REVIEW Libri Oncol., Vol. 34 (2006), N^{o} 1-3, 59 – 63

NEW STANDARDS IN THE CHEMOTHERAPY OF BREAST CANCER

TANJA ČUFER

Institute of Oncology, Ljubljana, Slovenia

Summary

During the last few years progress in breast cancer (BC) chemotherapy (CT) was made through the incorporation of taxanes into treatment schedules, the manipulation of dose-size and dose-density of our most active cytotoxic agents and recently, through the incorporation of trastuzumab into treatment schedules for all stages of BC. Further progress is foreseen by incorporating additional molecularly targeted therapies into treatment schemas and by improved molecular classification of disease based on gene expression profiles and signatures that might predict for prognosis and response to chemotherapy. In this review, the main findings related to these topics are summarized, currently recommended chemotherapy treatment options are discussed, and future directions of research are alighted.

KEY WORDS: *breast cancer, chemotherapy, molecularly targeted therapies*

NOVI STANDARDI U KEMOTERAPIJI RAKA DOJKE

Sažetak

Tijekom posljednjih nekoliko godina u kemoterapiji raka dojke postignut je napredak uvođenjem taksana u plan liječenja, mogućnošću prilagodbe veličine i učestalosti doziranja najdjelatnijih citotoksičnih lijekova, a odnedavno i uvođenjem trastuzumaba u protokole za sve stadije raka dojke. Daljnji se napredak očekuje od uvođenja dodatnih ciljanih bioloških terapija u shemu liječenja i boljom biološkom klasifikacijom bolesti koja se temelji na obilježjima genske ekspresije prema kojima bi bilo moguće dati prognozu i predvidjeti odgovor na kemoterapiju. U ovom preglednom članku ukratko su opisane glavne spoznaje na tu temu, raspravlja se o danas preporučljivim mogućnostima kemoterapijskog liječenja te pojašnjava u kojem smjeru će se kretati istraživanja u budućnosti.

KLJUČNE RIJEČI: *rak dojke, kemoterapija, ciljana biološka terapija*

INTRODUCTION

Breast cancer is a major health concern affecting millions of women around the globe: more than one million new cases were diagnosed in 2002 worldwide (1). It is the most common cause of cancer death among European women. Improvements in early diagnosis and in treatment have resulted in improved survival of all subsets of breast cancer patients. During the last few years progress in breast cancer (BC) chemotherapy (CT) was made through the incorporation of taxanes into treatment schedules, the manipulation of dose-size and dose-density of our most active cytotoxic agents and recently, through the incorporation of trastuzumab into treatment schedules for all stages of BC.

THE ROLE OF TAXANES

The addition of taxanes to anthracycline-based chemotherapy resulted in higher disease control rates and prolonged progression-free sur-

