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Adjuvant Chemotherapy of Early Stage Breast Cancer in Community-based Cancer Treatment Fields: CMF Compared with Anthracycline/Taxane-based Regimens

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Abstract

Background: The mortality rate from breast cancer has declined in recent years. The combination of cyclophosphamide, methotrexate, and 5-fluorouracil, as a pioneer adjuvant chemotherapy for breast cancer, followed by the introduction of anthracycline/taxane-based regimens have resulted in favorable outcomes for early-stage breast cancer. The current study aimed to compare breast cancer treatment outcomes between the cyclophosphamide, methotrexate, and 5-fluorouracil and anthracycline/taxane-based regimens.

Methods: In this cohort study, we extracted medical records of 1098 breast cancer patients who referred to oncology centers affiliated with Mashhad University of Medical Sciences from 1991 to 2011. We included patients with Stages I and II invasive cancers who were candidates for systemic chemotherapy. Patients were divided into the cyclophosphamide, methotrexate, and 5-fluorouracil or anthracycline/taxane-based arms. We considered median event-free survival, median overall survival, 5- and 10-year event-free survival, and 5- and 10-year overall survival as the study endpoints.

Results: The cyclophosphamide, methotrexate, and 5-fluorouracil arm had a median event-free survival of 190 months, with a 5-year event-free survival of 77% and 10-year event-free survival of 61%. The anthracycline/taxane arm had a median event-free survival of 212 months, a 5-year event-free survival of 74%, and a 10-year event-free survival of <61%. There were no significant differences between the two arms (P=0.3). The cyclophosphamide, methotrexate, and 5-fluorouracil arm had a 5-year overall survival of 87% and a 10-year overall survival of 76%, whereas the anthracycline/taxane-based arm had a 5-year overall survival of 83% and 10-year overall survival of <76% (P=0.2). Stage and estrogen receptor status significantly affected outcome in univariate analysis; however, the only important prognostic factor in multivariate analysis was disease stage.

Conclusion: Similar effectiveness exists between cyclophosphamide, methotrexate, and 5-fluorouracil and anthracycline/taxane-based regimens in terms of adjuvant treatment outcome for early-stage breast cancer. We can be confident that cyclophosphamide, methotrexate, and 5-fluorouracil is more favorable due to the infrequent adverse effects.

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Introduction

Since 1990, the death rate from breast cancer has decreased in the United States by 24% with similar reductions observed in other countries.[1] Mathematical models suggest that both the adoption of screening mammography and availability of adjuvant chemotherapy and tamoxifen have contributed approximately equally to this improvement.[2]

A number of adjuvant chemotherapy regimens are being developed where efficacy is the pivotal point and driving force for innovation of newer regimens. This can translate to decreases in the recurrence and mortality of breast cancer.

Adjuvant systemic treatment is recommended if a relevant reduction of the estimated risk of recurrence and death can be expected with an acceptable level of treatment-related adverse effects. A multiplicity of chemotherapy regimens is acceptable for adjuvant treatment of breast cancer.[3,4] Adjuvant chemotherapy that consists of multiple cycles of a combination of drugs is well established as an important strategy to lower the risk of breast cancer recurrence and improve survival in most cases.[5] Standard chemotherapy regimens are superior to less intensive regimens, even in elderly patients.[6]

Today, combinations of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF), as the pioneer of adjuvant chemotherapy for breast cancer, have been supplanted by 'third-generation' regimens that contain anthracyclines and/or taxanes. Numerous trials in treatment of early stage breast cancer introduced new chemotherapy protocols and combinations of anthracycline /taxane (A/T) based regimens. These studies mostly reported improved clinical outcome of early breast cancer treatment. However, the variations in patient compliance in clinical trials has not been specified. Strict treatment and patient selection are both types of biases that occur in clinical trials, whether these regimens for treatment of patients outside of clinical trials are superior compared with the older regimen of CMF has not been specified.

