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Treatment of HER-2 positive breast cancer

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ABSTRACT

HER-2 is considered a prognostic and predictive factor in early breast cancer, and it is fundamental for the decision about adjuvant systemic therapy. HER-2 is recognised as a strong predictive factor for the efficacy of chemotherapy-containing anthracyclines even if there are no prospective but only restrospective analysis from adjuvant chemotherapy trials comparing anthracyclines-containing chemotherapy to CMF or similar regimens. More contradictory is the role of HER-2 as predictive factor for the treatment with adjuvant chemotherapy-containing antharcyclines and taxanes compared to only anthracyclines. In the treatment of early breast cancer adjuvant trastuzumab reduces the risk of recurrence and death if added to chemotherapy. Trastuzumab can be administered in different ways but the concomitant administration with chemotherapy (taxanes), compared to sequential administration, reduces the risk of recurrence significantly. At the same time the risk of cardiotoxicity is increased using the concomitant instead of the sequential administration.

1. Role of anthracyclines in HER-2 disease

Oxford metanalysis demonstrates that anthracyclines-based chemotherapy compared to CMF and/or CMF-like regimens significantly reduces the risk of recurrence and death of 11% ($2p = 0.001$) and 16% ($2p < 0.00001$), respectively, with a corresponding absolute benefit of 3.4% and 4.2%, respectively.[1] Due to its own role of metanalysis, these results do not take into account the wide variability of the studies, in terms of different control arms, anthracyclines schedule (sequential or not to CMF), cumulative anthracycline doses, number of drugs associated to anthracyclines and number of cycles administered. Then, data coming from metanalysis should also be analysed considering the data coming from randomised trials. The First step is to exclude the suboptimal 1–21 days intravenous (i.v.) schedule (i.e. cyclophosphamide 600 mg/m^2, Methotrexate 40 mg/m^2, 5-fluorouracil 600 mg/m^2 all administered i.v. at day 1 every 21 d), and to consider only randomised trials in which the control arm is the classical CMF (i.e. cyclophosphamide 100 mg/m^2 orally from day 1 to 14, Methotrexate 40 mg/m^2 i.v. days 1 and 8, 5-fluorouracil 600 mg/m^2 i.v. days 1 and 8 every 28 d) or the 1–8 i.v. schedule (i.e. cyclophosphamide 600 mg/m^2, Methotrexate 40 mg/m^2 and 5-fluorouracil 600 mg/m^2 all administered i.v. at days 1 and 8 every 28 d). If these CMF-based regimens are compared with sequential schedule (doxorubcin or epiruibcin followed by CMF) or regimen with $\geqslant$6 cycles, with three drugs and with doxorubicin 60 mg/m^2 or epiruibcin 100 mg/m^2 per cycle, the reduction of death risk is higher with an hazard ratio of HR = 0.80 ($2p = 0.0004$) in favour of anthracyclines.[1] Recently, some authors argued that the role of anthracycline in early breast cancer patients could be restricted to HER2 positive disease. Gennari et al.[2] conducted a pooled analysis on 5354 patients, for whom HER-2 status was available, enrolled in randomised trials comparing anthracycline-based with non-anthracycline-based adjuvant chemotherapy. In HER-2 positive disease, anthracyclines demonstrated to be better both in terms of disease-free survival (HR = 0.71; 95% confidence interval (CI): 0.61–0.83, $p < 0.001$) and overall survival (HR = 0.73; 95%CI: 0.62–0.85, $p < 0.001$). On the contrary, in HER2 negative disease anthracyclines seemed not to improve disease-free survival (HR = 1.00; 95%CI: 0.90–1.11, $p = 0.75$) nor overall survival

