Journal of BUON **10:** 175-180, 2005

REVIEW ARTICLE

Adjuvant chemotherapy of breast cancer

S. Bešlija

Department of Medical Oncology, Institute of Oncology, Clinical Center of Sarajevo University, Sarajevo, Bosnia and Herzegovina

Summary

Breast cancer is the most common cancer and the second most common cause of cancer-related death in women. The last three decades have yielded marked progress in the diagnosis and management of breast cancer. Not only is the disease being detected at a much earlier stage, but the addition of systemic therapy has also improved survival. Cyclophosphamide (C), methotrexate (M) and 5-fluorouracil (F) (CMF) combination chemotherapy was among the first chemotherapy regimens found to prolong both disease-free survival (DFS) and overall survival (OS) when given in the adjuvant setting. The 2000 Oxford overview confirmed that anthracycline-based chemotherapy offers a survival advantage compared with CMF. Anthracycline-based therapies are better tolerated in terms of acute side effects but long-term sequels (cardiotoxicity, secondary leukaemia) are worrisome. It seems that more intensive three-drug regimens (FE[epirubicin]$_{100}$C, CEF, CA[adriamycin]F,) or the combination of E+CMF are more active in reducing the risk of relapse and death in breast cancer patients. The reported trials with taxanes demonstrated comparable reduction in the risk of recurrence and death, although administration of paclitaxel (T)-containing regimens appears to be most effective if administered on an every-2-week schedule with granulocyte colony-stimulating factor (G-CSF). The risk of febrile neutropenia is highest for the TAC regimen (~25%), although other trials have demonstrated that use of G-CSF will reduce this complication to about 3%.

Key words: adjuvant, breast, cancer, chemotherapy

Breast cancer is the most common cancer and the second most common cause of cancer-related death in women. The last three decades have yielded marked progress in the diagnosis and management of breast cancer. Not only is the disease being detected at a much earlier stage, but the addition of systemic therapy has also improved survival [1]. At diagnosis, many women with primary breast cancer already have distant micrometastases. With time, most of these women will progress to overt metastatic disease, even after surgery and radiotherapy. Systemic adjuvant therapy for early-stage breast cancer is thus used to prevent or delay disease progression and offers the prospect of cure by eliminating micrometastases.

CMF combination chemotherapy was among the first chemotherapy regimens found to prolong both DFS and OS when given in the adjuvant setting [2,3]. CMF given beyond 6 months did not reduce mortality or relapse rate, and there was little difference in the results between patients receiving CMF of 3 to 6-month duration. The many versions of CMF therapy, including those entailing oral or intravenous drug administration, appear generally equal, but it is quite possible that oral CMF could be superior, as suggested in studies of metastatic disease [4,5].

The 2000 Oxford overview [6] confirms the 1995 data that anthracycline(A)-based chemotherapy offers a survival advantage compared with CMF. A-based therapies are better tolerated in terms of acute side

Received 28-09-2004; Accepted 07-11-2004

Author and address for correspondence:

Semir Bešlija, MD
Department of Medical Oncology
Institute of Oncology
Clinical Center of Sarajevo University
Bolnicka 25
71000 Sarajevo
Bosnia and Herzegovina
Tel/Fax: +387 33 213 519
E-mail: sbeslija@onkokcus.bih.net.ba

effects [7], but long-term sequels (cardiotoxicity, secondary leukaemia) are worrisome [8,9]. To evaluate which A-based treatment is the best for use in standard clinical practice, the better approach could be an analysis of one-to-one comparison between A-based regimens and CMF. It seems that the more intensive three-drug A-based regimens ($FE_{100}C$, CEF, CAF) [10-12] or the combination of E+CMF [13] are more active in reducing the risk of relapse and death in breast cancer patients than CMF. Nevertheless, CMF remains a valid option for selected groups of patients (elderly, cardiac dysfunction, node-negative, hormone receptor-positive, HER2-negative).

