Is there a qualitative interaction between adjuvant trastuzumab and size of the primary tumor in breast cancer?
Minireview

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Received March 17, 2008

Benefit of adjuvant trastuzumab in breast cancer has been reported in four randomized trials of phase III, and these results are consistent in showing improvement in disease-free survival (DFS). Current evidence for homogeneity of this DFS benefit in subgroups of patients with the different size of the primary HER2-positive tumor treated according to the HERA trial is reviewed. It is evident that current published evidence is insufficient to rule out that there is a cohort of patients with HER2-positive disease who do not achieve a reduction in the risk of recurrence by adjuvant treatment with trastuzumab after completion of previous adjuvant chemo- and radiotherapy. An alternative interpretation of results of the HERA trial currently available in two primary reports (1-year, and 2-year median follow- up, respectively) is discussed. The risk factors of central nervous system (CNS) metastases in breast cancer and problem of CNS metastases in HER2-positive tumors are briefly reviewed. A hypothesis on the relations between brain metastases, their risk factors, the size of the primary tumor, and their impact on the DFS in patients with HER2-positive tumors treated with adjuvant trastuzumab is proposed based on the results of the HERA trial. Altogether, some direct evidence is presented here based on the published results of the HERA trial, and still more indirect evidence based on the information on related topics in literature, to show that current clinical practice of adjuvant trastuzumab in mono-therapy, which is based on assumption that there is a homogeneous benefit as for disease-free survival for all sizes of primary HER2-positive tumors above 1 cm, may not be based on such firm evidence as is commonly presented.

Key words: breast cancer; trastuzumab; adjuvant; brain metastases

The HER2/neu over-expressing breast carcinoma is a disease with an unfavorable prognosis. The outcome of treatment has changed with the introduction of the targeted therapy with trastuzumab in recent years. Albeit only about half of patients are responsive to this drug, and the median duration of the response in metastatic setting ranged between 9 and 12 months, the use of trastuzumab combined with some cytotoxic agents has lead to increased response rate and prolongation of overall survival in randomized studies [1]. The benefit of trastuzumab in adjuvant setting was subsequently documented in several large randomized trials. Results of four randomized trials of phase III with adjuvant trastuzumab are currently available [2–6]. These results are consistent in reporting a significant benefit as for disease-free survival (DFS), and an early impact on overall survival was even documented in two of the trials [2, 6]. These apparent benefits created a lot of optimism in the medical oncology community, and the adjuvant trastuzumab represents a paradigm for future studies in targeted therapy.

However, previous experience teaches us, that there is always some "but" and "if" associated with any treatment, and this is still more so in such heterogeneous and complex disease such as the breast cancer. The aim of this review is to point out some of the problems of the current clinical use of adjuvant trastuzumab and to show that not all current indications of adjuvant trastuzumab are based on such firm evidence as presented. Because we as physicians should require for our decision-making more than only indirect proofs, extrapolations and hopes, further research in this area is urgently needed. We are from Europe where the current practice of adjuvant trastuzumab is based predominantly on the results of the

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HERA trial [5–6]. Therefore we will discuss mainly the results of these studies with administration of the trastuzumab in mono-therapy for 52 weeks after the completion of (neo)adjuvant chemotherapy and/or radiotherapy, with concomitant administration of adjuvant hormonal therapy according to the standards.

Definition of the problem. Gelber and Goldhirsch have stated in their presentation at the 2007 St. Gallen Conference that: "The effectiveness of the targeted adjuvant treatment, trastuzumab, was so impressive that the trials reached their objectives earlier than anticipated, thus attenuating the opportunity to assess longer term effects and limiting the number of events available for subgroup analyses."[7] This is very true, and one should remember this statement while reading all paragraphs of this article. It was further stated in the same speech that "current evidence is insufficient to identify a cohort of patients with HER2-positive disease who would not achieve a reduction in the risk of recurrence."[7] There may be a problem with this statement. We don't feel to be the ones who could lead a polemic about the exact meaning of this sentence in the context of their whole speech on the symposium. On the other hand, one could paraphrase this statement in the manner that "currently available evidence is insufficient to rule out that there is a cohort of patients with HER2-positive disease who do not achieve a reduction in the risk of recurrence". We consider this statement to be valid in the context of the HERA trial, of which both speakers are co-authors [5–6].