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(HR = 1.03; 95%CI: 0.92–1.16, $p = 0.60$). On reading these data, it is important to underline the fact that the metanalysis by Gennari et al. was a retrospective analysis and it may be used only as 'hypothesis generating' to be prospectively tested in randomised manner. Moreover, several anthracyclines schedules were suboptimal: ACx4, PAF, alternating CMF/EV, EC or high dose EC, weekly epirubicin. Only CMF followed by doxorubicin, FEC and CEF included in this metanalysis can be considered optimal anthracyclines schedule. Actually, only the results of a retrospective analysis from one randomised trial, comparing an optimal regimen-containing anthracyclines and optimal CMF, demonstrate that the benefit of anthracyclines over CMF seems to be restricted to HER-2 positive breast cancer. Retrospective data from MA-5 study, comparing CEF (cyclophosphamide 100 mg/m^2 orally from day 1 to day 14, epirubicin 60 mg/m^2 i.v. days 1 and 8, 5-fluorouracil 600 mg/m^2 i.v. days 1 and 8 every 28 d) with oral CMF, demonstrate that risk reduction of recurrence and death is 0.52 ($p = 0.003$) and 0.65 ($p = 0.06$), respectively, in HER-2 positive disease, whilst is not statistically different is HER-2 negative disease.[3] Another study, BCIRG-006 trial,[4] was designed to assess the role of adjuvant trastuzumab added to chemotherapy-containing anthracyclines and taxanes (four cycles doxorubicin and cyclophosphamide followed by four cycles of docetaxel plus trastuzumab followed by trastuzumab for a total of 1 year) and to chemotherapy not containing anthracyclines (six cycles of Docetaxel, Carboplatin and trastuzumab followed by trastuzumab for a total of 1 year). After a median follow-up of 36 months (second interim analysis), the addition of trastuzumab to anthracyclines and taxanes reduces the risk of recurrence and death of 39% ($p < 0.0001$) and 41% ($p = 0.004$), respectively, as it reduces these risks of 33% ($p = 0.0003$) and 34% ($p = 0.017$), respectively, if added to docetaxel and carboplatin, compared to control arm AC followed by docetaxel. The difference between the two schedules containing trastuzumab was not statistically different neither in disease-free survival ($p = 0.42$) nor in overall survival ($p = 0.58$). An investigational analysis was conducted in patients with or without Topoisomerase-II co-amplification. Overall, 35% of patients had Topoisomerase-II co-amplified with HER-2. The difference in disease-free survival was not statistically significant between AC-TH and TCH in co-amplified or non co-amplified. In conclusion, optimal anthracycline-based regimens are better than optimal CMF regimens, and remain a gold standard treatment for all patients with early breast cancer, who are candidates for chemotherapy. Further studies are required to better select patients who may not benefit from anthracyclines.

