Should trastuzumab be administered concomitantly with anthracycline in women with early, HER2-positive breast cancer?

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Abstract: Clinical targeting of the human epidermal growth factor receptor 2 (HER2) has dramatically improved the outlook of a subset of about 15% of breast cancers carrying HER2 gene amplification and/or HER2 protein overexpression. Since the initial experiences with the anti-HER2 monoclonal antibody trastuzumab, it was clear that combination with conventional chemotherapy was required to exploit the full potential of HER2-targeting. However, prohibitive rates of cardiac toxicity were observed when trastuzumab was given concurrently with anthracyclines, which are compounds that have played a pivotal role in the treatment of breast cancer for decades. While most of the anti-HER2 programs have been designed as to avoid concomitance with anthracyclines, high rates of pathological complete remission (pCR) were obtained in carefully selected patients with operable breasts cancer receiving concomitant trastuzumab and anthracycline in the preoperative setting. A recently published randomized study compared directly the current standard of sequential anthracycline followed by concomitant taxane and trastuzumab with a reversed sequence of taxanes followed by anthracyclines with trastuzumab administered concurrently with the whole program as neoadjuvant treatment for patients with early, operable breast cancer. The practical question asked by this study was whether a potential increase in the efficacy of trastuzumab based regimens could be worth the risk of giving it in concomitance with anthracyclines. This editorial will review the background of this study and discuss the impact of its results on the current clinical practice and on future research in the field.

Keywords: Breast neoplasms; human epidermal growth factor receptor 2 (HER2); trastuzumab; pertuzumab; lapatinib; chemotherapy; anthracycline; metastatic; adjuvant; neo-adjuvant

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The monoclonal antibody trastuzumab, the first anti-human epidermal growth factor receptor 2 (HER2) therapy introduced in the clinic, has represented a major step forward in the treatment of breast cancer (1). *HER2* gene amplification, which almost invariably results in overexpression of its product, a transmembrane tyrosine-kinase receptor, is found in about 15% of breast cancers. This abnormality drives an aggressive clinical phenotype characterized, in the absence of specific targeting, by increased risk of relapse after surgery of localized disease, tendency to spread to distant organs with frequent visceral and central nervous system involvement, resistance to endocrine manipulation and short survival times in patients with metastatic disease (2). HER2-targeting with trastuzumab has resulted in a dramatic improvement in the life expectancy of women with metastatic disease and, with its introduction in adjuvant programs for operable disease, in a significant increase in cure rate. While newer anti HER2-agents are improving the clinical outlook of HER2-positive breast cancer patients beyond what was once hardly conceivable, much of the critical information on how to integrate anti HER2-therapy in the management