Subgroups and interactions. In general, subgroups need to be interpreted within the context of the trial, other studies, and the biological phenomena being investigated [8]. After reading the paper of D. Follmann about the analyses of subgroups and interactions in clinical trials [9] or some similar text, one could ask whether there is any reason for not performing the formal tests of qualitative interaction in large randomized trials, in case there is some uncertainty, based on merely comparing subgroup data in Forest plots, to rule out a heterogeneity of treatment effect, or if there might be a case where this heterogeneity is arguable on the sound biological basis. One can argue that these tests should be done in the original report of the results, but is it not a worth to do this exploration in some secondary papers because the decisions based on the results of the particular study have a huge impact worldwide?

Relation between the incidence of central nervous system (CNS) metastases and the size of the primary tumor in breast cancer. Tham et al. interpret the results of their large retrospective study dealing with risk factors of CNS metastases in breast cancer in the sense that the size of primary tumor has a limited role in the incidence of CNS metastases [10]. However, if one excludes the tumors of size 5 cm and above, the chi-square and Fisher exact tests performed for the data from this study both show a statistically significant difference in incidence of CNS metastases between T1 and T2 tumors (chi-square test: $p = 0.0402$, Fisher two-tailed and one-tailed: $p = 0.0402$, and 0.0231, respectively). This fact has also been proven in multivariate analysis performed by authors, where the T2 is independent risk factor for CNS metastases in relation to T1 tumors with hazard ratio (HR) of 1.5 and 95% confidence intervals (CI) of 1.1-2.0 ($p = 0.01$). The fact that also the primary tumors of 5 cm and above are not an independent risk factor for metastatic affection of CNS in this multivariate analysis may be explained by the generally accepted relation between the size of the primary tumor and the probability of metastatic spread. The tumors of 5 cm and above are associated with high probability of metastases in non-CNS visceral sites (in the descending order of incidence lungs, pleura, and liver), and patients die of these metastases before the manifestation of CNS metastases. (It is a similar mechanism with which the authors explain why there is the lower incidence of isolated CNS metastases as a primary recurrence in HER2-positive tumors compared to HER-negative tumors in their study). Theoretically, we can assume that such trend of an increase in risk of CNS metastases dependent on the size of primary tumor continues, in reality, also in tumors of size above 5 cm. We are not aware of any biological mechanism by which to explain a reversion in this increasing trend resulting in the decreasing of the risk to the levels comparable with the risk in T1 tumors.

Incidence of CNS metastases in HER2-positive breast cancer. Clinical experience suggests that HER2-positive tumors have high propensity for metastatic spread to the CNS. Each from us clinicians probably has some sad example of HER2-positive breast cancer patient in whom an apparently successful treatment has been terminated by the diagnosis of CNS metastases. One of us had a patient with loco-regionally advanced disease (initially T3N3M0), G3, Ki-67 75%, hormonally totally independent, HER2 3+ by immunohistochemistry, who achieved pathological complete response after neoadjuvant chemotherapy with doxorubicin and cyclophosphamide with sequential docetaxel, but presented with neurological symptoms during the course of the adjuvant radiotherapy on the chest wall and regional lymphatics. Supra- and infratentorial metastatic lesions with obstructive hydrocephalus were subsequently verified by the magnetic resonance imaging. The condition quickly progressed to the extent that the patient was not able to finish the palliative irradiation of cranium, and she died few weeks afterwards. This is an illustrative example of the "natural outcome" of this disease after achieving systemic control. Many clinicians tend to be rather nihilistic regarding any aggressive systemic treatment of HER2-positive tumors because of the similar experience. This is based on anecdotal evidence. What is, however, current objective evidence?

The results of the above-mentioned study of Tham et al. [10] are "somewhat confusing" as already stated above (lower incidence of isolated CNS metastases as a site of primary relapse in HER2-positive tumors compared to HER2-negative tumors if one takes as a reference the proportion of CNS metastases in group of patients with first recurrence in non-CNS

sites). The authors are arguing that this lower rate is due to the less active systemic treatment in most of the patients in this retrospective study (CMF regimen and hormonal therapy, mainly tamoxifen), and that results would be different if the more active systemic approaches would be used as it is now. The authors of this study also reported that HER2-expression has no impact on the probability of the metastatic spread to CNS [10]. This is the objective evidence from the largest study on the topic to date, and one would say that it is little contradictory to our own clinical experience.

On the other side, the study of Miller et al. investigating the benefit of screening for occult CNS metastases has indicated that the HER2-overexpression is a predictor of the higher risk of occult CNS metastases [11]. The sub-clinical disease in CNS can become to be clinically apparent in case of better systemic control with more effective therapy (chemotherapy regimens with anthracyclines and taxanes [12–13] or combinations with trastuzumab [14–15]).