2. Role of taxanes in HER-2 disease

Overall, taxanes added to anthracyclines as adjuvant chemotherapy for early breast cancer reduce the risk of recurrence from 14% to 36% with an absolute benefit of 4–7%, depending on trials, the use of paclitaxel or docetaxel and the sequential or concomitant schedules. Some studies (CALGB 9344, PACS 01 and BCIRG 001) have also demonstrated an improvement in overall survival of a relative 18–30% and an absolute 3–6%.[5–10] Different trials evaluated retrospectively the role of adding taxanes to anthracyclines as adjuvant chemotherapy in HER-2 positive disease. CALGB 9344[11] compared four cycles of AC (doxorubicin and cyclophosphamide) with different doses of doxorubicin (60 mg/m^2, 75 mg/m^2, 90 mg/m^2) to AC followed by four cycles of paclitaxel at 175 mg/m^2 every 3 weeks. In HER-2 positive disease Paclitaxel was associated with the reduction of recurrence and death risk of 41% ($p = 0.01$) and 43% ($p = 0.01$), respectively, independently from hormonal receptor status, whilst in HER-2 negative disease the difference was significant only if hormonal receptors were negative ($p = 0.002$). Another study, GEICAM 9906, shows different result compared to CALGB 9344. GEICAM 9906[12] compared four cycles of FEC (fluorouracil 600 mg/m^2, epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2 i.v. administered every 21 d) followed by paclitaxel 100 mg/m^2 for eight administrations to six cycles of FEC at the same doses. In HER-2 positive breast cancer, disease-free survival of FEC-P and FEC was 63% and 70%, respectively, even if the difference was not statistically significant (HR = 1.18, CI 95%: 0.71–1.98, $p = 0.52$), whilst opposite results were found with HER-2 negative breast cancer, with a statistically different disease-free survival of 82% and 74%, respectively, (HR = 0.65, CI 95%: 0.48–0.89, $p = 0.0075$). One possible explanation of this result is the different cumulative dose of anthracyclines received in the FEC arm and FEC-P arms, which was 540 mg/m^2 and 360 mg/m^2, respectively; this bias may have contributed to find these results in HER-2 positive disease. However, similar results were found in Intergroup trial E1199,[13] in which patients receiving four cycles of AC were then randomised to receive a different taxane with a different schedule (control arm: paclitaxel 175 mg/m^2 every 3 weeks, experimental arms: paclitaxel 80 mg/m^2 weekly, docetaxel 100 mg/m^2 every 3e weeks, docetaxel 35 mg/m^2 weekly). As compared to standard therapy (paclitaxel every 3 weeks), weekly paclitaxel was associated with a statistically significant improvement in disease-free survival (HR = 1.27, CI 95%: 1.03–1.57, $p = 0.006$) and overall survival (HR = 1.32, CI95%: 1.02–1.72, $p = 0.01$). Retrospective analysis on HER-2 status showed a statistically significant improved disease-free survival (HR1.33, CI 95%: 1.07–1.64, $p = 0.009$) and overall survival (HR = 1.34, CI 95%: 1.02–1.76, $p = 0.03$) in HER-2 negative disease but not in HER-2 positive disease neither in disease-free survival or overall survival. Differently from GEICAM 9906, all patients receive the same cumulative dose of doxorubicin (240 mg/m^2). The role of HER2 for taxanes efficacy is not further supported by the results coming from BCIRG-001,[9] a trial which randomised node positive breast cancer patients to receive six cycles of FAC (fluorouracil 500 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2 i.v. every 21 d) or TAC (Docetaxel 75 mg/m^2, doxorubicin 50 m/m^2, cyclophosphamide 500 mg/m^2 i.v. every 21 d). TAC was associated with a statistically significant improvement in disease-free survival independently from HER-2 status event if the reduction was greater for HER-2 positive disease (HER-2 positive: HR = 0.60, CI 95%: 0.41–0.88; HER-2 negative: HR = 0.76, CI 95%: 0.59–1.00). In conclusion, available data do not support the use of HER2 to select the choice to use or not to use a taxane in early breast cancer patients.

