary (stages I-III) HER2-positive (IHC 3+ and/or FISH) breast cancer primarily with lymph gland involvement (node-positive). The diagnosis took place according to criteria that apply to metastasised breast cancer[1,5]. Two studies also involved high-risk (tumour > 2 cm and oestrogen receptor-positive or progesterone receptor-positive, or tumour > 1 cm and hormone receptor-negative) patients without diseased lymph glands (NCCTG N9831 and HERA)[4,5]. Prior to the treatment with trastuzumab, in two studies (NCCTG N9831, NSABP B-31) patients were treated with the combination doxorubicin/cyclophosphamide (4 three-weekly cycles). The basic treatment was followed by taxan treatment lasting three months (table 1). In the NCCTG N9831 and NSABP B-31 studies, treatment with trastuzumab was initiated by starting the treatment with paclitaxel (table 1)[5]. In the third leg of the NCCTG N9831 study, only after treatment with paclitaxel did patients receive weekly trastuzumab treatment for one year[5]. In spite of the dissimilarity in the treatment with paclitaxel (weekly vs three-weekly), the provisional results of the NCCTG N9832 (groups A. and C.) and NSABB B-31 studies have been jointly analysed and published[5].

Table 1. Phase III studies in relation to the adjuvant use of trastuzumab on patients with breast cancer.

Study	Patients	Prior chemotherapy	Chemotherapy, with or without trastuzumab	Number of patients[1]
Inter-group NCCTG N9831 (Romond et al. 2005[5])	HER2-positibe, gland-positive, high-risk Gland-negative (N=3,000)	Doxorubicin/ cyclophosphamide (60/600 mg/m^2, q3w x 4)	A. Paclitaxel (80 mg/m^2, qw x12)	872
			B. Paclitaxel (80 mg/m^2, qw x12) ➔ Trastuzumab (qw, 52 weeks)[2]	981[4]
			C. Paclitaxel (80 mg/m^2, qw x12) + Trastuzumab (qw, 52 weeks)[2]	864

NSABP B-31 (Romond et al. 2005[5])	HER2-positive, gland-positive (N=2,700)	Doxorubicin/ cyclophosphamide (60/600 mg/m², q3w x 4)	A. Paclitaxel (175 mg/m², q3w x 4)	807
			B. Paclitaxel (175 mg/m², q3w x 4) + Trastuzumab (qw, 52 weeks)[2]	808
Herceptin Adjuvant (**HERA**) trial (Piccart-Gebhart et al. 2005[4])	HER2-positive, gland-positive, high-risk Gland-negative (N=5,090)	Every possible adjuvant chemotherapy whether or not in combination with radiotherapy	A. No further chemotherapy	1,693
			B. Trastuzumab (q3w, 52 weeks)[3]	1,694
			C. Trastuzumab (q3w, 104 weeks)[3]	1,674

[1] Evaluated on the basis of intention to treat.

[2] Booster dose (week 1): 4 mg/kg, followed by 2 mg/kg/week.

[3] Booster dose (week 1): 8 mg/kg, followed by 6 mg/kg once per 3 weeks.

[4] using randomisation.

The HERA study evaluated the effect of one or two years' adjuvant treatment with trastuzumab[4]. However, the set-up of this study is not the same as that of the above-mentioned studies, as the patients did not need to have been treated, prior to or after surgical treatment of the primary breast cancer (whether or not in combination with radiotherapy), with at least four cycles of a chemotherapy, summarily described, based mainly on the use of an antracyclin[4]. Just as in the second leg of the NCCTG N9831 study, treatment with trastuzumab was not started until the prior treatment (chemotherapy or radiotherapy) had been completed. However, trastuzumab was not administered on a weekly basis but per three weeks (table 1)[4]. Randomisation for the three groups took place at the latest by seven weeks after the start of the last chemotherapy or six weeks after terminating radiotherapy or the last surgical treatment[4].

