Novel Treatment Approaches for Managing Early-stage Breast Cancer – Maximising Safety and Outcome with Adjuvant Taxane-containing Chemotherapy Regimens

a report by
Zeba Aziz

Head, Oncology Department, Allama Iqbal Medical College

Breast cancer is the second most prevalent type of cancer after lung cancer and the fifth most common cause of cancer-related death.[1] In 2008, an estimated 182,460 cases of invasive breast cancer (125.3 per 100,000 women) and 40,480 deaths were expected in US.[2] In many Asian countries, breast cancer is the most common (or second most common after cancer of the cervix) female malignacy, and the leading cause of cancer-related death.[3] Although the incidence of breast cancer in Asian countries is lower than in western countries, there has been an increasing trend and the rise has particularly affected younger women.[4,5] Several studies from Asia have reported a lower median age (45–50 years) and advanced disease on presentation in breast cancer patients. In one series of 487 early breast cancer (EBC) patients at a North Indian institute, the median age at presentation was 47 years, with 16% of patients presenting with stage I and 74% with stage II disease.[6] Another Indian study reported that 50–70% of new patients present with locally advanced breast cancer (stage III) or metastatic breast cancer (MBC; stage IV) at diagnosis.[7] A Korean study analysing data from one centre between 1989 and 2004 reported that there was a continuous increase in the number of patients with breast cancer, with the median age of patients reported to be between 45 and 48 years in different studies.[8]

The proportion of EBC (stages 0 and I) increased from 34.2% in 1991 to 48.8% in 2003. In Taiwan, the age-adjusted incidence of invasive breast cancer has increased dramatically due to increased life expectancy.[9] There may also be a variation in the rate of oestrogen receptor (ER)-positive cancers among different racial groups. The incidence of ER- and progesterone receptor (PR)-positive cancers has been reported to be similar in Japanese and American women,[10] whereas a Chinese study indicated that the ER-positive rate, at 54%, was significantly lower than in Caucasian women.[11]

Adjuvant chemotherapy has had a significant impact on the management of EBC. This therapeutic strategy has been shown to reduce the risk of recurrence post-surgery and cancer mortality in certain subsets of patients with early-stage disease.[12] Since these earlier studies with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) and anthracycline-based regimens, the management of EBC has seen impressive progress with the introduction of the taxanes paclitaxel and docetaxel, aromatase inhibitors and, more recently, targeted therapy, which is being evaluated in this setting.

Although adjuvant chemotherapy is not suitable for all patients with EBC, the benefits of polychemotherapy after tumour resection were reinforced by an updated EBC Trialists' Collaborative Group meta-analysis, which showed that adjuvant chemotherapy reduced mortality by 38%.[13] Thus, adjuvant systemic chemotherapy is now widely accepted as an effective management strategy in varying and overlapping subsets of patients with EBC.

Taxanes were initially established as among the most active cytotoxic agents in MBC. Taxane single-agent therapy and combination therapy with anthracyclines were shown to have increased benefits over standard therapies in metastatic disease.[14–16] Consequently, taxanes are now widely used as a first-line treatment for advanced breast cancer. The activity of the taxanes in metastatic disease prompted investigations into its use as adjuvant therapy in EBC. Since the initial studies, taxanes have become a standard component of adjuvant chemotherapy regimens. Numerous taxane-containing adjuvant regimens have been studied and evolving research suggests that taxanes may be more beneficial in specific patient subsets with EBC. This article will discuss the continuing debate on the optimal adjuvant taxane-containing regimen, the evidence for the innovations in taxane strategies in EBC and the patient subgroups that will gain the greatest benefit from taxane therapy.

Classic Chemotherapy Regimens

Adjuvant chemotherapy in node-positive breast cancer was first carried out 30 years ago using a combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF).[17] The first randomised study compared no post-operative chemotherapy with 12 CMF cycles, demonstrating increases in 10-year disease-free survival (DFS) and overall survival (OS) (DFS 31.4–43.4%; p<0.001, OS 47.3–55.2%; p=0.10).[18] Meta-analyses by the EBC Trialists' Collaborative Group demonstrated that the CMF regimen reduced the relative risk (RR) of recurrence and death by 24 and 14%, respectively.[12,13] Accordingly, six cycles of CMF was the gold standard for adjuvant chemotherapy in breast cancer for a long time. The Milan research group investigated a new regimen by introducing four cycles of doxorubicin to the standard CMF combination. DFS was found to be significantly high (61% in the sequential arm and 38% in the alternating arm; p=0.001)[19]

