Neoadjuvant chemotherapy and concomitant trastuzumab in breast cancer: a pooled analysis of two randomized trials

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The aim of this meta analysis was to evaluate the benefit of adding concomitant trastuzumab to neoadjuvant (anthracycline and taxane-based) chemotherapy, which was assessed based on two published randomized controlled trials. The eligible patients were randomized to receive either neoadjuvant chemotherapy alone or with concurrent administration of trastuzumab. Relative risks (RRs) with 95% confidence intervals of pathologically complete response in breast and nodes, relapse-free survival, overall survival, and cardiotoxicity were calculated. The RR of obtaining a pathologically complete response in breast and nodes was 2.07 in the experimental arms (1.41–3.03; *P*=0.0002; *P* for heterogeneity 0.63; fixed effect model). The RR of being disease free was 0.67 in favor of the experimental arms (0.48–0.94; *P*=0.02; *P* for heterogeneity 0.22; fixed affect model). The RR of being alive was 0.67 in favor of the experimental arms (0.39–1.15; *P*=0.15). The RR of a cardiac event was 1.09 in the arms treated with chemotherapy and concomitant trastuzumab, but that is not significant (0.6–1.98; *P*=0.77). The addition of concomitant trastuzumab to neoadjuvant chemotherapy doubles the risk of obtaining a pathologically complete response in both breast and nodes compared with controls. Trastuzumab significantly reduces the risk of relapse and does not increase the risk of cardiotoxicity, despite being associated with anthracyclines. The largest benefit was observed in a locally advanced patient study. *Anti-Cancer Drugs* 22:128–135 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Neoadjuvant therapy, also named primary systemic (or preoperative) therapy, was initially introduced to reduce the size or the extent of inoperable breast cancer (BC) to make it operable and allow definitive surgery. Over the last two decades, chemotherapy has been shown to give equivalent survival benefits regardless of whether it was administered before or after surgery. Not only may the neoadjuvant approach allow an enhancement of breast conservation, it can also offer other advantages. The primary aim of neoadjuvant therapy in the treatment of breast cancer is to improve surgical outcomes, assess the response to the therapy and achieve long-term survival [1]. The response to the treatment in an individual patient may predict her long-term outcome. Despite the various definitions of pathologically complete response (pCR) in trials completed to date, it has been consistently shown that pCR is associated with improved disease-free survival (DFS) and overall survival (OS) [2–4]. Patients without residual invasive and noninvasive tumor cells in the breast and in axillary nodes have substantially improved their outcomes, compared with the patients with similar tumor stage and characteristics and extensive residual disease. The characteristics of the tumor can help predict whether the patient will respond to, and therefore benefit from, chemotherapy. The characteristics that may improve the response to neoadjuvant chemotherapy include absent or low expression of estrogen receptor, high Ki67 or another proliferation index, and high-grade and ductal pathology [5]. Better responses to neoadjuvant chemotherapy and high pCR rates are also more likely in women with tumors that amplify or overexpress the HER2/*neu* (HER2-positive) receptor or tumors that lack estrogen receptor, progesterone receptor, and HER2 (so called 'triple-negative' breast cancer), compared with the patients with low-grade tumors or tumors that express the estrogen receptor. The administration of the entire planned course of therapy is usually carried out before surgery over a period of 4–6 months [1].

The addition of trastuzumab to cytotoxic therapy has led to a considerable reduction in breast cancer recurrence and death rate in an adjuvant setting [6–8]. In particular, the addition of concurrent trastuzumab to chemotherapy (weekly paclitaxel) in sequence with anthracycline resulted in longer DFS compared with the sequential treatment, with a little difference in cardiac adverse events [9]. Patients with HER2-positive tumors, who are candidates for neoadjuvant chemotherapy, should probably undergo a trastuzumab-based regimen in the early course of the disease [10]. In addition, several small phase II studies have reported impressive pCR rates

