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# Effect of CMF-chemotherapy on blood coagulation in patients with breast cancer

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**BACKGROUND:** *Influences of CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy on blood coagulation were investigated in 30 patients receiving adjuvant chemotherapy and in 30 patients receiving chemotherapy for metastatic breast cancer.*

**METHODS:** *In plasma samples of 60 patients (median age 49.5), we evaluated the following parameters: 1) Markers of in vivo clotting activation thrombin-antithrombin complex ( ELISA) and D-dimer (ELISA), 2) Natural anticoagulants (protein C [PC] and antithrombin III [AT III] by chromogenic methods). The coagulation studies were performed at the beginning and at the end of the first cycle of CMF protocol.*

**RESULTS:** *Before CMF therapy, significant difference was observed between patients with early stage and patients with metastatic breast cancer in the PC ($p<0.01$), AT III ($p<0.01$) and TAT ($p<0.01$) levels. After CMF therapy, patients with stage II (adjuvant) disease manifested a significant decrease in the level of PC and AT III activity ($p<0.01$) and an increase in TAT level ($p<0.01$). In patients with disseminated breast cancer CMF therapy provoked an increased level of TAT and D-dimer with a decreased activity of protein C and antithrombin III. There was significant difference in value of TAT, D-dimer, protein C and antithrombin III between the patients with adjuvant and metastatic breast cancer patients after CMF chemotherapy.*

**CONCLUSION:** *Our results suggest that the application of cytotoxic therapy provokes hypercoagulable condition in breast cancer patients. This effect should be considered when chemotherapy is employed in advanced cancer patients at high risk for thrombosis, or in patients with other risk factors.*

**KEY WORDS:** *Breast Neoplasms; Blood Coagulation; Antineoplastic Agents*

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## INTRODUCTION

Cancer is often associated with abnormal activation of coagulation leading to a prothrombotic state (1-6). Thromboembolic disease has long been recognized as a complication of cancer. An increased incidence of thromboembolic events has been noted in women receiving chemotherapy for breast cancer (7-10). Weiss et al. noted a 5% incidence of thromboembolic disease in a cooperative group study of 433 breast cancer patients treated with adjuvant chemotherapy (11). Goodnough et al. reported a 17.6% incidence of thrombosis in 159 patients receiving a five-drug chemotherapy regimen for stage IV (metastatic) breast cancer (12).

Some chemotherapeutic agents used for cancer may induce thrombosis but their biological alterations in the hemostatic system are not well understood. The appreciation of a close link between treatment and thromboembolic complications has been difficult for the underlying increased tendency to thrombosis of cancer per se and required careful epidemiological evaluation (13-15). The main mechanisms of thrombogenesis associated with chemotherapeutic agents are: 1) The release of procoagulants and cytokines from tumor cells damaged by the cell-targeted treatment; 2) A toxic effect directed towards vascular endotheli-

Abbreviations:

CMF-Cyclophosphamide, Metothrexate, 5-fluorouracil; TAT-thrombin-antithrombin complex; PC-Protein C; AT III- Antithrombin III; UICC -International Union against Cancer; EORTC -European Organization for the Research and Treatment of Cancer; TNM-Tumor-Node-Metastasis; ECOG- Eastern Cooperative Oncology Group; ELISA- Enzyme-Linked Immunoadsorbent Assay.

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um; 3) the fall of naturally occurring anticoagulants (protein C, protein S, antithrombin III) (13,16-20).

This study evaluated alterations of coagulative parameters :1) Markers of *in vivo* clotting activation (thrombin-antithrombin complex [TAT] and D-dimer), 2. Natural anticoagulants (protein C [PC] and antithrombin III [AT III]) following CMF chemotherapy in patients with breast cancer. Topics of this study were: 1) Detection of laboratory markers of activation of coagulation during CMF chemotherapy; 2) Changes in the plasma level of natural coagulation inhibitors- protein C and antithrombin III; 3) Differences in plasma level of TAT, D-dimer, PC and AT III between patients with localized and patients with disseminated breast cancer during CMF chemotherapy.

## PATIENTS AND METHODS

Our research considered 60 patients with malignant breast tumors, diagnosed and treated at the Institute of Oncology in Sremska Kamenica from January 1997 to the end of 2000. All the patients received CMF chemotherapy: a) 30 of them were treated in adjuvant setting, b) the other 30 were treated for metastatic breast carcinoma.