Anthracyclines in the form of doxorubicin and epirubicin were introduced in clinical settings, and anthracycline-based regimens were found to be effective in treating patients, preventing relapse and death. Traditionally, the anthracycline-based regimens used are 5-fluorouracil, doxorubicin and cyclophosphamide (FAC), 5-fluorouracil, epirubicin and cyclophosphamide (FEC) and doxorubicin plus cyclophosphamide (AC). The annual risk of recurrence and death was reduced by 12 and 11%, respectively, with anthracycline regimens, equating to a 3.2 and 2.7% absolute reduction in recurrence and death, respectively, compared with the standard CMF regimen.[13] These small but real differences were seen with regimens containing three or more agents (e.g. CEF and CAF, FAC, FEC, etc.), whereas four cycles of two-drug regimens (e.g. AC or EC) appeared to be equivalent to six cycles of CMF.[19]

The need for new chemotherapy agents and approaches stemmed from the concerns raised about toxicity, dosage and the long-term benefit of using anthracycline regimens. Subsequently, in the last decade taxanes (specifically paclitaxel and docetaxel) have emerged as powerful compounds in breast cancer treatment.

The Taxane Era

The management approach of EBC has changed dramatically in the last few years. Due to the lack of cross-resistance with anthracycline, taxanes were initially tested as single agents in MBC and demonstrated significant activity in this setting. Chan et al. reported the use of docetaxel in an early phase II trial in anthracycline-naïve patients with MBC. Significant improvement in outcomes with docetaxel treatment was observed compared with doxorubicin treatment.[14] Single-agent therapy with docetaxel also demonstrated activity in anthracycline-resistant MBC.[20,21] Several randomised studies investigated docetaxel plus anthracycline regimens as first-line therapy in MBC and these studies demonstrated superior response rates compared with standard anthracycline-based regimens.[22–25] Paclitaxel was not as effective as doxorubicin in terms of disease and symptom control[15] as a single-agent therapy in anthracycline-naïve patients with MBC, but showed activity in anthracycline-resistant MBC.[26] Furthermore, paclitaxel plus anthracycline regimens were found to produce better response rates than older anthracycline-based regimens,[27,28] or were equivalent in activity.[29]

A recent meta-analysis of the above eight trials showed that taxane-based combination regimens were significantly better than anthracycline-based regimens in terms of response rates and progression-free survival (PFS), but not in terms of survival.[30,31]

Following the demonstration of activity in the metastatic setting, taxanes are being investigated as adjuvant therapy for EBC. The benefits of adding a taxane sequentially to an anthracycline-based regimen in EBC was first studied in the CALGB 9344 study.[32] The study assessed the efficacy of four cycles of paclitaxel following AC or four cycles of one of three increasing doses of doxorubicin post-operatively in patients with node-positive primary breast cancer. Sequential paclitaxel resulted in a hazard reduction of relapse and death of 17% (p=0.0023) and 18% (p=0.0064), respectively. There was no evidence of doxorubicin dose effect. This result led to the approval of paclitaxel use in adjuvant chemotherapy by the US Food and Drug Administration (FDA). Similar benefits were observed in the NSABP B28 study,[33] where a higher dose of paclitaxel was added sequentially to an AC regimen in post-operative node-positive breast cancer patients. In the GEICAM 9906 study, post-surgical FEC (four cycles) followed by paclitaxel (eight cycles weekly) demonstrated a significant increase in four-year DFS but not OS compared with the standard six cycles of adjuvant FEC.[34]

The first trials testing docetaxel in the adjuvant setting compared both concomitant dosing and sequential dosing schedules. The Breast Cancer International Researcxh Group (BCIRG) 001 study randomised women with node-positive EBC to either six cycles of docetaxel, doxorubicin and cyclophosphamide (TAC) or six cycles of FAC.[35] The TAC regimen was associated with improved five-year DFS and OS independent of hormone receptor status, and the results of BCIRG 001 led to FDA approval for docetaxel in the ajuvant setting for EBC. Three cycles of sequential docetaxel following three cycles of FEC was compared with six cycles of FEC post-operatively in the FNCLCC PACS 01 trial, which involved patients with node-positive EBC.[36] Sequential adjuvant docetaxel showed significantly improved DFS and OS compared with the adjvuant FEC regimen. A pooled analysis of the phase III taxane trials concluded that taxane-based adjuvant chemotherapy (both sequential and concomitant) for EBC appears to confer benefits in terms of improved DFS and OS over standard chemotherapy. Taxane-based adjuvant chemotherapy for EBC seems to add a significant benefit in both DFS and OS over standard chemotherapy.[37] A recent meta-analysis of published studies, reported relatively constant risk reductions for both recurrence and death for taxane chemotherapy in EBC.[38]

