

Trastuzumab as Adjuvant Treatment for Early Stage HER-2-positive Breast Cancer

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Abstract Her-2-positive breast cancers are associated with higher recurrence rates and increased mortality. Trastuzumab, a humanised monoclonal antibody targeting the extracellular domain of Her-2, is an important part of palliative first-line therapy. Combination therapy with taxanes improved response rates, progression-free as well as overall survival.

Based on those results, different groups initiated prospective randomised phase III trials evaluating the role of trastuzumab in the adjuvant setting. Again, significantly superior outcomes were observed in terms of recurrence-free and overall survival. Importantly however, a recently presented French trial showed no additional benefit of trastuzumab over conventional chemotherapy alone. As the mentioned adjuvant studies had huge differences in their respective designs, a number of questions remain unanswered; furthermore, those differences may account for disparities in both, efficacy and side effects.

In the neo-adjuvant setting, the addition of trastuzumab to conventional chemotherapy yielded pathologic complete remission rates of up to 60%. Therefore, pre-operative therapy regimens of Her-2-positive tumours today should incorporate trastuzumab.

As reported from earlier studies, cardiotoxicity appears to be the most significant side effect of trastuzumab treatment; this apparently is most prominent if the antibody is administered closely to an anthracycline.

In this chapter, current knowledge of the role of trastuzumab in the adjuvant setting is discussed.

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1 Introduction

Breast cancer remains the most prevalent cancer in women in both, developed and developing countries, and holds responsible for almost half a million deaths per year worldwide [1]. The history of targeted therapies for the treatment of breast cancer dates back to surgical oophorectomy in the late nineteenth century [2]. Today, a wide range of anti-hormonal agents and other targeted drugs, including trastuzumab, bevacizumab and lapatinib are available.

In the 1980s, it was established that patients suffering from Her (Human epidermal growth factor receptor)-2 positive tumours had a more aggressive course of disease [3–5]. Furthermore, it was discovered that Her-2 was a transmembrane growth factor receptor, which in conjunction with other members of the epidermal growth factor super-family (EGFR = Her1; Her3, Her4) will activate downstream signalling pathways important for cell growth and survival. Based on those findings, a humanised monoclonal antibody, trastuzumab (rhMab4D5), targeting Her-2 was developed.

1.1 *Role of Her-2 in Healthy Tissue*

Her-2 plays a number of physiological roles in healthy tissue. Among others, Her-2 signalling regulates cell differentiation, survival and cell repair mechanism [6]. Of note, cardiac myocytes seem to depend strongly on Her-2-activation in response to stress as caused by anthracyclines [7].

1.2 *Assessment of Her-2 Status*

Given the importance of Her-2 for tumour growth, reliable evaluation of patients' Her-status is paramount. Her-2-positivity is defined as either increased receptor expression or gene amplification. Two different methods are being used worldwide: immunohistochemistry (IHC) and fluorescence in situ hybridisation (FISH). Other options, including chromogenic in situ hybridisation (CISH) [8] or real-time polymerase chain reaction (RT-PCR) [9], are an established alternative to FISH, while gene expression profiles are still largely considered experimental.

Differences were observed between Her-2-testing in high- and low-volume centres [10]. Therefore, it is recommended that Her-2-status should be assessed in specialised institutions [11].

2 Trastuzumab

For 10 years, the use of trastuzumab is firmly established in Her-2-positive advanced breast cancer. The drug has dramatically increased response rate and progression-free survival as well as overall survival.

