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Anthracyclines in the adjuvant treatment of breast cancer: state of the art

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ABSTRACT

Anthracycline-based regimens form a cornerstone of the adjuvant and neoadjuvant treatment of breast cancer. Extensive data from clinical trials with long-term follow-up have shown that such regimens significantly prolong overall and disease-free survival, compared with non-anthracycline-based regimens. In recent years, however, the proven benefits of anthracyclines have been challenged because of concerns over toxicity, and evidence that the benefits may be confined to certain patient subgroups, such as those with over-expression of the *HER2* or *TOP2A* genes. Nevertheless, the available evidence suggests that it is premature to consider discarding anthracycline therapy. Although cardiotoxicity is a recognised limitation of long-term anthracycline treatment, clinically overt heart failure is uncommon and associated mortality is low. Similarly, the risk of acute myeloid leukaemia or myelodysplastic syndrome is low during anthracycline treatment. Although there are some data to suggest that the efficacy of anthracyclines may vary between patient subgroups, reliable prospective data to support this are sparse. Future prospective studies, and advances in the identification and validation of potential tumour biomarkers, can be expected to facilitate the targeting of anthracycline therapy to patients who are most likely to benefit.

1. Introduction

Anthracycline-based regimens have a central place in the adjuvant and neoadjuvant treatment of breast cancer. The most commonly used regimens include doxorubicin plus cyclophosphamide, and combinations of cyclophosphamide and fluorouracil with either doxorubicin (FAC or CAF) or epirubicin (FEC or CEF); many of these regimens have been supplemented in recent years by the addition of a taxane. Such regimens have been extensively investigated in numerous clinical trials with long-term follow-up. [1,2]

In the Early Breast Cancer Trialists' Collaborative Group meta-analysis, with data extending over 15 years' follow-up in more than 15,000 patients, polychemotherapy reduced breast cancer mortality by approximately 10%, and increased disease-free survival by approximately 12%, compared with no adjuvant chemotherapy in women under 50 years of age (Fig. 1). [2] In the same meta-analysis, data from randomised comparisons across all age groups showed that anthracycline-based regimens had clear benefits in reducing both breast cancer recurrence and mortality by an additional 3–4% at 10 years, when compared with cyclophosphamide, methotrexate and fluorouracil (CMF). [2]

As a result of such findings, anthracycline-based adjuvant therapy is now considered a standard of care in early breast cancer, [3] and should be considered for intermediate- and high-risk patients. Such patients may include younger patients, those with larger tumours

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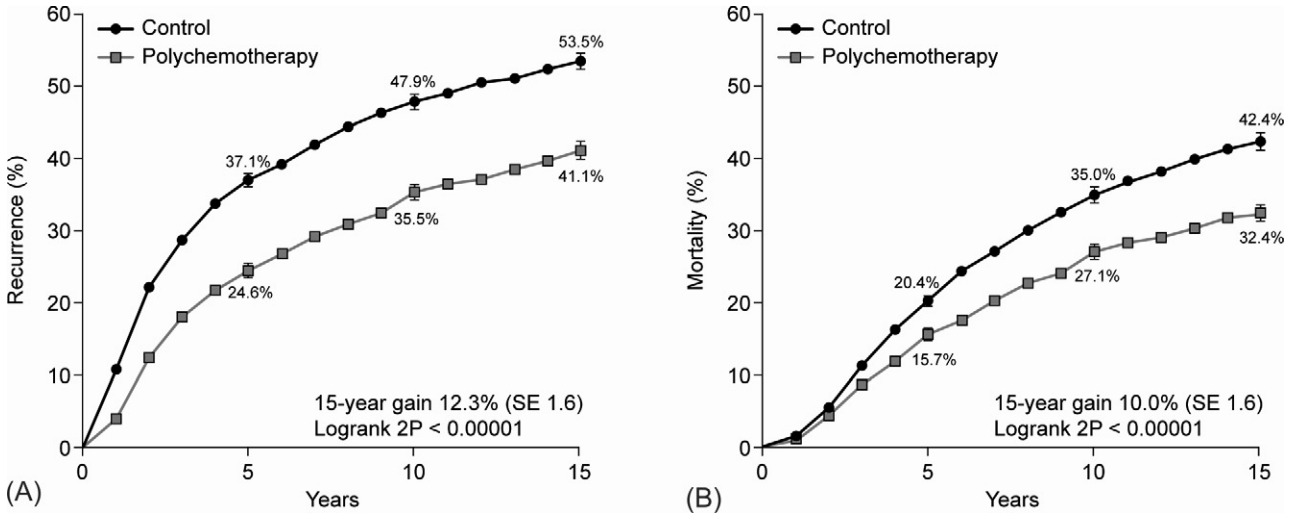