The GEICAM 9805 study conducted by the Grupo Espanol de Investigacion en cancer de Mama compared TAC with FAC regimens given every three weeks for six cycles in high-risk node-negative breast cancer patients.[39–41] Adjuvant TAC significantly improved five-year DFS compared with FAC (33 reduction in RR, hazard ratio [HR] 0.66; p=0.0202). This study is consistent with the previous data on the TAC regimen.

Following on from the initial studies that demonstrated promising activity, the focus has been on achieving the optimal dosing schedule and regimen to achieve improved outcomes with reduced side effect profiles and identifying the subset of patients most likely to benefit from taxane-based adjuvant polychemotherapy.

Reducing Adverse Effects, Improving Tolerability and Optimising Schedules

Taxane-based chemotherapy has been associated with more adverse events than anthracycline-based regimens, particularly febrile neutropenia, myelosuppression, asthenia and peripheral neuropathy. These side effects may lead to a significant deterioration of the health-related quality of life of patients.[42] In BCIRG 001 and PACS 01, 24.7 and 11.2% of patients in the docetaxel cohorts, respectively, were found to have febrile neutropenia.[35,36] Docetaxel toxicities can be managed by primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) and sequential versus concomitant administration. Primary prophylaxis with G-CSF was found to significantly alleviate incidences of febrile neutropenia,[42–45] as confirmed by the GEICAM 9805 trial.[42] The health-related quality of life (HRQoL) of patients treated with TAC improved with G-CSF prophylaxis.[42]

Sequential administration of docetaxel was favoured in the BIG 02-98 study, which randomised 2,887 patients with node-positive EBC to one of four regimens: four cycles of doxorubicin (A) followed by three cycles of CMF; four cycles of AC followed by three cycles of CMF; three cycles of A followed by three cycles of docetaxel (T) followed by three cycles of CMF; or four cycles of AT followed by three cycles of CMF. The incidence of febrile neutropenia was 8% in the sequential docetaxel arm compared with 12% in the AT arm (p=0.002).[46] DFS in the sequential docetaxel arm was better than that in the concurrent docetaxel arm and in the sequential control arm. It should also be noted that the BIG 02-98 study utilised a short-course adjuvant regimen. A similar trial, the Taxit 216 study, compared the effect of four cycles of epirubicin (E) followed by four cycles of CMF versus four cycles of E followed by four cycles of docetaxel then four cycles of CMF. Sequential administration of docetaxel in node-positive patients was found to be superior in terms of DFS after a five-year median follow-up. OS was also significantly improved, at a median of 62 months.[47,48] Haematological grade 3 and 4 toxicities were similar in both arms, except for febrile neutropenia, which was higher in the docetaxel arm (11 versus 6% in the non-docetaxel arm).

Two studies have investigated short-course concomitant adjuvant docetaxel-based regimens. The US Oncology (USO) 9735 trial investigated four cycles of TC versus four cycles of AC in 1,016 patients with stage I–III breast cancer. The study demonstrated a DFS and OS advantage for TC.[49,50] However, a greater incidence of febrile neutropenia was observed in the TC arm. The Eastern Co-operative Oncology Group (ECOG) 2197 study demonstrated no advantage for four cycles of AT compared with four cycles of AC. Grade 3 neutropenia associated with fever or infection occurred more often with AT.[51]

The phase III BCIRG 005 has investigated the relative benefits of concurrent versus sequential docetaxel adjuvant regimens, specifically 6 x TAC versus 4 x AC- 4 x T in patients with HER2-normal, node-positive EBC.[52] Data from the main efficacy analysis showed that adjuvant TAC is equivalent to AC–T in terms of DFS. These data suggest that while the sequential docetaxel regimen delivers a higher dose intensity (eight cycles), it is no more effective than the concurrent docetaxel regimen. The safety profiles of the two docetaxel-based adjuvant chemotherapy regimens were comparable, although a higher incidence of febrile neutropenia and G-CSF use was observed in the TAC arm.[52]