4.b. Phase III study adjuvant use – patients

In the studies below, patients were treated surgically (lumpectomy or mastectomy) prior to the adjuvant chemotherapy and treatment with trastuzumab. During the continued treatment with trastuzumab, most of the patients were also subjected to radiotherapy[4,5]. In the NCCTG N9831and NSABP B-31 studies, in total 1,672 patients were treated with trastuzumab[5]. The control group comprised the data of 1,679 patients. The number of patients between 40-50 and 50-60 years was pretty much the same (total ca. 67-69%). The remaining number was spread fairly evenly among the younger and the older patients. Between 1-3 lymph glands were afflicted in most patients (ca. 53%). The size of the tumour was in most cases < 2 cm (39%) or between 2 and 4 cm (45%). In most patients the tumour was histologically moderately (28%) or poorly (69%) differentiated. In slightly less than half of the patients, oestrogen receptors were present (48%), whilst in approximately 60% of the patients, progesterone receptors could be demonstrated. Approximately 11% of the patients were also treated with neo-adjuvant chemotherapy. Almost all the patients (98%) underwent the initial treatment with doxorubicin en cyclophosphamide after surgery. 97% of these patients started treatment with paclitaxel. This treatment was completed by 95% according to schedule. There were no individual differences between the various research groups with respect to the above-mentioned characteristics described above[5].

The HERA study (N evaluated=5.081) mainly involved patients treated with adjuvant chemotherapy (89%)[4]. Five percent of the patients received chemotherapy prior to surgical treatment, whilst six percent were treated chemotherapeutically both before and after the operation. The published results only involve the control leg (N=1.693) and the leg in which trastuzumab was administered during one year (N=1.694). In both groups most of the patients were between 35-50 and 50-60 years of age (resp. 44 and 32%). Of the remaining patients, most of them were older than 60 years (16%). In contrast to the two above-mentioned studies, no lymph glands were afflicted in most of the patients (ca. 32-33%)[5]. The number of patients with 1-3 afflicted lymph glands was pretty much the same as the number with four or more afflicted glands (29-29%). The size of the tumour was in most cases < 2 cm (39-40%) or between 2 and 4 cm (42-44%). In most of the patients the tumour was histologically moderately (32%) or poorly (60%) differentiated. Oestrogen receptors were present in slightly less than half of the patients (42-45%), whilst in approximately 32% of them, progesterone receptors could be demonstrated. Approximately three-quarters of the patients were treated with radiotherapy. Most of the patients (94%) had been treated prior to treatment with trastuzumab with an antracyclin either with (25-26%) or without (68%) a taxan. In patients treated only with antracyclin, epirubicin was the drug used most frequently (doxorubicin: 23-25%: median cumulative dose: 238-239 mg/m^2; epirubicin: 43-45%; median cumulative dose: 397-405 mg/m^2). With respect to the characteristics referred to above, there were no individual differences between the various study groups[4].

In the above-mentioned studies oestrogen receptor-positive patients were also treated, mostly after ceasing chemotherapy, with tamoxifen (20 mg/day). During a later stage of the studies, many post-menopausal patients were also treated with an aromatase inhibitor, as a result of an altered pharmacotherapeutic insight[1,4,5].

4.c. Phase III study – evaluation and study parameters

The therapeutic evaluation of trastuzumab in the adjuvant treatment of primary, HER2-positive breast cancer was based on the criteria efficacy, effectiveness, side effects, quality of life, experience, applicability and ease of use.

As surrogate parameter for general survival, disease-free survival was the primary endpoint of the phase III studies. Disease-free survival was defined as the time to the recurrence of the disease (local or metastised), the occurrence of another malign disease or death[4,5]. Secondary endpoints were general survival, the time to metastasis, death due to breast cancer, the occurrence of contralateral breast cancer, and death due to another primary malign disease.

4.d. Results

4.d.1 NCCTG N9831 and NSABP B-31

The results of the NCCTG N9831 and NSABP B-31studies involve an interim analysis after reaching a number of events relating to the primary endpoint parameter established in advance[5]. The median follow-up time was 2.0 years (N9831: 1.5; B-31: 2.4). Statistical evidence for a different result of the two studies could not be found. Certain important results of the combined interim analysis have been stated in table 2. For the group treated with trastuzumab, the percentage (Kaplan-Meijer estimate) three years after randomisation of disease-free patients still alive was calculated to be 87.1% compared with 75.4% in the control group (difference: 11.8% [95% BI: 8.1-15.4%]). After four years these percentages were respectively 85.3 and 67.1% (difference: 18.2% [95% BI: 12.7-23.7%). With respect to general survival, the percentages calculated after three years were: 94.3 vs. 91.7% (difference 2.5%; 95% BI: 0.1-5.0%), and after four years 91.4 vs.

