Never use anthracyclines with trastuzumab: it is time to reconsider the taboo

Luca Gianni

Breast Cancer Res Treat (2009) 117:599–601
DOI 10.1007/s10549-009-0402-5

INVITED COMMENTARY

Never use anthracyclines with trastuzumab: it is time to reconsider the taboo

Luca Gianni

Received: 3 March 2009 / Accepted: 9 April 2009 / Published online: 23 April 2009

The combination of an anthracycline and trastuzumab was an integral part of the pivotal trial that led to the registered approval of the monoclonal antibody for treatment of women with HER2-positive metastatic breast cancer [1]. In spite of improved efficacy associated with the combined use of doxorubicin and cyclophosphamide with trastuzumab, the incidence of 27% cardiac dysfunction and 16% symptomatic congestive heart failure (CHF) in that arm of the study brought to the conclusion that the HER2-directed monoclonal antibody should not be used in combination with an anthracycline outside of clinical trials [1, 2]. Such a conclusion was supported by the data, although the most relevant cardiac safety analysis was retrospective [2], and it was later confirmed by mechanistic insights that clarified the role of the HER2 receptor in the pathways of myocardial repair through neuregulin signaling, and the negative impact of HER2 blockade on myocardial damage such as the one caused by anthracyclines [3–5]. As an immediate consequence, all studies that tested the use of trastuzumab as adjuvant therapy avoided the concomitant use of the anthracyclines to limit the incidence and severity of cardiac events. The Breast Cancer International Research Group (BCIRG) even adopted a regimen without any anthracycline and found at the interim analysis so far released that women with *HER2* amplified gene derived benefit of the same order of magnitude with the docetaxel, carboplatin and trastuzumab combination than with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab [6]. Overall the use of trastuzumab in combination with anthracyclines has become a taboo.

In this issue of the *Journal* E. Stickeler et al. [7] publish a small but provocative study showing that the combination of pegylated lipomosal doxorubicin (PLD) and trastuzumab is feasible without excessive cardiac events and associated with promising antitumor activity. The study accrued only 16 of the 30 patients originally planned. In addition it was designed to enroll patients with prior exposure to a maximum of 400 mg/m^2 of doxorubicin or 600 mg/m^2 of the less cardiotoxic epirubicin, but only three of the women who participated in the trial had previously received anthracyclines [7]. On statistical and clinical grounds both aspects of the conduct of the trial substantially limit the wider applicability of the safety and efficacy findings of the report to the population of patients with HER2-positive breast cancer. However, as pointed out by the Authors [7], the study goes in the same direction of many other reports that are reconsidering the combination of anthracyclines and trastuzumab as a relevant treatment option for women with HER2 positive breast cancer. These studies were recently reviewed and all together challenge the tenet that combining anthracyclines and trastuzumab should be avoided [8].

There are indeed several reasons for revisiting the possibility of the combination. There appear to be a preferential antitumor activity of the anthracyclines in HER2-positive breast cancers [9, 10]. Such pattern of sensitivity has been linked to the frequent association between the *HER2* gene amplification and amplification of the *TOPOII* gene that encodes for a key intracellular target of the anthracyclines, the topoisomerase IIα enzyme [6, 11]. More recent reports have challenged such mechanistic interpretation [12, 13]. However, the appeal of combining trastuzumab with anthracyclines is still very high in the light of

This is a comment to doi: 10.1007/s10549-008-0306-9.

L. Gianni (✉)
Medical Oncology 1, Istituto dei Tumori di Milano,
Via Venezian 1, 20133 Milan, Italy
e-mail: luca.gianni@istitutotumori.mi.it

the outstanding therapeutic benefit associated with anthracyclines as a class in all stages of breast cancer presentation, and the worldwide diffusion of some anthracycline-containing regimens as the most popular adjuvant treatments.

On safety grounds, the simplest reason for revisiting the combination of anthracyclines and trastuzumab is that we have known for decades how to limit the incidence and severity of cardiac toxicity of anthracyclines and exploit their full therapeutic potential. The rule of thumb has always been that of keeping the exposure of the myocardium to a lifetime cumulative dose of anthracyclines below a threshold associated with acceptable risk. Although it is debatable where to set the threshold and what can be viewed as an acceptable risk, a lower exposure of the myocardium to anthracyclines can be accomplished in two ways: by decreasing their total administered dose, or by adopting an anthracycline formulation such as liposomal incapsulation that substantially lowers their distribution and penetration within the myocardium. There are examples of both approaches in the recent literature that described modalities of administration of anthracyclines with trastuzumab [8].