2.1 *Mechanism of Action*

Trastuzumab is a recombinant monoclonal humanised antibody targeting the extracellular domain of Her-2. Different mechanisms of action were suggested: Inhibition of downstream signalling pathways; internalisation and degradation of Her-2 receptor protein; p27 induction causing cell cycle arrest due to decreased cyclin-dependent kinase 2 (CDK2) activity; inhibition of DNA repair; and antibody-dependent cellular cytotoxicity (ADCC) [12]. In addition, trastuzumab sensitises tumour cells to the cytotoxic effects of conventional chemotherapy [13]. It is still unclear whether trastuzumab actually causes downregulation of Her-2, as some studies have demonstrated that receptor levels remain basically unchanged [12]. On the other hand, lapatinib, a tyrosine-kinase inhibitor of EGFR and Her-2, was observed to actively inhibit Her-2-internalisation, thereby exposing tumour cells to the immunologic effect of trastuzumab [14]. This mechanism may well hold responsible for the synergistic effect of lapatinib and trastuzumab, which has recently been reported in a randomised study [15].

Phase II clinical trials established the activity of trastuzumab as single-agent in Her-2-positive metastatic breast cancer [16, 17]. Based on those proof-of-principle studies, large randomised trials were initiated. Here, the combination of trastuzumab and taxanes was found superior in terms of response, progression-free and overall survival over chemotherapy alone [18, 19]. Accordingly, trastuzumab was approved as first-line treatment for Her-2-positive metastatic breast cancer in combination with taxanes.

2.2 *Mechanisms of Resistance*

Questions concerning mechanisms of resistance to trastuzumab-based therapy remain largely unresolved. Only one third of patients will initially respond to trastuzumab, suggesting de novo (primary) resistance [20]. Even in responders, acquired (secondary) resistance will eventually develop, as the majority of patients will experience disease progression within 1 year of treatment initiation [12].

A number of escape mechanisms were described, and trastuzumab resistance is likely a multifactorial process [12]. Known pathways conferring resistance comprise: Activation of insulin-like growth factor-1 (IGF-1) and its downstream

signalling pathways [21]; phosphatase and tensin homologue loss (PTEN) [22]; increased Akt signalling [23, 24]; steric hindrance of trastuzumab binding to Her-2 by cell surface proteins such as mucin-4 (MUC4) [12]; truncated Her-2 receptor (p95 Her-2), a receptor variant without extracellular domain due to alternative splicing [25]; and downregulation of p27 [12].

With alternative Her-2-targeted drugs becoming available (lapatinib, pertuzumab, trastuzumab-DM1, neratinib, ...), the question of specific mechanisms of resistance will gain importance and answers will ultimately help finding the optimal treatment approach for Her-2-positive tumours.

2.3 Combination of Chemotherapy with Trastuzumab in Advanced Breast Cancer

Based on preclinical studies conducted by Pegram et al., cytotoxic agents and trastuzumab were classed either as synergistic, agonistic or antagonistic [13]. Data were derived from cell culture as well as a tumour xenograft model. Based upon those results, special emphasis was put on combinations with taxanes, vinorelbine and platinum compounds (as for those substances a synergistic interaction was hypothesised).

As mentioned above, two randomised trials proved the combination of trastuzumab with either paclitaxel (H0648g) [18] or docetaxel (M77001) [19] superior to chemotherapy alone. In H0648g, patients who had not received prior adjuvant anthracycline-based therapy were treated with a combination of doxorubicin and trastuzumab. While this combination again was highly effective in terms of oncological end points, a surprisingly high rate of cardiotoxicity was observed.

3 Trastuzumab in the Adjuvant Setting

Due to the proven benefits of trastuzumab in the palliative setting, adjuvant trials were initiated evaluating the possible role of trastuzumab in the prevention of breast cancer recurrences. More than 13,000 women were included in a total of six prospective randomised phase III trials. Five studies showed a benefit for the respective trastuzumab groups in terms of progression-free survival and (with the exception of the FinHER-trial) overall survival. Those results have ultimately established trastuzumab as golden standard in the adjuvant therapy for Her-2-positive early breast cancer. Importantly, chemotherapy regimens and the timing of trastuzumab administration varied among the different studies. Therefore, a number of unanswered questions concerning the optimal way to administer adjuvant trastuzumab remain. Furthermore, the last trial to report, the French PACS 04 study, presented divergent results: Herein, no additional benefit was found with the addition of adjuvant trastuzumab. Respective designs of the adjuvant breast cancer trials are summarised in Fig. 1.