Dose-escalating regimens have been used to increase efficacy and prevent resistance to some chemotherapeutic agents. NSABP 22 and 25 trials indicate that cyclophosphamide doses > 600 mg/m^2 do not improve DFS or OS but do significantly increase toxicity [14,15]. Doses of doxorubicin > 60 mg/m^2 have shown no clear benefit and are not recommended outside of clinical trials [16]. Epirubicin has structural differences compared with doxorubicin and consequently different safety profile. Larger doses of epirubicin are required to produce the same degree of toxicity as doxorubicin.

Dose-dense treatment emphasizes manipulation of dose schedule by decreasing the time interval between cycles rather than dose level. The Cancer and Leukemia Group B (CALGB) clinical study 9741 (Intergroup C9741) [17] posed two questions: is combination chemotherapy superior to a sequence of single agents, and is dose density important? The first question was addressed by comparing the standard doxorubicin and cyclophosphamide combination (AC) followed by paclitaxel against the sequential administration of doxorubicin, then paclitaxel, then cyclophosphamide. All patients received 4 courses of these 3 agents (doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2, and paclitaxel 175 mg/m^2). The comparison revealed no significant differences between the 2 protocols. To determine the impact of dose density, the same patients were also randomized to receive their chemotherapy using 2- or 3-week intervals. The 2-week interval required growth factor support (filgrastim), whereas filgrastim was administered as needed in the every-third-week arm. Treatment using the 2-week interval was associated with improved DFS and OS, reduced rate of neutropenic fever (no doubt attributable to the growth factor support), and was of course one third shorter. Hence, a shorter, safer treatment was associated with improved disease-specific outcomes. This study was recently published [18] and a protocol-specified analysis was performed at a median follow-up of 36 months: 315 patients had experienced relapse or died, compared with 515 expected treatment failures. Dose-dense treatment improved the primary endpoint, DFS (risk ratio [RR] = 0.74; p=0.010), and OS (RR = 0.69; p=0.013). Four-year DFS was 82% for the dose-dense regimens and 75% for the others. There was no difference in either DFS or OS between the concurrent and sequential schedules. There was no interaction between density and sequence. Severe neutropenia was less frequent in patients who received the dose-dense regimens with the conclusion that dose density improves clinical outcomes significantly, despite the lower than expected number of events at this time. Sequential chemotherapy was as effective as concurrent chemotherapy.

This trial was correctly designed and performed but there is still a number of questions to be answered: we will have to wait for the data regarding long-term efficacy and toxicity; the trial did not have enough power to make an individual comparison between the 4 arms and is missing prospective stratification for estrogen receptor (ER) status. Finally, lacking are data regarding quality of life as well as cost/benefit ratio.

The use of high-dose chemotherapy is based on the hypothesis that high doses will overcome drug resistance, eradicate metastatic disease, and increase the proportion of women who are cured. According to the results from several randomized clinical studes [19-22], high-dose therapy cannot be considered standard for adjuvant therapy in any known group of women with high risk of relapse and has to be offered to the patients only in a clinical trial setting. Further studies and longer follow-up are awaited before any recommendations regarding the role of high-dose therapy can be established.

In recent years, the taxanes have been investigated in several trials of adjuvant therapy of women with node-positive breast cancer. The two major trials in which paclitaxel was used (NSABP B28 and CALGB-9344) provided evidence about the role of taxanes in adjuvant therapy [23,24]. In the CALGB 9344 trial, patients with node-positive disease were randomized to receive either 4 cycles of doxorubicin and cyclophosphamide (AC) or the same regimen followed by 4 cycles of paclitaxel. The patients were randomized in 3 dose levels of doxorubicin. The majority of the enrolled patients (94%) had ER-positive tumors and received tamoxifen following completion of chemotherapy. While the dose of doxorubicin did not have an impact on outcome, in the published article at a median follow-up of 69 months [25] the group of patients treated with paclitaxel have had significantly

greater 5-year DFS (70 *versus* 65%; p=0.0023) and OS (80 *versus* 77%; p=0.0064). The addition of paclitaxel yielded a statistically significant reduction in the risk of reccurence and death of 17% and 18%, respectively. An unplanned subgroup analysis showed that the paclitaxel arm was more affecting the reduction of the risk of relapse in patients with ER-negative tumors. The additional toxicity deriving from the sequential use of paclitaxel was generally modest.