Complications attributed to these regimens differ; many patients, because of adverse effects of alopecia, cardiac toxicity, and neuropathy prefer treatment with CMF since these complications are either not experienced or less encountered. This issue is especially important in our community where patients prefer to hide their disease. Preservation of their hair enables such patients to reach this purpose. This study assesses intravenous CMF versus A/T based regimens to determine probable differences in outcome of two comparable groups of patients. We intend to find the feasibility and conditions for replacement of A/T based regimens with intravenous CMF according to patient choice and clinical conditions.

Materials and Methods

This study was based on a historical cohort. We extracted information of breast cancer patients who attended the academic oncology centers at Omid, Emam Reza, and Ghaem Hospitals affiliated with Mashhad University of Medical Sciences from 1991-2011. All stages I and II invasive breast cancer patients considered candidates for systemic chemotherapy were included. They had received at least one cycle of the determined regimen. All other stages as well as stage-unclassified diseases were excluded.

We did not restrict the study based on dose, schedule and modifications to any of the regimens. All variations of CMF that included oral or intrvenous as well as 3- or 4-week courses were included. All protocles which included any kind of anthracyclines or taxanes in combination or subsequent to other regimens, even CMF, were considered in the A/T arm. These regimens included doxorubicin-cyclophosphamide (AC); doxorubicin-cyclophosphamide-5-fluorouracil (CAF); sequential CMF and doxorubicin; sequential CMF and CAF; epirubicin-cyclophosphamide-5-fluorouracil (ECF); sequential CMF and ECF; docetaxel-doxorubicin-cyclophosphamide (TAC); CAF/paclitaxel; CAF/docetaxel; ECF/paclitaxel; ECF/docetaxel; AC/paclitaxel; and AC/docetaxel. At the time of patient enrollment in this cohort study, no patient received adjuvant anti-HER2 therapy.

The potential prognostic factors of age, histological grade based on modified Bloom-Richardson scoring,[7] pathological and/or clinical stage based on AJCC version 2010,[8] ER status, HER2 status, and potential intervening treatment factors in the outcome from radiotherapy and hormone therapy, in addition to the type of chemotherapy were surveyed. Tumors were considered ER positive if at least 1% of the examined cells had ERs according to the immuno-histochemistry (IHC) analysis.[9,10] We based the criteria for HER2 according to IHC: 0 and 1+ (negative), 2+ (borderline), and 3+ (positive).[11]

Statistical analysis

We considered median event-free survival (EFS), median overall survival (OS), 5- and 10-year EFS, and 5- and 10-year OS to be the study endpoints. Event-free survival was defined from the date of diagnostic biopsy or surgery until local or distant recurrence, onset of a second primary cancer, or death. Overall survival was measured from the date of diagnostic biopsy or surgery until death. We used the chi-square tset to compare distribution of different variables among the subgroups; Kaplan-Meier[12] analyzed EFS and OS for these different groups of regimens. We used the log rank test to independently investigate the effect of each variable (age, histologic grade, disease stage, nodal status, and ER and HER2 status) on EFS and OS. Univariate and multivariate Cox regression analyses were used to find any significant prognostic factor in the population under study. *P*-values≤0.05 were considered significant.

Results

We included 1098 breast cancer patients in this study, 519 cases in the CMF arm and 579 cases in the A/T arm. The mean age of the patients was 48.4 years (range: 22 to 85 years). The median follow-up time was 52.5 months (range: 1 to 336 months) overall. The median follow-up was 63 months in the CMF arm, and 48 months in the A/T arm.

The median EFS for the CMF group was 190 months (95% CI: 156.34-220.46). In this group, the 5-year EFS was 77%, whereas the 10-year EFS was 61%. The median EFS for patients who received A/T based chemotherapy was 212 months (95% CI: 0). Patients in this group had a 5-year EFS of 74% and 10-year EFS of <61%. No significant differences existed between the two groups (*P*=0.3).