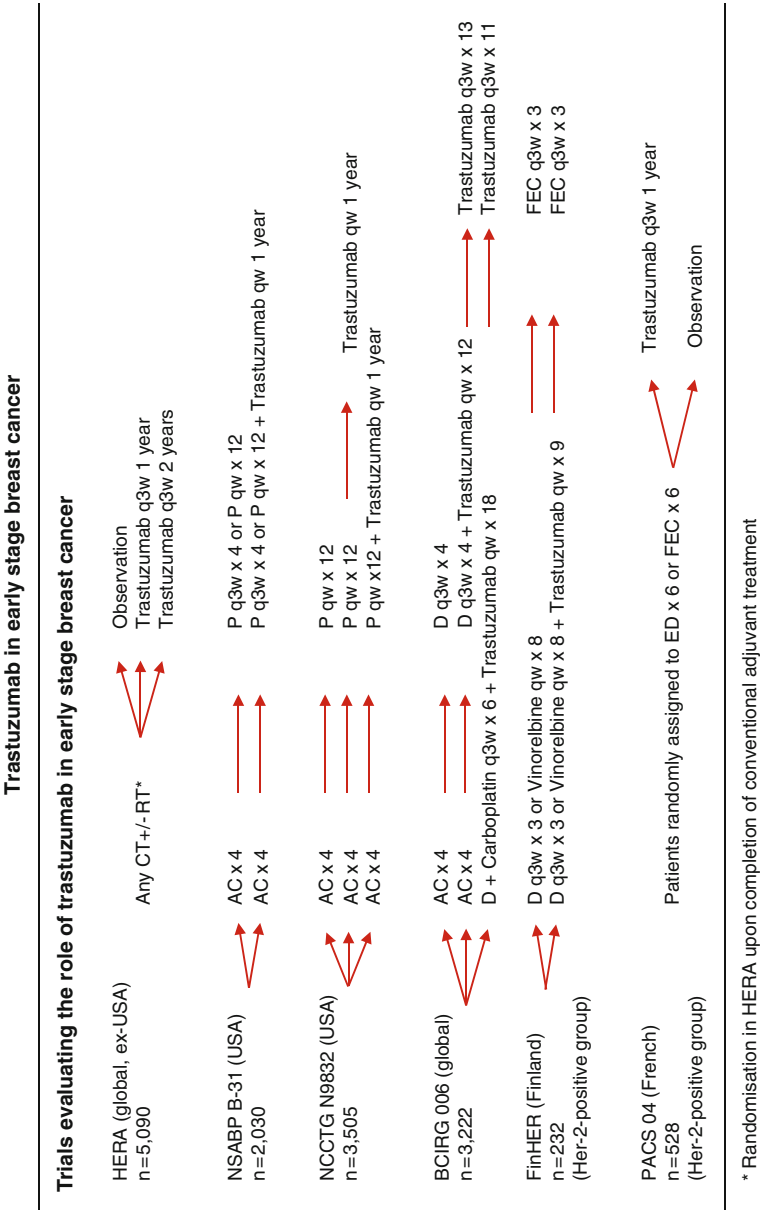


Fig. 1 *Trastuzumab in early stage breast cancer*. Abbreviations: *A* doxorubicin; *C* cyclophosphamide; *D* Docetaxel; *E* epidoxorubicin; *F* 5-FU; *P* paclitaxel; *q3w* every 3 weeks; *qw* weekly; *RT* radiotherapy