Another phase III study, NSABP B-30, also evaluated the benefits of concurrent versus sequential docetaxel adjuvant regimens on DFS and OS in operable, node-positive EBC.[53] The study also investigated whether a regimen without cyclophosphamide was at least as efficacious as regimens containing cyclophosphamide. NSABP B-30 contained three arms: 4 x AC - 4 x T, 4 x TAC and 4 x AT. The AC–T arm reduced mortality by 14%, which is a marginal benefit compared with the TAC regimen (pP=0.086). The AC–T arm also significantly decreased mortality by 17% compared with AT (p=0.034), while AT was shown to be as efficacious as TAC. In terms of DFS, AC-T significantly decreased DFS by 17 and 20% versus TAC and AT, respectively.[53] Again, no differences in DFS were observed between AT and TAC. Although the sequential docetaxel regimen was found to be marginally superior to the concurrent regimen, it should be noted that the TAC regimen used in NSABP B-30 was not the approved 6 x TAC. Interestingly, patients experiencing amenorrhoea for ≥6 months had significantly improved OS and DFS across all treatment arms.[54]

Dose-dense Chemotherapy and Taxanes

Innovations in adjuvant treatment strategies are critical for optimal outcomes. The post-operative dose-dense approach is intended to optimise the administration of a standard chemotherapy regimen. Dose-dense (dose of drug administered per unit of time [mg/m^2/week]) can be obtained by either increasing the dose or decreasing the interval between doses. This strategy, evaluated in the CALGB C9741 trial, has shown that paclitaxel chemotherapy given every other week (dose-dense schedule) obtained superior DFS (RR 0.74; p=0.010) and OS (RR 0.69; p=0.13) compared with conventional schedule (every three weeks). No significant increase in adverse events was observed.[55,56] However, this approach requires G-CSF prophylaxis and may be associated with toxicities not typically observed in conventional schedules.[57–59]

Data from the ECOG 1199 trial, a randomised trial of AC chemotherapy followed by either paclitaxel (weekly or every three weeks) or docetaxel (weekly or every three weeks), showed that weekly paclitaxel and docetaxel every three weeks conferred the best advantage in terms of lowest rates of disease recurrence. Weekly paclitaxel dosing was associated with the highest five-year OS. In terms of outcomes as a function of ER status, proportional gains were achieved in both ER-positive and -negative tumours for both weekly paclitaxel and docetaxel every three weeks.[60]

Prognostic Factors – Possibilities and Evidence

Breast cancer is a biologically heterogeneous disease. The 'one-size-fits-all' approach in adjuvant chemotherapy has been gradually eliminated in recent years. It is now increasingly refined and tailored based on the molecular characteristics of tumours and individual clinical circumstances. Numerous prognostic factors are involved and the right treatment must be identified to reduce the risk of recurrence.

Hormone Receptor Status

Hormone receptor status, ER and PR in breast cancer are believed to be important factors in improving chemotherapy outcome.[61,62] Unfortunately, very few clinical trials have used the receptor status as a stratification factor from the outset. Reduction of RR of recurrence with paclitaxel was more efficacious in HR-positive patients than in HR-negative patients in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B28 trial,[33] whereas reduction of RR of recurrence in the BCIRG 001 with doxcetaxel[35] trial was very similar in both HR-positive and -negative patients (0.72 and 0.69, respectively). In GEICAM 9906 trial, RR of recurrence with paclitaxel was again very similar between the two groups.[34] Similar results in patients with docetaxel were found in the PACS 01 trial[36,49,50] and the ECOG2197[51] trials. Pooled data from the BCIRG 001 and PACS 01 trials analysed retrospectively by Andre el al.[63] showed that RR of death was reduced by 30% (HR 0.70) in ER-positive patients and by 31% (HR 0.69) in ER-negative patients, thus concluding that docetaxel conferred proportional effects on the risk of recurrence or death based on ER expression. The ECOG 1199 study analysed outcomes as a function of ER status and found proportional gains were achieved in both ER-positive and -negative tumours for both weekly paclitaxel and docetaxel every three weeks.[60]