The median OS was not reached for both groups. Patients in the CMF arm had a 5-year OS of 87% and 10-year OS of 76%; patients in the A/T arm had a 5-year OS of 83% and less than 76% for 10-year OS (*P*=0.2; Figures 1, 2).

Univariate regression analysis indicated that

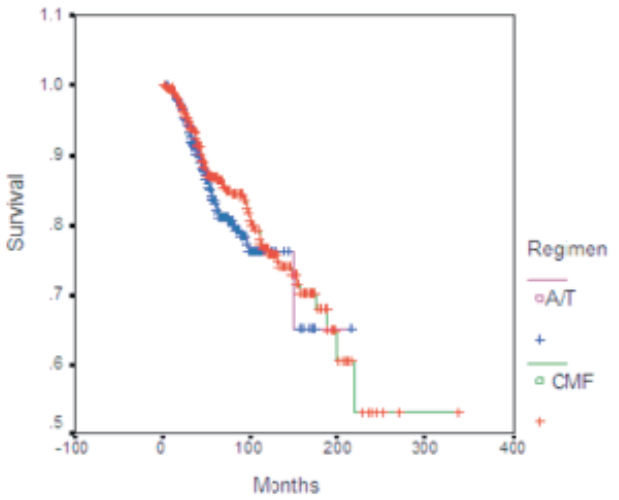

Figure 1. Diagram of overall survival (OS) analysis for cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) versus anthracycline/taxane (A/T) groups.

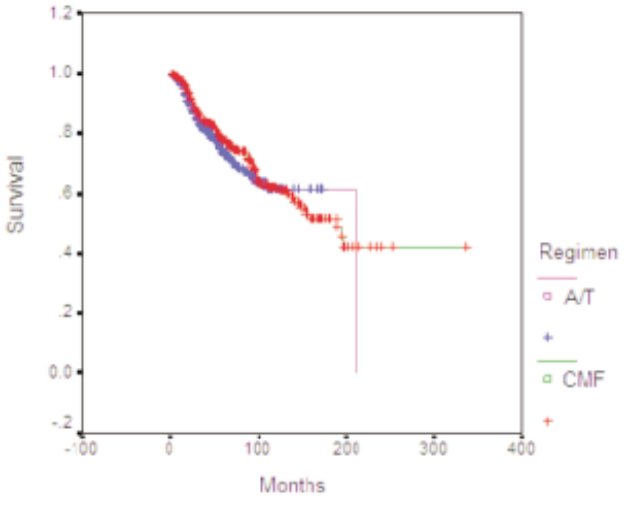

Figure 2. Diagram of event-free survival (EFS) analysis for cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) versus anthracycline/taxane (A/T) groups.

Table 1. Univariate regression analysis of potential prognostic factors.

Factors	Number (%)	HR	*P*-value
Age			
≤35 years	125 (11.5)	0.3	0.6
>35 years	965 (88.5)		
Histological grade			
1, 2, unknown	937 (85.3)	0.02	0.9
3	161 (14.7)		
Estrogen receptor			
Negative	369 (33.6)	4.08	0.04
Positive/unknown	729 (66.4)		
HER2 receptor			
Negative/unknown	960 (87.4)	0.6	0.4
Positive	138 (12.6)		
Stage			
I	157 (14.3)	4	0.04
II	941 (85.7)		
Chemotherapy regimen			
CMF	519 (47.3)	1.31	0.3
A/T	579 (52.7)		
Hormone therapy			
Yes	633 (60)	3.4	0.06
No	421 (40)		
Radiotherapy			
Yes	8267(22.6)	0.3	0.3
No	241 (87.4)		

CMF: Cyclophosphamide, methotrexate, and 5-fluorouracil

stage and ER status significantly affected outcome. Hormone therapy (HR=0.64, *P*=0.06) had an intermediate effect. HER2 status, age, histological grade, and radiotherapy treatment factors, as well as the type of chemotherapy had no prognostic efficacy (Table 1). Cox regression results indicated that the only important prognostic factor in this study was stage.