3.1 HERA

HERA (Herceptin Adjuvant) was the largest of the adjuvant trastuzumab studies. This international, non-US, adjuvant multicentre trial randomised a total of 5,102 patients following standard adjuvant therapy (a minimum of four cycles of adjuvant/neo-adjuvant chemotherapy with or without radiotherapy was required) to three treatment arms: Control, trastuzumab 12 months and trastuzumab 24 months. Disease-free survival was defined as primary study end point. It is noteworthy that in difference to the US-trials NSABP-B31 and NCCTG N9831, just over half of women had lymph-node positive disease. Therefore, information on the efficacy of trastuzumab in node-negative disease is largely derived from the HRA study. Initial data have been published in 2005. At 1 year of median follow-up, a relative reduction of recurrence risk of 46% was observed in the treatment group compared with control (hazard ratio [HR], 0.54; 95% confidence interval [CI], 0.43–0.67; $p < 0.0001$). Further, a trend towards prolonged overall survival was reported [26]. Despite a 51% crossover rate, this trend reached statistical significance at the second planned interim analysis at a median follow-up of 23.5 months (HR, 0.66; 95% CI, 0.47–0.91; $p = 0.0115$) [27].

A number of issues concerning specific aspects of the HERA trial need to be discussed: First, the sequential design might reduce the benefit of adjuvant trastuzumab, as there was no additional synergistic effect of chemotherapy plus trastuzumab combinations. Second, less than one-third of the study population had received prior anthracycline and taxane chemotherapy, rendering the administered chemotherapy protocols suboptimal. Third, patients were randomised upon completion of conventional chemotherapy, which may result in the selection of a more favourable cohort, as patients with early recurrences were not included into the study.

Still, HERA is a successful protocol proving the benefit of trastuzumab also in non-anthracycline and/or taxane pre-treated patients as well as in node-negative tumours.

3.2 NSABP B-31 and NCCTG N9831

NSABP B-31 was a two-arm, randomised phase III trial of four cycles of AC followed by four cycles of paclitaxel every 3 weeks (or 12 cycles of weekly paclitaxel) with or without trastuzumab. Trastuzumab treatment was initiated after completion of AC therapy, therefore concomitantly to paclitaxel. Only node-positive women were included. In contrast, NCCTG N9831 had a three-arm design. Two arms were identical to the corresponding arms of B-31, while a third arm initiated trastuzumab after the end of chemotherapy (HERA style). In the latter trial, also patients with high-risk node-negative disease were allowed, although their relative number was much lower than in HERA. Similar to B-31, treatment

again consisted of ACx4 followed by 12 cycles of weekly paclitaxel. Therefore, with FDA approval, a joint analysis comparing the two concurrent trastuzumab arms with the two control arms was conducted. A total number of 3,968 patients were included in the combined analysis, of which 93% had node-positive tumours.

After 2 years of median follow-up, patients treated with trastuzumab had a significantly longer disease-free survival as compared to the control group (HR, 0.48; 95% CI, 0.39–0.59; $p < 0.001$). Also, a significant benefit in terms of overall survival was observed (HR, 0.67; 95% CI, 0.48–0.93; $p = 0.015$) [28]. At a median follow-up of 2.9 years, despite a 21% crossover rate, updated results were similar: Risk of both, disease recurrence (HR, 0.48; 95% CI, 0.41–0.57; $p < 0.00001$) and death (HR, 0.65; 95% CI, 0.51–0.84; $p = 0.0007$) was significantly reduced [29].

Again, a number of aspects need to be considered. A small subsets of patients included in the joint analysis was identified Her-2-negative at central review. Furthermore, adjuvant AC→P might be considered a suboptimal adjuvant chemotherapy regimen.

3.3 *BCIRG 006*

A third trial was initiated by the BCIRG. This randomised three-arm open-label study conducted at centres in the US, Europe, South Africa, Asia and Venezuela had a slightly different design. Control arm consisted of ACx4 followed by four cycles of docetaxel every 3 weeks. This was compared to the same regimen plus trastuzumab (initiated after AC as in the North American studies) and a third (anthracycline-free) arm consisting of carboplatin, docetaxel and trastuzumab (TCH). A total of 3,222 patients were included, 71% had lymph-node-positive tumours.