Patients in study of Tham et al. had shorter overall survival after CNS metastases were diagnosed in case the tumor was HER2-positive [10] (one can assume that most of these patients had not systemic control of disease). Situation could be different today, because better systemic control is frequently obtained, and some studies show that an absence of extracranial disease could have a positive influence on the outcome of patients with CNS metastases [16]. The studies of smaller size are somewhat contradictory, e.g. as for the impact of the continuing in palliative trastuzumab in such cases [17–18].

The percentage of HER2 positive tumors in patients who had CNS metastases after previous non-CNS recurrence in the study of Tham et al. was 31% of all such patients with "secondary" CNS affection [10]. For comparison, the rate of HER2-positive primary tumors in early breast cancer patients is reported between 20-30% [19–20].

Details about the follow-up after the first distant event were reported in one of the studies with adjuvant trastuzumab administered concomitantly with paclitaxel (trial NSABP B-31), and this presented an opportunity to determine whether the imbalance in the higher incidence of isolated brain metastases as first events in the trastuzumab group was due to masking of the incidence of brain metastases in the control group as a result of earlier failures in other organs. The authors show that this imbalance in brain metastases as first events can be really attributed to earlier failures at other distant sites among patients in the control group without trastuzumab [2]. At the time of the primary report of this trial in 2005, brain metastases as a first or subsequent event were diagnosed in 28 patients in the trastuzumab group, as compared with 35 patients in the control group (HR 0.79; $p = 0.35$). Administration of the adjuvant trastuzumab concomitantly with paclitaxel had no influence on the overall incidence of brain metastases in this study.

Risk factors of CNS metastases in breast cancer. The study of Tham et al. [10] mentioned above is the largest one on the topic to-date. The authors have demonstrated in multivariate analysis that independent risk factors for CNS metastases are (in addition to T2 classification) age (HR 0.98, CI 95% 0.97-0.99, $p < 0.001$), lack of expression of estrogen receptors (HR 2.8, CI 95% 2.1-3.7, $p < 0.001$) and ductal histology compared to lobular histology (HR 2.5, CI 95% 1.1-5.5, $p = 0.02$). On the other hand, neither the number of positive lymph nodes, nor the adjuvant systemic therapy were shown to have any relation to the incidence of CNS metastases in breast cancer [10].

Subgroup analysis in the HERA trial. It is important to point out the fact that results of the HERA trial are often used in current clinical practice to define treatment of groups of patients, that were not eligible for this study, or for whom the study has not, with high probability, sufficient power to show the benefit. In the context of the present paper, this is valid mainly for the T4 tumors after completion of successful primary systemic therapy and subsequent local-regional treatments. A T4 primary tumor was one of the exclusion criteria in this study [5], and only T3 tumors were eligible in this study of all tumors of the size 5 cm and above. Moreover, the proportion of patient with T3 tumors was very low in this study, as compared with the lower T classification. Patients with positive supraclavicular lymph nodes were also excluded.

The results of subgroup analyses for disease free-survival have been reported in both primary reports (after 1-year [5], and 2-year median follow-up [6], respectively). However, these results were published only in the form of Forest plots, and it is not known if any formal tests for interaction have been performed on the data of this trial. Based on the published results a possibility of a qualitative interaction (or possibly a strong quantitative interaction) in at least one of the subgroups in the 2-year median follow-up report cannot be ruled out [6].

The description of the results of an investigation for heterogeneity in both reports is limited to the mere statement that "All CIs overlap (with) the overall result." The reports fail to comment on the fact that the lower limit of this CI in the T3 subgroup in the second report is 0.63 whereas the HR for the overall population is 0.64 [6]. Moreover, the CI has drifted toward a negative effect in the second report compared to the 1-year median follow-up report. The number of patients in this subgroup is low, and the results could be due to chance. On the other hand, the value of the estimated HR for the T3 subgroup in the second report is 1.14, and this contradictory effect fulfills the condition for suspicion of a qualitative interaction [9]. The evidence provided to us could be interpreted, conservatively saying, as weakening a general validity of the authors' statement that: "There was no evidence of substantial heterogeneity in the relative treatment effect on disease-free survival between subgroups, and there was no evidence of any subgroup in which trastuzumab was seen to be less efficacious than observation alone." A statistician should perform the tests of interaction (mainly Gail and Simon, Piantadosi and Gail, and Follmann and Proschan tests) to rule out formally such unexpected heterogeneity [9], and only if the benefit will be confirmed also for this subgroup, such

strong statement would be warranted. Otherwise, this is only a subjective interpretation of results of this industry-sponsored research.