86.6% (difference: 4.8% [95% BI: 0.6-9.0%). What is noticeable is that after four years a severe drop in mortalities is prognosticated. Concerning the occurrence of metastases, after three years these had not occurred in 90.4% of the patients treated with trastuzumab, compared with 81.5% of the patients in the control group (difference: 8.8% [95% BI: 5.5-12.1%]). After four years these percentages were 89.7 and 73.7% respectively (difference: 15.9% [95% BI: 11.0-20.8%)[5].

Table 2. Provisional results of the NCCTG N9831 and NSABP B-31 studies (Romond et al. 2005[5]).

Endpoint	Trastu-zumab (N)	Trastu-zumab (%)[1]	Control (N)	Control (%)[1]	Reduction (%)	Hazard ratio (95% BI)	P[2]
Diseased patients/ Disease-free survival	133	8.0	261	15.5	7.5	0.48 (0.39 – 0.59)[3]	<0.0001
Patients with breast cancer/time to recurrence of breast cancer	117	7.0	235	14.0	7.0	0.47 (0.38 – 0.59)	<0.0001
Patients with metastases/time to metastasis	96	5.7	193	11.5	5.8	0.47 (0.37 – 0.61)	<0.0001
Mortality/general survival	62	3.7	92	5.5	1.8	0.67 (0.48 – 0.93)[4]	0.015
Death due to breast cancer	53	3.2	79	4.7	1.5	0.66 (0.47 – 0.94)	0.02
Occurrence of contralateral breast cancer	4	0.2	6	0.4	0.2	0.64 (0.18 – 2.27)	0.48
Occurrence of a different primary malign disease	5	0.3	20	1.2	0.9	0.24 (0.09 – 0.64)	0.002

[1] number of patients on the basis of intention to treat (trastuzumab: N=1,672; control; N=1,679).

[2] P-values are dualistic. BI: reliability interval.

[3] Hazard ratio calculated for the first symptom of disease observed.

[4] Hazard ratio calculated for death.

Discussion: the gains from treatment with trastuzumab, shown by the near doubling of the disease-free survival, is mostly due to a 50% decrease in the number of patients with disease relapse, whether or not in a metastasized state. The gain in overall survival is somewhat smaller. What is striking is that treatment with trastuzumab greatly reduces the chance, however small, of the development of a second malignant disease. For the various sub-groups, particularly with respect to the presence or lack of hormone receptors, no distinguishing effect of trastuzumab was observed. On the basis of provisional results, the various treatment schedules of paclitaxel do not seem to affect the results of treatment with trastuzumab.

Conclusion: in HER2-positive patients with mainly lymph gland-positive breast cancer, the risk of disease relapse is reduced by approximately 50%, independent of the hormone receptor stratus due to the addition of trastuzumab to the chemotherapeutic treatment with paclitaxel following treatment with doxorubicin/cyclophosphamide. The number of patients that die from the disease is reduced by almost one-third.

4.d.2 HERA

The results of the HERA study involve an interim analysis after reaching an *a priori* determined number of events in relation to the primary endpoint[4]. The median duration between diagnosis and the start of treatment with trastuzumab was 8.4 months (inter-quarter range: 7.1–9.6 months). The median duration of follow-up was 1.0 year (0-36 months). A number of important results of the interim analysis are mentioned in table 3. The number of disease phenomena that occurred in the group treated with trastuzumab for one year (B.) was equal to that in the group (C.) treated for two years (see table 1). No further results were announced for the last group (C.)[4]. No distinguishing effect of trastuzumab was observed for the various sub-groups.

Table 3. Provisional results of the HERA study (Piccart-Gebhart et al. 2005[4]).

Endpoint	Trastu-zumab (N)	Trastu-zumab (%)[1]	Control (N)	Control (%)[1]	Reduction (%)	Hazard ratio (95% BI)	P[2]
Diseased patients/ Disease-free survival	127	7.5	220	13.0	5.5	0.54 (0.43– 0.69)[3]	<0.0001
Patients with metasta-ses/time to metastasis	85	5.0	154	9.1	4.8	0.49 (0.38 – 0.63)	<0.0001
Mortality/general survival	29	1.7	37	2.2	0.5	0.76 (0.47 – 1.23)[3]	0.06
Death due to breast cancer	23	1.4	34	2.0	0.6		
Occurrence of contralateral breast cancer	6	0.4	7	0.4	0		
Occurrence of a different primary malign disease	3	0.2	6	0.4	0.2		

[1] number of patients on the basis of intention to treat (trastuzumab: N=1,694; control; N=1,693).