Of interest is the inclusion of an anthracycline-free regimen. In the light of cardiac safety concerns, this seems an attractive option in patients with known pre-existing cardiac conditions. Currently however, anthracycline-free regimens cannot be considered a standard in the adjuvant therapy of breast cancer.

Updated results were presented at the 2006 San Antonio Breast Cancer Symposium [30]. At a median follow-up of 36 months, both trastuzumab groups were significantly superior over AC→docetaxel in terms of recurrence-free (HR, 0.61; 95% CI, 0.48–0.76; $p < 0.0001$ [AC→docetaxel+trastuzumab]; HR, 0.67; 95% CI, 0.54–0.83; $p = 0.0003$ [TCH]) as well as overall survival (HR, 0.59; 95% CI, 0.42–0.85; $p = 0.004$ [AC→docetaxel+trastuzumab]; HR, 0.66; 95% CI, 0.47–0.93; $p = 0.017$ [TCH]).

3.4 *FinHER*

A total of 1,010 women with node-positive or high-risk node-negative breast cancers were accrued to this randomised, controlled, open-label trial. The study was designed to compare the relative benefits of three cycles of docetaxel

administered every 3 weeks to twelve cycles of weekly vinorelbine before receiving three cycles of FEC. Two hundred and thirty-two Her-2-positive patients were further randomised to nine cycles of weekly trastuzumab or control. Recurrence free survival was defined as primary end point.

While there was only a trend towards improved overall survival, a significant reduction in recurrence-free survival events was observed in patients receiving trastuzumab (HR, 0.42; 95% CI, 0.21–0.83; $p = 0.01$) [31]. In the overall population, docetaxel was significantly more active than vinorelbine in the adjuvant treatment of breast cancers.

This trial, while interesting, is limited by the small number of Her-2-positive patients as well as the non-significant improvement of overall survival. Therefore, further trials challenging the optimal duration of trastuzumab treatment must be awaited. For now, the golden standard remains treatment for 12 months.

3.5 *PACS 04*

This study is important, as it was the first – and hitherto only – trial not to report an additional benefit of trastuzumab. In total, 3,010 women with node-positive breast cancer were randomised to six cycles of epirubicin plus docetaxel or six cycles of FEC (epirubicin 100 mg/m²). No results from this randomisation became available yet. The 528 Her-2-positive patients included were further randomised to trastuzumab for 1 year versus control upon availability of their respective Her-2-status. Similar to HERA, patients started trastuzumab after the completion of conventional adjuvant chemotherapy and irradiation.

At a median follow-up of 4 years, there was no added benefit observed for the addition of trastuzumab over chemotherapy alone in terms of recurrence-free survival (HR, 0.86; 95% CI, 0.61–1.22; $p = 0.41$) as well as overall survival (HR, 1.27; 95% CI, 0.68–2.38) [32].

While the study may be underpowered to detect a small advantage for the trastuzumab group, it may appear reasonable to ask whether the HERA-style sequential approach might have added to these results.

3.6 *Discussion of Adjuvant Trials*

When considering the above presented studies, despite PACS 04 results, there is clear-cut evidence in support of trastuzumab for 12 months in the adjuvant setting. Due to different designs of the adjuvant trials, a number of questions concerning the optimal use of trastuzumab remain unanswered.

In the light of BCIRG 006, it is intriguing to further evaluate the potential future role of an anthracycline-free regimen.

