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Making the right choice in the adjuvant chemotherapy of primary breast cancer

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ABSTRACT

During the last few years, significant progress has been made in the adjuvant chemotherapy of primary breast cancer. When compared with anthracycline-based regimens, the addition of taxanes significantly improved disease-free survival and overall survival, and some studies suggest that many women could be treated without anthracyclines. In patients with HER2-positive tumours, adjuvant trastuzumab produced a significant reduction of mortality and recurrence in comparison with no adjuvant trastuzumab.

Despite these dramatic achievements in the treatment of early breast cancer, several questions remain to be answered, and individualisation of adjuvant therapy should be further improved. In this regard, the application of new technologies (i.e. genomics and proteomics) may be of great value.

1. Introduction

In the adjuvant treatment of primary breast cancer, the Oxford Overview showed that combination chemotherapy was more effective than single agents, that 4–6 months of treatment using the same regimen produced optimal benefit, that regimens containing an anthracycline were superior to regimens lacking anthracyclines and that for women with hormone receptor-positive breast cancer, the combination in sequence of chemotherapy and endocrine therapy provided an additive benefit.[1]

During the last years, other clinical trials have addressed a number of new questions related to the adjuvant chemotherapy of breast cancer, including the role of taxanes and the value of dose-dense administration of chemotherapy. At the same time, the exciting results obtained with trastuzumab in patients with HER2-positive metastatic breast cancer led to a new generation of adjuvant trials in this subset of patients, whose results, whilst confirming the beneficial effects of trastuzumab-based treatment in the adjuvant setting, raised several important questions regarding the optimal administration of treatment and the related toxicity.

Despite these important achievements, overtreatment with consequent adverse events and costs is common in the adjuvant breast cancer setting, because of the lack of an accurate method of identification of patients at real risk of relapse. Fortunately, in the recent years, significant improvement in the understanding of molecular biology of breast cancer has opened the way to better define subsets of patients with different prognoses and drug sensitivities, and this will hopefully allow to improve our clinical decision making in early breast cancer.

We will summarise some of the most important advances in the adjuvant chemotherapy of patients with primary breast cancer, particularly those with HER2-positive tumours.

2 Adjuvant chemotherapy

The latest Oxford Overview demonstrated that adjuvant chemotherapy significantly reduced the risk of recurrence and death in women with operable breast cancer, regardless

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of age, stage, nodal status, hormone receptor status and menopausal status. Anthracycline-containing regimens were generally more effective than earlier combinations of cyclophosphamide (C), methotrexate (M) and fluorouracil (F).

In fact, the absolute difference of recurrence and breast cancer mortality between anthracycline-based and CMF chemotherapy was about 3% at 5 years and 4% at 10 years. Anthracycline-containing regimens included doxorubicin (A) or epirubicin (E), and were generally given for about 6 months with other cytotoxic agents (e.g. FAC or FEC). They became the standard adjuvant therapy for the majority of patients with operable breast cancer, as well as the reference treatment for comparison in trials using new chemotherapy regimens.

In an attempt to improve the treatment results, several randomised trials evaluated the effects of taxanes in combination or in sequence with anthracycline-containing regimens.

Generally, these trials showed significant longer disease-free survival (DFS) for the taxane arms, but only rarely a clear advantage in overall survival (OS) was evidenced. This was observed in a recent meta-analysis evaluating 13 randomised trials including 22,903 patients.[2] The pooled HR estimate was 0.83 ($p < 0.001$) for OS, and the risk reduction was not influenced by type of taxane (paclitaxel or docetaxel), oestrogen receptor (ER) expression, number of metastatic lymph nodes and patient's age/menopausal status. The use of a taxane resulted in an absolute 5-year risk reduction of 5% for DFS and 3% for OS. The administration schedule, concomitant or sequential, did not seem to influence outcome.