We took into consideration the wide heterogeneity among the two treatment groups and performed a sub-analysis for potential intervening factors. Comparisons between the two treatment

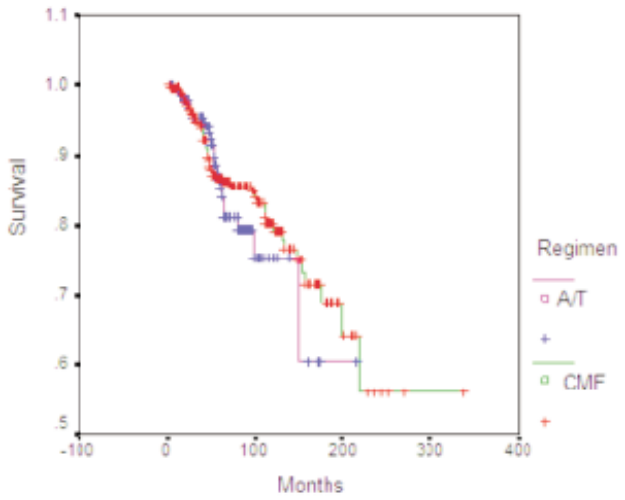

Figure 3. Overall survival (OS) in cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) versus ADR/Taxane arms amongst patients >35 years, HER2 negative or unknown, ER positive or unknown, and grades 1, 2, or unknown.

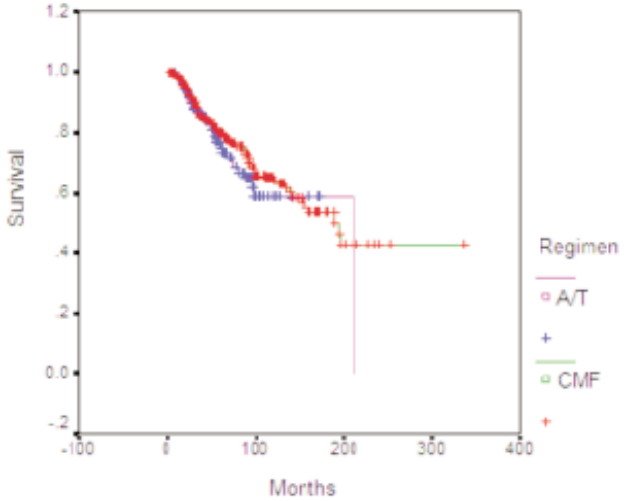

Figure 4. Event-free survival (EFS) in cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) versus ADR/Taxane arms in patients >35 years, HER2 negative or unknown, ER positive or unknown, and grades 1, 2 or unknown.

Table 2. Survival rates of the CMF and A/T treatment groups based on potential interventional factors.