Fig. 1 – Effects of polychemotherapy versus no adjuvant chemotherapy (control) among patients under 50 years of age on entry in a meta-analysis of 194 randomised trials of adjuvant chemotherapy or hormonal therapy.[2] (A) 15-year breast cancer recurrence, and (B) 15-year breast cancer mortality. SE, standard error. Reprinted from Early Breast Cancer Trialists' Collaborative Group (EBCTCG). 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. Copyright ©2005, with permission from Elsevier and the EBCTCG.

or node-positive disease, oestrogen or progesterone receptor-negative, or human epidermal growth factor receptor-2 (HER2 [also known as c-erbB-2])-positive tumours, and those with poor prognostic features such as lymphovascular invasion.

Despite the proven benefits of anthracycline-based adjuvant therapy, a greater understanding of tumour biology in recent years and concerns about anthracycline-related toxicity have led to suggestions that this strategy should be replaced by other treatment options in many patients.[3] The available evidence suggests that this conclusion is premature.[3] Although cardiotoxicity is a recognised limitation of long-term anthracycline therapy, the incidence of clinical heart failure among all patients below the age of 70 years is low (<1%),[2] and the associated mortality is also low. In the meta-analysis cited above, the annual mortality rate from cardiovascular causes was 0.08% in anthracycline-treated patients, compared with 0.06% in those receiving other regimens.[2] However, data show that older women aged 66–70 years can have higher rates of cardiac morbidity.[4]

The risk of cardiotoxicity may be reduced by patient screening and using newer agents, which are associated with a decreased risk of cardiac adverse events. Similarly, although concerns have been expressed about an increased risk of acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS) in anthracycline-treated patients, it should be noted that such events are rare and typically occur early in the course of treatment; this is in contrast to the recognised occurrence of late leukaemia associated with alkylating agents. In an analysis of three trials of anthracycline-based therapy in node-positive patients, older patients (>65 years) were significantly more likely to die of AML or MDS than younger patients.[5]

This paper reviews recent studies of adjuvant or neoadjuvant treatment with anthracyclines in breast cancer, which have provided important insights into the potential benefits and limitations of anthracyclines in this setting.

2. Comparisons between anthracyclines and other regimens

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-15 study compared the efficacy and tolerability of 2 months' treatment with doxorubicin and cyclophosphamide (AC) and 6 months' treatment with CMF.[6] After 3 years' follow-up there was no significant difference between the AC and CMF regimens in disease-free survival (62% vs 63%, respectively) or overall survival (83% vs 82%). However, the two treatments had different toxicity profiles, with nausea and vomiting being more common and severe with the CMF regimen. This study helped to establish AC as an effective and well-tolerated option for the adjuvant treatment of breast cancer. The subsequent National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) MA5 study compared FEC and CMF in patients with node-positive disease.[7] After 5 years, both disease-free and overall survival were significantly longer with FEC than with CMF (disease-free survival: 63% vs 53%, $P = 0.009$; overall survival: 77% vs 70%, $P = 0.03$). FEC was associated with significantly higher incidences of alopecia and febrile neutropenia compared with CMF, but there were no

episodes of congestive heart failure with FEC compared with one episode in the CMF group. There was, however, an unexpectedly high rate of acute leukaemia in the FEC group (1.4%).