The specific issue of schedule was recently addressed by the BIG 02-98 trial testing the incorporation of docetaxel (T) into anthracycline-based adjuvant regimens and companing sequential versus concurrent schedules.[3] Patients ($n = 2887$) with node-positive breast cancer were randomised to four arms: sequential control (4 A → 3 CMF); concurrent control (4 AC → 3 CMF); sequential T (3 A → 3 T → 3 CMF); concurrent T (4 AT → 3 CMF). DFS was better in the sequential T arm than in the sequential control arms (HR = 0.79, $p = 0.0035$), whereas it was similar in the two concurrent arm (HR = 0.93, $p = 0.48$). Moreover, the sequential T arm had a slightly better DFS in comparison with the concurrent T arm (HR = 0.83). Subgroup analysis did not show any evidence of different effects with regard to efficacy of T according to age, lymph node status and hormonal receptor status. Additional follow-up will be required to evaluate wether a statistically significant difference in OS will emerge. The higher DFS observed in the sequential T arm compared with concurrent T arm may be a consequence of a dose–response relationship, a higher anthracycline cumulative dose, a longer duration of treatment or a lack of chemoresistance development due to the sequential drug use according to the Norton-Simon hypothesis.

In an attempt to avoid the cardiac toxicity related to anthracycline administration, the US Oncology group has run a prospective randomised trial to compare 4 cycles of AC with a non-anthracycline regimen of 4 cycles of docetaxel and cyclophosphamide (TC) in 1016 node-positive and high-risk node-negative breast cancer patients.[4] After a median follow-up of 7 years, patients treated with TC had a statistically significant improvement in DFS in comparison with those treated with AC (81% versus 75%). Overall survival for patients in TC arm was 87%, compared with 82% for women treated with AC, which was a statistically significant difference.[5]

3. Adjuvant therapy in HER2-positive patients

Considering the benefit of trastuzumab-based regimens in advanced breast cancer, five prospective randomised trials (NSABP – B31, NCCTG N9831, HERA, BCIRG 006 and FinHer) have recently been completed and early results have been published, all demonstrating a significant benefit in patients receiving trastuzumab.

A recent meta-analysis of these five randomised trials showed a significant reduction of mortality ($p < 0.00001$), recurrence ($p < 0.00001$) and metastases rates ($p > 0.00001$) in favour of trastuzumab-containing regimens. There were more grade III or IV cardiac toxicity after trastuzumab (4.5%) versus no trastuzumab (1.8%). The likelihood of cardiac toxicity was 2.45-fold higher in trastuzumab arms, but this result was associated with heterogeneity.[6]

The issue of cardiac toxicity in adjuvant trials using regimens including anthracyclines and trastuzumab has received a great attention.

All patients enrolled in the five adjuvant trastuzumab trials were subject to prospective cardiac monitoring. Both the B-31 and N9831 trials assessed the incidence of NYHA class III/IV cardiac heart failure (CHF) or cardiac death. In the recent update of the N9831 trial, the 3-year incidence of CHF was 0.3%, 2.8%, 3.3% in the control, sequential and concurrent trastuzumab arm, respectively.[7] In the B-31 trial this toxicity occurred in 0.8% of the control arm and in 4.1% of the trastuzumab arm.

In the BCIRG 006 trial, a NYHA grade III/IV CHF was observed in 1.8% of the patients in the AC → TH arm, and in 0.3% of the patients treated with AC → T or TCH, the arm not including an anthracycline (AC → TH versus TCH, $p < 0.0015$).

In the HERA trial, after 2 years of follow-up, the incidence of NYHA Class III/IV CHF in the 1-year trastuzumab arm was 0.6% compared with 0.0% in the control arm, whilst a symptomatic CHF was recorded in 2% versus 0.1% of the patients ($p < 0.0001$).[8]

No significant cardiotoxicity has been reported in the small FinHer trial.

The overall risk of severe CHF reported in HERA trial was lower than that in B-31 or N9831, and one of the possible explanation might be the longer interval between discontinuing anthracyclines and starting trastuzumab. The mechanism of cardiac dysfunction associated with trastuzumab is not clearly understood. Cardiomyocyte injury from anthracyclines is thought to be mediated through free-radical injury, resulting in permanent ultrastructural changes and poor cellular and clinical reversibility. Trastuzumab cardiac damage might occur through triggering myocyte apoptosis and abrogating mitochondrial function by activation of the mitochondrial apoptotic pathway through the BCL–X proteins, lowering ATP levels and causing subsequent contractile dysfunction.[9] Current data suggest that trastuzumab cardiotoxicity can be reverted by discontinuing trastuzumab and initiating standard cardiological care.