At the Institute of Oncology in Sremska Kamenica the following cytostatic CMF scheme was applied: cyclophosphamide 300 mg/m$^2$ days 1-5, methotrexate 20 mg/m$^2$ days 1, 3 and 5, 5-fluorouracil 500 mg/m$^2$ days 2 and 4. Chemotherapy was repeated in every 28 days.

Criteria for inclusion of patients in our studies were: radical mastectomy, which was done in 40 patients (66.7%), segmental resection in 20 patients (33.3%) and axillary dissection in all patients. Histological diagnosis of breast cancer was confirmed: ductal carcinoma in 44 patients (73.3%), lobular carcinoma in 7 (11.7%) and mixed (ductal and lobular) in 9 patients (15%). For the diagnosis of metastatic disease the following examinations were done: routine laboratory tests, chest X ray, ultrasonography of abdomen, bone scan, also computed tomography of the chest and abdomen, magnetic resonance of CNS and, if necessary, magnetic resonance of bones. Histological verification of the outspread of disease was established by cytological examination of pleural puncture, liver and bone biopsy. The stage of disease was established according to the criteria of UICC and EORTC from 1997. Of 60 examined patients, 30 were in stage II (adjuvant) and 30 with metastatic disease. Patients' median age was 49.5 (range, 30-71 years); of 60 patients 32 (53.3%) and 28 (46.7%) were in pre-and postmenopausal status, respectively.

The median age of the patients with stage II (adjuvant) breast cancer was 48 years (range, 35-71 years), and of patients with stage IV it was 52 years (range, 30-65 years). Patients who previously received adjuvant chemotherapy were not treated with radiation or hormonal therapy. Twelve of 30 patients with metastatic breast cancer received hormonal therapy (Tamoxifen) but radiation was applied in all patients (Table 1). Patients started with CMF treatment at least 28 days after the end of previous therapy.

No patients presented clinically evident signs of thromboembolic disease, disseminated intravascular coagulation (DIC), and hemorrhage syndrome, and they were not treated with anticoagulant therapy.

**Table 1.** Characteristics of patients groups

| | Stage II (adjuvant) (%) | Stage IV (%) |
|---|---|---|
| Number of patients | 30 (50) | 30 (50) |
| Mediana age (range) | 48 (35-71) | 52 (30-65) |
| Premenopausal | 18 (30) | 14 (23) |
| Postmenopausal | 12 (20) | 16 (27) |
| Histological type | | |
| Ductal | 24 (40) | 20 (33.3) |
| Lobular | 2 (3.4) | 5 (8.3) |
| Mixed (ductal and lobular) | 4 (6.7) | 5 (8.3) |
| ECOG status | | |
| 0-2 | 30 (50) | 21 (35) |
| 3-4 | – | 9 (15) |
| Previous hormonal therapy | | 11 (18.3) |
| Previous radiation therapy | – | 30 (50) |
| Previous chemotherapy | – | – |

The following parameters were studied:

1. Markers of *in vivo* clotting activation thrombin-antithrombin complex and D-dimer,
2. Natural anticoagulants (protein C and antithrombin III).

All tests were performed before CMF chemotherapy and immediately after the first cycle.

### Laboratory tests

To avoid diurnal variation, blood was always collected in the morning (between 7 a.m. and 9 a.m.). Blood samples obtained by untraumatic venepuncture were put into plastic tubes containing one-ninth volume of balanced citrate. Hematological parameters were measured in citrated plasma after centrifugation of 3,000 g at 40°C for 20 min. The obtained plasma was immediately frozen and stored at -70˚C.

Thrombin-antithrombin complex was measured by enzyme-linked immunoadsorbent assay (ELISA; Enzygnost TAT [Behring]). Normal range: 2-4 $\mu$g/L.

D-dimer was measured by the latex agglutination assay for the semi-quantitative determination of fibrin D-dimer in human plasma or serum (ACCUCLOT TM D-dimer SIGMA). Normal range: < 250 ng/ml.

Antithrombin III was measured by the chromogenic substrate Berichrom-Antithrombin III (Behring) for Chromotimer (Behring). Normal range: 80-120%. Protein C was measured by the chromogenic substrate Berichrom-Protein C (Behring) for Chromotimer (Behring). Normal range: 70-140%.