More recently, a further trial compared the AC regimen with a combination of docetaxel and cyclophosphamide (TC).[8] This trial is noteworthy in that a relatively high proportion of patients (16%) were aged 65 years or older, and 48% of patients had node-negative disease. After 7 years' follow-up, the taxane-based regimen was associated with significant improvements in disease-free survival (hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.56–0.98, P = 0.033) and overall survival (HR 0.69, 95% CI 0.50–0.97, P = 0.032), compared with AC, and was generally well tolerated. These improvements in survival were seen in all patient subgroups, irrespective of age, hormone receptor status, HER2 status and previous therapy. It should be noted, however, that as yet these findings have not been replicated in other trials.

3. Should anthracyclines be restricted to certain patient populations?

A number of studies have suggested that the benefits of anthracyclines may be confined to, or at least particularly apparent in, patients with HER2-positive disease. However, this conclusion is based largely on retrospective studies; the available data suggest that most patients can benefit from anthracycline therapy irrespective of their HER2 status, although HER2-positive patients may derive the greatest benefits.

3.1. *HER2-positive patients*

Several studies have investigated the relationship between HER2 status and anthracycline responsiveness. In a study comparing low (30 mg/m^2), moderate (40 mg/m^2) and high (60 mg/m^2) doses of doxorubicin, in combination with cyclophosphamide and fluorouracil, significant dose–response relationships were seen only in patients with over-expression of HER2.[9] The possibility that HER2 over-expression might be a predictor of responsiveness to doxorubicin was tested in a retrospective analysis from the NSABP B-11 study, which compared the effects of L-phenylalanine mustard plus fluorouracil, alone or in combination with doxorubicin.[10] The addition of doxorubicin was associated with significant improvements in disease-free survival and distant disease-free survival in patients with HER2 over-expressing disease, but not in women with HER2-negative tumours.

Recently, two further studies have suggested that only patients with HER2 over-expression benefit from anthracycline therapy. The first was a retrospective analysis from the NCIC CTG MA5 study, described above, in which HER2 expression was measured by means of fluorescence *in situ* hybridisation (FISH), immunohistochemical analysis and polymerase chain reaction (PCR) analysis.[11] Adjuvant FEC provided a superior improvement in relapse-free and overall survival, compared with CMF, in patients with HER2-amplified disease, whereas there was no significant difference in outcome between the two treatments in women whose tumours lacked HER2 amplification (Fig. 2). The second study was a meta-analysis of eight randomised trials comparing anthracycline-based and non-anthracycline-based chemotherapy in women with early breast cancer; information on HER2 status was available from 5354 of 6564 patients.[12] In patients with HER2-positive tumours (n = 1536), anthracyclines were associated with significantly longer disease-free survival (HR for relapse 0.71, 95% CI 0.61–0.83, P < 0.001) and overall survival (HR for death from any cause 0.73, 95% CI 0.62–0.85, P < 0.001), compared with comparator regimens. In contrast, anthracyclines had no significant effect on either disease-free survival (HR 1.00, 95% CI 0.90–1.11, P = 0.75) or overall survival (HR 1.03, 95% CI 0.92–1.16, P = 0.60) in patients with HER2-negative tumours. On the other hand, a caveat of the meta-analysis was that the doses of alkylating agents among the different studies were not well balanced, and therefore a small benefit in the HER2-negative population cannot be excluded.

3.2. *TOP2A status*

Although such findings suggest that HER2 over-expression may be predictive of the response to anthracyclines, it is important to recognise that other factors may also influence responsiveness, and these may confound studies of the impact of HER2 expression. One such factor is topoisomerase II alpha (TOP2A) expression. TOP2A is the molecular target of anthracyclines, and plays critical roles in segregation, condensation and superhelicity during cell division.[13] The *HER2* and *TOP2A* genes both lie on the long arm of chromosome 17 and are frequently co-amplified.[3]

The Breast Cancer International Research Group (BCIRG) 006 study randomised 3222 patients to receive either a control arm of doxorubicin and cyclophosphamide followed by docetaxel (AC → T) or one of two trastuzumab-containing arms: doxorubicin and cyclophosphamide followed by docetaxel plus trastuzumab (AC → TH), or docetaxel, carboplatin and trastuzumab (TCH).[14,15] Approximately one third of the patients showed co-amplification of *HER2* and *TOP2A*. The results of the study confirmed the benefit of the two trastuzumab-containing regimens compared with the AC → T arm without trastuzumab.[14,15] However, among patients with tumours that co-amplified the *TOP2A* gene, the outcome data were essentially identical regardless of whether trastuzumab was included in the regimen. By contrast, among patients with disease that did

