available at www.sciencedirect.com

SCIENCE DIRECT®

journal homepage: www.ejconline.com

Current Perspective

Adjuvant trastuzumab therapy for HER2-overexpressing breast cancer: What we know and what we still need to learn

*Martine J. Piccart-Gebhart**

Medicine Department, Jules Bordet Institute, Rue Heger-Bordet, 1, Boulevard de Waterloo 125, 1000 Brussels, Belgium

ARTICLE INFO

Article history:
Received 21 April 2006
Accepted 27 April 2006
Available online 27 June 2006

Keywords:
Breast cancer
Adjuvant therapy
Trastuzumab
Clinical trials

ABSTRACT

With the reporting of five studies with different and complementary designs, but all demonstrating a similar and striking benefit from the targeted drug trastuzumab in HER2-overexpressing breast cancer, the year 2005 has profoundly marked the history of randomised adjuvant breast cancer trials. In view of the halving in recurrence risk, obtained at the real but small risk of cardiotoxicity, these results are generating hope in women affected with this aggressive form of the disease. But at the same time these results pose real challenges to healthcare authorities faced with the high cost of the anti-HER2 monoclonal antibody. These results also leave oncologists and patients to deal with a complex treatment tailoring process that needs to take into account risk of an early relapse as well as the benefit versus risk of trastuzumab according to the different patterns of administration used in the clinical trials.

1. Introduction

The rational development of trastuzumab, a humanised anti-HER2 monoclonal antibody and the second molecular targeted therapy for breast cancer after tamoxifen, started in 1984 with the identification of the HER2-neu oncogene.[1] This was soon followed by its cloning[2,3] and the demonstration that an anti-HER2 monoclonal antibody is able to inhibit neu transformed cells.[4] The bench-to-bedside process was initiated in 1987 when the correlation of HER2 amplification with poor prognosis in breast cancer was found;[5] it received considerable attention in the late 1990s and early 2000 when trastuzumab, given in combination with chemotherapy, was shown to improve survival of metastatic HER2-positive disease,[6] and it culminated in 2005 by the demonstration that adjuvant trastuzumab – in 5 randomised clinical trials – reduces the risk of recurrence of HER2-positive disease by roughly 50%, a magnitude rarely observed in breast cancer trials.[7–10] These trials are analysed and discussed below.

2. Published and/or reported adjuvant trastuzumab trials: similarities, differences and design issues

Table 1 summarises the design of the published trials, namely the HERceptin® Adjuvant (HERA) trial,[7] the combined North American trials, NSABP-B31 and NCCTG/N9831,[8] the BCRIG 006 trial[9] and the Finnish trial.[10]

While a total of 13,353 patients were accrued, a substantial number of patients are not included in the current analysis: 1694 patients belonging to the 2-year trastuzumab arm of the HERA trial (the data for which are still accumulating); 842 patients enrolled in the sequential chemotherapy → trastuzumab arm of the N9831 trial (an arm unsuitable for combined analysis with NSABP-B31); 334 patients with pending follow-up (325 in B31 and N9831 and 9 in HERA); and, finally, 152 patients excluded from N9831 because of enrolment in the control arm during its temporary closure due to safety concerns of the concomitant trastuzumab-chemotherapy arm.

* Tel: +32 2 541 32 06; fax: +32 2 538 08 58.
E-mail address: martine.piccart@bordet.be.
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2006.04.008

Table 1 – Adjuvant trastuzumab trials: designs and patient characteristics

	HERA	Combined populations B31 // N9831	BCIRG 006	Finnish trial
Accrual / patients included	5090/3387	2043/1736 // 2766/1615	3222/3222	232/232
Median follow-up (months)	12	24	23	36
Treatment regimens	Any accepted CT regimen H 1 year after completion of CT H 2 years after completion of CT (not included in analysis)	AC × 4 → P × 4 AC × 4 → P × 4 + H Note: P given 3 weekly AC × 4 → P × 12 AC × 4 → P × 12 + H starting concurrently with P AC × 4 → P × 12 + H starting after P (not included in analysis) Note: P given weekly	AC × 4 → D × 4 AC × 4 → D × 4 + H starting concurrently with D DC[b] × 6 + H Note: D given 3 weekly	V weekly × 8 or D 3 weekly × 3 with or without concomitant H weekly × 9 → then FEC 3 weekly × 3
Trastuzumab schedule	Every 3 weeks	Weekly / weekly	Weekly with CT, then every 3 weeks	Weekly
Primary endpoints	DFS	OS / DFS (DFS for combined analyses)	DFS	RFS
HER2 testing	Centralised IHC ± FISH	IHC a/o FISH in 'approved' laboratories	Centralised FISH	Centralised CISH
Age < 50 years (% with)	51	51	52	NA
Node-negative disease (% with)	32[a]	5.7	29[b]	16[c]
Grade 3 tumours (% with)	60	69	NA	65
Taxane-based chemotherapy (% with)	26	100	100	50
Planned endocrine therapy (% with)	46	52	54	NA
Normal cardiac function	At completion of locoregional therapy and chemotherapy	At completion of AC × 4	After surgery	After surgery
Participating countries (*n*)	39	1	40	1

