TREATMENT

Trastuzumab in the adjuvant treatment of breast cancer

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Abstract

Four large randomized trials to assess efficacy and toxicity of trastuzumab in adjuvant systemic therapy of breast cancer have been initiated. Results clearly demonstrate, that adjuvant treatment of trastuzumab significantly improves outcomes for women with HER2 positive breast cancer. The clinically most significant adverse events of trastuzumab are serious-infusion related reactions and cardiotoxicity. Benefit for patient should be considered according to advantage versus risk *(Tab. 1, Fig. 2, Ref. 17)* Full Text (Free, PDF) *www.bmj.sk*.

Key words: adjuvant treatment, breast cancer, trastuzumab, HER2.

Trastuzumab is a humanized IgG1 -kappa monoclonal antibody with high affinity for the extracellular domain of the human epidermal growth factor receptor 2 (HER2). The HER2 is a member of the epidermal growth factor receptor (EGFR) family of four transmembrane tyrosine kinases (HER1, HER2, HER3, HER4) that mediate growth, differentiation and survival of cells (Fig. 1). HER2 has no identified ligand and functions as a partner. The HER2 receptor forms homo- or heterodimers with other members of the receptor family, such as HER3 or HER4. Heterodimers (HER2 with HER3 or HER4) bind specific ligands, neuregulin/heregulin. HER2 receptor dimerisation leads to receptor stimulation, which starts a signal cascade leading to cell proliferation and differentiation. In humans the HER2 receptor is present in normal tissue, but is pathologically overexpressed due to gene amplification. This overexpression occures in approximately 20 to 30 percent of breast cancers. HER2/*neu* oncogene is located on chromosome 17 and causes up to 100 times the usual level in the expression of HER2. Trastuzumab binds with high affinity to HER2 and leads to internalisation of the HER2-trastuzumab complex and downregulation of the receptor's cell surface expression. It further inhibits the HER2-induced signal transduction via the ras/raf/MAPkinase and the PI3-kinase/AKT pathways. In vitro, trastuzumab shows anti-angiogenic activity by reducing vascular endothelial growth factor production and increasing the expression of the anti-angiogenic factor thrombospondin-1. The efficacy of trastuzumab requires an intact Fc antibody domain, suggesting that antibody-dependent cell-mediated cytotoxicity plays a role. Besides trastuzumab decrease ability of cells to repair DNA damage after platinum therapy or ionizing radiation. Taken together, trastuzumab acts through a complex system of mechanism influencing receptor expression, signal transduction, angiogenesis, immune response and inhibition of DNA repair.

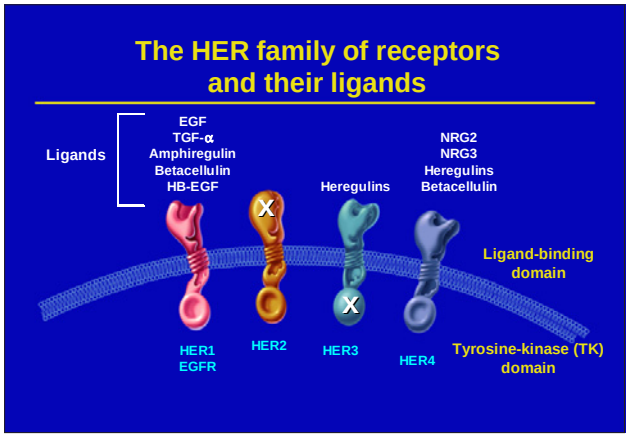

Fig. 1. The HER family of receptors and their ligands (Baselga, 2004).