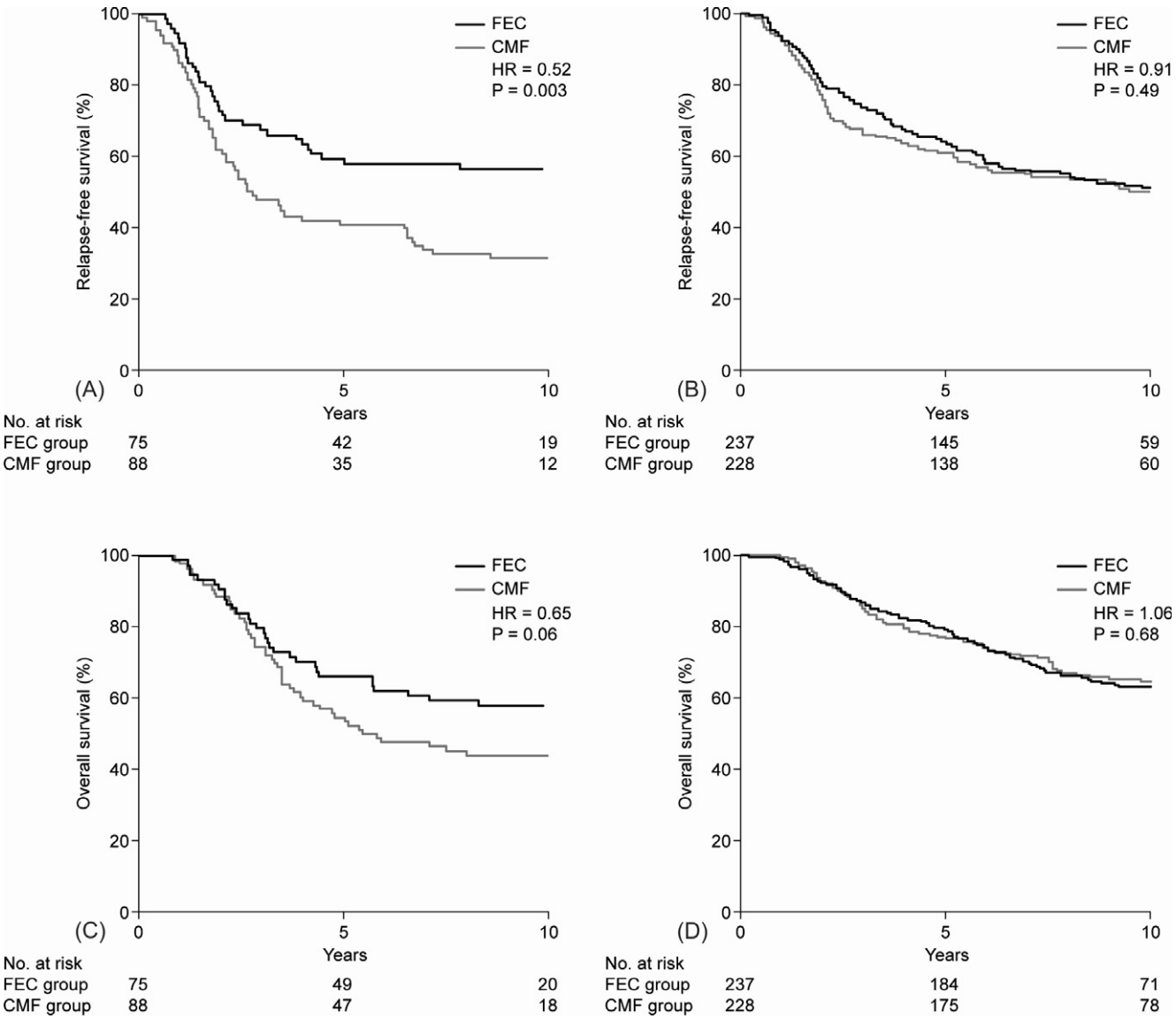

Fig. 2 – Effect of HER2 status on survival in the NCIC CTG MA5 study. [11] **(A) Relapse-free survival, HER2-amplified disease; (B) relapse-free survival, HER2-non-amplified disease; (C) overall survival, HER2-amplified disease; (D) overall survival, HER2-non-amplified disease. FEC, fluorouracil, epirubicin, cyclophosphamide; CMF, cyclophosphamide, methotrexate, fluorouracil; HR, hazard ratio. Reprinted with permission from Pritchard KI, et al. HER2 and responsiveness of breast cancer to adjuvant chemotherapy. *N Engl J Med* 2006;354:2103–11. Copyright ©2006 Massachusetts Medical Society. All rights reserved.**

not co-amplify the *TOP2A* gene, the difference in the rates of disease-free survival between the trastuzumab-containing arms and the AC→T control arm was even larger compared with the combined population in the study. [15] These data might suggest that, in patients with HER2 over-expression, the benefits of anthracyclines are largely related to TOP2A status. [15]

Furthermore, in another subset analysis of the NCIC CTG MA5 trial, 438 tumours were assessed for *TOP2A* alterations and *HER2* amplification by FISH. In patients whose tumours showed *TOP2A* alterations (either amplifications or deletions), treatment with FEC was statistically significantly superior to treatment with CMF in terms of relapse-free survival. In contrast, patients without *TOP2A* amplification or deletion did not appear to benefit from epirubicin. [16]

The issue is complicated, however: a recently presented analysis using representational oligonucleotide microarray analysis (ROMA) has suggested that FISH may overestimate TOP2A expression, and that co-amplification of *TOP2A* and *HER2* may therefore be uncommon. [17] A recent meta-analysis of four trials of adjuvant therapy showed that in HER2-positive patients TOP2A status had only a modest, borderline statistically significant predictive value for anthracycline responsiveness. [18]

The only study to have prospectively investigated the predictive value of *TOP2A* amplification in anthracycline-treated patients was the TOP trial, which involved 149 pa-