### Statistical analysis

All statistical analyses were performed using the BMDP software 1990 Revision package. Results are expressed as the mean ± SD and median. Comparisons of means between paired data were performed using the matched paired *t* test. Comparisons between groups of quantitative data were performed using the Mann-Whitney rank sum *U* test (two groups of non-paired data). Chi-squared and Wilcoxon matched pairs tests were used.

## RESULTS

Sixty women with breast cancer were treated with CMF chemotherapy, and were considered eligible.

The pretreatment level of TAT was in normal range in 90% (27/30) of patients treated with adjuvant chemotherapy and it was increased in 56.7% (17/30) of patients treated for metastatic disease.

D-dimer was noted in 50% (15/30) of patients receiving adjuvant chemotherapy and in 56.7% (17/30) of patients with disseminated breast carcinoma.

The pretreatment plasma level of natural coagulation inhibitors PC and AT III were in normal range with almost all patients.

The median pretreatment value of TAT in patients receiving adjuvant chemotherapy was 2.82 $\mu$g/L, whilst in patients with stage IV it was 4.45 $\mu$g/L. There was significant difference in pretreatment values of TAT between patients on adjuvant setting and patients with stage IV breast carcinoma (Table 2).

**Table 2.** The pre-treatment values of hemostatic parameters quantified in patients with stage II (adjuvant) (N=30) and in the patients with stage IV (N=30) breast carcinoma

| Hemostatic parameters | Groups | Median | Ranges | P value[a] |
|---|---|---|---|---|
| TAT | Stage II | 2.82 | 2.16-8.55 | |
| | Stage IV | 4.45 | 2.75-7.32 | p<0.01 |
| Protein C | Stage II | 121.93 | 53.91-142.23 | |
| | Stage IV | 99.52 | 90.23-120.45 | p<0.01 |
| AT III | Stage II | 113.93 | 64.08-134.72 | |
| | Stage IV | 94.30 | 84.3-107.19 | p<0.01 |

[a]P value from the Mann-Whitney rank sum test

The median pretreatment value for protein C was 121.93% in patients with stage II (adjuvant), whilst in patients with stage IV it was 99.52%. Comparisons revealed that the pretreatment value of protein C was statistically significantly higher in patients with stage II (adjuvant) than in patients with stage IV breast carcinoma (Table 2).

There was significant difference in pretreatment value of AT III between patients with stage II (adjuvant) and stage IV breast cancer. The patients with localized breast carcinoma showed significant elevations of AT III when compared with patients with disseminated breast carcinoma (Table 2).

There was no statistically significant difference in pretreatment value of D-dimer between patients with stage II (adjuvant) and patients with stage IV breast carcinoma (Chi-square test; p=0.60).

The pretreatment levels of TAT were within normal range (2.16-8.55 $\mu$g/L) in all patients who received adjuvant therapy for breast carcinoma and increased in 33% of patients (2.32-7.68 $\mu$g/L) after the first cycle of chemotherapy. There was significant difference in TAT value between pre- and post-treatment value (Table 3). The average difference between the pre- and post-treatment value was 0.616±0.98 $\mu$g/L.

**Table 3.** Results of coagulation tests in 30 patients with stage II (adjuvant) breast carcinoma before and after CMF chemotherapy (mean ± SD)

| Hemostatic parameters | Before therapy | After therapy | P value[a] |
|---|---|---|---|
| TAT µg/L | 3.15±1.24 | 3.76±1.30 | p<0.01 |
| Protein C % | 116.83±21.25 | 95.75±12.39 | p<0.01 |
| ATIII % | 111.74±15.08 | 94.63±18.15 | p<0.01 |

[a]P value from the matched paired T test

At the beginning of the first cycle of CMF therapy, protein C levels were in normal range in most patients treated with adjuvant chemotherapy for breast carcinoma and it remained in normal range after the termination of chemotherapy. Protein C level decreased in almost all patients during CMF therapy. There was significant difference in Protein C activity between pre- and post-treatment value (Table 3). The average difference between the pre- and post-treatment value was 21.08±13.50%.

At the beginning of therapy antithrombin III was increased in 33% (10/30) of patients who received adjuvant CMF therapy but it was decreased in 20% (6/30) of patients after the termination of chemotherapy. Before and after chemotherapy, statistically relevant difference existed for mean level of antithrombin III (Table 3). The average difference between the pre- and post-treatment value was 17.11±13.30% (Table 4).