[2] P-values are dualistic. BI: reliability interval.

[3] Hazard ratio calculated for death.

For the group treated during one year with trastuzumab, the percentage calculated (Kaplan-Meijer estimate) two years after randomisation of patients still alive and disease-free was 85.8 % compared with 77.4% in the control group (difference: 8.4% [95% BI: 2.1-4.8%]). With respect to the occurrence of metastases, these had still not occurred after two years in 90.6% of the patients treated with trastuzumab compared with 82.8% of the patients in the control group (difference: 8.8% [95% BI: 5.5-12.1%]). With respect to the estimated general survival, after two years there was no difference between both groups: the calculated percentages are 96.0 and 95.1%[4].

Discussion: the most important differences with the study[5] described above are the participation of a large group (32%) of patients whose lymph glands were not affected, the possibility that patients had undergone radiotherapeutic treatment prior to the treatment with trastuzumab and the less strict definition of chemotherapy, so that the number of patients treated with a taxan was relatively low. Due to the looser criteria, patients may have received an average of only four instead of six chemotherapy treatment cycles. Furthermore, epirubicin was used much more often than doxorubicin. In comparison with the other studies, the start of treatment with trastuzumab was delayed. Finally, the follow-up duration of the HERA study at the moment of the interim-report was only one year. It is particularly due to the short follow-up (1 vs. 2 years) that the results of the HERA study cannot properly be compared with those of the two studies discussed early and it is not possible to determine whether, and how, the differences

between the three studies do actually affect the treatment results. However, what is noticeable is that with respect to disease-free survival the results show a great deal of correspondence.

Final conclusion regarding the results: The addition of one year's treatment with trastuzumab to the chemotherapeutic treatment of primary operated breast cancer reduces the risk that the disease recurs by approximately 50%. This also applies to the number of patients in whom metastasis occurs. These effects of trastuzumab seem to occur independently and are not related to the severity of the disease, the hormone receptor status, the use of tamoxifen or aromatase inhibitors and the use of radiotherapy. In two of the three studies, treatment with trastuzumab led to a significant improvement and, in spite of the short duration of the follow-up, probably to a clinically relevant increase in general survival. There is as yet no clarity about the optimum duration of the adjuvant treatment with trastuzumab, whether or not given in combination with paclitaxel (upon initiation) following prior treatment with the combination doxorubicin/cyclophosphamide or a different antracyclin-containing treatment.

4.e. Side effects

The percentage of patients that ceased treatment in the NCCTG N9831 and NSABP B-31 studies due to side effects other than cardiac ones was 2.3%[5]. In the HERA study 8.5% of the number of patients in the group treated with trastuzumab stopped treatment prematurely, mainly as a result of side effects (5.5%)[4]. In view of the relatively low dropout percentages and the large number of patients (> 90%) who continued taking the entire medication schedule, the treatments investigated seem to be reasonably well tolerated.

4.e.1. Cardiac side effects

The most important side effect of trastuzumab is the reduction in the heart function, causing a reduction in the left ventricle ejection fraction (LVEF) which can eventually lead to congestive heart failure. In treating metastised breast cancer the occurrence of congestive heart failure is closely associated with the prior use of antracyclins, in particular doxorubicin. Trastuzumab should therefore not be given simultaneously with an antracyclin, whilst the cumulative administered dose of doxorubicin is limited to 450-550 mg/m^2. At this level the incidence of cardiotoxicity is 5-10% (dropouts due to cardiotoxicity in the NCCTG N9831 and NSABP B-31 studies after chemotherapy: 6.7%)[5]. However, it has recently become apparent that considerable cardiotoxicity already occurs at cumulative doses of less than 300 mg/m^2 (Swain et al. 2003[7]; Ewer & Lipmann 2005[8]). In the studies the average cumulative dose (± 240 mg/m^2)[4] or the maximum cumulative dose achieved by most patients of 240 mg/m^2 was far under this value. What is also important for assessing cardiotoxicity is that patients with a reduced heart function were excluded from participation in the studies.