Risk factor	Treatment arms	Number	Median OS (months)	Median EFS (months)	5-year OS (%)	5-year EFS (%)	10-year OS (%)	10-year EFS (%)	*P*-value
Age (years)									
≤35									
	CMF	44	190	NR	94	74	69	55	0.2
	A/T	81	NR	NR	75	-	-	-	
>35									
	CMF	470	NR	190	85	77.7	76.5	51.7	0.5
	A/T	494	NR	NR	84	75	-	-	
Grade									
1, 2, unknown									
	CMF	483	NR	190	87	78	76.5	-	0.3
	A/T	453	NR	212	82	74	-	-	
3									
	CMF	36	NR	148	78	69	-	-	0.7
	A/T	125	NR	NR	85	73	-	-	
Estrogen Receptor									
Negative									
	CMF	120	NR	148	81	73	68	-	0.3
	A/T	248	NR	NR	82	72	-	-	
Positive/unknown									
	CMF	399	NR	194	87.5	78.5	77.5	62	0.7
	A/T	340	NR	NR	83	75	-	-	
HER2 Receptor									
Negative/unknown									
	CMF	500	NR	190	86	77	76	61	0.1
	A/T	459	NR	NR	83.3	73	-	-	
Positive									
	CMF	19	NR	144	76	-	-	-	0.3
	A/T	119	NR	NR	80	-	-	-	
Stage									
I									
	CMF	98	NR	NR	91	86.4	-	-	0.6
	A/T	50	NR	NR	90	82	-	-	
II									
	CMF	421	NR	190	85	75	74	58	0.4
	A/T	519	NR	NR	81	72	-	-	
Hormone therapy									
No									
	CMF	189	NR	196	84	73	74.5	-	0.5
	A/T	231	150	NR	80	71	-	-	
Yes									
	CMF	317	NR	190	87.5	79	75	-	0.7
	A/T	316	NR	NR	85	78	-	-	
Radiotherapy									
No									
	CMF	126	NR	148	81	67	65	-	0.7
	A/T	115	NR	NR	82	70	-	-	
Yes									
	CMF	378	NR	194	87.5	79.5	77	63.5	0.1
	A/T	448	NR	NR	83.3	74.5	-	-	

A/T: Anthracycline/taxane based chemotherapy; CMF: Cyclophosphamide, methotrexate, and 5-fluorouracil; OS: Overall survival; EFS: Event-free survival; NR: Not Reached

groups in stage I versus stage II, ER positive versus ER negative or unknown, and hormone therapy versus no hormone therapy showed no differences between the CMF versus A/T arms (Table 2).

Cases younger than 35 years, HER2 positive, ER negative, and grade 3 which also were less engaged in the CMF group were set aside. Analysis showed no significant differences in outcome between CMF with a 5-year OS of 86% and 5-year EFS of 79.5% versus A/T chemotherapy with a 5-year OS of 85% and 5-year EFS of 75.7% among patients older than 35 years, HER2 negative/unknown, ER positive/unknown, and grades 1 or 2/unknown (Figures 3, 4).

Discussion

This study surveyed patients treated in university hospital clinics and analyzed the two most comparable groups of patients treated with different regimens of CMF and A/T. We took into consideration the important differences in treatment-related complications for both types of treatments and the willingness of our patients to receive the CMF regimen, particularly because of sparing alopecia. We sought to determine by the results of this study if a significant difference existed in treatment outcome. Relatively crude analysis indicated that CMF regimens with a 5-year EFS of 77% and 5-year OS of 86.4% compared to A/T regimens with a 5-year EFS of 74%, and 5-year OS of 83% did not significantly differ. However, most patients with potentially adverse prognostic factors received A/T protocols whereas those with better factors received CMF. Therefore, it was necessary to examine the two most comparable groups to avoid selection bias. Analysis again showed no significant differences between the two treatment groups after refinement of these intervening factors. Univariate analysis results indicated that ER status and disease stage were significant intervening factors. Multivariate analysis showed that disease stage was the only independent prognostic factor. No other potential risk factors, including the type of chemotherapy, were shown to be important. Few patients with the potential adverse prognostic factors of young age, HER2 positive status, ER negative status, and histologic grade 3 were included in the CMF arm. Therefore, we could not conclude that CMF regimens were not inferior compared with A/T regimens, at least in these groups of patients. However, the two treatment arms were considered equally effective among patients older than 35 years, ER positive or unknown, HER2 negative or unknown, and grades 1and 2 or unknown.