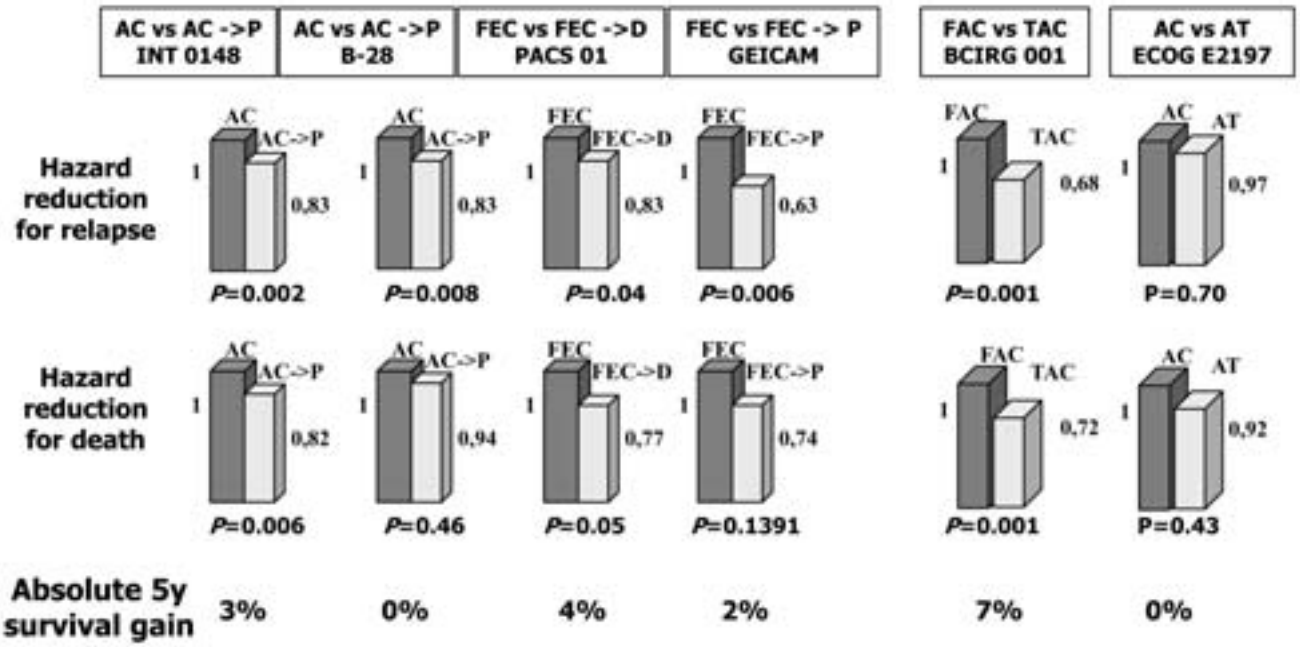

Figure 1. Taxane benefits in six large adjuvant trials with more than 4.5 year follow-up

vival of patients with metastatic disease. However, the clear guidelines for optimal use of taxanes in metastatic setting are still lacking. According to the results of the meta- analysis performed in 3953 patients enrolled in 11 trials the incorporation of taxanes alone or in combination with anthracyclines in the first line therapy for metastatic breast cancer (MBC) resulted in better objective response rate and time to progression but in increased overall survival (2). Since the goal of therapy in MBC is still palliation of symptoms with possible prolongation of life, the use of more toxic taxane-anthracycline combinations should be judged on the individual basis for each patient, taking into consideration patient's age, performance status, extend of disease and previous therapy.

The addition of taxanes to anthracycline-based chemotherapy resulted in significantly lower risk of relapse in 6 large prospective trials with more than 4.5 year follow-up (INT 0148, NSABP B-28, BCIRG 001, PACS 01, GEICAM, and ECOG E2197) (3-8). However, in only three out of six trials significant survival gain of 3 to 7% was observed (3, 5, 6) (Figure 1), with most of the trials showing that the benefit of taxanes may be confined to HR-low tumors . Although many would argue that there is now "level 1" evidence that incorporation of taxanes into A-based regimens improves survival, some discomfort persists in view of the suboptimal control arm in three out of four trials; of note, only the PACS 01 trial used a proper control arm, consisting in six cycles of FEC 100. Subset analysis of INT 0148 showed that the benefit of adding taxane to anthracycline is confined to the subset of ER-low tumors. Interestingly, the only trial showing a strong effect of the taxane regimen in ER-positive patients is BCIRG trial, which is also the only one with reported higher rate of amenorrhea in taxane containing arm. The threshold for using anthracycline and taxane-based regimens is lower for women with ER-absent or low tumors or showing other aggressive biological features. Preference should be given to regimens that have been subjected to a 5 year follow-up: namely the sequence of AC→ paclitaxel or docetaxel, the sequence of FEC→ docetaxel and the TAC regimen. In the large E1199 adjuvant trial, comparing AC followed by either paclitaxel or docetaxel, every 3 week or weekly, no significant difference in terms of DFS benefit was observed among two taxanes (9). So far, none of these treatment options seems to be associated with an increased risk of leukemia or myelodysplastic syndrome or congestive heart failure. Long-term functional

cardiac assessment and cognitive function assessment, however, are still lacking.

DOSE - DENSITY AND DOSE-SIZE MODIFICATIONS

Dose dense application of chemotherapeutic agents and "metronomic" chemotherapy, which refers to frequent administration of small doses of cytotoxic drugs are two elegant concepts under active evaluation. In CALGB 9741 trial the dose-dense application of AC→ paclitaxel with GCSF support resulted in a significant risk reduction for relapse (RR=0.80; 95% CI= 0.67-0.96), but not for death (RR= 0.85; 95% CI= 0.68-1.05); the subset analyses according to HR revealed that the benefit is confined to ER negative tumors (10). So far, no major differences in toxicity between the dose dense and standard schedules have been reported. However, before any major changes in standards of care occur, these results should be independently confirmed and all efforts should be made in order to identify the subgroups of patients most likely to benefit from the expensive dose-densification approach. More frequent, weekly administration of paclitaxel proved superior to once-every 3-weeks administration in CALGB9840 metastatic disease trial (11) and in the recently reported adjuvant INT E1199 trial (9).

