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ORIGINAL ARTICLE

The influence of steroid receptors status on disease outcome in early breast cancer patients treated with adjuvant cyclophosphamide, methotrexate and fluorouracil chemotherapy

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Summary

Purpose: *To assess the influence of steroid receptors (SR) status on disease outcome of early breast cancer patients treated with adjuvant cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy.*

Patients and methods: *Sixty-six node-negative patients with grade 3 invasive breast carcinoma and 95 patients with 1-3 involved axillary lymph nodes regardless of tumor grade received adjuvant CMF chemotherapy. The endpoints of this analysis were disease-free survival (DFS) and overall survival (OS). Statistical analysis included log rank test and Cox regression models.*

Results: *The median follow–up period was 81 months (range 6-208). Patients with progesterone receptor (PR) - negative tumors had better DFS compared to women with PR-positive tumors (log rank test, p=0.033). Estrogen receptor (ER) - negative and PR-negative patients in the node-negative subgroup had better DFS than ER-positive and PR-positive patients (for ER: log rank test, p=0.009, and for PR: log rank test, p=0.004). However, positive lymph nodes were the only significant predictor of disease progression among patients receiving CMF therapy (Likelihood Ratio test, p <0.001). Women under 40 bearing SR-positive breast cancer had a trend toward worse DFS (log rank test, p=0.054) compared to older SR-positive premenopausal women.*

Conclusion: *We can not unequivocally reveal the influence of SR status on disease outcome in early breast cancer patients treated with adjuvant CMF, although SR-positive patients in the node-negative group were shown to have worse DFS in comparison to SR-negative ones. However, nodal status remained the only independent predictor of disease progression in these patients.*

Key words: adjuvant chemotherapy, breast cancer, CMF, cytotoxic agents, steroid receptors, survival

Introduction

Breast cancer is the most common solid tumor in women, the mortality of which began to decline during the last decade in developed countries. This is partly the result of efficacious treatment of operable breast cancer, which almost always includes adjuvant systemic therapy that may be introduced after the radical operation with or without postoperative radiotherapy.

Since the results from the NSABP-B05 study had shown that adjuvant monochemotherapy (L-phenylalanine mustard) was superior to no adjuvant therapy, it became clear that some early breast cancer patients needed further adjuvant systemic therapy after radical surgical resection [1]. At the same time, Bonadonna et al. revealed that a combined regimen consisting of cyclophosphamide, methotrexate and fluorouracil improved the outcome in premenopausal

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breast cancer patients [2,3]. This was confirmed by the Early Breast Cancer Trialists' Collaborative Group report on the significance of adjuvant chemotherapy in breast cancer patients [4]. Results of this meta-analysis also showed that polychemotherapy is superior to monochemotherapy, although the prolonged duration of adjuvant chemotherapy (8-24 months) did not improve survival in comparison with a shorter adjuvant course (4-6 months).

Bonadonna's chemotherapy schedule [2] was later called a "classical CMF regimen". From that time on, various schemes of the CMF regimen were investigated either in adjuvant or in metastatic settings, with controversial results. It was reported that lower doses of this chemotherapy combination were inferior to full doses of the same cytotoxic drugs in metastatic breast cancer [5]. However, a European Organization for Research and Treatment of Cancer (EORTC) trial revealed that lower doses of CMF had some activity in the adjuvant setting [6]. Hence, it was proposed that dose intensity (DI) of the combination is crucial for its activity [7].

The predictive value of SR status regarding response to endocrine therapy has been well recognized earlier. The view that SR content has no influence on response to chemotherapy has prevailed until recently when subgroup analyses of some adjuvant studies showed that SR-positive tumors are not as sensitive to chemotherapy as are SR-negative breast cancers [6,8-12].

The purpose of our study was to evaluate the disease outcome in relation to SR status in a group of node-negative and node-positive early breast cancer patients treated from 1985 to 1994 at the Institute of Oncology and Radiology of Serbia with adjuvant CMF chemotherapy alone.