A cohort randomized study by Bonadonna et al. examined a group of invasive breast cancer patients. They had a median follow-up of 28.5 years and reported that adjuvant CMF caused a significant reduction in the relative risk of relapse and death compared with surgery alone. CMF proved beneficial in all subgroups of patients in terms of prognostic factors.[13]

Hutchins et al. conducted a randomized clinical trial (RCT) with high risk and node-negative breast cancer patients. CAF showed no improvement in disease-free survival (DFS) compared to CMF. CAF produced a negligible effect on OS.[14]

However, an Oxford Overview of multiple clinical trials established the superiority of anthracycline-based chemotherapy over CMF-based chemotherapy. According to their report, the anthracycline-containing regimens showed a statistically significant Improvement of 3% in 5-year survival.[15]

The last St. Gallen Consensus stated that patients with luminal A-like disease could be treated with any of the standard regimens that included CMF and AC. The same regimen could also be used in patients with low burden luminal B disease. Regimens used for high burden luminal B-like disease should generally comprise anthracyclines and taxanes, which was almost similar to other breast cancer subtypes.[14]

Other studies currently recommend that a CMF chemotherapy regimen may be a good option in elderly patients and those with cardiac contraindications, while anthracyclines may be recommended for most patients, especially HER2 positive patients.[6,16]

Improvement in disease survival was a major advantage for the introduction of taxanes as early-stage breast cancer treatment. Taxanes significantly improved outcomes in women with node-positive breast cancer.[17]

In 2006, Bria et al. conducted a pooled analysis of phase III trials. They evaluated the advantages of taxane-based adjuvant chemotherapy. The authors reported absolute benefits of 3.3% to 4.6% for DFS and 2.0% to 2.8% for OS in favor of taxenes. The numbers of patients needed to be treated in order to one patient benefit were 23 to 31 for DFS and 36 to 50 for OS.[18]

A meta-analyses by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) evaluated the efficacy of different adjuvant chemotherapy regimens for breast cancer. In the group of taxane regimens, patients that received four separate cycles of a taxane in addition to a constant background chemotherapy regimen had an 8-year breast cancer mortality of 21.1% compared to 23.9% in the control group (2p=0.0005).[19]

In accordance with current study, a retrospective multicenter study of community-based adjuvant chemotherapy for breast cancer found no significant differences regarding survival among CMF, anthracycline-based, and anthracycline/taxane-based regimens in N0 and 1-3 lymph node positive (N1) diseases.[20]

Several retrospective analyses suggested that taxanes might be particularly effective in patients with ER-negative or HER2-positive early-stage breast cancer. Chemotherapy regimens that combined anthracyclines and taxanes have been mainly investigated in patients with node-positive breast cancer. Some studies proposed that the sequential use of these treatments might be superior to concomitant use of anthracyclines and taxanes.[21,22]

Selection of an appropriate chemotherapy regimen is complicated due to the numerous contributing molecular factors that influence the basis of the decision-making process. These factors include the rate of hormone receptor positivity, status of HER2 receptors, histological grade, and clinicopathological factors.

On the other hand, patients` preferences and treatment complications are of significant importance when the response to chemotherapy is moderate, or when the absolute benefit of the therapeutic regimen is low. This may be the reason that anthracyclines and taxanes are not preferred treatments in patients with cardiac diseases and neuropathic disorders, respectively.

Alopecia is an extremely concerning, common adverse effect of antineoplastic treatment which becomes increasingly noticeable six weeks after the beginning of chemotherapy. Hair will grow back to baseline within three months of treatment cessation.[23] Recently, permanent and severe alopecia has been reported as a complication of an FEC100-docetaxel regimen used for breast cancer.[24,25]

According to previous studies, cardiotoxicity is also a possible complication of chemotherapy, especially in patients with a previous history of heart disease. These include arrhythmias, dilated cardiomyopathy, angina, or myocardial infarction. The most common implicated agents include anthracyclines and related compounds.[26] The symptoms may be initially subclinical and possibly result in congestive heart failure.[27]

In addition to these complications, patients treated with paclitaxel have complained of sensory neuropathy, especially numbness and tingling, which peaked at the third day. A more severe pain experienced with the first dose of paclitaxel has indicated a greater risk for chronic neuropathy.[28] Paclitaxel-induced myalgia and arthralgia are associated with individual doses.[29]

This survey is important because the complications of these two regimens are different. Numerous patients prefer the CMF regimen due to infrequent adverse effects such as alopecia, cardiac toxicity, and neuropathy.