Human Epidermal Growth Factor Receptor-2 Status

Understanding of human epidermal growth factor receptor-2 (HER2) as a predictive factor and target of treatment is a recent development. The HER2 gene encodes for the HER2 protein, a tyrosine kinase inhibitor. Overexpression of the HER2 protein can be established by using immunohistochemistry (IHC) and fluorescence *in situ* hybridisation (FISH) is used to measure HER2 gene amplification. Trastuzumab, an HER2 antibody, and lapatinib, a tyrosine kinase inhibitor potentially play a vital role in adjuvant chemotherapy to achieve a maximum DFS.[64]

Results from the combined NSABP B-31/North Central Cancer Treatment Group (NCCTG) N9831 study[65] showed significant improvements in both DFS (p<0.001) and OS (p=0.02) with trastuzumab. Similar results were obtained in the Herceptin Adjuvant (HERA) trial.[66] Trastuzumab for one year significantly improved DFS (p<0.0001) and OS (p=0.11). The combination of trastuzumab and docetaxel was found to achieve a 60% objective response rate, and 22% of patients were alive after four years.[67] Subgroup analysis in the BCIRG 007 trial also suggests similar benefits.[64] Hayes et al. reported that in a subgroup analysis of the CALGB 9344 trial, the interaction between HER2 positivity and the addition of paclitaxel to the treatment was associated with an HR for recurrence of 0.59 (p=0.01). HER2-positive patients benefited from paclitaxel, regardless of ER status, but HER2-negative or ER-positive patients did not benefit.[68] Use of lapatinib in HER2 overepression obtained a response rate of 62%.[69] The combination of trastuzumab and vinorelbin was found to be well tolerated and cost-effective.[70,71] A small study called the FinHER trial randomised high-risk

node-negative patients to three cycles of chemotherapy (docetaxel or vinorelbine) with or without trastuzumab every week for nine weeks followed by three cycles of standard chemotherapy. Andersson et al. discussed the opinion of clinical experts on five case studies with variable predictive factors and concluded that HER2 was one of the most important to predict outcome. Trastuzumab, mostly in conjuction with taxanes, has enhanced the curative potential of adjuvant therapy.[66]

Based on results from the joint analysis of the NSABP B31 and NCCTG N9831 trials, the FDA approved the new regimen of AC-TH (doxorubicin and cyclophosphamide followed by paclitaxel [T] and trastuzumab [H]) for the adjuvant treatment of patients with early-stage HER2-positive, node-positive breast cancer. More recently, data from the phase III BCIRG 006 have led to FDA approval for two further new trastuzumab-based regimens for the adjuvant treatment of early-stage HER2-positive node-positive or node-negative (ER/PR-negative or with one high-risk feature) breast cancer. The first is the AC-TH regimen, and the second is the the TCbH regimen (docetaxel and carboplatin [Cb] combined with trastuzumab). BCIRG 006 compared three regimens: the standard AC-T regimen of 4 x AC followed by 4 x docetaxel; AC-TH, 4 x AC – 4 x docetaxel plus trastuzumab followed by trastuzumab monotherapy to complete one year of trastuzumab treatment; or TCbH, 6 x docetaxel plus carboplatin plus trastuzumab, then trastuzumab monotherapy to complete one year of trastuzumab treatment.[72] At 36-month follow-up, the AC-DH regimen significantly improved both DFS (39%) and OS (a significant 42% reduction in the risk of death) compared with the AC-T control arm. In the TCbH arm, DFS and OS were significantly improved (33 and 34% reduction in the risk of death, respectively) compared with the AC-T control arm. No statistically significant differences were observed in DFS or OS between the TCbH and AC-TH.[72]

Herceptin is associated with cardiotoxicity and the rate of cardic dysfunction increases when anthracyclines and trastuzumab are used concurrently.[73] Furthermore, cardiotoxicity remains an important clinical issue with sequential therapy. In the NCCTG N9831 study, the three-year cumulative incidence of cardiac events in the concurrent paclitaxel/trastuzumab AC-TH arm was 3.3% and 2.8% in the AC-T-H arm, compared with 0.3% in th AC-T arm.[74] In NSABP B-31, the three-year cumulative incidence of cardiac events were 4.1% (concurrent paclitaxel/trastuzumab) versus 0.8% (chemotherapy alone).[75] In comparison, the anthracycline-free regimen utilised in BCIRG 006, TCbH, was associated with a five-fold lower risk of cardiotoxicity compared with AC-TH. The three-year cumulative incidence of symptomatic cardiac events and congestive heart failure was lower in the TCH arm compared with the AC-TH arm (0.3, 1.9 and 0.4% for AC-T, AC-TH and TCbH, respectively).[72] Thus, BCIRG 006 showed that a non-anthracycline regimen containing docetaxel, carboplatin and trastuzumab is as effective as an anthracycline-containing regimen but with a lower risk of cardiotoxicity.