Table 1. Patient characteristics

Characteristic	*No. of patients (%)*
Number of patients	161 (100)
Age (years)	
Median	47
Range	28-66
Nodal status	
Node-negative	66 (41)
Node-positive	95 (59)
Menopausal status at diagnosis	
Premenopausal	93 (58)
Postmenopausal	68 (42)
Tumor size (cm)	
≤ 2	56 (35)
2-5	92 (57)
> 5	13 (8)
Tumor grade	
1	4 (3)
2	84 (52)
3	73 (45)
ER status	
Negative	78(48)
Positive	45 (28)
Unknown	38 (24)
PR status	
Negative	96 (60)
Positive	27 (16)
Unknown	38 (24)
Combined SR status	
Both SR absent	38 (24)
ER and/or PR present	85 (52)
Unknown	38 (24)

For abbreviations see text

Patients and methods

Patients and therapy

This retrospective analysis included 66 women who had node-negative disease with grade 3 ductal or lobular invasive breast carcinoma, and 95 women with 1-3 involved lymph nodes regardless of tumor grade (Table 1). According to the Protocol for Diagnosis and Treatment of Cancers of the Institute for Oncology and Radiology of Serbia at that time [13], women with node-negative early breast cancer did not receive adjuvant systemic therapy unless their tumors were of histological grade 3. In that case adjuvant CMF chemotherapy was introduced if PR status was negative. Node-positive PR-negative patients were treated with chemotherapy and in case of 1-3 positive nodes, CMF therapy for 6 or 12 cycles was usually given. None of analyzed patients received adjuvant endocrine therapy.

All patients received a median number of 6 cycles of adjuvant CMF modified as follows: cyclophosphamide 500 mg i.v. bolus, days 1-4 (total dose 2000 mg/cycle); methotrexate 35 mg i.v. bolus, days 1 and 4 (total dose 70 mg/cycle); and 5-fluorouracil 500 mg i.v. bolus, days 1-4 (total dose 2000 mg/cycle) every 4 weeks, irrespective of the body surface.

According to the guidelines for the treatment of breast cancer at that time, postoperative radiotherapy of the chest wall and/or regional lymph nodes (supraclavicular/infraclavicular field and/or parasternal region) was applied almost exclusively to postmenopausal patients. Only 9 out of 93 premenopausal patients were postoperatively irradiated, while 40 out of 68 postmenopausal patients received postoperative

radiotherapy, mostly in the node-positive subgroup.

Patients' files were the source documents for collecting data about the disease outcome of the analyzed patients. If no recorded data appeared in the patients' files, the survival data were provided by the Municipal Death Registry Books.

Steroid receptors

SR contents in primary tumors were analyzed by the classical biochemical DCC method [14]. SR values were considered positive if the ER content was ≥ 10 fmol/mg protein and the PR content was ≥ 20 fmol/mg protein. According to the recommendations for the treatment of breast cancer at that time [14], adjuvant chemotherapy was given if the PR content of the primary tumor was below the cut-off limit. Since SR status could not be determined from 1992 to 1995, although frozen tumor sections were collected and stored, the following policy in the adjuvant treatment of these patients was accepted: all premenopausal and postmenopausal patients of younger age with short-lasting amenorrhea were to be treated with CMF. SR content in some patients with unknown SR at the time of diagnosis was determined retrospectively during the follow-up period when the first relapse of disease occurred, or for the purpose of this analysis in patients without disease progression.

Statistical analysis

The endpoints of this study were DFS and OS. DFS was defined as the period from breast cancer operation till either local recurrence or distant metastases. OS was defined as the period from the operation until death of any reason. Kaplan-Meier function estimates were plotted to compare the survival distributions (time until progression and time until death) by each predictor variable. Univariate statistical analysis by the log rank test was used to assess the importance of classic prognostic factors: ER and PR contents, nodal status, tumor histology, size, and tumor grade, menopausal status, age. Cox regression models were used to identify variables associated with progression and death and to estimate hazard ratios in the analyzed patients.

Results

The median follow–up period of the whole group of 161 patients was 81 months (range 6-208) and the 5-year DFS and OS were 64.9% (95% CI 57.5%-73.1), and 79.4% (95% CI 73.1%-86.3), respectively. Sixty-six out of 161 analyzed patients experienced disease relapse (Table 2). As far as SR status was concerned, the whole number of SR-positive (ER+/PR+ and ER+/PR– and ER–/PR+) patients not receiving adjuvant endocrine therapy was 50 (31%), and among them 33/93 (35%) were premenopausal and 17/68 (25%) were postmenopausal. The precise data about SR-positive patients with disease relapse is given on Table 3. Among premenopausal SR-positive patients, 18 out of 93 (19%) were under 40 years of age. Eight of these patients (44%) experienced disease relapse.