of these patient comes from the early experiences with trastuzumab. As single agent, trastuzumab showed modest activity in women with HER2-positive metastatic breast cancer (1). Response rates ranging from 15% to 35% were observed according to the load of previous treatments for metastatic disease. However, as preclinical studies suggested, and for reasons that are still not completely understood, the full potential of HER2-targeting with this monoclonal antibody could be exploited by combining it with conventional chemotherapy (3). This rationale was explored in a pivotal randomized trial that led to the approval of the monoclonal antibody trastuzumab (4). In this study, women with HER2 positive breast cancer were randomized to chemotherapy with or without concomitant trastuzumab as first line therapy for metastatic disease. The chemotherapy schema was different according to whether patients had received anthracyclines in the adjuvant setting. In case of no prior exposure, the chemotherapy schema consisted of AC (doxorubicin 60 mg/m^2 or epi-doxorubicin 75 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks for six or more cycles). Those who had received an anthracycline in the adjuvant setting received paclitaxel at the dose of 175 mg/m^2 every 3 weeks for 6 or more cycles. This study provided evidence that trastuzumab could improve response rate, progression-free survival (PFS) and overall survival (OS), compared with chemotherapy alone. However, and unexpectedly, trastuzumab resulted associated with significant cardiac dysfunction, with a 27% incidence of left ventricular ejection fraction (LVEF) depression, including a 16% incidence of heart failure (New York Heart Association Class III and IV) in the anthracycline-containing arm. Notably, the corresponding figures in the AC alone arm were 8% and 3%, respectively. Although significantly less frequently, cardiac toxicity was observed also in the paclitaxel plus trastuzumab arm (overall 13%, NYHA class III and IV 2%). These findings prompted a systematic retrospective analysis of all the trastuzumab trials conducted at the time and research to elucidate the role of HER2 in cardiac function (5). Trastuzumab was confirmed to induce LVEF depression. However, differently from anthracycline-induced cardiomyopathy which is characterized by irreversible myofibrillar damage, trastuzumab effect was mostly reversible upon withdrawal of this antibody (5). Molecular biology studies revealed that HER2 is involved in embryonic cardiac development (6). Furthermore, the epidermal growth factor receptor (EGFR) family, which includes HER2, is involved in repairing the oxidative damage related to anthracycline exposure (7). Therefore, pharmacological inhibition of the physiological function of HER2 in the heart could account for the toxicity observed when anthracycline and trastuzumab were administered together (7). The lessons from these initial experiences have been carried forward over the years up to present time, having had a profound influence on the design of any anti HER2 therapeutic strategy. Screening for pre-existing cardiac conditions that could predispose patients to cardiac toxicity, avoidance of concomitance with anthracyclines, regular cardiac monitoring and proactive cardiac pharmacologic intervention to support LVEF are considered both in clinical trial design and in the current clinical practice, regardless of the anti HER2-compound used (8). Tackling trastuzumab-related cardiac toxicity was a relevant issue when trastuzumab was studied in the adjuvant setting, where anthracycline are an important component of the chemotherapy regimens. In fact, a meta-analysis of studies comparing anthracycline-based *vs.* cyclophosphamide, methotrexate, 5-fluorouracil (CMF)-like adjuvant treatments found that the major efficacy of the former regimens was restricted to women with HER2-positive breast cancer (9). Beyond strict cardiac inclusion criteria, trialists dealing with trastuzumab-based experimental arms used different approaches (8): administering trastuzumab after anthracyclines and concomitantly with taxanes, developing anthracycline-free adjuvant chemotherapy regimens, where trastuzumab could be administered concomitantly with the complete chemotherapy program, or administering trastuzumab after the completion of chemotherapy, regardless of the regimen used. Because partial or no overlap between trastuzumab and chemotherapy could be seen as a potential limitation to the full exploitation of trastuzumab-based therapy, a number of authors tried to evaluate the feasibility of anthracyclines, either conventional or liposomal, administered concomitantly with trastuzumab in the metastatic setting (10). While these experiences could not convincingly demonstrate the safety and convenience of these regimens, the results of a small study conducted ad M.D. Anderson Cancer Center caused quite a stir in the field (11). Women with HER2-positive operable breast cancer were randomized to neoadjuvant chemotherapy consisting of four cycles of paclitaxel (225 mg/m^2 as a 24-hour continuous infusion every 3 weeks) followed by four cycles of FEC_{75} (5-fluorouracil 500 mg/m^2, epi-doxorubicin 75 mg/m^2, and cyclophosphamide 500 mg/m^2 every 3 weeks for four cycles) with or without concomitant trastuzumab (24 weeks of treatment). The study was prematurely