A, adriamycin; CISH, chromogenic *in situ* hybridisation; C, cyclophosphamide; Cb, carboplatin; CT, chemotherapy; D, docetaxel; DFS, disease-free survival; E, epiadriamycin; F, 5-fluorouracil; FISH, fluorescence *in situ* hybridisation; H, Herceptin®(trastuzumab); HR, hazard ratio; IHC, immunohistochemistry; NA, not available; OS, overall survival; P, paclitaxel; RFS, relapse-free survival; T, trastuzumab; V, vinorelbine.

a Only if tumour size > 1 cm.

b Only if other concomitant risk factors (grade > 1, hormone receptors lacking).

c Only if size > 20 mm and PgR negative.

Because trastuzumab was administered after chemotherapy in the HERA trial, its findings apply to the wide variety of chemotherapy regimens used throughout the world. The HERA design, however, delays the start of trastuzumab until a median time of 8 months after surgery, which contrasts with a median time of 4 months in the trastuzumab-treated patients of B31 and N9831, and 1 month in the Finnish trial and in the platinum-taxane arm of BCRIG-006. The important question of optimal timing of adjuvant trastuzumab is likely to remain unanswered, however. Indeed, its early administration in the North American and Finnish trials requires its use concurrently with *specific* chemotherapy regimens hypothesised to enhance the effectiveness of trastuzumab.[11,12]

Another difference between the trials relates to the schedule of taxanes and trastuzumab: 3-weekly (B31-BCRIG 006) or weekly (N9831) for the taxane, which is either paclitaxel (B31/N9831) or docetaxel (BCRIG 006) and 3-weekly (HERA), weekly (B31-N9831) or both (BCRIG 006) for trastuzumab.

The impact of these differences on outcome is unlikely to be important, though, in view of the recently reported results of the large Eastern Cooperative Oncology Group (ECOG) 1199 trial. This study shows similarities in disease-free-survival for docetaxel and paclitaxel whether given 3-weekly or weekly.[13] The results, however, are at an early stage, and a separate analysis for hormone receptor negative disease is still lacking. We also now know about the long half-life of trastuzumab and its similar anti-tumour activity in advanced breast cancer, whether given weekly or 3-weekly. However, a head-to-head comparison of these two schedules has never been performed.[14–17] It is interesting to note that the long half-life of trastuzumab implies sustained trastuzumab levels in the blood of the Finnish patients while receiving FEC chemotherapy (5-fluorouracil, epirubicin and cyclophosphamide), a unique feature of this provocative small trial, which may have benefited from anthracycline-trastuzumab synergy.

3. Patient populations

Table 1 highlights similarities and differences in patient characteristics across the five trials. Similarities include young age (median around 50 years), high proportion of high-grade tumours (60–70%) and planned endocrine therapy in view of positive hormone receptors in roughly 50% of the patients.

Table 2 – Adjuvant trastuzumab trials: cardiotoxicity

	HERA		NSABP-B31		NCCTG-N9831			BCIRG 006		
Treatment arms	Observation	1 year H	AC → P	AC → PH	AC → P	AC → PH	AC → P → H	AC → T	TCbH	AC → TH
Women at risk (*n*)	1710	1677	814	850	670	579	718	1050	1056	1068
Cardiac deaths (*n*)	1	0	1	0	1	0	1	0	0	0
CHF NYHA Class 3–4 (*n*)	0	9	4	31	1	20	16	3	4	17
%	0	0.5	0.8	4.1	0.3	3.5	2.5	0.2	0.4	1.6

Note: no CHF class 3–4 and no cardiac death reported in the Finnish trial. Cumulative incidences at 3 years reported in NSABP-B31 and NCCTG-N9831.
CHF, congestive heart failure; NYHA, New York Heart Association; HERA, HERceptin® Adjuvant trial; A, doxorubicin; C, cyclophosphamide; Cb, carboplatin; H, Herceptin®(trastuzumab); P, paclitaxel; T, docetaxel.