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when trastuzumab was added to neoadjuvant anthracycline and taxane-based regimens. In the past, the use of concomitant trastuzumab and anthracycline-based regimens had been initially abandoned after the release of the data collected from a pivotal phase III trial in advanced disease setting. That trial showed an unexpectedly high number of adverse cardiac events [11]. In total, 13% of all patients had symptomatic or asymptomatic cardiac heart failure (CHF): 27% in the combination group versus 8% in the anthracycline monotherapy group, and 13% in the combination paclitaxel–trastuzumab group versus 1% in the paclitaxel monotherapy group. Moreover, CHF severity turned out to be worse in the anthracycline combination group than in the anthracycline monotherapy group (New York Heart Association grade III/IV CHF 16 versus 3%, respectively), and in the paclitaxel combination group than in the paclitaxel monotherapy group (New York Heart Association grade III/IV CHF 2 versus 1%, respectively). Subsequent data on individual patients with advanced disease, who were enrolled into seven early phase II/III trials, confirmed these findings [12,13]. Although cardiac-related deaths were overall rare (0.8%, 10 cases among 1219 patients), all patients but one have received trastuzumab.

To date, there are only two published trials [14–16] that explore, in a randomized manner, the added value and feasibility of concomitant trastuzumab in a neoadjuvant chemotherapy regimen (anthra based and taxane based). In these trials (one American and one European), two different populations have been sampled: operable and locally advanced BC, respectively. The regimens were similar, with a sequential administration of anthracycline and taxanes either with or without concomitant trastuzumab. The aim of this pooled analysis was to evaluate the benefit (if there is any) of chemotherapy plus trastuzumab in terms of pCR, relapse, survival, and toxicity.

Methods

Data source

The deadline for the trial publication of this analysis was May 30, 2010. The MEDLINE database has been searched using the following keywords: 'breast cancer', 'neoadjuvant chemotherapy', and 'trastuzumab' without restriction data. The American Society of Clinical Oncology (*www.asco.org*) annual meeting abstracts have also been retrieved.

Study selection

The relevant clinical trials have been carefully manually selected based on the following criteria: (i) chemotherapy (anthracycline-based) combined with concomitant trastuzumab versus chemotherapy alone; (ii) patients with pathologically confirmed BC and untreated earlier; and (iii) randomized controlled trial. No language restrictions were applied.

Clinical endpoints

The data extracted from each trial include (Table 1) author, year of publication, study design, race, patient's characteristics (medium age, Eastern Cooperative Oncology Group performance status, or Karnofsky performance status, whether the HER2 expression has been evaluated as an entry criterion by the fluorescence in-situ hybridization method or the immunohistochemistry techinque, chemotherapy regimens, number of patients in trastuzumab-chemo and chemo-alone groups, the percentage of patients acquiring pCR in breast and nodes [(bn)pCR], median OS and DFS or event-free survival (EFS), hazard ratios for OS and DFS or EFS and their 95% confidence intervals, specific grade III/IV cardiotoxicity data.

The main goal of Buzdar's trial was to show that the addition of trastuzumab to chemotherapy would lead to a 20% improvement in pCR rates (from 21 to 41%). The planned sample size was 164 patients. The prognostic factors were similar in the two groups. After 34 patients had completed the therapy, the trial's Data Monitoring Committee stopped the trial because of the superiority of trastuzumab plus chemotherapy. The main goal of Gianni's trial was to compare EFS, defined as time from randomization to disease recurrence or progression (local, regional, distant, or contralateral) or death from any cause, in patients with HER2-positive disease treated both with and without trastuzumab.

Statistical analysis

The relative risks (RRs) of pCR, OS, and progression-free survival have been calculated using the 5.0.24 version of RevMan (Cochrane IMS, Copenhagen: Nordic Cochrane Centre, Cochrane Collaboration, 2008). A statistical test with a P value lower than 0.05 was considered significant. A RR of more than 1 showed more pCRs in trastuzumab-chemo arms, whereas a RR of less than 1 showed a lower risk of relapse or survival in trastuzumab-chemo arms. To investigate the statistical heterogeneity between the trials, the standard χ^2 Q-test was applied (significant differences between studies indicated by $P < 0.10$). The results were generated using the fixed-effect model. A random-effect model has been used in case of the significant statistical heterogeneity. All P values were two sided. All confidence intervals had two-sided probability coverage of 95%. The search strategy was extensive, but it has not been possible to detect any publication bias because of the limited number of trials, even though a funnel plot and Begg and Egger's tests have been carried out.