Table 1 Selected neoadjuvant trials with anti HER2-therapy

Author	Study arms	N	pCR[1] rate (%)	LVEF drop >10% points to below an LVEF of 50%	CHF (%)
Buzdar (11)	T→FEC	19	25.0	26.00[2]	0
	TH→FECH	23	66.7	30.00[2]	0
Gianni (12)	AT→T→CMF	118	19.0	17.00[2]	0
	ATH→TH→CMF	117	38.0	27.00[2]	2.0
Untch (13)	ECH→DH	308	30.2	0.40	2.6
	ECL→DL	307	44.6	1.40	0.3
Guarneri (14)	TH→FECH	36	25.0	3.00	0
	TL→FECL	36	26.3	0	0
	THL→FECHL	46	46.7	0	0
Buzdar (15)	FEC-TH	138	56.5[3]	7.90[4]	0
	TH-FECH	142	54.2[3]	10.60[4]	0
Schneeweiss (16)	FECHP→DHP	72	50.7	5.60	0
	FEC→DHP	75	45.3	5.30	2.7
	DCHP	76	51.9	3.90	0
Ismael (17)	DH→FECH	263	34.2	2.12	0
	DscH→FECscH	260	39.2	2.40	0.75
Baselga (18)	TH	149	27.6	0.60	0
	TL	154	20.0	0.60	0
	THL	152	46.8	0.60	0
Gianni (19)	DH	107	21.5	0.90	
	DHP	107	39.3	2.80	0
	HP	107	11.2	0.90	1.0
	DP	96	17.7	1.00	0

[1], no residual disease in the breast and the axilla; [2], overall incidence of LVEF drop of >10 percentage points; [3], pCR defined as no residual invasive disease in the breast; [4], as reported by the cardiac review panel; [5], one case of New York Heart Association grade II CHF. pCR, pathological complete remission; LVEF, left ventricular ejection fraction; CHF, congestive heart failure; T, paclitaxel; FEC, 5-fluorouracil, epirubicin and cyclophosphamide; H, trastuzumab; A, doxorubicin; CMF, cyclophosphamide, methotrexate and 5-fluorouracil; L, lapatinib; D, docetaxel, P, pertuzumab; scH, subcutaneous trastuzumab.

closed after the accrual of just 42 patients because of an unprecedented rate of pCR in the "all concomitant" trastuzumab and chemotherapy arm of 66.7%, compared with 25% in the chemotherapy alone arm (*Table 1*). Subsequent follow-up of patients treated with that regimen showed a high rate of freedom from disease progression (20). Most importantly, authors did not find a strong signal towards cardiac toxicity. After the MD. Anderson study other groups studied concomitant regimens confirming high rates of pCR and an acceptable profile of cardiac toxicity (*Table 1*) (12-14,16,17). Furthermore, a small, but provocative study from Finland used an "all concomitant" adjuvant regimen of taxanes or vinorelbine followed by FEC and trastuzumab given for 9 weeks only (21). Hazard ratios for event-free survival (EFS) and OS were in the same range of those reported in the registration trials, where trastuzumab was not combined with anthracycline and given in general for one year. Also in this case, no signal for increased cardiac toxicity was observed in the trastuzumab arm of the study.

These results suggested revisiting the concept of full concomitance between trastuzumab and anthracycline-based therapy, as an approach to optimize the efficacy of trastuzumab in the setting of early breast cancer. One important consideration regarding the cardiac concerns associated with trastuzumab treatment is that patients in small trials of neoadjuvant chemotherapy may represent a selected population that only partially overlaps with the "real world" patients. Population based studies reveal that, because of frequent cardiac conditions which, by themselves, do not represent a contraindication to treatment, the incidence of cardiac toxicity despite all the precautions is