Differences relate to the proportion of node-negative disease (very low in the B31/N9831 combined trial and absent in the Finnish trial, while substantial in HERA and BCRIG 006); the use of taxanes (systematic in B31 / N9831 and BCIRG 006, while used in ⩽50% of patients in the European-led trials); and the geographic distribution around the world (very wide only in HERA and BCIRG 006). It is worth recalling that, by design, women with highly significant cardiac risk factors were excluded from all trials in view of the documented adverse interaction between trastuzumab and anthracyclines in advanced disease.[6] The same was true for women with cardiac dysfunction (measured by echocardiography or MUltiple Gated Acquisition (MUGA) scan); however, the timing of cardiac function assessment differed substantially among the trials since it took place either after surgery, or after 3 months of doxorubicin-based chemotherapy or at completion of locoregional therapy *and* chemotherapy (Table 2). The most favourable selection, in this regard, occurred in the HERA trial.

4. Safety and compliance

With the exception of hypersensitivity, which has been seen mainly and only occasionally with the first infusion, cardiotoxicity (principally congestive heart failure (CHF)) is the most important adverse effect of trastuzumab. Its incidence is around 1.4% in women receiving the drug as single agent.[15–17] Cardiac dysfunction (symptomatic or not) occurs in 13% and 27% percent of patients receiving trastuzumab concomitantly with paclitaxel or anthracyclines, respectively.[6] For this reason, all investigations of trastuzumab in the adjuvant setting required careful cardiac monitoring and stopping rules specified for cardiotoxicity.

Table 2 summarises the most notable cardiotoxicity results reported so far with adjuvant trastuzumab use. Although cross-trial comparisons are hazardous and need to be made with caution, it appears from Table 2 that: (i) concomitant administration of trastuzumab with a *non-anthracycline* based regimen, such as TCH (docetaxel, carboplatin, Herceptin®), carries a very low risk of severe CHF, namely, in the range of what is observed with the non-trastuzumab regimens (0–0.3%); (ii) sequential administration of anthracycline-taxane based chemotherapy and trastuzumab may be associated with a slight increase in risk (1.4% in the sequential arm of N9831); this, however, is not clearly seen in the HERA trial (0.5%), which has a shorter follow-up; (iii) concomitant administration of trastuzumab and a taxane following 4 cycles of doxorubicin-cyclophosphamide induces a risk of severe CHF ranging from 1.5% with docetaxel (BCIRG 006) to 2.4% with weekly paclitaxel (N9831), and 3.4% with 3-weekly paclitaxel. What is unclear is whether those figures reflect truly different risks, or fluctuations related to different cardiac risk factors (e.g. diabetes, smoking, hypertension) in the patient populations.

Unexpected or poorly manageable side-effects have not been seen in any of the trials, with the exception of 9 cases of, possibly trastuzumab-induced, interstitial pneumonitis in NSABP-B31 and N9831 resulting in 2 toxic deaths, as well as 2 fatal incidences of pneumonia in the TCH arm of BCRIG 006. In the HERA trial, no such events were reported, but a slightly higher rate of infections, in general, occurred in the trastuzumab group when compared with the observation group (1.7% versus 0.6%).

Compliance has been excellent: more specifically, patient-initiated discontinuation of trastuzumab (for reasons other than toxicity or progression) occurred in 2.5% of the HERA patients and 6% of the patients in B31/N9831. The follow-up of all of the large trials is too short to analyse the rates of secondary leukaemias.

5. Efficacy

The highly reproducible and striking therapeutic benefit of adjuvant trastuzumab is shown in Table 3: 39–52% reductions in the rates of recurrences – all highly statistically significant – are observed in the trials at median follow-up times ranging from 1 year to 36 months. Importantly, these early recurrences are distant in roughly two-thirds of the cases and are essentially incurable. A statistically significant survival benefit is currently seen only in B31/N9831.