Results

Selected trials

A total of 45 trials were retrieved from the primary search after electronic searching on May 30, 2010, and two trials were selected for full review [14–16]. The other trials

Table 1 Characteristics of two study populations

Author/year (ref.)	Phase and no of patients	Age (median)/ race/PS	Stage	CT schedule	HER2 status (IHC/FISH)	Objectives/ median follow-up	% (bn) pCR	DFS (median)	OS (median)	% cardiotoxicity
Buzdar *et al.* [15,16]	III/42 (19 CT alone & 23 CT + T)	48 and 52 years/white 26/ 42 PS: n.a.	II & IIIA	Paclitaxel 225 mg/m^2 × 4 cycles → FEC × 4 cycles ± weekly trastuzumab	37/42 FISH +ve 4/42 IHC + ve 1/42 IHC + ve/ FISH-ve	↑ of 20% of pCR/36 months	65.2 vs. 26.3% in CT + T and CT alone arms	100 vs. 85.3% at 3 years in CT + T and CT alone arms	100 vs. 95% in CT + T and CT alone arms	12/42 >10% reduction in EF; No CHF
Gianni *et al.* [14]	III/235 (117 CT + T & 118 CT alone)	57% > 50 years 43% <50 years	100% locally advanced or inflammatory	AT × 3 cycles → T × 4 cycles → CMF × 3 cycles ± T q 3 weeks during CT & for a total of 1 year	IHC 3 + or FISH +ve	EFS/3.2 years	38 vs. 19% in CT + T and CT alone arms	71 vs. 56% EFS at 3 years in CT + T and CT alone arms (HR 0.59; 95% CI 0.38–0.9) P=0.013	HR 0.62 (P=0.114)	All cardiac events: 11% in 2 arms; Left ventricular dysfunction 2 vs. 0% in CT + T and CT alone arms

AT, adriamycin/paclitaxel; (bn)pCR, pathologically complete response of breast and nodes; CHF, cardiac heart failure; CMF, cyclophosphamide/methotrexate/fluorouracil; CT, chemotherapy; DFS, disease free survival; EF, ejection fraction; EFS, event free survival; FEC, fluorouracil/epirubicin/cyclophosphamide; FISH, fluorescence in situ hybridization; HR, hazard ratio; IHC, immunohistochemistry; OS, overall survival; PS, performance status; T, trastuzumab.

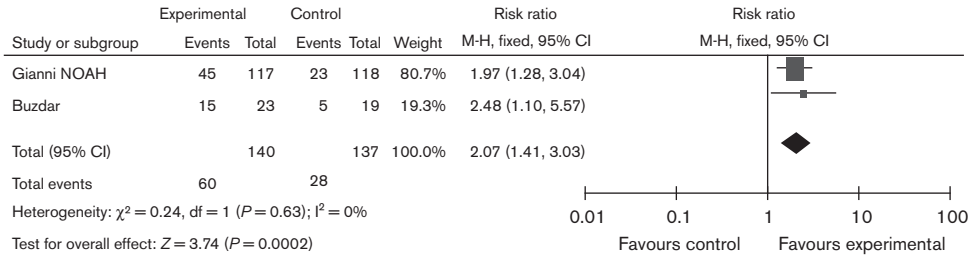
have been excluded because they were not randomized, including the patients with metastatic disease, and did not include any arm with concomitant trastuzumab and anthracyclines. Forty-two patients have been analyzed in Buzdar's trial and 235 in Gianni's trial ($n = 279$ total). In particular, 138 patients received chemotherapy plus trastuzumab and 132 patients received chemotherapy alone in their allocated arms.