The small size of the sample in the T3 subgroup represents an objective obstacle to arrive at a conclusion even after completing a battery of statistical tests. Thus, what could be a clinical point of view on this suspicion? We suggest here to try to look at this problem from the perspective of brain metastases. Assuming that systemic treatment with adjuvant trastuzumab is not able to influence the probability of developing CNS metastases from the occult to the clinically manifested stage, we could see the only effect of the adjuvant trastuzumab in mono-therapy in first years after early breast cancer diagnosis as for CNS dissemination to be able to demasque these occult brain metastases by means of diminishing the rate of non-CNS recurrences. The whole problem would be de-generated then to the investigation for the subgroup of patients that have high risk of occult brain metastases already at time of starting adjuvant trastuzumab in mono-therapy. A growth of these CNS metastases would be able to erase an additive benefit of the adjuvant trastuzumab on the systemic level as for the DFS.

Brain metastases in the HERA trial. The hypothesis of inhomogeneity of benefit of adjuvant trastuzumab that is, at least partly, associated with lack of control of CNS metastases by this monoclonal antibody presented here is based on three pillars. First, in the HERA trial the number of CNS metastases as the primary recurrence is proportionally higher in the trastuzumab group compared to controls [5–6] (in 2-year median follow-up: 26 versus 22 pts, respectively, i.e. 2% versus 1%). This is an established and commonly accepted fact also in other trials with adjuvant trastuzumab [21].

Second, if we take an exploratory look at the data, it is possible to interpret some of the parameters in DFS subgroup analysis that have CIs crossing 1.00, as the risk factors for developing the CNS metastases. The first such risk factor is the size of the primary tumor. Applying the logic described above that the risk of brain metastases in breast cancer is, generally, increasing beyond the primary size of 5 cm, the results of the HERA trial may be interpreted in the T3 subgroup as meaning unchanged or even decreased DFS [6]. Better systemic control achieved by means of continuing in adjuvant trastuzumab, as compared with observation only, is significant enough to allow for manifestation of brain metastases. It is very difficult to estimate what effect on this phenomenon would have stopping trastuzumab earlier than after 52 weeks. We are awaiting the results of the 2-year arm in the HERA trial. Similarly, the behavior of the DFS curve in the years after stopping the adjuvant trastuzumab in mono-therapy could be difficult to explain. Moreover, one should take into account that authors decided to handle the size of the primary tumor as a categorical variable (although this is more acceptable than the arbitrary value of 4 cm used in American trials [2]). However, the preferred approach should be to handle this parameter as a continuous variable, as the results of multivariate analysis with continuous variables are generally more reproducible and better comparable with other studies. In such situation, one can freely argue that still some part of the T2 subgroup could have similar behavior like the T3 subgroup. This is very important because the T2 patients represent about half of all patients in this study. The risk of CNS metastases in the T2 patients is, generally, rather high. Tham et al. [10] reported that proportion of relapses in CNS (including the HER2-positive tumors) for primary breast tumors of size 2.1 – 5.0 cm is 16.4% of all relapsed patients (166 with CNS metastases compared to 849 with non-CNS recurrence). And this risk does not appear to be lower in the case of systemic control. In Tham's study, the stratification by T classification for comparing incidence of CNS metastases in the full systemic control compared to metastatic condition was of borderline significance, $p = 0.05$ [10]. In general, other studies reported rather higher proportion of CNS metastases in the case of systemic control [12-15]. Therefore performing an analysis of the relation between the T classification as continuous parameter and the risk of CNS metastases in the setting of the good systemic control (group with trastuzumab), and slightly inferior systemic control (control group in HERA) could be very informative. In this respect, a report on numbers of the primary CNS relapses in intention-to-treat analysis in the HERA trial stratified according to the TNM T stage would be interesting.