INCORPORATION OF TRASTUZUMAB

Not surprisingly, the addition of targeted therapy, namely trastuzumab, revolutionized the results of systemic therapy in BC. In metastatic disease the addition of trastuzumab to taxanes resulted in superior response rates, time to progression and survival (12, 13). In M77001 trial a significant improvement in median survival of 6, 5 months was achieved by the addition of trastuzumab to docetaxel (13). Four large multicenter adjuvant trials: NSABP B31/ NCCTG N9831, HERA, BCIRG 006 and Fin-HER, uniformly confirmed a huge benefit of trastuzumab when combined with chemotherapy in early BC (14-18). With a very brief follow-up of 24 to 38 months, all four trials showed highly significant reductions in the risk of recurrence (with hazard ratios of relapse ranging from 0,42 to 0,61), with significant prolongation of overall survival already observed in the joint analysis of NSABP B31 and NCCTG N9831 trial and in the HERA trial (14,16). The major concern goes to cardiotoxicity, the rate of which was between 0.5 -3.4% in adjuvant trastuzumab trials (Table 2). Cardiotoxicity was found to be higher in older women, women with pre-existing cardiac diseases and in women with previous anthracycline exposure or concomitant taxane-trastuzumab therapy. Despite the exiting results obtained with adjuvant

Table 1.

RESULTS OF ADJUVANT TRASTUZUMAB TRIALS

NSABP B31/NCCTG 9831		
DDFS	HR = 0.47	2p = 8 X 10 -10
OS	HR = 0.67	2p = 0.015
HERA		
DFS	HR = 0.63	p < 0.0001
OS	HR = 0.63	p < 0.0051
BCIRG 006		
AC → TH		
DFS	HR = 0.49	p < 0.0001
OS	ND	
TCH		
DFS	HR = 0.61	p < 0.0001
OS	ND	
Fin-HER		
RFS	HR = 0.42	p = 0.01
OS	HR = 0.41	p = 0.07

DDFS: Distant-disease free survival; RFS: Relapse-free survival; DFS: Disease-free survival; OS: Overall survival; HR= Hazard Ratio.

Table 2.

CARDIOTOXICITY IN ADJUVANT TRASTUZUMAB TRIALS

Trial, Regimen	No. of women at risk	Class 3-4 CHF NYHA No. of pts (%)
HERA		
Observation	1693	0 (0)
T X 1 y	1694	9 (0.5)
NSABP B31		
AC → P	872	3 (0.3)
AC → P + T	864	30 (3.4)
NCCTG N9831		
AC → P	807	0 (0)
AC → P + T	808	20 (2.4)
AC → P → T	842	12 (1.4)
BCIRG 006		
AC → D	1050	3 (0.2)
DCb + T	1056	4 (0.3)
AC → D + T	1068	17 (1.5)

T: trastuzumab; A: anthracycline, C: cyclophosphamide; P: paclitaxel; D: docetaxel; Cb: carboplatin

trastuzumab, there are still several unresolved questions about the optimal use of trastuzumab in the adjuvant setting, such as the best modality of trastuzumab administration, the duration of therapy, the long-term efficacy and toxicity.