Table 2. Characteristics of patients with disease relapse

Characteristic	*No. of patients (%)*
Number of patients with disease relapse	66/161 (41)
First relapse site	
Local relapse	9/66 (14)
Bones	15/66 (23)
Soft tissues	5/66 (7.5)
Viscera	14/66 (21)
Multiple sites	1/66 (1.5)
CNS*	22/66 (33)
Menopausal status in relapsed patients	
Premenopausal	38/93 (41)
Postmenopausal	28/68 (41)
Therapy of first relapse	
Tamoxifen	37/66 (56)
Chemotherapy	15/66 (23)
Chemotherapy + tamoxifen	6/66 (9)
No therapy	8/66 (12)

*central nervous system

Table 3. Characteristics of SR-positive patients with disease relapse

Characteristic	
SR-positive patients, n (%)	
Premenopausal	15/33 (45)
Postmenopausal	10/17 (59)
DFS in premenopausal SR-positive patients (months)	
Median	48
Range	16-180
OS in premenopausal SR-positive patients (months)	
Median	70
Range	16-186
DFS in postmenopausal SR-positive patients (months)	
Median	37.5
Range	19-114
OS in postmenopausal SR-positive patients (months)	
Median	83
Range	19-114

For abbreviations see text

Table 4. Univariate analysis of classical prognostic factors in relation to DFS and OS in patients treated with adjuvant CMF chemotherapy

Prognostic factor	*p-value*	
	DFS	*OS*
Nodal status: node-negative vs. node-positive	0.003	0.275
Tumor histology: ductal vs. lobular carcinoma	0.400	0.768
Tumor size: < 2 cm vs. 2-5 cm vs. >5 cm	0.136	0.043
Tumor grade: grade 1 vs. grade 2 vs. grade 3	0.042	0.553
Menopausal status: premenopausal vs. postmenopausal	0.947	0.944
ER status: ER-negative vs. ER-positive	0.068	0.68
PR status: PR-negative vs. PR-positive	0.033	0.655

For abbreviations see text

Among all the tested prognostic factors in the analyzed group, log rank test showed nodal status, tumor grade and PR status to be of statistical significance for DFS, but not for OS (Table 4). Age as well as menopausal status had no influence on DFS and OS. Patients with grade 3 tumors appeared to have significantly better DFS than patients with grade 1 or 2 breast cancer (log rank test, p=0.042). However, the interaction between tumor grade and nodal status was found to be statistically significant (log rank test, p=0.025).

Patients with PR-negative tumors had better DFS compared to women with PR-positive tumors (log rank test, p=0.033). There was no evidence (log rank test, p=0.068) that ER status had any influence on DFS. OS was affected neither by ER, nor by PR status. The number of SR-positive patients was unequally distributed among node-negative and node-positive subgroups, while the number of ER-negative and PR-negative patients was similar in both subgroups (Table 5). Due to these differences, we tested the importance of interaction between SR-status and nodal status. ER-negative and PR-negative patients in the node-negative subgroup had better DFS than ER-positive and PR-positive patients (for ER: log rank test, p=0.009, and for PR: log rank test, p=0.004; Figure 1). OS remained unaffected by SR status in both node-negative and node-positive patients. There was no difference in DFS and OS between patients with total lack of SR (ER0/PR0) and patients with SR present in their primary tumors.