In the NSABP B28 trial [24], 3059 patients with node-positive disease were randomized to receive 4 cycles of doxorubicin and cyclophosphamide (AC), or the same regimen followed by 4 cycles of paclitaxel at a dose of 225 mg/m^2. Tamoxifen was administered to all patients aged > 50 years, as well as to younger women with ER-positive disease. The patients of this study represented a better risk group compared with the CALGB study in terms of number of positive nodes and hormone receptor positivity. The initial analysis of the NSABP B28 trial showed no difference in outcome between patients treated with AC alone and those treated with AC and paclitaxel [25]. A more recent update at a median follow-up of 64 months showed that patients receiving paclitaxel had a statistically significant reduction in the risk of relapse but they did not have statistically significant reduction in the risk of death [26].

The absolute benefit of adding paclitaxel in the adjuvant treatment of breast cancer remains uncertain, mainly due to the control regimen used in both trials which seems to be suboptimal. Patients in the control arms in both of these trials received only 4 cycles of treatment compared with 8 received in the experimental arm. Four cycles of AC have been shown to be equivalent to, but not more effective than 6 cycles of CMF, as mentioned above. Three-drug anthracycline-containing combinations administered for 6 or more cycles have been shown to be superior to 6 cycles of CMF [10-12].

The first large trial that evaluated the use of docetaxel in the adjuvant setting was reported by Nabholtz et al. (Breast Cancer International Research Group - BCIRG 001) [27]. They compared 6 cycles of standard 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) chemotherapy (500, 50, and 500 mg/m^2, respectively, every 3 weeks) *versus* docetaxel, doxorubicin, and cyclophosphamide (TAC) (75, 50, and 500 mg/m^2, respectively, every 3 weeks). This study provided evidence that docetaxel may have an important role when used as a component of adjuvant therapy for patients with high-risk operable or locally advanced breast cancer. There were 3 important points that might limit the application of the TAC regimen. First, the febrile neutropenia rate was very high (24%), suggesting that patients may need to be selected carefully for this regimen. Second, surprisingly TAC was found not to be beneficial in patients at highest risk (>3 positive nodes), a group in which clinicians would most likely accept a higher toxicity rate if the treatment was more effective. Finally, the trial did not include patients older than 70 years. On the other hand, there was clear benefit when this docetaxel-based regimen was used in patients with ER and/or PR-positive disease, which was not the case when paclitaxel was used sequentially following doxorubicin-cyclophosphamide in such patients. All these considered, however, this study suggests that TAC may be a reasonable alternative for the group that demonstrated clear benefit: relatively young women with 1-3 positive axillary nodes, irrespective of hormone receptor status.

On the latest San Antonio Breast Cancer Meeting, Mackey and colleagues from the BCIRG reported an update of the BCIRG 001 trial [28]. This report represents an update with 55 months median follow-up at a second interim analysis preplanned to occur after 400 events, compared with 33 months at the first interim analysis performed after about 300 recurrences; in the current analysis, 92% of patients have been followed for at least 4 years. The results were compared with those of the first interim analysis (Table 1). In the first analysis, TAC was associated with a significant reduction in the risk of recurrence but not death (p=0.11, log rank test), although the risk of death was significantly reduced in a preplanned Cox proportional hazard model adjusted for baseline prognostic factors. In the updated analysis, TAC was now associated with a significant reduction in the risk of both recurrence and death (log rank test). In a Cox analysis adjusted for prognostic factors, TAC was again associated with a significant improvement in DFS (hazard ratio for recurrence 0.72; p=0.0010) and OS (hazard ratio for death 0.70; p=0.008), a finding that is nearly identical to that of the initial report. Also similar to the original report, subgroup analysis revealed benefit for the TAC arm in patients with 1-3 positive axillary nodes, hormone receptor-positive or negative disease, and HER2/neu-positive or negative disease, but not in patients with 4 or more positive axillary nodes; the latter group comprised 568 patients, and the lack of benefit for this group remains somewhat surprising. However, the study is not powered to address the difference in the 4+ node subgroup until the final analysis is planned after 580 events.