FUTURE DIRECTIONS

Further progress can be achieved by the introduction of new chemotherapeutic agents and new targeted drugs and by the incorporation of individualized treatment strategies based on molecular markers of prognosis and response to therapy in our daily practice. As the result of a major shift on thinking, in 2005 St. Gallen consensus the risk of relapse is no more the major determinant of treatment decision (19); it comes second after determination "endocrine-responsiveness" of each particular patient. This paradigm shift comes from the growing evidence that endocrine-nonresponsive, i.e. hormone receptor-negative patients benefit much more from chemotherapy (20) and that there is a subset of HR-rich patients with excellent prognosis when treated by hormonal therapy alone. There are preliminary data showing that gene expression profiles and signatures might be an excellent predictor for prognosis and response to each particular therapy, the hypotheses being currently tested in prospective manner in the large MINDACT trial; but there is still a long way to go before we will be able to tailor therapy in each particular patient.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. Cancer J Clin 2005; 55: 74-108.
2. Piccart M, Burzykowski T, Buyse M, et al. Meta-analysis of taxanes alone or in combination with anthracyclines versus non taxane-based regimens as first-line therapy of patients with metastatic breast cancer: a lesson from the past and a message for the future. Eur J Cancer 2006; 4 (Suppl 2): 178 (Abstr 434).
3. Henderson CI, 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: 976-83.
4. Mamounas EP, Bryant J, Lembersky BC et al. Paclitaxel following doxorubicin/cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. Proc Am Soc Clin Oncol 2003; 22:4 (Abstr 12).
5. Martin M, Pienkowski T, Mackey J et al. TAC improves disease free survival and overall survival over FAC in node positive early breast cancer patients, BCIRG 001: 55 months follow-up. Proc SABCS 2003; 82:1 (Abstr 43).
6. Roché H, Fumoleau P, Spielmann M, et al. Five years analysis of the PACS 01 trial: 6 cycles of FEC100 vs 3 cycles of FEC100 followed by 3 cycles of docetaxel for the adjuvant treatment of node positive breast cancer. Proc SABCS 2004; 88:1 (Abstr 27).
7. Martin M, Rodriguez-Lescure A, Ruiz A, et al. Multicenter, randomized phase III study of adjuvant chemotherapy for node positive breast cancer comparing 6 cycles of FE90C versus 4 cycles of Fe90C followed by 8 weekly paclitaxel administration: interim efficacy analysis of GEICAM 9906 trial. Proc SABCS 2005; (Abstr 39).
8. Goldstein L, OžNeill A, Sparano J, et al. E2197: Phase III AT (doxorubicin/docetaxel) vs. AC (doxorubicin/cyclophosphamide) in the adjuvant treatment of node positive and high risk node negative breast cancer. Proc Am Soc Clin Oncol 2005; (Abstr 512).
9. Sparano JA, Wang M, Martino S, et al. Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node-positive or high-risk node-negative breast cancer: results of North American Breast Cancer Intergroup trial E1199. Proc SABCS 2005; (Abstr 48).
10. Hudis C, Citron M, Berry D, et al. Five year follow-up of INT C9741: dose-dense chemotherapy is safe and effective. Proc SABCS 2005; (Abstr 41).
11. Seidman AD, Berry D, Cirrincione C, et al. CALGB 9840: Phase III study of weekly paclitaxel via 1-hour infusion versus standard 3h infusion every third week in the treatment of metastatic breast cancer, with trastuzumab for HER2 positive MBC and randomized for trastuzumab in HER2 normal MBC. Proc Am Soc Clin Oncol 2004; 22:6 (Abstr 512).
12. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001; 344: 783-92.
13. Marty M, Cognetti F, Maraninchi D, et al. Randomized Phase II Trial of the Efficacy and Safety of Trastuzumab Combined With Docetaxel in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer Administered As First-Line Treatment: The M77001 Study Group. J Clin Oncol 2005; 23: 4265-74.
14. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005;353:1673-84.

15. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005;353:1659-72.
16. Smith IE, on behalf of HERA.ASCO 2006: Clinical Science Symposium.
17. Slamon D, Eiermann W, Robert N, et al. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (ACT) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (ACTH) with docetaxel, carboplatin and trastuzumab (TCH) in her2 positive early breast cancer patients: BCIRG 006 study. Proc SABCS 2005;94:5 (Abstr 1) .
18. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al. Adjuvant docetaxel or vinorelbin with or without trastuzumab for breast cancer. N Engl J Med. 2005; 354:809-20.
19. Goldhirsch A, Glick JH, Gelber RD, et al. Meeting highlights: international expert consensus on the primary therapy of early breast cancer 2005. Ann Oncol 2005; 16(10):1569-83.
20. Berry DA, Cirrincione C, Henderson IC et al. Effects of improvements in chemotherapy on disease-free and overall survival of estrogen-receptor negative, node-positive breast cancer: 20-year experience of the CALGB U.S. Breast Intergroup. Proc SABCS 2004 88:1 (Abstr 29)

Author's address: Tanja Čufer, MD, PhD, Institute of Oncology, Zaloška 2, 1000 Ljubljana / Slovenia;
Phone: +386 1 5879 220; Fax: +386 1 5879 305;
e-mail: tcufer@onko-i.si