Also, the aspect of treatment duration is not resolved yet. While the HERA-trial evaluated longer treatment – the third arm (trastuzumab for 24 months) has not yet reported – FinHER is suggesting that less than 1 year of treatment might be sufficient. This question was also probed in E2198, a pilot trial examining the cardiac side effects of paclitaxel plus trastuzumab prior to doxorubicin plus cyclophosphamide (AC) in Her-2-positive patients. Patients received paclitaxel plus weekly trastuzumab for 10 weeks followed by four cycles of AC. Upon completion of chemotherapy, one arm received trastuzumab for a further 52 weeks. Disease-free survival and overall survival were comparable between the two groups. The authors concluded that while the trial was not designed or powered to test for non-inferiority of short-course trastuzumab, a significant advantage for prolonged trastuzumab administration was not observed. Currently, two major trials are ongoing directly comparing short- versus long-course therapy. Up until results from those studies become available, the matter is open to speculation and 12 months of adjuvant trastuzumab remains the golden standard.

Obviously, another important issue concerns the optimal time-point of trastuzumab initiation. In HERA and PACS 04, biological therapy was started upon completion of chemotherapy and irradiation. All other trials had a shorter or longer course of concurrent therapy. The obvious advantage of such a design is the minimisation of post-surgery trastuzumab delays (1–4 months versus 8 months in HERA) [11], furthermore, preclinical models had suggested a synergistic effect of trastuzumab when administered in conjunction with certain chemotherapeutic agents [13]. PACS 04, using a sequential design, indeed reported no benefit of trastuzumab. When considering the results of the above-mentioned studies, patients with early relapses, who are assumed to derive the largest benefit from concomitant treatment, were not included into the HERA study population due to the randomisation after the end of conventional therapy. This might have added to the positive results of the HERA trial. On the other hand, it is reasonable to assume that a longer time-span between anthracycline exposure and initiation of trastuzumab might reduce cardiac toxicity. It is hoped for that result from the sequential treatment arm of N9831 when available will provide further insight into the relative risks and benefits of the two different approaches.

Another largely unresolved question concerns the concurrent administration of trastuzumab with radiotherapy. Again, preclinical data suggest a radiosensitising effect of concurrent trastuzumab [33]. Currently, no data are available from prospective randomised studies. Yet, in a subgroup analysis of N9831 concurrent adjuvant radiotherapy and trastuzumab were not associated with increased acute adverse events, including cardiac side effects. Still, authors concluded that further follow-up is required to assess late adverse events [34]. Therefore, for the moment being, the combination of adjuvant irradiation and trastuzumab appears safe, and may enhance irradiation activity.

Only a very limited number of small-size tumours (pT1a, pT1b) were included in the above-mentioned trials. Therefore, it is not possible to give a final recommendation concerning those patients and chemotherapy plus trastuzumab may not be necessary in node-negative tumours smaller than 1 cm in size [35]. However, a

combined retrospective analysis of approximately 1,000 women with tumours <1 cm suggests that even in this relative good-risk subgroup, Her-2-positive patients had 5.09 (95% CI, 2.56–10.14; $p < 0.0001$) times the risk of recurrence and 7.81 times (95% CI, 3.17–19.22; $p < 0.0001$) the risk of distant recurrence compared with patients with hormone receptor-positive tumours, leaving this matter to debate [36].

With the establishment of antibody therapy in early stage Her-2-positive breast cancer, recurrence rate was reduced by approximately 50%. Despite this success, a number of patients will still experience disease recurrence during antibody therapy or upon follow-up. Therefore, there is an urgent need to answer the question, whether trastuzumab should be re-induced in those individuals. Data from the RHEA (Re-treatment after Herceptin Adjuvant) phase II trial, which is currently ongoing, will hopefully provide information concerning this problem [37].

4 Trastuzumab in the Neo-adjuvant Setting

First reported in 1973 in inoperable breast cancer, the concept of pre-operative treatment has evolved into the use in operable disease with the objective of increasing the rate of breast conserving surgeries [38]. Different studies lead to the assumption that pathologic complete response (pCR) might act as surrogate for improved survival [39–41]. Due to the high efficacy of trastuzumab in the metastatic setting, it was reasonable to evaluate the effect on pCR in a neo-adjuvant setting. Early phase II trials reported pCR rates in the range of 18–39% [42–45].