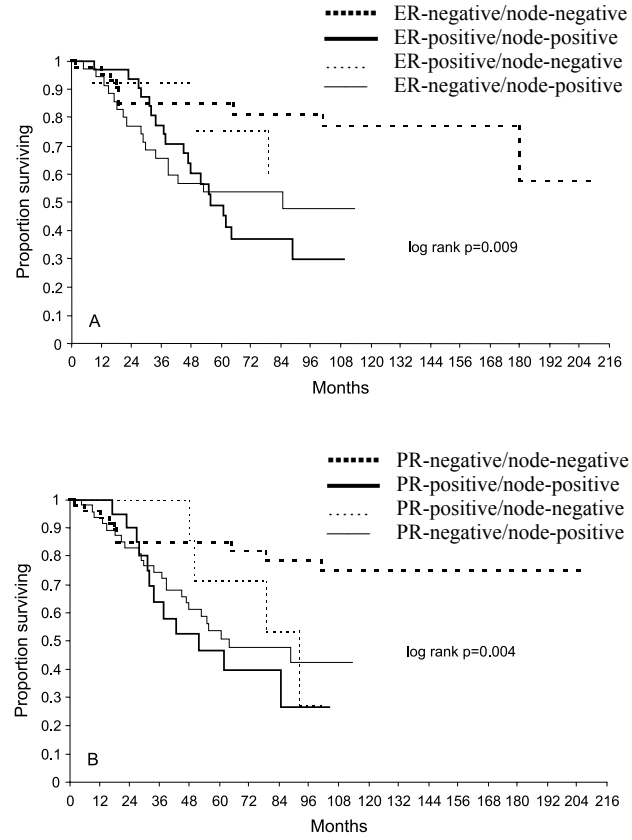

Figure 1. DFS according to nodal status and ER status (A), and nodal status and PR status (B) in patients treated with CMF.

Since a substantial percentage of our patients had SR-positive disease and were not treated with adjuvant endocrine therapy, we performed the following analyses to evaluate: 1) if there was a difference between

Table 5. Distribution of ER and PR status in subgroups of patients with known SR status according to nodal status

Nodal status	*ER-negative*	*ER-positive*	*PR-negative*	*PR-positive*
Node-negative, n (%)	43/56 (77)	13/56 (23)	49/56 (87.5)	7/56 (12.5)
Node-positive, n (%)	35/67 (52)	32/67 (48)	47/67 (70)	20/67 (30)

For abbreviations see text

pre- and postmenopausal SR-positive patients, and 2) if there was a difference between premenopausal SR-positive patients aged under 40 and premenopausal women over 40, to see if secondary amenorrhea might have had some influence on disease outcome in patients receiving adjuvant CMF. There was no difference in DFS and OS between SR-positive premenopausal and SR-positive postmenopausal patients. However, in a subgroup of premenopausal patients with SR-positive breast cancer, a trend toward worse DFS was noticed in women under 40 in comparison to older premenopausal women (log rank test, p=0.054). Five out of 18 women under 40 had SR-positive tumors, and all of them experienced disease relapse. On the contrary, only in 2/9 SR-negative patients disease relapse was noticed during the follow-up period. There was no significant difference in OS between the two SR-positive premenopausal subgroups of patients.

Node-positive patients had significantly worse DFS than node-negative ones (log rank test, p=0.003). Involved lymph nodes were the only significant predictor of disease progression among patients receiving CMF (Likelihood Ratio test, $p < 0.001$). Hazard ratio for an individual with positive lymph nodes relative to one with negative lymph nodes was 2.28 (95% CI 1.30-3.98). There was no evidence that the addition of PR and the interaction between PR and nodal involvement further contributed to the modeling of hazard for progression, given that the involvement of lymph nodes was already present in the model. None of the variables was found to have a significant effect on the hazard of death in the same group of patients.

Discussion

Our results demonstrate that the nodal status is the only independent prognostic factor for DFS in node-negative patients with grade 3 tumors and in patients with 1-3 positive nodes treated with adjuvant CMF chemotherapy. Positive nodal status doubled the hazard of disease progression at any given time in patients who received adjuvant chemotherapy. There was no significant difference in OS between node-negative and node-positive subgroups. This might suggest that the prognosis in some patients of node-negative and node-positive subgroups overlaps because of the presence of other prognostic factors related to the tumor, not investigated in the analysis.

Patients with grade 3 tumors appeared to have significantly better DFS than patients with grade 1 or 2 breast cancer. Since the majority of patients with grade 3 tumors had negative nodal status and the majority of patients with grade 2 breast cancers had positive nodal status, these results should be taken cautiously. Furthermore, the analysis of nodal status - tumor grade interaction confirmed that only the lymph nodes status was of significance for DFS.