tients with oestrogen receptor-negative breast cancer who received neoadjuvant therapy with epirubicin.[19] *TOP2A* amplification, measured by FISH, was observed in 9.4% of patients, all of whom also showed over-expression of HER2; amplification of *TOP2A* was a strong ($P \leqslant 0.001$) predictor of pathological complete response (pCR). However, such results should be regarded with caution, as predictors of pCR might not be able to identify patients who are truly resistant to anthracyclines, as pCR only detects high sensitivity.

3.3. Basal-like phenotype breast cancer

As new molecular subtypes of breast cancer are being identified, research is focusing on evaluating the respective benefit of certain therapies in such subsets.[20] In a retrospective analysis from the NCIC CTG MA5 trial, 5-year overall mortality was significantly higher in FEC-treated patients with disease expressing a core basal-like phenotype cancer (negative for hormone receptors and HER2, positive for CK5/6 and epidermal growth factor receptor), compared with patients with other phenotypes (HR 1.8, $P = 0.02$); by contrast, in CMF-treated patients there was no significant difference in mortality between patients with different phenotypes.[21] However, it must be emphasised that the doses of alkylating agents differed between the two arms, and this may explain the lower benefit of anthracyclines.

4. Conclusions

Anthracyclines remain a cornerstone of adjuvant or neoadjuvant therapy for breast cancer, although their prolonged use is limited by late toxicities, notably cumulative cardiotoxicity. Although some retrospective analyses and limited prospective data have suggested that their effectiveness may be restricted to certain patient subgroups, reproducible prospective data to support this suggestion are sparse. Adjuvant trials may provide new insights into this issue, including the currently ongoing NSABP B-46 study (NCT00887536), which randomises patients with node-negative or high-risk node-positive and HER2-negative breast carcinoma to either docetaxel and cyclophosphamide or docetaxel, doxorubicin and cyclophosphamide (± bevacizumab), and the recently completed Cancer and Leukemia Group B (CALGB) 40101 study (NCT00041119), in which patients were randomised to four or six cycles of either doxorubicin and cyclophosphamide or paclitaxel.