6. Subsets that benefit most from trastuzumab

Trastuzumab does not alter the natural history of all cases of HER2-overexpressing breast cancer: experience with the drug in advanced disease tells us that *de novo* resistance does exist. Unfortunately, our current knowledge of resistance mechanisms is still limited.[18]

Collection of tumour blocks and serum is ongoing in the context of the adjuvant trials. It is hoped that translational

Table 3 – Adjuvant trastuzumab trials: efficacy results

	HERA		B31 + N9831		BCIRG006			Finnish trial	
	Observation (n = 1693)	H × 1year (n = 1694)	Control (n = 1679)	H × 1 year (n = 1672)	AC-T	AC-TH	TCH	Control (n = 115)	H × 9 weeks (n = 116)
Events* for DFS									
Patients with events	220	127	261	133	147	77	98	27	12
Distant events	154	85	193	96	113	52	67	26	8
Events for OS	37	29	92	62	36	20	28	14	6
HR for DFS	0.54		0.48		0.61 (0.47–0.79)			0.42	
(95% CI)	(0.43–0.57)		(0.39–0.59)		0.49 (0.37–0.65)				
P-value	<0.0001		<0.0001		<0.0001		= 0.0002	0.01	
HR for OS	0.74		0.67					0.41	
95% CI	0.47–1.23		0.48–0.93		NA				
P-value	0.26		0.015					0.07	
Median follow-up	1 year		2 years		≈ 2 years			36 months	

A, doxorubicin; C, cyclophosphamide; H, Herceptin®(trastuzumab); NA, not available; T, docetaxel.
* Defined in all trials as breast cancer relapses, second malignancies, deaths; the Finnish trial uses recurrence-free survival instead.

research conducted with these samples will help to identify 'molecular signatures' of success or failure of trastuzumab. At the 2005 San Antonio Breast Cancer Symposium, S. Paik presented preliminary but fascinating results obtained from NSABP-B31 related translational research: tumours with co-amplification of c-Myc and HER2 seem to derive the greatest benefit from adjuvant trastuzumab, a phenomenon explained by the fact that trastuzumab can turn on the pro-apoptotic function of deregulated c-Myc.[19]

7. Adjuvant chemotherapy 'optimisation' for HER2-positive disease

The magnitude of the trastuzumab's treatment effect is substantial in all trials and raises the question of whether less aggressive and safer chemotherapy regimens could be developed in the future. A very interesting, although retrospective, analysis carried out by the BCRIG 006 investigators, suggests that co-amplification of the topoisomerase II alpha gene occurs in one-third of HER2-positive patients and may confer a therapeutic advantage to anthracycline-based regimens; HER2-positive patients who are not co-amplified for topoisomerase II alpha do not appear to derive this same benefit and may be ideal candidates for efficacious, non-anthracycline-based regimens.[9] If independently and prospectively confirmed, this observation would have important implications for clinical practice. There is also growing interest in the investigation of liposomal anthracyclines in the HER2 patient population, since these agents might decrease the risk of cardiac toxicity.

8. Pending questions related to adjuvant trastuzumab

Numerous questions in connection with adjuvant trastuzumab are pending and point to the tremendous amount of work that still needs to be done in HER2-positive breast cancer. They include: (i) Is there an optimal time to initiate trastuzumab? (ii) Will the strong trastuzumab effect weaken over time? (iii) Can we do as well with less trastuzumab (6 months) or better with more trastuzumab (2 years)? (iv)Who does not benefit from trastuzumab? (v) Is there heterogeneity in the magnitude of trastuzumab benefit? (vi) Can we design 'softer' and safer chemotherapy regimens? (vii) Can we avoid chemotherapy in selected women? (viii) Can we further improve results with other targeted therapies?

Data emerging from the control arms of the trastuzumab trials are likely to enrich our understanding of the 'natural history' of chemotherapy-only treated women with HER2-overexpressing breast cancer, at least in the cases where no crossover to trastuzumab will take place. A first look at this group in the HERA trial showed substantially different risks of relapse at 2 years according to hormone receptor (HR) and nodal status: this risk was 33% for women with $\geqslant$4 positive nodes (independent from HR status); 25% for women with HR-negative disease and 1–3 positive nodes; 18% for HR negative and node-negative disease; and around 10% for women with HR-positive disease and either node-negative or 1–3 node-positive disease.[20] These figures should by no means be used as a means to deny trastuzumab to certain subgroups of patients; however, they may assist the clinician and the patient in selecting earlier or later time points for the initiation of adjuvant trastuzumab. This could be especially valuable when anthracyclines are planned, considering that the risk of cardiotoxicity is probably lower with later initiation of trastuzumab (as done in the HERA trial).

9. Take-home messages for the clinician

There is level 1 evidence that adjuvant trastuzumab is an effective therapy, the benefit of which exceeds the risks in most patients. Nevertheless, a careful benefit versus risk assessment needs to be done for each individual woman and for each of the strategies studied so far: upfront trastuzumab with carboplatin and docetaxel; 4 cycles of an anthracycline regimen followed by trastuzumab in combination with a taxane; or administration of trastuzumab at completion of chemotherapy.