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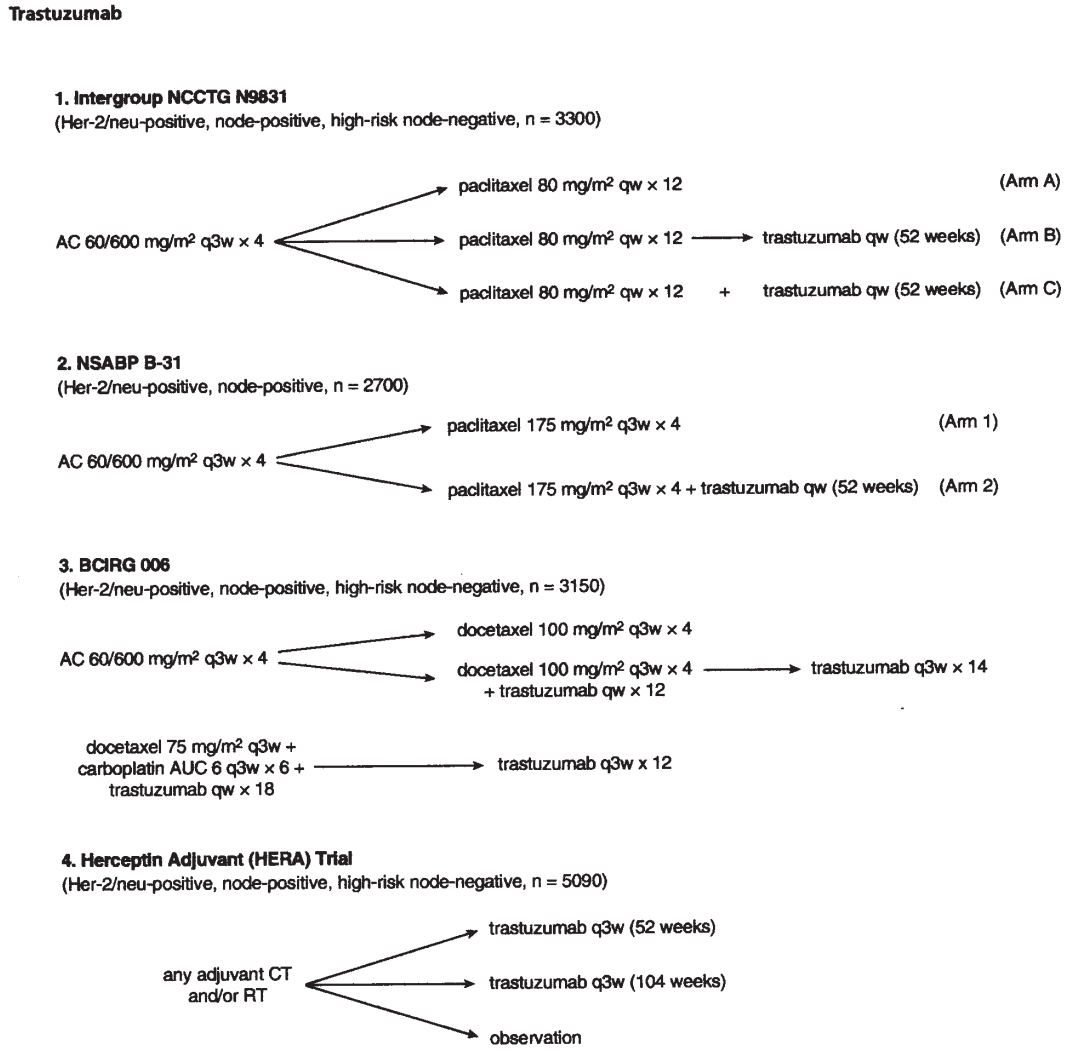

Fig. 2. Clinical trials in adjuvant treatment of breast cancer – trastuzumab (according to Rueckert et al, 2005).
AC – doxorubicin/cyclophosphamide, AUC – area under the curve, CT – chemotherapy, q3w – every three weeks, qw – every week, RT – radiotherapy.

Trastuzumab is produced by genetically engineered Chinese hamster ovary (CHO) cell line. Trastuzumab is human in 95 %. The mean half-life is 28.5 days with a washout period of up to 20 weeks.

HER2/*neu* gene amplification can be detected by fluorescence in-situ hybridisation (FISH), chromogenic in-situ hybridisation (CISH) or HER2 protein overexpression by imunohistochemistry (IHC). As HER2 or HER2/*neu* positive patients we consider those, who have FISH+, CISH+ or IHC3+. If IHC is 2+, positivity or negativity should be confirmed by FISH. Clinical use of trastuzumab is strictly restricted to HER2 positive breast cancer patients, determined as described above.