Summary and Conclusions

Adjuvant breast cancer therapy has undergone a plethora of advances in the past decade. While head-to-head comparisons of taxanes in the adjuvant setting can be difficult due to the large number of variables involved in the clinical trials, including doses and schedules, it is clear from the available data that taxanes show promise in extending DFS and have acceptable toxicity profiles. They can be added sequentially after an anthracycline or substituted for doxorubicin or 5-fluorouracil. Dose-dense scheduling, especially with just taxanes, has provided interesting data and may benefit patients with early-stage disease, although these data need to be supported by further studies. Despite extensive efforts focused on targeted therapy, the available data are too inconsistent to establish the right regimen for each patient. No single regimen so far has been able to claim superiority. The next Oxford Overview meta-analysis will hopefully provide further insights. Searching for reliable molecular indicators of responsiveness should be the focus of future trials to enable clinicians to target specific taxanes and strategies to subsets of patients. New agents and tools have enabled clinicians to individualise chemotherapy. These new advances raise numerous questions – what is the right adjuvant combination, dose, duration and method of prophylaxis, and what are the predictive and genomic factors? These questions need to be resolved through translational research, with the ultimate goal of achieving maximum benefit for the patient. ■

1. World Health Organization, Cancer Fact sheet No. 297, 2008. Available at: www.who.int/mediacentre/factsheets/fs297/en/index.html
2. American Cancer Society, Cancer Facts & Figures 2008, Atlanta: American Cancer Society; 2008. Available at www.cancer.org/docroot/STT/content/STT_1x_Cancer_Facts_and_Figures_2008.asp
3. Agarwal G, et al., *World J Surg*, 2007;31:1031–40.
4. Minami Y, et al., *Int J Cancer*, 2004;108:901–6.
5. Ahn SH, *Arch Surg*, 2004;139:27–30.
6. Raina V, et al., *Indian J Cancer*, 2005;42:40–45.
7. Chopra R, *J Clin Oncol*, 2001;19(18S):106–11S.
8. Son BH, et al., *Arch Surg*, 2006;141:155–60.
9. Shen YC, et al., *Cancer Epidemiol Biomarkers Prev*, 2005;14:1986–90.
10. Nomura Y, et al., *Cancer Res*, 1977;37:106–10.
11. Chow LW, Ho P, *J Surg Oncol*, 2000;75:172–5.
12. *Lancet*, 1998;352:930–42.
13. *Lancet*, 2005;365:1687–1717.
14. Chan S, et al.,*J Clin Oncol*, 1999;17:2341–54.
15. Paridaens R, et al., *J Clin Oncol*, 2000;18:724–33.
16. Ghersi D, et al., *Br J Cancer*, 2005;93:293–301.
17. Bonadonna G, et al., *N Engl J Med*, 1976;294:405–10.
18. Bonadonna G, et al., *Breast Cancer Res Treat*, 1985;5:95–115.
19. Buzzoni R, et al., *J Clin Oncol*, 1991;9:2134–40.
20. Ravdin PM, et al., *J Clin Oncol*, 1995;13:2879–85.
21. Bonneterre J, et al., *Eur J Cancer*, 1999;35:1431–9.
22. Bonneterre J, et al., *Br J Cancer*, 2004;91:1466–71.
23. Mackey JR, et al., *Proc Am Soc Clin Oncol*, 2002;21:137.
24. Nabholtz JM, et al., *J Clin Oncol*, 2003;21:968–75.