We must consider some limitations of this study. This was a retrospective, nonrandomized study. In order to find a survival difference of 2%-3%, it was necessary to include more than 3000 patients, which was far from our accrual rate in this study. The different arms of the study were

not exact in terms of the patients' characteristics. The median follow-up of 52.5 months was not long enough. Breast cancer patients should be followed for longer time periods. This was not a randomized clinical trial; however, the aim of the study was to examine the results of different chemotherapy regimens out of clinical trials and in a community-practice setting with a variety of patients, where, rough prescription of schedules and doses are not possible compared to clinical trials.[1]

Conclusion

The CMF regimen had similar effectiveness with anthracycline and taxane based regimens on outcomes of adjuvant treatment for early stage breast cancer in a community-based practice. However, elevated risk features such as high histological grade, HER2 positive status, ER negative disease, and perhaps younger patients show that this treatment protocol probably is not the preferred regimen, although it could not translate to its inferiority. We can say with confidence that the CMF chemotherapy regimen which is more favorable for most patients due to its toxicity profile is a potent cost effective treatment in a large group of early breast cancer patients.

Conflict of Interest

No conflict of interest is declared

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References

1. Burstein, HJ; Harris, JR; Morrow, M. Malignant tumors of the breast. In: Devita, VT; Theodore, SL; Rosenberg, SA, editors. Devita, Helman, and Rosenberg's cancer principles & practice of oncology. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2011.p. 1431-1433.
2. Berry DA, Cronin KA, Plevritis SK, Fryback DG, Clarke L, Zelen M, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med.* 2005;353(17):1784-92.
3. Aebi S, Davidson T, Gruber G, Cardoso F; ESMO Guidelines Working Group. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2011;22 Suppl 6:vi12-24.
4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Clarke M, Coates AS, Darby SC, Davies C, Gelber RD, et al. Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer: patient-level meta-analysis of randomised trials. *Lancet.* 2008;371(9606):29-40.
5. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Peto R, Davies C, Godwin J, Gray R, Pan HC, et al. Comparisons between different poly-chemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet.* 2012;379(9814):432-44.
6. Muss HB, Berry DA, Cirrincione CT, Theodoulou M, Mauer AM, Kornblith AB, et al. Adjuvant chemotherapy in older women with early-stage breast cancer. *N Engl J Med.* 2009;360(20):2055-65.
7. Bloom HJ, Richardson WW. Histological grading and prognosis in breast cancer; a study of 1409 cases of which 359 have been followed for 15 years. *Br J Cancer.* 1957;11(3):359-77.
8. Edge, S; Byrd, D; Compton, C; Fritz, A; Greene, F; Trotti, A. Cancer staging manual. American Joint Committee on Cancer (AJCC). 7th ed. New York: Springer; 2010.
9. Hammond ME, Hayes DF, Wolff AC. Clinical Notice for American Society of Clinical Oncology-College of American Pathologists guideline recommendations on ER/PgR and HER2 testing in breast cancer. *J Clin Oncol.* 2011;29(15):e458.
10. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *Arch Pathol Lab Med.* 2010;134(6):907-22.
11. Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *Arch Pathol Lab Med.* 2014;138(2):241-56.
12. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958; 53(282):457-81.
13. Bonadonna G, Moliterni A, Zambetti M, Daidone MG, Pilotti S, Gianni L, et al. 30 years' follow up of