This report confirms that TAC chemotherapy may be a reasonable treatment option for patients with operable node-positive breast cancer. The results reported for BCIRG 001 are contrasted with results from

Table 1. Comparison of first and second interim analyses – BCIRG 001 [17,18]

	Initial report	*Current report*
Planned interim analysis	First	Second
Median follow-up period (months)	33	55
No. of recurrences	289	389
No. of deaths	133	221
Hazard rate - recurrence*	0.68 (p=0.0002)	0.72 (p=0.0010)
Hazard rate – death*	0.71 (p=0.049)	0.70 (p=0.008)

*Cox proportional hazard model (adjusted for nodal status)

3 other phase III trials that have evaluated taxane-containing therapy for node-positive breast cancer (Table 2). All trials demonstrate comparable reduction in the risk of recurrence and death, although administration of the paclitaxel-containing regimens appears to be most effective if administered on an every 2-week schedule with G-CSF. The risk of febrile neutropenia is highest for the TAC regimen (~25%), although other trials have demonstrated that use of G-CSF will reduce this complication to about 3%.

Finally, there are about 24000 women who are enrolled in clinical trials, which will give us the answers regarding the optimal use of taxanes in the adjuvant setting.

The successful introduction of trastuzumab, a recombinant humanized monoclonal antibody directed to the HER2 protein [29-31] has led to the design of trials studying the use of trastuzumab in the adjuvant setting. There are many prospective clinical studies that will investigate the possible role of trastuzumab in different combinations with cytotoxic drugs. There are many open questions: cardiotoxicity, confirmation of the preclinically proven activity with some drugs which are not so active in breast cancer (platinum), duration of therapy and the future role of the every 3 weeks administration. Additionally, analysis of retrospective data suggests that HER2 overexpressing tumors may be particularly sensitive to anthracyclines and anthracycline dose intensity, and less responsive to CMF. There is no doubt that HER2 overexpressing tumors are associated with a worse prognosis and more aggressive course but the predictive value of this receptor still has to be answered.

Conclusion

A large number of questions remains and some answers will hopefully appear over the next few years regarding the best use of adjuvant chemotherapy in breast cancer patients. These issues include the role of taxanes in the adjuvant therapy, the possible benefits of a dose-dense schedule of agents, the maturation of studies of high-dose chemotherapy and the determination of a possible benefit with the use of trastuzumab in the adjuvant setting.

Future generations of clinical trials will highlight the need to optimize the integration of traditional breast cancer therapies with new-targeted strategies. Improved individualization of adjuvant therapy based on the identification of new and reliable predictive markers is our best hope for enhancing cure rates in the next decade.

The treatment planning for all patients with breast cancer has to be multidisciplinary (Breast Care Unit) and has to offer participation in clinical trials to patients who are very well informed about their disease.

Table 2. Phase III randomized adjuvant taxane breast cancer trials

Study	*No. of patients*	*Median follow-up (months)*	*Comparison*	*5-year DFS (%)*	*5-year OS (%)*
CALGB 9344 [23]	3,121	69	AC x 4	65	77
			AC x 4 → P x 4	70*	80*
NSABP B 28 [26]	3,060	65	AC x 4	72	85
			AC x 4 → P x 4	76*	85
BCIRG 001 [28]	1,491	55	TAC x 6	75*	87*
			FAC x 6	68	81
CALGB 9741 [18]	2,005	36	Dose-dense arms II and IV	82†	92
			Standard arms I and III	75*	90*

DFS: disease-free survival; OS: overall survival; CALGB: Cancer and Leukemia Group B; AC: doxorubicin and cyclophosphamide; P: paclitaxel; NSABP: National Surgical Adjuvant Breast and Bowel Project; FAC: fluorouracil, doxorubicin, and cyclophosphamide; BCIRG: Breast Cancer International Research Group; TAC: docetaxel, doxorubicin, and cyclophosphamide
*p <0.05; †82% (4-year DFS)