In the first study, each patient has received four cycles of paclitaxel followed by four cycles of fluorouracil, epirubicin, and cyclophosphamide. Paclitaxel was administered (225 mg/m^2) as a 24-h continuous intravenous (IV) infusion; the cycles have been repeated every 3 weeks for four cycles. Administration consisted of fluorouracil (500 mg/m^2 IV) on days 1 and 4, cyclophosphamide (500 mg/m^2 IV) on day 1 only, and epirubicin (75 mg/m^2) on day 1 only. The patients randomly assigned to the trastuzumab arm of the study received trastuzumab at a dose of 4 mg/kg IV on day 1 of the first treatment cycle, administered over 90 min. Subsequent doses of weekly trastuzumab were administered at a dose of 2 mg/kg over 30 min. Trastuzumab was administered before chemotherapy. A total of 24 doses of trastuzumab were administered on a weekly basis. In the second trial, all patients received doxorubicin (60 mg/m^2; given first) plus paclitaxel (150 mg/m^2) infused over 3 h, every 3 weeks for three cycles, followed by paclitaxel (175 mg/m^2) administered every 3 weeks for four cycles. Cyclophosphamide (600 mg/m^2), methotrexate (40 mg/m^2), and fluorouracil (600 mg/m^2) were then administered on days 1 and 8 every 4 weeks for three cycles. Surgery followed by radiotherapy was scheduled for all patients after the completion of chemotherapy. Patients with estrogen or progesterone receptor-positive disease also received adjuvant tamoxifen (20 mg per day) for 5 years. The patients who were scheduled to receive trastuzumab have received a loading dose of 8 mg/kg of body weight infused intravenously over 90 min, followed by 10 cycles of 6 mg/kg over 30 min every 3 weeks alongside chemotherapy. Trastuzumab may have been administered every 4 weeks during chemotherapy with cyclophosphamide, methotrexate, and fluorouracil. After surgery, to complete 1 year of trastuzumab treatment, additional cycles of trastuzumab were scheduled, starting before or during radiotherapy (at the investigator's discretion).

Efficacy comparison

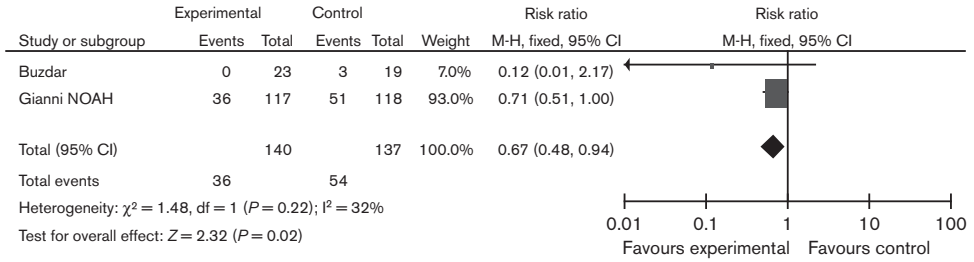
The RR of obtaining [(bn) pCR] was 2.07 in the experimental arms (1.41–3.03; $P = 0.0002$; P for heterogeneity 0.63; fixed effect model). The RR of being relapse free was 0.67 in favor of the experimental arms (0.48–0.94; $P = 0.02$; P for heterogeneity 0.22 fixed-affect model). The RR of being alive was 0.67 in favor of the experimental arms (0.39–1.15; $P = 0.15$; Figs 1–3).

Fig. 1



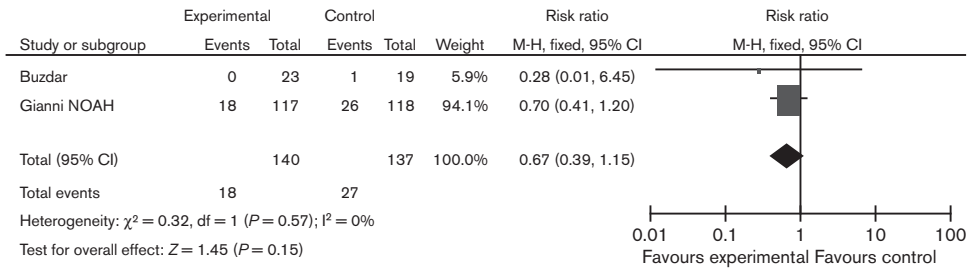
Forrest plot of risk ratio of pathologically complete response in breast and nodes in the experimental and control arms. CI, confidence interval; df, degree of freedom; NOAH, neoadjuvant herceptin; M-H, Mantel–Haenszel.