There are some unresolved questions concerning the optimal trastuzumab administration in adjuvant treatment of breast cancer, including the optimal timing of initiation in patients who have completed adjuvant chemotherapy, the relative effectiveness of simultaneous and sequential administration with other chemotherapeutic agents, and whether there is a subgroup of patients in whom chemotherapy is not mandatory. Optimum adjuvant trastuzumab duration remains to be established by randomised trials, although the FinHer trial suggests that a short trastuzumab administration is effective, and further data will be available from the 2-year trastuzumab arm of the HERA trial.

To avoid treatment cardiotoxicity, the use of non-anthracycline containing regimens has been suggested, due to the results of BCIRG 006 trial indicating similar efficacy for TCH and AC → TH treatments, with less cardiotoxicity for the non-anthracycline arm. In this regard, of great interest is the possibility of a 'targeted' anthracycline use. The topoisomerase 2A (TOPO 2A) gene is often co-amplified with HER2 gene (30–90% of cases), whilst it is rarely amplified (5–10%) in HER2 non-amplified tumours. The TOPO 2A gene product is an enzyme which is a major target for anthracyclines. A recent analysis of the BCIRG 006 trial compared efficacy of treatment in TOPO2–HER2 co-amplified tumours with non-co-amplified tumours, and found that co-amplified tumours (35% of the total) had significantly improved DFS compared with non-co-amplified tumours.[10] In non-co-amplified tumours, a DFS advantage was observed in the trastuzumab-containing arms (AC → TH and TCH) versus the control arm (AC → T). These data indicate the possibility of omitting anthracyclines in non-co-amplified tumours, thus reducing the cardiac risk. Nevertheless, further prospective studies are needed to confirm these findings.

4. Conclusions and future perspectives

The results of several large randomised trials and meta-analyses have showed a substantial benefit from adjuvant chemotherapy in women with operable breast cancer, in terms of both disease recurrence and survival. The use of targeted drugs, such as trastuzumab, has led to a major contribution in improving treatment results in specific subsets of patients. However, the individualisation of adjuvant treatment should be further improved. In this regard, the application of new technologies (i.e. genomics and proteomics) may be of great value.

Genomic profiling of breast cancer is already being employed in the adjuvant setting, and various genomic profiles are under clinical development as predictors of tumour sensitivity to specific treatments, such as tamoxifen, taxanes, FAC and AC.

It is hoped that the ongoing studies and a better molecular characterisation of the disease will lead the clinicians towards more specific treatment options for patients with operable breast cancer.

Conflict of interest statement

None declared.

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;**365**:1687–717.
2. De Laurentis M, Cancello G, D'Agostino D, et al. Taxane-based combinations as adjuvant chemotherapy of early breast cancer: a meta-analysis of randomized trials. *J Clin Oncol* 2008;**26**:44–53.
3. Francis P, Crown J, Di Leo A, et al. Adjuvant chemotherapy with sequential or concurrent anthracycline and docetaxel: Breast International Group 02-98 randomized trial. *J Natl Cancer Inst* 2008;**100**:121–33.
4. Jones SE, Savin MA, Holmes FA, et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. *J Clin Oncol* 2006;**24**:5381–7.
5. Tuma R. Anthracycline therapy may be avoidable in early breast cancer, new studies suggest. *J Natl Cancer Inst* 2008;**100**:459–61.
6. Viani GA, Afonso SL, Stefano EJ, et al. Adjuvant trastuzumab in the treatment of her-2-positive early breast cancer: a meta-analysis of published randomized trials. *BMC Cancer* 2007;**7**:153.
7. Perez EA, Suman VJ, Davidson NE, et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. *J Clin Oncol* 2008;**26**:1231–8.
8. Smith I, Procter M, Gelber R, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet* 2007;**369**:29–36.
9. Grazette LP, Boecker W, Matsui T, et al. Inhibition of ErbB2 causes mitochondrial dysfunction in cardiomyocytes: implications for herceptin-induced cardiomyopathy. *J Am Coll Cardiol* 2004;**44**:2231–8.
10. Slamon D, Eiermann W, Robert N, et al. BCIRG 006 study: 2nd Interim analysis phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC → T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC → TH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2neu positive early breast cancer patients. In: *San Antonio breast cancer symposium*; 2006 abstract 52.