References

1. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: An overview of the randomized trials. Lancet 1998; 352: 930-942.
2. Bonadonna G, Brusamolino E, Valagussa P et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 1976; 294: 405-410.
3. Bonadonna G, Valagussa P, Moliterni A et al. Adjuvant cyclophosphamide, methotrexate and fluorouracil in node positive breast cancer: The results of 20 years of follow-up combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 1995; 332: 901-926.
4. Lindeman GJ, Boyages J, Driessen C, Langlands AO. Intravenous or oral adjuvant CMF for node-positive breast cancer. Aust N Z J Surg 1992; 62: 556-562.
5. Engelsman E, Klijn JC, Rubens RD et al. «Classical» CMF versus a 3-weekly intravenous CMF schedule in postmenopausal patients with advanced breast cancer. An EORTC Breast Cancer Cooperative Group Phase III Trial (10808). Eur J Cancer 1991; 27: 966-970.
6. Early Breast Cancer Trialists' Collaborative Group: Analysis overview results. Fifth Meeting of the Early Breast Cancer Trialists' Collaborative Group, Oxford, United Kingdom, September 21-23, 2000.
7. 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 node positive breast cancer patients with tamoxifen non-responsive tumors: Results from the National Surgical Adjuvant Breast and Bowel Project B-15. J Clin Oncol 1990; 8: 1483-1496.
8. Chambers SK, Chopyk RL, Chambers JT et al. Development of leukemia after doxorubicin and cisplatin treatment for ovarian cancer. Cancer 1989; 64: 2459-2461.
9. Lenaz I, Page JA. Cardiotoxicity of adriamycin and related anthracyclines. Cancer Treat Rev 1976; 3: 111-120.
10. French Adjuvant Study Group: Benefit of a high-dose epirubicin regimen in adjuvant chemotherapy for node-positive breast cancer patients with poor prognostic factors: 5-year follow-up results of French Adjuvant Study Group 05 randomized trial. J Clin Oncol 2001; 19:602-611.
11. 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: 2651-2658.
12. Coombes RC, Bliss JM, Wils J et al. Adjuvant cyclophosphamide, methotrexate, and fluorouracil versus fluorouracil, epirubicin, and cyclophosphamide chemotherapy in premenopausal women with axillary node-positive operable breast cancer: Results of a randomized trial. The International Collaborative Cancer Group. J Clin Oncol 1996; 14: 35-45.
13. Poole CJ, Earl HM, Dunn A et al. NEAT (National Epirubicin Adjuvant Trial) and SCTBG BR9601 (Scottish Cancer Trials Breast Group) phase III adjuvant breast trials show a significant relapse-free and overall survival advantage for sequential ECMF. Proc Am Soc Clin Oncol 2003; 22: 4 (abstr 13).
14. Fisher B, Anderson S, Wicherham DL et al. Increased intensification and total dose of cyclophosphamide in a doxorubicin-cyclophosphamide regimen for the treatment of primary breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-22. J Clin Oncol 1997; 15: 1858-1869.
15. Fisher B, Anderson S, DeCillis A et al. Further evaluation of intensified and increased total dose of cyclophosphamide for the treatment of primary breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-25. J Clin Oncol 1999; 17: 3374-3388.
16. Wood WC, Budman DR, Korzun AH et al. Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast carcinoma. N Engl J Med 1994; 330:1253-1259.
17. Citron M, Berry D, Cirrincione C et al. Superiority of dose-dense (DD) over conventional scheduling (CS) and equivalence of sequential (SC) vs. combination adjuvant chemotherapy (CC) for node-positive breast cancer (CALGB 9741, INT C9741). Program / abstracts 25th Breast Cancer Symp; Dec 11-14, 2002; San Antonio, Texas (abstr 15).
18. Citron M, Berry D, Cirrincione C et al. Randomized Trial of Dose-Dense Versus Conventionally Scheduled and Sequential Versus Concurrent Combination Chemotherapy as Postoperative Adjuvant Treatment of Node-Positive Primary Breast Cancer: First Report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003; 21: 1431-1439.
19. Hortobagyi GN, Buzdar A, Champlin R et al. Lack of efficacy of adjuvant high dose (HD) tandem combination chemotherapy (CT) for high-risk primary breast cancer (HRPBC): a randomized trial. Proc Am Soc Clin Oncol 1998; 18: 2a (abstr 471).
20. Peters WP, Rosner G, Vredenburgh J et al. A prospective, randomized comparison of two doses of combination alkylating agents as consolidation after CAF in high-risk primary breast cancer involving ten or more axillary lymph nodes: Preliminary results of CALGB 9082/SWOG 9114/NCIC MA-13. Proc Am Soc Clin Oncol 1999; 18: 1a (abstr 2).
21. The Scandinavian Breast Cancer Study Group 9401. Results from a randomized adjuvant breast cancer study with high-dose chemotherapy with CTCb supported by autologous bone marrow stem cells vs dose-escalated and tailored FEC therapy. Proc Am Soc Clin Oncol 1999; 18:2a (abstr 3).
22. Rodenhuis S, Bontenbal M, Beex L et al. Randomized phase III study of high-dose chemotherapy with cyclophosphamide, thiotepa, and carboplatin in operable breast cancer with 4 or more axillary lymph nodes. Proc Am Soc Clin Oncol 2000; 19:74a (abstr 286).
23. Henderson IC, Berry DA, Demetri GD et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol 2003; 21: 976–983 [Abstract/Free Full Text].
24. Thomas E, Buzdar A, Theriault R et al. Role of paclitaxel in adjuvant therapy of operable breast cancer: preliminary results of a prospective randomized clinical trial. Proc Am Soc Clin Oncol 2000; 19: 74a (abstr 285).
25. Eifel P, Axelson JA, Costa J et al. National Institutes of Health Consensus Development Conference Statement: Adjuvant therapy for breast cancer, November 1–3, 2000. J Natl Cancer Inst 2001;93:979–989 [Abstract/Free Full Text].