25. Bontenbal M, et al., *J Clin Oncol*, 2005;23(28):7081–8.
26. Rivera E, et al., *Cancer*, 2000;89:2195–2201.
27. Jassem J, Pet al., *J Clin Oncol*, 2001;19:1707–15.
28. Sledge GW, et al., *J Clin Oncol*, 2003;21:588–92.
29. Biganzoli L, et al., *J Clin Oncol*, 2002;20:3114–21.
30. Lück H, et al., *Proc Am Soc Clin Oncol*, 2000;19:280.
31. Piccart-Gebhart MJ, et al., *J Clin Oncol*, 2008;26(12):1980–86.
32. Henderson IC, et al., *J Clin Oncol*, 2003;21:976–83.
33. Mamounas EP, et al., *J Clin Oncol*, 2005;23:3686–96.
34. Martín M, et al., *J Natl Cancer Inst*, 2008;100:805–14.
35. Martín M, et al., *N Engl J Med*, 2005;352:2302–13.
36. Roché H, et al., *J Clin Oncol*, 2006;24:5664–71.
37. Bria E, et al., *Cancer*, 2006;106:2337–44.
38. De Laurentiis M, et al., *J Clin Oncol*, 2008;26:44–53.
39. Martin M, et al., Program and abstracts of the 2008 Breast Cancer Symposium; September 5–7, 2008;153.
40. Martin M, et al., *Ann Oncol*, 2008;19(Suppl 8):viii77.
41. Martin M, et al., *J Clin Oncol*, 2008;26(15S): abstract 542.
42. Martín M, et al., *Ann Oncol*, 2006;17:1205–12.
43. Lyman GH, *J Natl Compr Canc Netw*, 2005;3:557–71.
44. Aapro MS, et al., *Eur J Cancer*, 2006;42:2433–53.
45. Smith TJ, et al., *J Clin Oncol*, 2006;24:3187–1205.
46. Francis P, et al., *J Natl Cancer Inst*, 2008;100:121–33.
47. Bianco AR, et al., *J Clin Oncol*, 2006;24 (18S): abstract LBA520.
48. Cognetti F, et al., *Ann Oncol*, 2008;19(Suppl. 8):viii77.
49. Jones S, et al., *J Clin Oncol*, 2006;24:5381–7.
50. Jones S, et al., *Breast Cancer Res Treat*, 2007;106(Suppl. 1): abstract 12.
51. Goldstein LJ, et al., *J Clin Oncol*, 2008;26:4092–9.
52. Eiermann W, et al., *Cancer Res*, 2009;69(Suppl. 2): abstract 77.
53. Swain SM, et al., *Cancer Res*, 2009;69(Suppl. 2): abstract 75.
54. Ganz PA, et al., *Cancer Res*, 2009;69 (Suppl. 2): abstract 76.
55. Citron ML, et al., *J Clin Oncol*, 2003;21:1431–9.
56. Hudis C, et al., *Breast Cancer Res Treat*, 2005;94 (Suppl. 1):S20.
57. Dang CT, et al., *Clin Cancer Res*, 2004;10:5754–61.
58. Bardia A, et al., *J Clin Oncol*, 2006;24:e18–19.
59. Tolaney SM, et al., *J Clin Oncol*, 2006;24:5330–31.
60. Sparano JA, et al., *J Clin Oncol*, 2007;25(18S): abstract 516.
61. Albain K, et al., *Breast Cancer Res Treat*, 2004;88(Suppl. 1): abstract 37.
62. Berry DA, et al., *JAMA*, 2006;295:1658–67.
63. Andre F, et al., *J Clin Oncol*, 2008;26:2636–43.
64. Andersson M, et al., *Breast*, 2008;17:S1–11.
65. Romond EH, et al., *N Engl J Med*, 2005;353:1673–84.
66. Piccart-Gebhart MJ, et al., *N Engl J Med*, 2005;353:1659–72.
67. Marty M, et al., *J Clin Oncol*, 2005;23:4265–74.
68. Hayes DF, et al., *N Engl J Med*, 2007;357:1496–1506.
69. Spector NL, et al., *J Clin Oncol*, 2006;24(18S): abstract 502.
70. Chan A, et al., *Br J Cancer*, 2006;95:788–93.
71. Bernardo G, et al., *J Clin Oncol*, 2004;22(14S): abstract 731.
72. Slamon D, et al., *Breast Cancer Treat Res*, 2006;100(Suppl. 1): abstract 52.
73. Seidman A, et al., *J Clin Oncol*, 2002;20(5):1215–21.
74. Perez EA, et al., *J Clin Oncol*, 2008;26:1231–8.
75. Tan-Chiu E, et al., *J Clin Oncol*, 2005;23:7811–19.