Finally, clinicians should remember the stringent conditions under which HER2 overexpression and/or amplification was assessed in the clinical trials described here. The worst case scenarios are: (i) offering trastuzumab to a false-positive case; (ii) omitting trastuzumab in a false-negative case. Working with a highly experienced laboratory is therefore the cornerstone for daily clinical practice.

Conflict of interest statement

None declared.

REFERENCES

1. Schechter AL, Stern DF, Vaidyanathan L, et al. The neu oncogene: an erb-B-related gene encoding a 185,000-Mr tumour antigen. *Nature* 1984;**312**:513–6.
2. Semba K, Kamata N, Toyoshima K, Yamamoto T. A v-erbB-related protooncogene, c-erbB-2, is distinct from the c-erbB-1/epidermal growth factor-receptor gene and is amplified in a human salivary gland adenocarcinoma. *Proc Natl Acad Sci USA* 1985;**82**:6497–501.
3. Coussens L, Yang-Feng TL, Liao YC, et al. Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with neu oncogene. *Science* 1985;**230**:1132–9.
4. Drebin JA, Link VC, Weinberg RA, Greene MI. Inhibition of tumor growth by a monoclonal antibody reactive with an oncogene-encoded tumor antigen. *Proc Natl Acad Sci USA* 1986;**83**:9129–33.
5. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987;**235**:177–82.
6. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;**344**:783–92.
7. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;**353**:1659–72.
8. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005;**353**:1673–84.
9. Slamon D, Eiermann W, Robert N, et al. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC TH) with docetaxel, carboplatin and trastuzumab (TCH) in her2 positive early breast cancer patients: BCIRG 006 study. *Breast Cancer Res Treat* 2005;**94**(suppl 1):S5. (abst 1).
10. Joensuu H, Kellokumpu-Lehtinen P-L, Bono P, et al. Trastuzumab in combination with docetaxel or vinorelbine as adjuvant treatment of breast cancer: the FinHer trial. *Breast Cancer Res Treat* 2005;**94**(suppl 1). (abst 2).
11. Baselga J, Norton L, Albanell J, Kim YM, Mendelsohn J. Recombinant humanized anti-HER2 antibody (Herceptin) enhances the antitumor activity of paclitaxel and doxorubicin against HER2/neu overexpressing human breast cancer xenografts. *Cancer Res* 1998;**58**:2825–31.
12. Pegram M, Hsu S, Lewis G, et al. Inhibitory effects of combinations of HER-2/neu antibody and chemotherapeutic agents used for treatment of human breast cancers. *Oncogene* 1999;**18**:2241–51.
13. Sparano JA, Wang M, Martino S, et al. From the Eastern Cooperative Oncology Group (ECOG), Southwest Oncology Group (SWOG), Cancer and Acute Leukemia Group B (CALBG), and the North Central Cancer Treatment Group (NCCTG). Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node-positive or high-risk node-negative breast cancer: results of North American Breast Cancer Intergroup Trial E1199. 28th San Antonio Breast Cancer Conference 2005, abstract 48.
14. Cobleigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J Clin Oncol* 1999;**17**:2639–48.
15. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 2002;**20**:719–26.
16. Baselga J, Carbonell X, Castaneda-Soto NJ, et al. Phase II study of efficacy, safety, and pharmacokinetics of trastuzumab monotherapy administered on a 3-weekly schedule. *J Clin Oncol* 2005;**23**:2162–71.
17. Leyland-Jones B, Gelmon K, Ayoub JP, et al. Pharmacokinetics, safety, and efficacy of trastuzumab administered every three weeks in combination with paclitaxel. *J Clin Oncol* 2003;**21**:3965–71.
18. Cardoso F, Piccart MJ, Durbecq V, Di Leo A. Resistance to trastuzumab: a necessary evil or a temporary challenge? *Clin Breast Cancer* 2002;**3**(4):247–57.
19. Kim C, Bryant J, Horne Z, Geyer CE, Wickerham DL, Wolmark N, et al. Trastuzumab sensitivity of breast cancer with co-amplification of HER2 and cMYC suggests pro-apoptotic function of dysregulated cMYC in vivo. San Antonio Breast Cancer Symposium 2005 – General Session. *Breast Cancer Res Treat* 2005;**94**(suppl 1). (abst 46).
20. The HERA Study team. Trastuzumab (H:Herceptin®) following adjuvant chemotherapy (C+) significantly improves disease-free-survival (DFS) in early breast cancer (BC) with HER2 overexpression: the HERA trial. *Breast Cancer Res Treat* 2005;**94**(suppl 1). (abst 11).