The principle of combining trastuzumab with doxorubicin for a limited number of cycles until a maximum cumulative dose of 240 mg/m^2 in a regimen that also included paclitaxel was successfully tested by Bianchi et al. [14] after observing that all episodes of congestive heart failure reported in the pivotal trial occurred after a total dose of 360 mg/m^2 of doxorubicin in combination with trastuzumab [1, 2]. The report of Bianchi et al. [14] led to a randomized trial in women with locally advanced breast cancer that has recently documented a significantly improved efficacy in a population of women in whom more than 25% had inflammatory breast cancer [15] [NOAH trial]. The superior efficacy shows that trastuzumab adds on the therapeutic effects of anthracyclines in contrast with the findings of the BCIRG-006 trial, where trastuzumab did not improve the efficacy of the anthracycline regimen in the subset of women with tumors carrying co-amplification of *HER2* and *TOPOII* [6]. The observation of safety and excellent therapeutic benefit of the NOAH trial is in line with the findings reported by Buzdar et al. in a trial of trastuzumab combined with sequential paclitaxel followed by fluorouracil, epirubicin and cyclophosphamamide that was discontinued because, based on preliminary findings of antitumor activity, it was found unethical to negate trastuzumab to the patients randomized to control therapy [16]. In a different approach in the HERCULES study the combination of trastuzumab and cyclophosphamide with two doses of epirubicin (60 or 90 mg/m^2 per cycle) was given with good cardiac tolerability for as many or more than 10 cycles [17]. The cardiac safety and good antitumor activity of coadministering cyclophosphamide, epirubicin at 90 mg/m^2 for four cycles and concomitant trastuzumab as preoperative therapy was also shown in the interim analysis of the GeparQuattro trial by the GBG/AGO German Intergroup study [18].

A similar scenario of good cardiac tolerability and very promising therapeutic effects is emerging from the studies that adopted liposomal anthracyclines with trastuzumab. The data reported by Stickeler et al. find support in other small trials in which either pegylated [19–21] or non-pegylated doxorubicin [22] was combined with trastuzumab. Of note, in a Phase I/II trial that built on the combination of doxorubicin, paclitaxel and trastuzumab of the NOAH study and substituted the naked anthracycline with the non-pegylated liposomal formulation TLC-D99 the Authors reported an outstanding objective response rate of 98.1% in 69 patients with HER2-positive metastatic breast cancer, and a median time to progression exceeding 22 months at the cost of very good cardiac tolerability [23].

Collectively several hundred patients have received trastuzumab concomitantly with anthracycline-containing regimens since the release of the data of the pivotal trial [1]. The merged data set seems to dispel the concern of excessive cardiac risk and supports the concept that "naked" classical anthracyclines and liposomal doxorubicin can be usefully and successfully administered with trastuzumab provided that patients are adequately selected to have a normal cardiac function, and that the total dose of anthracyclines is kept at or around the total cumulative dose of 240 mg/m^2 of doxorubicin or doxorubicin cardiotoxic equivalents. The clinical results are so promising to justify renewed attention to the possibility of widening the indication of trastuzumab to also include the co-administration with anthracyclines. Such scenario will have to wait for the results of prospective randomized tests that in some cases are already ongoing, as in the Breast cancer Adjuvant Caelyx Herceptin (BACH) study [8], or in the announced trial that will prospectively test in women with metastatic breast cancer the combination of trastuzumab and paclitaxel verses TLC-D99, trastuzumab and paclitaxel [23]. The time for reconsidering the taboo of never combining trastuzumab with anthracyclines has come.

Disclosure Luca Gianni is Advisor to Roche, Genentech, Wyeth and GSK.