As far as SR status is concerned, the opinion that SR-positive tumors are sensitive to both chemotherapy and endocrine therapy has been changing in recent years [6,8-12]. Univariate analysis in our study showed that breast cancer patients with PR-positive tumors treated with adjuvant CMF chemotherapy had significantly lower DFS than PR-negative patients. Although it seems that those results might support the hypothesis that SR-negative and SR-positive tumors are of different tumor phenotypes with different sensitivity to chemotherapy, we found that the influence of the nodal status on disease outcome was more important than SR status. This means that node-positive patients had a worse prognosis than node-negative patients irrespective of SR status.

However, SR status seemed to have significantly different influence in node-positive and node-negative patients. It appeared to be quite important in the node-negative subgroup of patients: ER-negative, as well as PR-negative patients treated with adjuvant CMF had significantly better DFS, but not OS, compared to ER-positive and PR-positive patients. There was no difference in OS between SR-positive and SR-negative subgroups, probably because SR-positive patients received endocrine therapy upon disease relapse (65% of patients received tamoxifen upon disease relapse), which might result in prolonged survival in the metastatic phase of the disease.

According to the guidelines for the treatment of breast cancer [13] at the time when our patients received chemotherapy, patients with ER-positive/PR-negative tumor phenotype did not routinely receive endocrine therapy. Almost one third of the patients had ER-positive/PR-negative tumor phenotypes or their SR-positive disease was recognized later during follow-up, and all of them were withheld from appropriate and effective adjuvant endocrine therapy [15,16]. However, some medical oncologists are still prone to believe that chemotherapy is more efficacious in breast cancer patients irrespective of SR status. This was shown to be true in Italy, where an accurate analysis of adherence to evidence-based guidelines for adjuvant treatment of early breast cancer patients in routine practice was recently done [17], showing that 19% of all SR-positive patients did not received adjuvant hormonotherapy. Although the National Guidelines for the Treatment of Breast Cancer was developed more than 5 years ago, the analysis of the

adherence to the protocol has not yet been performed in Serbia.

We did not find significant difference in disease outcome between pre- and postmenopausal patients. Although no influence of adjuvant chemotherapy on survival in postmenopausal women was reported in some studies [3], the possible reasons for this might be that lower doses of cytotoxic drugs were administered to these patients, or there was lack of compliance with oral cyclophosphamide. On the other hand, CMF was found to be a feasible regimen also in patients over 50 years old [18]. According to these views, the influence of chemotherapy-induced amenorrhea in premenopausal women is overestimated.

The endocrine effect of adjuvant chemotherapy in our patients was evaluated in relation to the age of women treated with chemotherapy and SR status of their primary tumors. It is well known that chemotherapy-induced secondary amenorrhea directly depends on patient's age. Although no data about the menopausal status after adjuvant chemotherapy in the analyzed group of premenopausal patients were available, we have reported amenorrhea secondary to adjuvant FAC/FEC therapy to be achieved in only 33% of premenopausal patients aged under 40 [19].

Our results point once again that SR status has a significant influence on disease outcome in very young patients treated with adjuvant chemotherapy alone. Among 18 patients under 40, all 5 SR-positive patients experienced disease relapse, and this subgroup had a trend toward worse DFS in comparison with older SR-positive premenopausal patients. OS was not affected in this subgroup of women, probably due to the introduction of endocrine therapy after the occurrence of disease relapse. Although obtained on a small number of patients, our results support the hypothesis that young premenopausal patients with SR-positive breast cancer treated with adjuvant chemotherapy need also adjuvant endocrine treatment [20]. This means that adjuvant chemotherapy does not exert endocrine effect in very young patients due to the lack of secondary-induced amenorrhea.

Although level-1 evidence-based superiority of adjuvant anthracycline regimens over CMF therapy has been established earlier, from our point of view it is quite important to evaluate the results obtained in routine practice. The weak points of our study were the relatively small number of patients and, unfortunately, a substantial portion of patients that were lost to follow-up. We believe this is a general problem in developing countries, deserving our full attention.

This retrospective analysis showed that the nodal status remained the only independent prognostic factor in patients treated with adjuvant CMF chemotherapy. The influence of SR status was not unequivocally proved, although there was a trend supporting the fact that ER/PR-positive patients treated with adjuvant chemotherapy alone had a worse outcome than ER/PR-negative patients, at least in the subgroup of patients with grade 3 breast cancer without involved regional lymph nodes and younger-aged premenopausal women.

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