Although cardiac mortality in all studies was negligible (table 4), the subsequent use of doxorubicin and trastuzumab in the NCCTG N9831and NSABP B-31 studies led to a clear increased number of patients with congestive heart failure NYHA class III or IV (table 4)[5] (Tan-Chiu et al. 2006[9]). The relatively low percentage of patients with heart failure in the HERA study seems to be related to the relatively extensive use of epirubicin (66%) and/or the longer period of time between the course of antracyclin and the start of treatment with trastuzumab[4].

Table 4. Severe cardiac side effects as a result of the use of trastuzumab after prior treatment with doxorubicin

Study	LVEF sufficient at start	Patients who dropped out after DC (%)	Trastuzumab (after antracyclin)			Control		
			CHF (%)	Cardiac death (%)	Total (%)	CHF (%)	Cardiac death (%)	Total (%)
N9831			20 (2.3)	1	30 (2.9)	0	0	0
B-31	3,497	233 (6.7)	31(4.1)	0	31 (4.1)	4	1	5 (0.8)
HERA	3,387	--	9 (0.6)	0	10 (0.6)	0	1	1 (0.1)

[1] CHF NYHA class III and IV.

An asymptomatic drop in the LVEF was observed in many patients. In the NCCTG N9831 and NSABP B-31 studies the administration of trastuzumab was interrupted or prematurely terminated in respectively 164 (14.2%) and 54 (4.7%) of the patients due to the occurrence of an asymptomatic reduction in the LVEF or other cardiac side effects (mainly CHF NYHA I-IV)[5,9]. In the NSABP B-31 study alone 102 (14.1%) patients terminated treatment with trastuzumab prematurely due to an asymptomatic drop in the LVEF[9]. Analysis of the cardiotoxicity of the NSBAP B-31 study shows that a considerable proportion of the patients treated with trastuzumab had still been receiving medicinal treatment six or more months after ceasing treatment[9]. In the HERA study there were signs of symptomatic heart failure (incl. CHF NYHA III/IV) in 29 patients (1.7%; P< 0.001); vs. 1 patient (0.06%) in group A). A drop in the LVEF of 10% or more was observed in 113 (7.1%) of the patients treated with trastuzumab as compared with 34 (2.2%; P< 0.001) patients in the control group[4]. In patients from the NSABP B-31 study, it seems that the occurrence of cardiotoxicity was related to age: heart failure occurred more frequently in older patients (> 50 years) than in younger patients[9]. Further predictive value was provided by the LVEF after ceasing treatment with doxorubicin and cyclophosphamide[9].

4.e.2. Other side effects

Apart from the cardiac side effects caused by the use of trastuzumab in the NCCTG N9831 and NSABP B-31 studies, there were no other specific side effects. Interstitial pneumonitis did occur in respectively five (N9831) and four (B-31) patients as a result of which one patient died in both studies[5]. In the HERA study there were more severe side effects in the patients treated with trastuzumab than in the control group (7.9 vs. 4.4%; P< 0.001), in particular infections and vascular problems[4].

Discussion & conclusion: in comparison with the oncolytics used in the studies mentioned here, the use of trastuzumab only led to a limited degree of severe side effects. One exception to this, however, is the damage to the heart function which was seen, particularly in the form of an asymptomatic drop in the left ventricle ejection fraction, in a considerable number of patients (10-20%). This results in heart failure, sometimes severe (NYHA class III and IV), developing in 1-3% of the patients treated with doxorubicin and trastuzumab. Patients older than 50 years seem to be more sensitive to this than younger patients. A matter of concern is the question to which extent the drop in the left ventricle ejection fraction is reversible. The NSBAP B-31 study shows that many patients with heart failure were still receiving medicinal treatment six months after the diagnosis of this side effect. In contrast to this, Ewer and Lippmann[8] recently claimed that the myocardial dysfunction observed in patients with metastised breast cancer who had been treated with trastuzumab, was usually of a reversible nature (2-4 months) (see also Ewer et al. 2006[10]). Prior screening and monitoring of the heart function is necessary during treatment with doxorubicin and trastuzumab. For the moment, an additional requirement exists to continue monitoring the heart function even after treatment has ceased. The reason for this is the persistent nature of the drop in the left ventricle ejection fraction that has been observed in the adjuvant treatment of primary breast cancer.