References

1. Slamon DJ, Leyland-Jones B, Shak S et al (2001) Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344(11):783–792

2. Seidman A, Hudis C, Pierri MK, Shak S, Paton V, Ashby M, Murphy M, Stewart SJ, Keefe D (2002) Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol 20(5):1215–1221
3. Sawyer DB, Zuppinger C, Miller TA et al (2002) Modulation of anthracycline-induced myofibrillar disarray in rat ventricular myocytes by neuregulin-1b and anti-erbB2. Potential mechanism for trastuzumab-induced cardiotoxicity. Circulation 105:1551–1554
4. Peng X, Chen B, Lim CC, Sawyer DB (2005) The cardiotoxicology of anthracycline chemotherapeutics: translating molecular mechanism into preventative medicine. Mol Interv 5(3):163–171
5. Ewer MS, VooletichMT DurandJB et al (2005) Reversibility of trastuzumab-related cardiotoxicity: newinsights based on clinical course and response to medical treatment. J Clin Oncol 23:7820–7826
6. Slamon DJ, Mackey J, Robert N et al. (2007) Role of anthracycline-based therapy in the adjuvant treatment of breast cancer: efficacy analyses determined by molecular subtypes of the disease. 30th San Antonio Breast Cancer Symposium, December 13–16 (abstract 13)
7. Stickeler E, Klar M, Watermann D, et al. (2009) Pegylated liposomal doxorubicin and trastuzumab as 1st and 2nd line therapy in Her2/neu positive Metastatic Breast Cancer: A Multicenter Phase II Trial. Breast Cancer Res Treat (this issue)
8. Rayson D, Richel D, Chia S, Jackisch C, van der Vegt S, Suter T (2008) Anthracycline-trastuzumab regimens for HER2/neu-overexpressing breast cancer: current experience and future strategies. Ann Oncol 19(9):1530–1539
9. Muss HB, Thor AD, Berry DA, et al. (1994) c-erbB-2 expression and response to adjuvant therapy in women with node-positive early breast cancer. N Engl J Med. 1994 May 5;330(18):1260–6. Erratum in: N Engl J Med 331(3):211
10. Moliterni A, Ménard S, Valagussa P et al (2003) HER2 overexpression and doxorubicin in adjuvant chemotherapy for respectable breast cancer. J Clin Oncol 21(3):458–462
11. Gennari A, Sormani MP, Pronzato P et al (2008) HER2 status and efficacy of adjuvant anthracyclines in early breast cancer: a pooled analysis of randomized trials. J Natl Cancer Inst 100(1):14–20
12. McArthur HL, Tan LK, Patil S, et al. (2008) High resolution representational oligonucleotide microarray analysis (ROMA) suggests that TOPO2 and HER2 co-amplification is uncommon in human breast cancer. 31st San Antonio Breast Cancer Symposium, December 10–14 2008 (abstract 2023)
13. Bartlett JMS, Munro A, Dunn JA, et al. (2008) Chromosome 17 polysomy (Ch17) as a predictor of anthracycline response: emerging evidence from the UK NEAT adjuvant breast cancer trial. 31st San Antonio Breast Cancer Symposium, December 10-14 2008 (abstract 45)
14. Bianchi G, Albanell J, Eiermann W et al (2003) Pilot trial of trastuzumab starting with or after the doxorubicin component of a doxorubicin plus paclitaxel regimen for women with HER2-positive advanced breast cancer. Clin Cancer Res 9:5944–5951
15. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer: primary efficacy analysis of the NOAH trial. 31st San Antonio Breast Cancer Symposium, December 10–14 2008 (abstract 31)
16. Buzdar AU, Ibrahim NK, Francis D et al (2005) Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol 23:3676–3685
17. Untch M, Tjulandin S, Jonat W, et al. (2007) Evaluation of first-line trastuzumab in combination with epirubicin/cyclophosphamide for patients with HER2-positive metastatic breast cancer. 30th San Antonio Breast Cancer Symposium, December 13–16 2007 (abstract 4058)
18. Untch M, Rezai M, Loibl S, et al. (2007) Evaluating the efficacy and safety of trastuzumab given concomitantly to epirubicin/cyclophosphamide® docetaxel ± capecitabine as neoadjuvant treatment of HER2 overexpressing primary breast cancer. First analysis of the GBG/AGO intergroup-study "GeparQuattro". Breast Cancer Res Treat 106:2007 (suppl 1; abstract 5053)
19. Chia S, Clemons M, Martin LA et al (2006) Pegylated liposomal doxorubicin and trastuzumab in HER-2 overexpressing metastatic breast cancer: amulticenter phase II trial. J Clin Oncol 24:2773–2778
20. Wolff A, Bonetti M, Sparano J et al (2003) Cardiac safety of trastuzumab (H) in combination with pegylated liposomal doxorubicin (D) and docetaxel (T) in HER2-positive metastatic breast cancer (MBC): preliminary results of the Eastern Cooperative Oncology Group trial E3198. Proc Am Soc Clin Oncol 22:A70
21. Andreopoulou E, Gaiotti D, Kim E et al (2007) Feasibility and cardiac safety of pegylated liposomal doxorubicin plus trastuzumab in heavily pretreated patients with recurrent HER2-overexpressing metastatic breast cancer. Clin Breast Cancer 7:690–696
22. Theodoulou M, Campos SM, Batist G et al (2002) TLC D99 (D, Myocet) and herceptin (H) is safe in advanced breast cancer (ABC): final cardiac safety and efficacy analysis. Proc Am Soc Clin Oncol 21:55a
23. Cortes J, DiCosimo S, Climent MA et al (2009) Nonpegylated liposomal doxorubicin (TLC-D99), paclitaxel, and trastuzumab in HER-2-overexpressing breast cancer: a multicenter phase I/II study. Clin Cancer Res 15(1):307–314