**Table 4.** Results of coagulation tests in 30 patients with stage IV breast carcinoma before and after CMF chemotherapy(mean ± SD)

| Hemostatic parameters | Before therapy | After therapy | P value[a] |
|---|---|---|---|
| TAT | 4.68±1.33 | 7.21±2.16 | p<0.01 |
| Protein C | 90.73±5.84 | 81.83±5.85 | p<0.01 |
| ATIII | 94.48±5.56 | 87.22±4.61 | p<0.01 |

[a]P value from the matched paired T test

Cross-linked fibrin derivatives (D-dimer) were noted before chemotherapy in 15 of 30 patients who received adjuvant therapy for breast carcinoma, and in 19 of 30 patients after chemotherapy. There was no significant difference in D-dimer between pre- and post-treatment value.

Before chemotherapy an increase of TAT was noted in 17 of 30 patients with disseminated breast carcinoma, and it was increased in 27 of 30 patients after the first cycle of CMF

chemotherapy. When the value of TAT after treatment was compared with the pretreatment value, a significant difference was observed (Table 4). The average difference between pre- and post-treatment value was 2.53±1.36 $\mu$g/L.

The pretreatment level of natural coagulation inhibitor protein C was within normal range with almost all patients and it remained in normal range after the first chemotherapy cycle finished. Protein C activity was significantly reduced after the termination of chemotherapy when compared to pretreatment activity (Table 4). The average difference between the pre- and post-treatment value was 19.38±10.26%.

Before and after CMF chemotherapy, antithrombin III level was in normal range within all patients with stage IV breast carcinoma. There was significant difference in antithrombin III value between pre- and post-treatment value (Table 4). The average difference between the pre- and post-treatment value was 7.25±4.64%.

D-dimer was observed before chemotherapy in 17 of 30 patients with disseminated breast carcinoma, and in 24 of 30 patients after the termination of chemotherapy. There was significant difference between pre- and post-treatment D-dimer value (Wilcoxon matched pairs test: $p < 0.01$).

The median values, ranges of the parameters studied in patients with stage II (adjuvant) and patients with stage IV after CMF chemotherapy are presented in Table 5. There was significant difference in TAT post-treatment value between patients with stage II (adjuvant) and those with stage IV breast carcinoma (Table 5). TAT value was increased in patients with metastatic breast carcinoma. Protein C activity was significantly decreased in patients with disseminated breast carcinoma (Table 5). Antithrombin III was significantly decreased in patients with stage IV breast carcinoma (Table 5). There was no significant difference in D-dimer value after chemotherapy between patients with stage II (adjuvant) and patients with stage IV breast carcinoma.

**Table 5.** Results of coagulation tests in 30 patients with stage II (adjuvant) and stage IV of breast carcinoma after CMF chemotherapy

| Hemostatic parameters | Groups | Median values | Ranges | P value[a] |
|---|---|---|---|---|
| TAT | Stage II | 3.29 | 2.32-7.68 | |
| | Stage IV | 7.68 | 3.76-11.23 | p<0.01 |
| Protein C | Stage II | 97.79 | 64.37-126.48 | |
| | Stage IV | 82.11 | 71.3-96.78 | p<0.01 |
| AT III | Stage II | 96.00 | 47.85-127.57 | |
| | Stage IV | 88.17 | 75.76-97.45 | p<0.01 |

[a]P value from the Mann-Whitney rank sum test

## DISCUSSION

Malignancy is known to be associated with an increased incidence of thromboembolic disease. It has been shown that iatrogenic influences, such as surgery (21), radiotherapy (9) and chemotherapy (17-20,22) potentially increase the risk for thrombosis in cancer. Previous reports have implicated an association of chemotherapy and increased incidence of thrombosis in women with breast cancer (17-19). Patients with breast cancer are found to develop thrombosis in 2.2% to 17.6% of cases when treated with CMF chemotherapy, and the risk is highest in patients treated for metastatic disease (12,23). These observed incidences were far greater than the average incidences in similar cancer patients not receiving chemotherapy. The etiology of the increased incidence of thromboembolic events in breast cancer patients receiving chemotherapy is not known. The potential risk of chemotherapeutic agents for increasing tendency to develop thrombosis is difficult to evaluate as other risk factors often predispose cancer patients to thromboembolic complications.