26. Mamounas EP, Bryant J, Lembersky BC et al. Paclitaxel (T) following doxorubicin/ cyclophosphamide (AC) as adjuvant chemotherapy for node-positive breast cancer: Results from NSABP B-28. Proc Am Soc Clin Oncol 2003; 22: 4 (abstr 12).
27. Nabholtz JM, Pienkowski T, Mackey J et al. Phase III trial comparing TAC (docetaxel, doxorubicin, cyclophosphamide) with FAC (5-fluorouracil, doxorubicin, cyclophosphamide) in the adjuvant treatment of node positive breast cancer patients: interim analysis of the BCIRG 0001 study. Proc Am Soc Clin Oncol 2002; 21 (abstr 141).
28. Martin M, Pienowski T, Mackey J et al. TAC improves disease-free survival and overall survival over FAC in node positive breast cancer patients, BCIRG 001: 55 months follow up. Breast Cancer Res Treat 2003; 82 (Suppl 1): (abstr 43).
29. Slamon D, Leyland-Jones B, Shak S et al. Addition of Herceptin TM (humanized anti-HER2 antibody) to first line chemotherapy for HER2 overexpression of metastatic breast cancer (HER2 + MBC) markedly increases anticancer activity: a randomized multinational controlled phase III trial. Proc Am Soc Clin Oncol 1998; 17 (abstr 377).
30. Cobleigh MA, Vogel CL, Tripathy D et al. Efficacy and safety of Herceptin TM (humanized anti-HER2 antibody) as single agent in 222 women with HER2 overexpression who relapsed following chemotherapy for metastatic breast cancer. Proc Am Soc Clin Oncol 1998; 17 (abstr 376).
31. Baselga J, Tripathy D, Mendelsohn J et al. Phase II study of weekly intravenous recombinant humanized anti-p185HER2 monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer. J Clin Oncol 1996; 14: 737-744.