HER2 is a prognostic factor, because is associated with aggressive disease and poor clinical outcome. As well as prognostic it has also predictive value, because it indicates relative sensitivity to anthracycline and taxane based therapies and decreased sensitivity to CMF (cyclophosphamide, metotrexate, 5-fluorouracil). About half of HER2 positive breast cancers also express the steroid hormone receptors (estrogen, progesteron). Levels of steroid hormone receptors are typically lower than in HER2 negative, hormone-receptor positive tumors that is why HER2 positive breast cancer is relatively resistant to tamoxifen.

Efficacy

Efficacy of trastuzumab was firstly confirmed in large multicentre clinical trials for metastatic breast cancer. Trastuzumab significantly improved clinical outcomes as a single agent (second and third line therapy) as well as in combination with chemotherapy (first line). Based on these results trastuzumab was approved for use in patients with HER-2 amplified or overexpressed metastatic breast cancer as monoterapy (second line or later) or in combination with paclitaxel (first line) by FDA in United States in 1998.

Trastuzumab also showed efficacy as monotherapy in first line treatment (Vogel and colleagues), but response rate was half

Tab. 1. Results of disease-free survival and overall survival in individual trials. BCIRG* 006 comparison of ACT versus TCH arm; BCIRG 006 comparison of ACT to AC-TH arm. Results from HERA trial are at 2 years of follow-up. NA – not available.

	Disease-free survival (absolute difference) at 3 years	Overall survival (absolute difference) at 3 years	Disease-free survival (absolute difference) at 4 years	Overall survival (absolute difference) at 4 years
JOINT	11.8	2.5	18.2	4.8
BCIRG*	3.0	NA	7.0	NA
BCIRG	9.0	NA	11.0	NA
HERA	6.3	2.7	NA	NA

of that of the chemotherapy plus trastuzumab, overall survival was similar (Slamon trial and colleagues).

According to adjuvant setting of trastuzumab, results of four big randomised studies phase III with trastuzumab in adjuvant treatment of breast cancer were published (NSABP B-31, NCCTGN 9831, HERA, BCIRG 006) (Fig. 2). In all trials hormone receptor positive as well as hormone receptor negative patients were enrolled. Hormone receptors positive patients were treated with adjuvant endocrine therapy, mostly tamoxifen after chemotherapy unless contraindicated. Only in B-31 trial tamoxifen was administered concurrently with chemotherapy, until an amendment on January 14, 2003 required hormonal therapy to be started after chemotherapy according to fidings of Southwest Oncology Group trial 8814. Aromatase inhibitors in postmenopauzal women were allowed in the last years in all 4 studies. Radiotherapy was administered in all trials with slight differences (if indicated).

In BCIRG 006 there were 3222 patients randomised, node positive or high risk node negative. Study compared following arms: 4 cycles of doxorubicin plus cyclophosphamide followed by 4 cycles of docetaxel every three weeks (AC-T), 4 cycles of doxorubicin plus cyclophosphamide followed by 4 cycles of docetaxel every three weeks plus 1 year of trastuzumab (AC-TH) beginning with the first dose of docetaxel. The third one consisted of docetaxel plus carboplatin 6 cycles every three weeks plus 1 year of trastuzumab beginning with the first dose of docetaxel (TCH). Although excluding of anthracyclines decreased occurrence of cardiac adverse events, efficacy was superior in anthracycline arm (disease-free survival: hazard ratio of 0.49 with AC-TH and 0.61 with TCH).

N9831 (2043 patients) compared three regimens: The chemotherapy was the same in all arms (4 cycles of doxorubicin plus cyclophosphamide followed by weekly paclitaxel 12 weeks. Trastuzumab was used in arms B and C. The difference between this two arms was the beginning of administration of trastuzumab. Trastuzumab was strarted after completion of paclitaxel in arm B and in arm C paclitaxel and trastuzumab started concomitantly.