Fig. 2



Forrest plot of risk ratio of relapse in the experimental and control arms. CI, confidence interval; df, degree of freedom; NOAH, neoadjuvant herceptin; M-H, Mantel–Haenszel.

Fig. 3



Forrest plot of risk ratio of survival in the experimental and control arms. CI, confidence interval; df, degree of freedom; NOAH, neoadjuvant herceptin; M-H, Mantel–Haenszel.

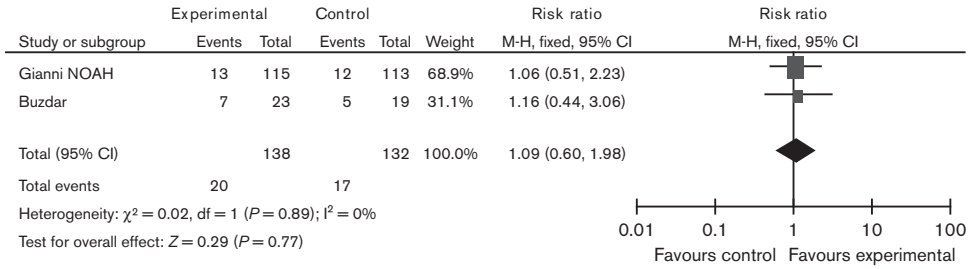
Cardiac safety

Cardiac adverse events were reported in both trials. In Buzdar's trial, greater than 10% decrease in the left ventricular ejection fraction was observed in five and seven patients, respectively, in the chemo-alone arm and the trastuzumab-plus chemotherapy arm. Left ventricular ejection fraction decreased to baseline values in all the patients who had undergone follow-up cardiac studies except for one, whose ejection fraction remained at normal low levels. No cardiac failure was reported. In Gianni's trial, two patients experienced a grade II decrease (asymptomatic) during the treatment and the follow-up, and other two (1.7%; 95% confidence interval 0.5–6) a reversible grade III decrease (congestive heart failure, classified as New York Heart Association class III). Cardiac events showed similar characteristics in both the arms (11%). The RR of a cardiac event was 1.09 (0.6–1.98; $P = 0.77$; Fig. 4).

Discussion

Patients with locally advanced BC have poor rates of DFS (not exceeding 50–60%) depending on tumor characteristics

Fig. 4



Forrest plot of risk ratio of cardiotoxicity in the experimental and control arms. CI, confidence interval; df, degree of freedom; NOAH, neoadjuvant herceptin; M-H, Mantel–Haenszel.

and nodal status. In general, the most frequent type of treatment failure is because of distant metastases, and the majority of them appear within 2 years of the diagnosis. Thanks to an increase in the use of multimodality therapy, including chemotherapy, radiation therapy, and surgery, the survival rate for this patient population has improved significantly. A multimodality treatment approach (systemic therapy then surgery and radiotherapy) can provide an improved control of locoregional and systemic disease. The response to neoadjuvant therapy may lead to improved overall outcomes in patients with locally advanced BC by performing definitive local therapy. The neoadjuvant approach provides equivalent DFS and OS rates in patients with primary operable disease and in those patients treated with adjuvant therapy, but it is associated with improved rates of breast-conserving therapy [17].

In the past, the standard of treatment for operable and locally advanced BC involved the administration of anthracycline-based chemotherapy [e.g. fluorouracil, doxorubicin (epirubicin), and cyclophosphamide schedule] for 3–4 cycles and a subsequent surgical reevaluation. As of now, there is no ideal regimen to be prescribed during the neoadjuvant phase, but the medical literature states that the addition of a taxane to an anthracycline-based neoadjuvant platform results in higher pCR rates and survival benefit [18,19]. There seems to be no difference in the survival rates in women with locally advanced disease who undergo chemotherapy before or after surgery. Neoadjuvant chemotherapy results in complete and partial RRs ranging from 80 to 90%. Patients with large lesions are more likely to have partial responses. pCRs do occur in 20–40% of the cases and are more likely to be observed in patients with smaller tumors. A pCR in the primary tumor is often predictive of a complete axillary lymph node response. Patients with locally advanced BC, who have a pCR in the breast and, in particular, axillary nodes, have a significantly improved DFS compared with those who have less than a pCR. However, a pCR does not entirely eliminate the risk of recurrence. In particular, HER2-positive BC has poor prognosis and the addition of trastuzumab during the neoadjuvant phase of the treatment has the aim of blocking the micro-metastatic process early and increasing locoregional and distant control. After the release of trastuzumab-adjuvant data, all the patients with HER2-positive disease started receiving 1 year of adjuvant trastuzumab even though, so far, only two randomized trials have investigated whether any added benefit can be achieved from trastuzumab, when offered in addition to neoadjuvant chemotherapy, surgery, radiotherapy, and eventually adjuvant trastuzumab as well.