randomised studies of adjuvant CMF in operable breast cancer: cohort study. *BMJ.* 2005;330(7485):217.
14. Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol.* 2015;26(8):1533-46.
15. 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(9472):1687-717.
16. Hutchins LF, Green SJ, Ravdin PM, Lew D, Martino S, Abeloff M, et al. Randomized, controlled trial of cyclophosphamide, methotrexate, and fluorouracil versus cyclophosphamide, doxorubicin, and fluorouracil with and without tamoxifen for high-risk, node-negative breast cancer: treatment results of Intergroup Protocol INT-0102. *J Clin Oncol.* 2005;23(33):8313-21.
17. Henderson IC, Berry DA, Demetri GD, Cirrincione CT, Goldstein LJ, Martino S, 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(6):976-83.
18. Bria E, Nistico C, Cuppone F, Carlini P, Ciccarese M, Milella M, et al. Benefit of taxanes as adjuvant chemotherapy for early breast cancer: pooled analysis of 15,500 patients. *Cancer.* 2006;106(11):2337-44.
19. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Peto R, Davies C, Godwin J, Gray R, Pan HC, et al. Comparisons between different poly-chemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet.* 2012;379(9814):432-44.
20. Schwentner L, Wöckel A, König J, Janni W, Blettner M, Kreienberg R, et al. Assessing the impact of CMF-like/Anthracycline-based/Anthracycline-Taxane-based/ dose-dense chemotherapy in dependency of positive axillary lymph nodes/hormone receptor-status/grading/T-stage on survival - A retrospective multi-centre cohort study of 3677 patients receiving adjuvant chemotherapy. *Eur J Cancer.* 2014;50(17):2905-15.
21. Francis P, Crown J, Di Leo A, Buyse M, Balil A, Andersson M, et al. Adjuvant chemotherapy with sequential or concurrent anthracycline and docetaxel: Breast International Group 02-98 randomized trial. *J Natl Cancer Inst.* 2008;100(2):121-33.
22. Swain SM, Jeong JH, Geyer CE Jr, Costantino JP, Pajon ER, Fehrenbacher L, et al. Longer therapy, iatrogenic amenorrhea, and survival in early breast cancer. *N Engl J Med.* 2010;362(22):2053-65.
23. Kanti V, Nuwayhid R, Lindner J, Hillmann K, Stroux A, Bangemann N, et al. Analysis of quantitative changes in hair growth during treatment with chemotherapy or tamoxifen in patients with breast cancer: a cohort study. *Br J Dermatol.* 2014;170(3):643-50.
24. Kluger N, Jacot W, Frouin E, Rigau V, Poujol S, Dereure O, et al. Permanent scalp alopecia related to breast cancer chemotherapy by sequential fluorouracil/epirubicin/cyclophosphamide (FEC) and docetaxel: a prospective study of 20 patients. *Ann Oncol.* 2012;23(11):2879-84.
25. Prevezas C, Matard B, Pinquier L, Reygagne P. Irreversible and severe alopecia following docetaxel or paclitaxel cytotoxic therapy for breast cancer. *Br J Dermatol.* 2009;160(4):883-5.
26. Smith LA, Cornelius VR, Plummer CJ, Levitt G, Verrill M, Canney P, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. *BMC Cancer.* 2010;10:337.
27. Barrett-Lee PJ, Dixon JM, Farrell C, Jones A, Leonard R, Murray N, et al. Expert opinion on the use of anthracyclines in patients with advanced breast cancer at cardiac risk. *Ann Oncol.* 2009;20(5):816-27.
28. Loprinzi CL, Reeves BN, Dakhil SR, Sloan JA, Wolf SL, Burger KN, et al. Natural history of paclitaxel-associated acute pain syndrome: prospective cohort study NCCTG N08C1. *J Clin Oncol.* 2011;29(11):1472-8.
29. Garrison JA, McCune JS, Livingston RB, Linden HM, Gralow JR, Ellis GK, et al. Myalgias and arthralgias associated with paclitaxel. *Oncology (Williston Park).* 2003;17(2):271-7; discussion 281-2, 286-8.