In addition, there is an entire group of interesting risk factors (ER+/PR-, ER-/PR+, pre-menopausal status and age < 35 years) that were shown to represent risk factors for CNS metastases in multivariate or univariate analysis in the study of Tham et al. [10], with the exception of ER-/PR- subgroup that is also a proven risk factor [10], but at the same time these patients benefit from adjuvant trastuzumab in mono-therapy [5–6]. This may seem confusing, but is not contradictory with regard to the whole theory of brain metastases. The hormonally independent HER2-positive tumors can be in a strong risk for CNS involvement one considers the logic of masking as these patients can achieve DFS benefit from adjuvant trastuzumab in mono-therapy. It may be assumed that in this group the benefit of systemic control with trastuzumab that is not possible to achieve at least partially by means of hormonal therapy like in the other breast tumors, is large enough to overweight the negative impact of the more frequent brain metastases. This absence of even only partial response to hormonal therapy is clinically very important because of extremely high absolute risk of visceral metastases in these patients. For this reason absolute benefit of adjuvant chemotherapy is consistently better for hormonal unresponsive disease [22].

The third pillar of the hypothesis presented here reflects the differences in the systemic treatment before starting adjuvant trastuzumab in mono-therapy. There were three systemic pre-treatment subgroups in the HERA trial [5–6]. The subgroup of patients without anthracyclines is small, and the CIs of this group in both primary reports are very wide, so it is

probably safer to avoid any comment on it. More interesting are both subgroups with anthracyclines. The benefit of adjuvant trastuzumab as for DFS appears to be quite apparent in the subgroup of anthracyclines-only pre-treated patients [5–6]. On the other hand, the subgroup with anthracyclines and taxanes has wide CIs in both primary reports, and with upper CI limits crossing in both cases the HR 1.00. However, important is the behavior of lower CI limits in both reports. The situation here is very similar to the results of T3 subgroup, there is a difference between this lower limit and the HR for the overall population in magnitude of only 0.01 in one of the reports, but the worse value is reported for the 1-year median follow-up in this case [5]. The concern regarding the lack of formal tests of interaction (to rule out an eventual qualitative interaction or a strong quantitative one) is also valid here, but we would like rather to focus attention to the clinical interpretation of these results. If one assumes that there is no specific drug-drug interaction due to the sufficiently large period between administration of any chemotherapy and the trastuzumab, then the eventually formally proven attenuation of the DFS benefit of trastuzumab in this subgroup is possible to explain by obtaining sufficient systemic control by means of sole chemotherapy with combination regimens. This beneficial effect of the chemotherapy is limited in time, however. This could be also the mechanism of the increased DFS benefit for the trastuzumab group in the anthracyclines and taxanes subgroup during the follow-up [5–6]. If this is true, then the incidence of the brain metastases as first site of recurrence should be very similar in both groups, at least in the 1-year median follow-up report. Unfortunately, authors of the HERA trial have again not provided us with such stratification of CNS recurrences [5–6]. It would be helpful to document the "natural" incidence of CNS metastases in the setting of the full systemic control. This may be a legitimate demand, because neither anthracyclines, nor taxanes or trastuzumab are able to cross the intact blood-brain barrier [10].

Based on the hypothesis described above, it would be interesting to report results of the HERA trial also in form of "combined" subgroups analyses. Clinically highly important questions are aiming mainly at the subgroup analyses of DFS of patients with T3 tumors treated with anthracyclines plus taxanes versus the remaining patients, and still more so of patients with T2 or T3 tumors treated with anthracyclines plus taxanes versus the remaining patients. If at least one of these subgroups will have fully significant lack of DFS benefit in simple comparison of the respective lower limits of CIs of HRs for overall population, there would be already sufficiently strong evidence to start asking whether it is beneficial to administer the trastuzumab mono-therapy in adjuvant setting to these groups of patients, as both acquired resistance on trastuzumab [19–20], and cardio-toxicity of trastuzumab [21] should be taken into account. In this case, another clinical trial would be warranted to show whether it will not be better to wait with trastuzumab till the time of relapse, and to start it in palliative indication only. Otherwise, in any case, the formal testing for qualitative interaction published in form of some secondary paper would be helpful in next step of reporting the results of the HERA trial.

Conclusion

Some direct evidence based on the results of the HERA trial, and still more indirect evidence based on the information available for related topics in literature is presented here to show, that current clinical practice of adjuvant trastuzumab in mono-therapy based on the assumption of a strong significance in statistical testing for absent heterogeneity as for disease-free survival benefit of this treatment, and on the concluding from this that there is a homogeneous benefit as for DSF for all sizes of primary HER2-positive tumors above 1 cm, is not firmly scientifically based. Any firm proofs for changing this approach or even discussing some new approaches are beyond the scope of this article.

Supported by the research project MZO 00179906 (Ministry of Health of the Czech republic).

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