These two trials, here pooled for a combined data analysis, target two different populations of BC patients (stage II–IIIA and locally advanced BC, respectively). In particular, 69% of the trastuzumab arm in Gianni's trial is consists of T4 noninflammatory and inflammatory BC. In the past, the most striking benefit achieved from the multimodality approach was seen in patients with inflammatory BC, with 5-year survival rates of 35–50% reported for a multimodality treatment including primary chemotherapy followed by surgery, radiation therapy, and additional adjuvant systemic therapy. The medical literature provides data taken from phase II (nonrandomized) trials that show that the addition of trastuzumab to nonanthracycline-based chemotherapy in particular confers a high rate of response and pCR, despite a general concern about the cardiotoxicity of concomitant anthracycline/trastuzumab regimen, which made it hard to design trials based on such an intensive regimen.

The pooled analysis of Buzdar and Gianni's trials shows that, with a median 3-year follow-up, the addition of neoadjuvant and concomitant trastuzumab to anthracycline/taxane based chemotherapy is safe, and that DFS and the EFS rates are 100 and 71%, respectively in two trials [the last value is lower because of the more advanced stage of the disease in the neoadjuvant herceptin (NOAH) trial]. In particular, by adding neoadjuvant trastuzumab, the RR of having [(bn)pCR] is 200% higher (RR 2.07; $P = 0.0002$; fixed-effect model with P for heterogeneity 0.63) and the RR of relapse is 33% lower

($P = 0.02$; fixed-effect model with P for heterogeneity 0.22). Overall, no significant survival advantage was observed (RR 0.67; $P = 0.15$ non significant). In particular, no differences in the RR of cardiac events (all grade) have been observed between the trastuzumab and the non-trastuzumab arms (RR 1.09; $P = 0.77$).

The analysis of these data shows that the rate of [(bn)pCR], the most predictive benefit of neoadjuvant chemotherapy, has risen from 26 to 65% and from 19 to 38% in the two trials. This reflects the double RR of having a [(bn)pCR] at pathological examination and might explain the high rate of DFS at a 3-year follow-up (33% lower risk of being relapse free from combined analysis). Overall, the survival rate at the moment is not different. These data have two possible explanations: one, the relatively short follow-up and two, the addition of 1 year of adjuvant trastuzumab in the NOAH trial after the randomized phase III trial data had been released. However, the data on the DFS benefit are of similar magnitude of the ones obtained in the HERA trial at a 2-year follow-up [6].

Robidoux *et al.* [20] have recently published data taken from a phase II trial that investigated the effects of neoadjuvant nanoparticle albumin-bound paclitaxel followed by administration with fluorouracil, epirubicin, and cyclophosphamide in 66 patients with locally advanced BC. Patients with HER2-positive disease have received concomitant trastuzumab. In the HER2 plus group, the pCR in breast was 58% (11 out of 19), similar to the one observed in Buzdar's trial. A pCR in the breast and the axilla was obtained in 36.4% of the patients. A similar but lower rate of [(bn)pCR] was obtained in the GETN(A)-1 trial that tested trastuzumab, carboplatin, and docetaxel in stage II–III noninflammatory BC administered as neoadjuvant therapy [21]. The rate of pCR was 39% (27/70 patients) in tumor and nodes and 43% in 56 centrally confirmed HER2-positive BCs. No symptomatic cardiac dysfunctions have occurred. In an updated version of this and the Taxotere Herceptin (TAXHER-S01) study [22], no differences have been observed in the survival or in the survival without relapse according to the type of chemotherapy. Pathological CR has significantly influenced survival without relapse ($P = 0.03$) and the survival without local recurrence ($P = 0.04$), but not OS or survival without metastatic relapse. In the GeparQuattro trial [23], in which capecitabine was added to the sequential epirubicin and cyclophosphamide, and docetaxel regimen with trastuzumab administered to all the 445 HER2-positive (operable or locally advanced) BC patients, the rate of [(bn)pCR] was 29%. The replacement of standard anthracycline formulations with liposomal formulations might improve both the therapeutic index and the effectiveness of the treatment [24–29]. As liposomal anthracyclines/trastuzumab schedules have shown high activity and cardiac safety several times in the metastatic setting, they could be also applied to the neoadjuvant setting.