In our study observed the changes of markers of clotting activation-TAT and D-dimer, and natural clotting inhibitors protein C and antithrombin III during CMF chemotherapy in breast cancer patients. At the beginning of CMF chemotherapy, marker of activation of clotting-TAT was significantly increased while there was no difference in D-dimer levels in patients with disseminated breast cancer in comparison with patients with localized disease. The higher levels of natural clotting inhibitors (PC and AT III) were noted in patients who received adjuvant therapy for breast carcinoma when compared with the values of patients with metastatic disease. As we know, in advanced breast cancer disease there is a natural tendency towards thrombosis. In most of the patients with metastatic cancer subclinical activation of blood coagulation is evident (3,6,24). This was a background for the consideration of our results.

After CMF chemotherapy, in majority of patients on adjuvant setting significant increases in TAT levels were noted, followed by significant decreases in PC and AT III levels. The value of natural inhibitor of coagulation was within normal range. The increase TAT level indicated activation of blood coagulation during CMF chemotherapy. Our results were similar with the results of other studies (7,9,16-20,22).

The mechanisms for depression of natural inhibitors of coagulation noted in our patients are unclear. The first possible mechanism could involve the known inhibition of DNA and RNA synthesis by CMF chemotherapy leading to decrease in protein synthesis in the liver, and lowering of plasma levels of protein C and antithrombin III (25). In addition, we cannot exclude the possibility of functional disorder of natural inhibitor of blood coagulation. Also, we cannot exclude the possibility of functional disorder of protein C as a resistance to activated protein C or a disorder in carboxylation of PC in liver under the influence of 5-FU (26). The other possible mechanism could be the initiation of intravascular coagulation by cytostatics. In malignant diseases the incidence of disseminated intravascular coagulation (DIC) is increased (3-5, 8). Decrease of plasma levels of PC and AT III (27) is evident at

DIC. In our study, however, we did not measure the antigenic level of protein C and antithrombin III, so we were able to evaluate their activity alone, which was declined after chemotherapy. Enhanced values of TAT are also observed at intravascular coagulation (27). The increase of TAT values, noticed in our study, could suggest the activation of coagulation. As a result of initiation of coagulation the thrombin is produced and neutralized by antithrombin III, linking to it and forming TAT. During this process antithrombin III is consumed, declining its level in plasma. This could be the acceptable explanation of the results in our study. The third mechanism could be a disorder in absorption and metabolism of vitamin K caused by cytostatics, which could explain decrease of protein C noticed in our study (28). In any case, reduction of activity of the two inhibitors suggests the presence of thrombophilic state.

In more than half of patients with metastatic breast cancer pretherapeutic values of TAT are elevated, and implicate the raised production of thrombin. Our results are similar to results of other authors (8,23,27,28). After the therapy, in higher percentage of patients TAT level is elevated. The cause of these processes might be either the coagulation activation or declined antithrombin activity, or both of them. In our work, we found that in this group of patients the activity of AT III and PC, powerful inhibitors of coagulation, was significantly lowered after CMF therapy (12,29-31). These changes move the equilibrium of coagulation mechanism towards prethrombotic state.

D-dimer is detected in 60% of patients before the therapy, and after the therapy in 80% of patients. The study of Falanga et al., reporting similar data about increased values of D-dimer before therapy that remain on high level after therapy, confirms our results (28). The presence of D-dimer proves that proteolytic digestion of fibrin under the influence of plasmin is performed *in vivo* and fibrinolytic system is activated (32). In the meantime, D-dimer indirectly shows presence of thrombin and activation of coagulation process. In our study, increased thrombin activity in patients with stage IV of breast cancer was registered, and this could explain the higher level of D-dimer.

The alterations in coagulation parameters due to chemotherapy were similar between patients with metastatic and localized disease. The coagulation studies in these patients showed low-grade intravascular clotting activation and a reduction of antithrombin III and protein C. The increase of TAT levels following CMF chemotherapy was noted in majority of patients with breast cancer. The decrease in plasma protein C and antithrombin III levels as a result of chemotherapy was observed in almost all of our patients. None of our patients developed clinically apparent thrombotic event.

## CONCLUSION

This study provides suggestive evidence of an effect of chemotherapy towards hypercoagulability. The results of this study indicate that before therapy, hypercoagulable state is present in stage IV of breast cancer. After chemotherapy, abnormalities of hypercoagulation markers persist which was not indicated in stage II. This observation suggests for caution when using anticancer drugs in some patients. In advanced breast cancer patients, where an increased incidence of thrombosis occurs naturally, the combination of chemotherapy with other drugs that are reported to induce hypercoagulability, especially in patients with other additional risk factors, should be carefully evaluated.

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