3. Trastuzumab as adjuvant treatment in HER-2 disease

Adjuvant trastuzumab for early breast cancer has been studied associated with different schedules of adjuvant chemotherapy and this fact can have condition the results in terms of efficacy. HERA trial randomised node positive breast cancer, treated with $\geqslant$4 cycles of (neo)adjuvant chemotherapy, followed by adjuvant radiotherapy (if needed), to no further systemic therapy, 1 or 2 years of trastuzumab. After a median follow-up of 1 and 2 years, adjuvant trastuzumab was associated to an absolute improvement in terms of disease-free survival of 8.4% and 6.3%, respectively. From the first to the second year, benefit in recurrences had a decrease of a relative 25% and absolute 2%.[14,15] From this point of view, the result of the combined analysis of US trials (NSABP B-31 and NCCTG 9831) is different. After a median follow-up of 2.0 and 2.9 years the absolute benefit in terms of disease-free survival is 11.7% and 12.8%, respectively, with a further improvement of a relative 9% and an absolute 1%.[16,17] The benefit shown by US trials', which remains over time, could be a consequence of the type chemotherapy schedule associated with trastuzumab. In NSABP B-31 and NCCTG 9831 (with the exclusion of sequential arm of N9831 that was not considered for the combined analysis) all patients were treated with a sequential schedule of anthracyclines and taxanes (i.e. four cycles of doxorubicin and cyclophosphamide, followed by 12 administrations of weekly Paclitaxel at 80 mg/m^2 or four cycles of 3-weekly Paclitaxel at 175 mg/m^2). Trastuzumab was administered concomitantly to Paclitaxel and then sequentially for a total of 1 year and this type of administration can produce a more definitive treatment. In fact, NCCTG 9831 compared 1 year of trastuzumab administered concomitant or sequential to Paclitaxel. The results, after a median follow-up of 1.5 years, show that concomitant schedule is associated with a significant improvement in terms of disease-free survival (HR = 0.64, $2p = 0.0114$).[18] This finding seems to clarify the role of adjuvant trastuzumab administered concomitantly to chemotherapy. Another important consideration is the type of chemotherapy administered with trastuzumab. In the HERA trial, the type of chemotherapy was at physician discretion. Patients treated with anthracyclines (68% of the population study) followed by trastuzumab, compared to patients treated with only chemotherapy, received an improvement in terms of disease-free survival of 43%, statistically significant (HR = 0.57, CI 95%: 0.46–0.71). Patients treated with regimens containing anthracycline and taxanes (26% of the population study) had a more little benefit and were not statistically significant (HR = 0.80, CI 95%: 0.59–1.10). Similar results were shown by NCCTG 9831 trial. This trial randomised breast cancer patients to AC (doxorubicin and cyclophosphamide) followed by weekly Paclitaxel or to the same schedule with 1 year of trastuzumab administered for 1 year. Trastuzumab was administered concomitantly with weekly Paclitaxel and then for other 40 weeks or sequentially to weekly Paclitaxel for 52 weeks. Trastuzumab added to chemotherapy and administered with a concomitant schedule was associated with a significant difference in disease-free survival (HR = 0.64, CI 95%:0.46–0.91; $p = 0.0114$) compared to trastuzumab administered sequentially. Interestingly, trastuzumab was not associated with an improved disease-free survival compared to control if administered with a sequential schedule (HR = 0.87, CI 95%:0.67–1.13; $p = 0.2936$). Similar results were shown by PACS-04,[19] that is phase III trial, randomizing early breast cancer patient to six cycles of FEC (5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2 every 3 weeks) versus six cycles of TE (Docetaxel 75 mg/m^2 plus epirubicin 75 mg/m^2 every 3 weeks). A second randomisation, after the results of trastuzumab in metastatic breast cancer was done: trastuzumab was administered sequentially to chemotherapy for 1 year and compared to observation. After a median follow-up of 48 months, adjuvant trastuzumab was associated with no significant improvement in disease-free survival (HR = 0.86, CI 95%:0.61–1.22; $p = 0.41$). The possible conclusions of these results are two. The first: trastuzumab is not associated with a better outcome if administered sequentially to chemotherapy containing anthracyclines and taxanes. The second: only the concomitant administration of trastuzumab and taxanes (Paclitaxel) has been associated with benefit in disease-free survival. Confirmatory data about the efficacy of concomitant administration of chemotherapy and trastuzumab come from the results of FINHER trial,[20] a small trial, in which patients were randomised to receive three cycles of Docetaxel or Vinorelbine before three additional cycles of FEC (fluorouracil, epirubicin and cyclophosphamide). A second randomisation was done for cases HER-2 positive by FISH to receive or not trastuzumab for a total of 9 weeks administered concomitantly with Docetaxel or Vinorelbine. After a median follow-up of 36 months, the administration of trastuzumab was associated with an improvement of disease-free survival of 58% ($p = 0.01$) and a trend for better overall survival ($p = 0.07$). The question is how a short administration of trastuzumab could be protective in terms of reduction of the risk of recurrence. However one of the possible keys of lecture is that the concomitant administration seems to be a very effective treatment.

4. Cardiotoxicity of adjuvant trastuzumab

The first consideration about cardiotoxicity induced by trastuzumab is given by the analysis of NSABP B-31[21,22] in which patients received trastuzumab together with weekly Paclitaxel after four cycles of AC (doxorubicin and cyclophosphamide). Patients could receive adjuvant trastuzumab after AC if they were asymptomatic, with a left ventricular ejection fraction (LVEF) upper to the normal limit and with a decline from baseline (before AC) $\leqslant$15%. With these inclusion criteria for receiving trastuzumab, 7.5% (149/1978) of patients, considering investigational and control arm, had one or more of these criteria not satisfied and automatically excluded from the treatment with trastuzumab. Between patients who received adjuvant trastuzumab in NSABP B-31, 15.5% discontinued treatment caused by asymptomatic or symptomatic cardiac toxicity (1.9% in the first quarter, 6.3% in the second quarter, 5.3% in the third quarter, 2.0% in the fourth quarter). Globally, after a median of 3 years from day 1 of the fifth cycle (the beginning of Paclitaxel), the incidence of cumulative cardiac events (defined as the appearance of cardiac death or