The design of NSABP B-31 (1633 patients for arm A and C) was very similar to N9831. The same chemotherapy was used, but paclitaxel was given in 3 weeks. After approximately three years from beginning of the trial it was allowed to use also weekly paclitaxel regimen at the discretion of the investigator. Trastuzumab was administered with the first dose of paclitaxel. In both trials trastuzumab treatment continued during radiotherapy. Initially, both trials included node positive patients, as of May 2, 2003 high risk node-negative women were eligible for N9831 study. Because the studies were very similar, National Cancer Institute in USA and Food and Drug Administration approved a joint-analysis to combine data from B-31 and N9831 studies. Control group of both studies was compared with the trastuzumab group. Group B of N9831 was excluded in the joint analysis, because trastuzumab was not given concurrently with paclitaxel. Disease-free survival showed clear advantage for trastuzumab group, 18.2 % in absolute difference and 4.8 % overall survival at four years.

HERA trial compared one or two years of trastuzumab therapy given after completion of adjuvant therapy with observation after adjuvant therapy. 5102 node positive and negative patients were randomised, but results are available only from 3401 patients treated or observed one year. The data of women treated for 2 years are not yet available. The absolute difference in this trial at two years is 6.3 % disease-free survival and 2.7 % overall survival.

Despite of differences in the design, all trials showed highly significant relative reductions in the disease-free survival. In the joint analyses, the benefit of adjuvant trastuzumab occured in all HER2 positive breast cancer patients and no evidence of substantial differences in relative treatment effect between subgroups was noticed. HERA study showed, that patients with tumor larger than 5 cm had any benefit of administering the trastuzumab after chemotherapy in relation to disease-free survival.

The benefit of adjuvant treatment for overall survival with trastuzumab was confirmed in joint analyses as well as in HERA study (Tab. 1).

Trastuzumab is worldwide approved for adjuvant treatment of breast cancer for women with HER-2 positive breast cancer after operation, chemotherapy (adjuvant or neoadjuvant) and radiotherapy (if applicable). On the other hand some questions remain still open.

What is the optimal schedule of administration of trastuzumab: concurrent or sequential? Simultaneously administration of chemotherapy with trastuzumab (N9831, B-31, BCIRG 006) as well as sequential administration (N9831, HERA) significantly improved disease-free survival. Results of the N9831 study suggests, that concurrent chemotherapy plus trastuzumab may be superior to sequential tharapy. Trastuzumab may amplify chemoterapy's pro-apoptotic effect and has a synergistic activity for

some chemotherapy agents. BCIRG 006 substudy results demonstrated, that co-amplification of the topoisomerase II alpha gene occurs in ~35 % of HER2 positive patients and may confer a therapeutic advantage to anthracycline-based trastuzumab combination regimens. However concurrent therapy with antracyclines can be associated with greater cardiotoxicity.

Appropriate duration and scheduling of trastuzumab are also unknown. In all studies trastuzumab was administered for one year, but in HERA trial trastuzumab was given in one arm for 2 years. The results of this arm are not available now. Current data support one year of therapy, but definitive results needs further observation.

In BCIRG study trastuzumab was started with paclitaxel treatment. Loading dose was 4 mg/kg and followed by weekly doses of 2 mg/kg. After completion of chemotherapy three weekly administration was used with loading dose of 8 mg/kg subsequently trastuzumab treatment continued with 6 mg/kg doses. NSABP B-31 and N9831 trials used weekly administration of trastuzumab (4 mg/kg loading dose followed by 2 mg/kg), HERA used 3 weekly regimen, first dose of 8 mg/kg, the second and all subsequent maintanance doses were 6 mg/kg. In the metastatic setting three weekly schedule showed efficacy, side effects and pharmacokinetics similar to those of the weekly schedule. The recent results do not allow to make the conclusion of which mode of administration is better in adjuvant setting.