higher than that reported in clinical trials (22). For all these reasons, whether increasing the potential efficacy of trastuzumab based regimens is worth the risk of giving it in concomitance with anthracyclines has remained an open issue until recently. A randomized study from the Institution that first showed the potentiality of the "all concomitant" approach has provided a convincing response (15). The Z1041 trial randomized a total of 282 women with early, HER2-positive breast cancer to either a sequential arm of four cycles of FEC_{75} followed by weekly paclitaxel (80 mg/m^2/week for 12 weeks) plus 12 weekly administrations of trastuzumab (4 mg/kg loading dose, followed by weekly doses of 2 mg/kg) or to a concomitant arm of weekly paclitaxel (same schedule as above) followed by four cycles of FEC_{75} with weekly trastuzumab started with paclitaxel and administered for a total of 24 weeks. Upon completion of treatment patients were schedule to undergo surgery and, then, advised to continue trastuzumab for up to one year. The primary study end-point was pCR in the breast and the study was powered on the hypothesis that the concomitant schedule could increase the pCR rate by 20% or more, from an expected 25% in the sequential arm. Patients were meticulously selected on the basis of strict cardiac criteria, including no history of myocardial infarction, congestive heart failure (CHF), cardiomyopathy, or cardiac disease requiring drug treatment; severe conduction abnormality, valvular disease, cardiomegaly, ventricular hypertrophy on electrocardiography, or poorly controlled hypertension. The striking finding of this trial was that doubling the duration of trastuzumab and giving it in full concomitance with a taxane and anthracycline-based chemotherapy yielded a high pCR that was similar to that achieved by patients in the more conventional sequential arm, were trastuzumab duration was just a half (12 weeks) (*Table 1*). In fact, pCR rate in the latter arm was largely higher than expected. The study also confirmed the cardiac feasibility of trastuzumab with anthracyclines, with caveats to consider regarding the selection of patients (see above). The results of the Z1041 trial mirror those of the previously published TRYPHAENA trial (*Table 1*) (17), where HER2-inhibition consisted of trastuzumab and the other anti HER2 monoclonal antibody pertuzumab and confirm that whether anti HER2 therapy should be administered in full concomitance with a sequence of anthracycline and taxanes is no longer an issue. On a more general level, they also suggest that further manipulation of the classical ingredients of the HER2-therapy recipe (anthracycline, taxanes, concomitance and duration) will hardly result in an increase in pCR, and possibly, in cure rate. In fact, two studies using single agent chemotherapy and double HER2 targeting with either the tyrosine-kinase inhibitor lapatinib or pertuzumab showed impressive rates of pCR obtained after just 16 weeks of treatment (*Table 1*). In those two studies, an anthracycline-based regimen was administered after surgery, before resuming HER2-targeting. A relevant scientific issue would be assessing the role of further anthracycline therapy in those patients achieving pCR in the neoadjuvant setting. In fact, not all patients who achieve a pCR show long-term EFS, but for a proportion of them anthracycline and their fearsome general and cardiac toxicity could be possibly avoided. On the other hand, as a slightly better DFS and OS favouring AC followed by docetaxel plus trastuzumab over the anthracycline-free docetaxel, carboplatin and trastuzumab was observed in the Breast Cancer International Research Group (BCIRG) 006 trial (23). This suggests the existence of a subset of HER2 positive tumors that may be better cured with anthracycline-containing regimens combined with HER2 targeting.

For now, clinicians managing operable HER2-breast cancer patients at risk of relapse are reinforced in their prescribing patterns by the results of the Z1041 study. However, the real challenge, especially in the era of multiple HER2-targeting strategies, is to tailor treatment intensity to clinical and biological features of the tumor. There is increasing recognition that breast cancer in general, and HER2 positive breast cancer in particular can be further grouped on the basis of their molecular heterogeneity (24). Deciphering this heterogeneity has several obvious implications in the process of optimizing the toxicity/benefit and cost/effectiveness ratios of treatment for HER2-positive breast cancer. In this respect, considering that adjuvant anti HER2 therapy is increasingly offered to patients with small, node-negative, HER2 positive tumors, depotentiation of the chemotherapy component of programs should became a major focus for research. Once again, however, translational research is called into cause in the eternal quest for biomarkers that could help stratify patients according to the likelihood to derive benefit from a specific treatment approach. Unfortunately, the jury is still out for the most promising candidate biomarker of potential sensitivity to anthracycline, the topoisomerase 2 gene status or protein expression (25). Yet, further research in this direction should be pursued to define those patients for whom anthracycline could be safely omitted and those, conversely, for whom these drugs still represent a life-saving option.

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