Such prospective data are urgently needed to fully characterise the potential benefits of anthracyclines. Continuing advances in the identification and validation of potential biomarkers are likely to facilitate the acquisition of these data.[13]

5. Conflict of interest statement

None declared.

References

1. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 1998;**352**:930–42.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). 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.
3. Gianni L, Norton L, Wolmark N, Suter TM, Bonadonna G, Hortobagyi GN. Role of anthracyclines in the treatment of early breast cancer. *J Clin Oncol* 2009;**27**:4798–808.
4. Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol* 2007;**25**:3808–15.
5. Muss HB, Berry DA, Cirrincione C, et al. Toxicity of older and younger patients treated with adjuvant chemotherapy for node-positive breast cancer: the Cancer and Leukemia Group B Experience. *J Clin Oncol* 2007;**25**:3699–704.
6. Fisher B, Brown AM, Dimitrov NV, et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. *J Clin Oncol* 1990;**8**:1483–96.
7. Levine MN, Bramwell VH, Pritchard KI, et al. Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1998;**16**:2651–8.
8. Jones S, Holmes FA, O'Shaughnessy J, et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research Trial 9735. *J Clin Oncol* 2009;**27**:1177–83.
9. Muss HB, Thor AD, Berry DA, et al. c-erbB-2 expression and response to adjuvant therapy in women with node-positive early breast cancer. *N Engl J Med* 1994;**330**:1260–6.
10. Paik S, Bryant J, Park C, et al. erbB-2 and response to doxorubicin in patients with axillary lymph node-positive, hormone receptor-negative breast cancer. *J Natl Cancer Inst* 1998;**90**:1361–70.
11. Pritchard KI, Shepherd LE, O'Malley FP, et al. HER2 and responsiveness of breast cancer to adjuvant chemotherapy. *N Engl J Med* 2006;**354**:2103–11.
12. Gennari A, Sormani MP, Pronzato P, et al. HER2 status and efficacy of adjuvant anthracyclines in early breast cancer: a pooled analysis of randomized trials. *J Natl Cancer Inst* 2008;**100**:14–20.

13. Oakman C, Moretti E, Di Leo A. Re-searching anthracycline therapy. *Breast Cancer Res Treat* 2010;**123**:171–5.
14. Slamon D, Eiermann W, Robert N, et al. 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 HER2 positive early breast cancer patients: BCIRG 006 study. *Breast Cancer Res Treat* 2005;**94**(Suppl 1):S5.
15. Slamon D, Eiermann W, Robert N, et al. BCIRG 006: 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. *Breast Cancer Res Treat* 2006;**100**(Suppl 1):abs 52.
16. O'Malley FP, Chia S, Tu D, et al. Topoisomerase II alpha and responsiveness of breast cancer to adjuvant chemotherapy. *J Natl Cancer Inst* 2009;**101**:644–50.
17. McArthur HL, Tan LK, Patil S, et al. High resolution representational oligonucleotide microarray analysis (ROMA) suggests that TOP2A and HER2 coamplification is uncommon in human breast cancer. *Cancer Res* 2009;**69**(Meeting Abstract Supplement):abs 2023.
18. Di Leo A, Isola J, Piette F, et al. A meta-analysis of phase III trials evaluating the predictive value of HER2 and topoisomerase II alpha in early breast cancer patients treated with CMF or anthracycline-based adjuvant therapy. *Breast Cancer Res Treat* 2008;**107**(Suppl):705.
19. Desmedt C, Di Leo A, de Azambuja E, et al. Multifactorial approach to predicting resistance to anthracyclines. *J Clin Oncol* 2011;**29**:1578–86.
20. Rouzier R, Perou CM, Symmans WF, et al. Breast cancer molecular subtypes respond differently to preoperative chemotherapy. *Clin Cancer Res* 2005;**11**:5678–85.
21. Cheang M, Chia SK, Tu S, et al. Anthracyclines in basal breast cancer: the NCIC-CTG trial MA5 comparing adjuvant CMF to CEF. *J Clin Oncol* 2009;**27**(Suppl 15S):519.