In a phase III trial, patients received four cycles of paclitaxel every 3 weeks followed by four cycles of 5-FU, epirubicin and cyclophosphamide (FEC) with or without weekly trastuzumab for 24 weeks. The trial was terminated prematurely after the first 34 patients completed therapy, because a significant difference in terms of pCR favouring the trastuzumab arm was observed (66.7% versus 25%; $p = 0.02$) [46]. The German GeparQuattro trial randomised patients to four cycles of epirubicin plus cyclophosphamide (EC) followed by four cycles of docetaxel with or without capecitabine. Her-2-positive patients were treated with trastuzumab every 3 weeks concurrently to chemotherapy. pCR rates at surgery were 31.8% with trastuzumab and 15.4% without trastuzumab ($p < 0.001$). Importantly, none of the patients included on the trial experienced congestive heart failure or a decrease in left ventricular ejection fraction <45% [47]. The Austrian Breast and Colorectal Cancer Study Group (ABSCG) has now completed recruitment of ABSCG 24, a neo-adjuvant trial comparing six cycles of standard epirubicin plus docetaxel (ED) to ED with the addition of capecitabine. Her-2-positive patients had a further randomisation to trastuzumab versus control [37]. Results are not available yet, but are expected to be presented at the 2009 San Antonio Breast Cancer Symposium.

A meta-analysis of eight neo-adjuvant trials conducted by the German Breast Group and AGO (Arbeitsgemeinschaft Gynäkologische Onkologie; Working group Gynaecologic Oncology) included a total of 6,634 patients, 1,407 of which were Her-2-positive; 671 of those had received neo-adjuvant trastuzumab, while the remaining 736 had not. pCR rates reported were 41.1% in trastuzumab-treated patients, as compared to 27.7% [48].

While similar to the adjuvant setting the optimal combination of chemotherapy plus trastuzumab awaits further clarification, it appears reasonable to accept trastuzumab as golden standard even in the pre-operative setting.

5 Side Effects of Adjuvant Trastuzumab Therapy

The main issue of trastuzumab-related side effects regard cardiac toxicity. This problem was first reported in the pivotal metastatic trial, with the highest frequency in patients treated with a combination of doxorubicin plus trastuzumab [18]. In the adjuvant setting, approximately 5% of patients are expected to develop some form of cardiac function impairment, and 1% may develop symptomatic congestive heart failure (CHF) [26, 28, 49]. In most cases, the systolic dysfunction appears to be reversible [50], still, a close monitoring of patients on trastuzumab treatment is mandatory. At highest risk for a drop of left ventricular ejection fraction (LVEF) are patients of old age and those with known hypertension; further risk factors include pre-existing diabetes, coronary heart disease, and valvular dysfunction [11, 50].

When comparing the rates of cardiac dysfunction in HERA to results from the combined analysis of NSABP B-31 and NCCTG N9831, it is noteworthy that cardiac side effects appear less pronounced in the HERA study [51]. It is possible that the sequential design of HERA may hold responsible for this observation; furthermore, the number of patients receiving anthracyclines as adjuvant treatment was lower in the HERA study [11, 26]. Randomisation in HERA occurred upon completion of conventional treatment, and the eligibility threshold of LVEF was more stringent in HERA ($\geq 55\%$ as compared to $\geq 50\%$) [51]. This might have excluded patients with worse LVEF, thereby apparently reducing cardiac side effects.