Toxicity

The most common adverse events were hypersensitivity reactions, which has been seen mainly and occasionally with the first infusion. Infrequently severe hypersensitivity reaction including anaphylaxis, urticaria, bronchospasm, angioedema, hypotension were reported. The most significant adverse event associated with trastuzumab is cardiac dysfunction from mild to severe. In BCIRG 006 there was a statistically significant higher incidence of cardiac events in AC-TH in comparison to AC-T, but not in TCH in comparison to AC-T (AC-T: 0.86 %, AC-TH: 2.62 %, TCH: 1.04 %). There is also a statistically significant higher incidence of asymptomatic and persistent LVEF (left ventricular ejection fraction) declines in AC-TH in comparison to AC-T and TCH. In N9831 and NSABP B-31 the result were very similar, the cumulative three year incidence of congestive heart failure NYHA (New York Heart Association) III or IV increased by about 3 % in trastuzumab arms, in the HERA trial only for 0.6 %.

It seems that cardiac toxicity can be a consequence of using trastuzumab close to doxorubicin. For this reason careful cardiac monitoring is essential. Only a little and slight differencies were reported between treatment groups. However rare cases of severe pulmonary toxicities were observed.

Conclusion

Efficacy was confirmed in node-negative as well as high-risk node-negative or node-positive patients. Although decision of the treatment must be considered according to risk versus benefit for every patient. For patients with HER2 positive, lymph node-positive breast cancer addition of trastuzumab to the adjuvant systemic treatment should be beneficial, unless trastuzumab contrainidicated. For HER2 positive node-negative patients addition of trastuzumab to adjuvant therapy should be considered. The benefit should exceed the risk of toxicity.

References

Baselga J. HER-targeted therapies: using tumour biology to guide drug development Targeting Breast Cancer with Care, Prague, 2004.

Burstein HJ. The Distinctive Nature of HER2-Positive Breast Cancers. New Engl J Med 2005; 353: 16: 1652—1654.

Dittrich Ch. Signal transduction inhibition in breast cancer with special emphasis on HER2 and trastuzumab (Herceptinr) in Abstracts State of the Art Treatment of Breast Cancer, Vienna, 2005, 11—14.

Hanna W, Gelmon K. Current Oncology 2002; 9 (Suppl 1): 2—17. In: Vijver M (Ed). What can the HER 2 experience teach us about tumor diagnosis? Targeting Breast Cancer with Care, Prague, 2004.

Hortobagyi GN. Trastuzumab in the Treatment of Breast Cancer, New Eengl J Med 2005; 353: 16: 1734—1736.

Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al. Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer. New Engl J Med 2005; 353: 16: 1659—1672.

Roberts P. Trastuzumab adds to adjuvant chemotherapy for resected HER2-positive breast cancer in, January 2006 original article.

Romond EH, Perez EA, Bryant J et al. Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer. New Engl J Med 2005; 353: 16: 1673—1684.

Romond EH, Perez EA, Bryant J et al. Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer. New Engl J Med 2005; 353: 16: 1673—1684.

Ross JS et al. Oncologist, 2003, 8: 307—325. In: Vijver M (Ed). What can the HER 2 experience teach us about tumor diagnosis? Targeting Breast Cancer with Care, Prague, 2004.

Rueckert S, Ruehl I, Kahlert S, Konecny G, Untch M. A monoclonal antibody as an effective therapeutic agent in breast cancer: trastuzumab. Expert Opin Biol Ther 2005; 5 (6): 853—866.

Slamon D, Eierman W, Robert N. Phase III Trial Comparing AC-T with AC-TH and with TCH in the Adjuvant Treatment of HER2 positive Early Breast Cancer Patients: First Interim Efficacy Analysis, SABCS, 2005.

Sledge GW. Targeting HER-2 in the Adjuvant Setting, Orlando, ASCO, 2005.

Smith JE and HERA study team, Trastuzumab Following Adjuvant Chemotherapy in HER2-Positive Early Breast Cancer (HERA Trial): Disease-Free and Overall Survival after 2 Year Median Follow-Up. Atlanta ASCO 2005.

Summary of product characteristics, Herceptin, 1.7.2006.

Vijver M. What can the HER 2 experience teach us about tumor diagnosis? Targeting Breast Cancer with Care, Prague, 2004.

Yeon HC, Pegram MD. Anti-erB-2 antibody trastuzumab in the treatment of HER-amplified breast cancer, Investigational New Drugs 2005; 23: 391—409.

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