4.f. Quality of life
As yet no data on the quality of life have been published from the studies discussed in this evaluation.

4.g. Experience
Trastuzumab has been used, alone or in combination with a taxan, for the treatment of metastised breast cancer since 1999. Sufficient experience has been obtained with trastuzumab.

4.h. Costs
One flacon of 150 mg trastuzumab per treatment is sufficient for most patients (3-weekly dose is 3x the weekly dose). Including the booster dose, the costs of adjuvant treatment per patient for one year are 53 x 704 = 37,312 Euro (AIP excl. VAT [Z-Index February 2006]). These costs are in addition to those of the necessary chemotherapeutic treatment with, for example, doxorubicin/cyclophosphamide and docetaxel or paclitaxel (see 4.a.).

5. Specific details
The results of a fourth phase III study (BCIRG 006) have only been published in abstract form (Slamon et al. 2005)[11]. In this study the set-up of two of the three study legs is comparable with that of the NCCTG N9831 and NSABP B-31 studies, but paclitaxel is replaced by docetaxel. In a third leg, the effect of the combination of an antracyclin-free treatment (carboplatin/docetaxel) with trastuzumab is investigated. The provisional results of this study indicate that the effect of treatment with docetaxel is the same as treatment with paclitaxel[11].
The results of a phase II/III study were recently published (Joensuu et al. 2006)[12] in which, following an operation, the effect was investigated of a short-lasting treatment with trastuzumab (1x per week during 9 weeks; with vs. without) together with docetaxel (3 cycles) or vinorelbine (3 cycles), following by FEC (3 cycles). After a median follow-up duration of three years it turned out that subsequent treatment with docetaxel plus FEC (3 cycles) was more effective than treatment with FEC plus vinorelbine (3 cycles; 91 vs. 86%; HR prior to the recurrence of the disease or death: 0.58; 95% BI: 0.40-0.85; P=0.005). With respect to general survival there was no difference between these treatments (HR: 0.66: 95% BI: 0.38-1.17; P=0.15). In patients with an HER2-positive cancer, disease-free survival was longer when trastuzumab was added to the treatment with docetaxel or vinorelbine (89 vs. 78%; HR: 0.42; 95% BI: 0.21-0.83; P=0.01). The 'short' treatment with trastuzumab that was implemented in this way was not associated with a reduction in the LVEF or heart failure. Due particularly to the small number of patients, it is not clear what consequences the results of this Finnish study will have for the set-up of the adjuvant treatment of primary operated HER2-positive breast cancer with chemotherapy and trastuzumab[12].

In the meantime the provisional results have also been published for two phase II studies in which the neo-adjuvant use of trastuzumab in combination with, sequentially, paclitaxel (4 cycles) and FEC (4 cycles) or with docetaxel alone (6 cycles) was investigated (Buzdar et al. 2006[13]; Coudert et al. 2006[14]). The addition of trastuzumab led to a greatly increased response (CR+PR)[11] or a high response as such[14].

6. CFH-evaluation

Due to the 50% reduction in the risk of the recurrence of the disease and the likelihood that general survival will increase in the long term, a one-year treatment with trastuzumab in addition to sequential chemotherapy with the combination

doxorubicin/cyclophosphamide and paclitaxel or other schedules mentioned in the guideline[1] can be used on women with HER2-positive primary breast cancer that has been treated surgically. There is a not inconsequential risk of cardiac side effects. In 10-15% of the patients, trastuzumab causes a reduction in heart function, which is usually asymptomatic but possibly long-term, and which in some patients (1-3%) can turn into congestive heart failure. Apart from prior screening and monitoring of the heart function during treatment, it is therefore also necessary to continue monitoring the heart function after treatment has ceased. The exact place of trastuzumab in the adjuvant treatment of breast cancer will become increasingly clear during the next few years, partly depending on the results of further safety studies. The possible advantages of using this drug for this indication should be weighed up against the possible disadvantages involved. Within this framework the combination of chemotherapy and trastuzumab has a therapeutic added value on women with HER2-positive primary breast cancer who have been treated surgically.

7. Literature

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