congestive heart failure, CHF) was 4.0% in the group treated with trastuzumab and 0.9% in the control arm. Considering the cardiotoxicity data after the completion of trastuzumab, the respective incidences were 3.3% versus 0.5%. From these data we can observe that cardiotoxicity seems to concentrate during treatment with trastuzumab and the possibility to observe it after is low. In fact, after the year of treatment with trastuzumab, only a further 0.5% and 0.4%, respectively, of cardiac events occurred. Another cardiac safety analysis is based on the results of NCCTG 9831[23] trial in which HER-2 positive breast cancer was treated with AC followed by either weekly Paclitaxel alone or weekly Paclitaxel followed by trastuzumab for 1 year or weekly Paclitaxel administered concomitant with trastuzumab for 12 weeks followed by trastuzumab alone for 40 weeks. In this trial we have the unique direct comparison between sequential versus concomitant administration of trastuzumab. Of the 2992 completing AC, with similar results of NSABP B-31, 5.0% had LVEF decreasing disallowing trastuzumab (decrease below normal limit: 2.4%, decrease >15%: 2.6%). Between patients receiving trastuzumab, cumulative incidence of congestive heart failure or cardiac death at 1 year after AC occurred in 0%, 1.6% and 3.3%, respectively, and after 3 years in 0.3%, 2.8% and 3.3%, respectively. These results seem to be similar to the result of NSABP B-31: congestive heart failure occurred early, with most of the events before the end of adjuvant trastuzumab. After trastuzumab the possibility of events decreased dramatically. Interruption of trastuzumab because of symptomatic or asymptomatic cardiac events was necessary in 18.8% (17.2% asymptomatic and 1.6% symptomatic) of patients in the sequential arm and in 28.9% (25.6% asymptomatic and 3.3% symptomatic) of patients in the concomitant arm. Globally, an absolute 10% of patients of difference between sequential and concomitant administration of trastuzumab interrupted it. Based on these data, considering another 5% of patients who never received trastuzumab because of LVEF decrease after AC, from 24% to 33% of patients could not receive the planned treatment with trastuzumab without any interruptions. Similar data are shown by NSABP B-31: in the concomitant arm until 23% of patients could not complete treatment with trastuzumab without interruption. In the HERA trial[24] patients received $\geqslant$4 four cycles in most cases of chemotherapy-containing anthracyclines (94%) associated with taxanes (26%). Trastuzumab was administered for 1 or 2 years sequentially to chemotherapy (and radiotherapy if done) and compared to control arm. No data are actually available for patients who received 2 years of trastuzumab. One year of trastuzumab was associated with a significant increase of cardiac death or congestive heart failure (trastuzumab: 2.1%, control: 0.2%), a similar data of 2.8% of the sequential arm of NCCTG 9831. In HERA trial the proportion of patients who interrupted trastuzumab because of cardiac disorders was 4.3%, a percentage that, compared to 18.8% of sequential arm of NCCTG 9831, was lower. Another important consideration is the analysis of cardiac safety of BCIRG-006,[4] which compared two regimens containing trastuzumab administered for 1 year with or without anthracyclines. There were no cases of cardiac death. There were 20 cases of CHF versus 4 in the anthracyclines arm and TCH arm, respectively, with a statistically significant difference ($p = 0.0015$) and 18.0% versus 8.6% relative declines of LVEF >10%, respectively ($p < 0.0001$). Similar disease-free survival and overall survival were registered with these two regimens, but with a less cardiac toxicity with TCH. However, this schedule cannot be applied in patients with cardiac risk factors in order to reduce cardiac toxicity because patients enrolled in this study were free from cardiac problems.

Conflict of interest statement

None declared.

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