Further adverse events reported were mainly concerning anaphylactic reactions; furthermore, the HERA trial reported a minimal increase of infections (22 patients [1.3%] versus 7 patients [0.4%] in the control group) [26], and the combined analysis of NSABP B-31 and NCCTG N9831 trials observed rare cases of interstitial pneumonitis that in some cases appeared to be related to trastuzumab therapy (four cases in B-31 and five in N9831). In BCIRG 006, there were no significant differences in grade 3 or 4 haematologic or non-haematological adverse events among the three treatment arms [52]. Also, in the FinHER trial, no differences were observed in the respective trastuzumab and non-trastuzumab groups [31]. Interestingly, a recently published paper evaluated gastrointestinal side effects of trastuzumab (i.e. nausea, vomiting, diarrhoea, abdominal pain). Those were observed in as

much as 12% of trastuzumab administrations. As only 46 patients were available for this retrospective chart review, however, further prospective evaluation of those symptoms appears necessary [53]. A single case report is available describing a case of trastuzumab-induced hepatopathy in an otherwise healthy women receiving adjuvant therapy for breast cancer [54]. This report, however, has not been verified in prospective studies.

6 Ongoing Studies

Lapatinib is an orally available tyrosine kinase inhibitor blocking the tyrosine kinase domains of EGFR and Her-2. Lapatinib in combination with capecitabine was found superior over chemotherapy alone in terms of response rate and progression-free survival [55]. Furthermore, patients in the combination group experienced significantly less brain metastases. This is mirrored by another trial suggesting direct activity of lapatinib on cerebral lesions [56].

In the adjuvant setting, the ALLTO trial (BIG 2-06/N063D; NCT00490139) is currently ongoing. This prospective randomised phase III study incorporates four treatment arms: A standard arm of trastuzumab for 1 year is compared with lapatinib for 1 year, lapatinib for 12 weeks followed by trastuzumab for 6 months (sequential) or trastuzumab in combination with lapatinib (concurrent). Recruitment is well on the way, and study completion is expected for June 2010 [37].

Bevacizumab is a humanised monoclonal antibody targeting vascular endothelial growth factor (VEGF). Increased signalling via the ras/raf/MAPKinase signalling pathway, as is the case in Her-2-positive disease, will increase HIF-1 α and consequently VEGF [57–60]. This mechanism may be blocked by trastuzumab. Based upon this rationale, a randomised multicentre study is currently on the way, evaluating docetaxel plus trastuzumab with or without bevacizumab in the first line metastatic setting (AVAREL; A Study of Avastin (Bevacizumab) in Combination With Herceptin (Trastuzumab/Docetaxel) in Patients With HER-2-Positive Metastatic Breast Cancer; NCT00391092) [37]. Meanwhile, a randomised adjuvant study was initiated (BETH; Bevacizumab and Trastuzumab Adjuvant Therapy in Her-2-positive Breast Cancer; NCT00625898) [37].

Other important studies were mentioned already: The SOLD (Synergism or Long Duration; NCT00593697) and PHARE (Protocol of Herceptin Adjuvant with Reduced Exposure; NCT00381901) studies are directly comparing long-versus short-term trastuzumab treatment [37]. In this context, results from the 2-year trastuzumab arm of the HERA trial are also eagerly awaited. NCCTG N9831 again will hopefully resolve questions regarding the superiority of a concomitant versus a sequential approach for administering chemotherapy and trastuzumab. The RHEA trial is challenging the problem of trastuzumab re-induction in patients who progressed after adjuvant trastuzumab therapy.

7 Conclusion

Targeting Her-2 with trastuzumab has dramatically changed the prognosis of patients with Her-2-positive breast cancer, both in advanced and in early stage disease. Meanwhile, three prospective randomised phase III trials have reported superior overall survival when trastuzumab is added to conventional chemotherapy.

Still, questions remain concerning the potential role of anthracycline-free chemotherapy regimens (which might reduce cardiac toxicity), the optimal time point of trastuzumab initiation, the combination of trastuzumab and irradiation, the role of trastuzumab in tumours smaller than 1 cm and the optimal duration of trastuzumab therapy. A number of important trials are still ongoing and will hopefully resolve some of those questions.

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