Thus, other schedules without anthracyclines or with alternative taxanes could be implemented in phase III trials. The addition of higher amounts of the agent (capecitabine) does not seem to increase the benefit. It seems, instead, that taxanes followed by anthracyclines provide a higher pCR rate than that observed in the reverse sequence, but this hypothesis has yet to be confirmed in a randomized manner.

Finally, this analysis proves that cardiac toxicity should no longer be considered as a limiting concern. In fact, despite the concurrent use of doxorubicin, paclitaxel, and trastuzumab, the incidence of symptomatic cardiac failure in the NOAH trial was low ($< 2\%$) and less than expected (2.8–4.1%) based on adjuvant trials in which trastuzumab was given concurrently with paclitaxel after the completion of doxorubicin [30,31] and as monotherapy after the completion of chemotherapy (2%) [6]. In Buzdar's trial, the rate of cardiac heart failure in randomized patients reported in the updated version at a 36-month follow-up was 0% with no new safety concerns.

These data convincingly confirm that it is possible to prevent excessive cardiac toxicity by administering a cumulative dose of anthracycline below the safety limit for cardiotoxicity (180 mg/m^2 of doxorubicin and 300 mg/m^2 of epirubicin). As different numbers of cycles and agents (10 and 8 cycles; 6 and 5 agents, respectively) have been used in the NOAH and Buzdar's trials, what the proper duration of the preoperative treatment should be is still being debated, as well as the hypothesis that locally advanced BC requires prolonged and noncross resistant chemotherapy while operable early BC can be treated with a shorter duration therapy despite the addition of trastuzumab.

Conclusion

The results achieved through the pooled analysis of the only two randomized trials that compared the concomitant use of chemotherapy (anthracycline-based) and trastuzumab confirm that this approach is safe and provide benefits if added to the standard locoregional treatment and adjuvant trastuzumab. By combining chemotherapy and trastuzumab from the first cycle, it is possible to improve the rate of (bn)pCR proved to be a predictive factor of the OS and to decrease the risk of progression or relapse by 33%, but not to improve the survival data, probably because of the short duration of the follow-up of the two trials (3 years) and perhaps the adjuvant component of the trastuzumab treatment administered to patients after the release of the data on the benefits of adjuvant trastuzumab. In particular, this approach does not increase cardiotoxicity in a significant manner. Particular attention must be paid to the fact that neoadjuvant trastuzumab provided significant benefits,

particularly in locally advanced BC cases, the more numerous group in Gianni's trial. In fact, the inflammatory BC population with the worst prognosis achieved the greatest benefit from the addition of trastuzumab (HR = 0.27). This benefit could result in a survival gain with longer follow-up. In conclusion, trastuzumab should be given to patients with HER2-positive locally advanced and inflammatory BC (and maybe early BC) together with neoadjuvant chemotherapy, even when anthracycline based, without concern for cardiac safety. Nevertheless, two questions are still unanswered. First, is the addition of neoadjuvant trastuzumab necessary if standard (1 year) adjuvant trastuzumab is administered after neoadjuvant chemotherapy alone? And second, what should the proper duration of adjuvant trastuzumab therapy be after approximately 6 months of neoadjuvant trastuzumab therapy? An answer needs to be found for these questions through appropriate randomized trials.

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