Original article

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Tamoxifen-induced tissue factor pathway inhibitor reduction: a clue for an acquired thrombophilic state?

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Background: Current understanding of hemostatic systems enables us to better explore the enigmatic pathobiology of tamoxifen (TAM)-induced thrombotic diathesis. We have therefore aimed to assess the hemostatic changes in breast cancer patients receiving TAM on an adjuvant basis.

Patients and methods: The study population consisted of 43 female patients with hormone receptor-positive breast cancer who received TAM 20 mg/day as part of their adjuvant treatment. Mean age was 52 ± 12 years (range 25–74). Twenty-one patients (49%) were premenopausal. Plasma samples were collected prior to and following 6 months of TAM therapy and were assayed for total tissue factor pathway inhibitor (TFPI), free TFPI, lipid-bound TFPI, thrombomodulin, D dimer, activated protein C resistance (APC res), factors VIIa, II, V, VII and X, and global fibrinolytic capacity (GFC).

Results: Median total TFPI decreased significantly from 48.5 ng/ml to 36.2 ng/ml ($P = 0.001$), free TFPI from 10 to 7.6 ng/ml ($P = 0.001$) and lipid-bound TFPI from 39.1 to 28.7 ng/ml ($P = 0.001$). There were significant decreases in the levels of factor II ($P = 0.03$), factor V ($P = 0.001$), factor VII ($P = 0.06$), thrombomodulin ($P = 0.01$) and D dimer ($P = 0.001$). However, APC res times were significantly prolonged ($P = 0.04$). The remaining parameters that we have studied were not significantly affected.

Conclusion: Our findings suggest that TAM tends to activate the coagulation pathway by counteracting major molecules involved in coagulation inhibition, namely TFPI and TM. As reflected by unchanged GFC, the drug appears to impair the expected compensatory activation of the fibrinolytic system, which removes fibrin polymers resulting from coagulation activation.

Key words: breast cancer, hemostasis, hypercoagulability, tamoxifen, TFPI, venous thromboembolism

Introduction

Tamoxifen (TAM) has been effectively used in the treatment of hormone receptor-positive early and advanced breast cancer for 30 years. Its favorable impact on survival is now well established [1, 2]. Recent studies also suggest that it may prove useful in the prevention of breast cancer in high-risk women [3]. On the other hand, TAM increases the risk of venous thromboembolism (VTE) about two-fold [4]. Thrombotic diathesis is further enhanced when TAM is used simultaneously with cytotoxic chemotherapy [5, 6]. Though this side effect was noted shortly after the introduction of this agent into daily practice, the underlying mechanisms have still not been precisely elucidated.

Effects of TAM on some hemostatic factors have been investigated in healthy subjects as well as in breast cancer patients. Antithrombin and protein C levels have been found to be decreased in breast cancer patients using TAM [7–9]. Mannucci et al. [10] also showed similar decrements in levels of both proteins in healthy women in a randomized, placebo-controlled prevention trial, as did Cushman et al. [11]. Furthermore, the latter study demonstrated for the first time that activated protein C resistance (APC res) was developed with TAM use.

Apart from the induction of APC res, the profile of hemostatic derangements induced by TAM has not been thoroughly investigated. In this study, we assessed a spectrum of parameters of coagulation and fibrinolysis in patients with breast cancer before and after 6 months of adjuvant TAM treatment, in order to obtain have a comprehensive overview of the hemostatic system in this setting and to observe the changes brought about by this agent.

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Patients and methods

Fifty-three consecutive female patients with early breast cancer who were scheduled for adjuvant TAM treatment were enrolled after giving informed consent. Patients with hereditary or acquired thrombophilia and/or a history of vascular thrombosis, organ failure, and those receiving antiaggregant/anticoagulant therapy were excluded.

A total of 10 patients were subsequently excluded. The reasons were: development of metastases in five, discontinuation of TAM after subsequent discovery of hormone receptor negativity in two, establishment of a diagnosis of cirrhosis in one and two patients were lost to follow-up. In total, 43 patients were considered evaluable.

Every patient underwent gynecological examination prior to the initiation of TAM therapy. Follow-up visits were scheduled every 3 months, and medical history, physical examination, blood counts, liver function tests, chest X-ray and abdominal ultrasonography were performed. TAM was administered at a daily dose of 20 mg to all patients. Total tissue factor pathway inhibitor (TFPI), free TFPI, lipid-bound TFPI, thrombomodulin, D dimer APC res, factors VIIa, II, V, VII and X, and global fibrinolytic capacity (GFC) were chosen as the study parameters and were assessed before the initiation of TAM and after 6 months of treatment. Pretreatment and 6 months posttreatment levels of total TFPI, free TFPI, lipid-bound TFPI, thrombomodulin, D dimer and APC res were assayed in all of the 43 patients; factors II, V, VII, X and GFC in 39 patients and factor VIIa in 26 patients.

The collection of blood samples was performed at least 14 days after any surgery, chemotherapy or radiotherapy to minimize the possible impact of these interventions on the hemostatic parameters. After the collection of venous blood samples into tubes containing 0.129 M sodium citrate, they were immediately centrifuged at 3000 *g*, at 4°C for 10 min and stored at −80°C until assayed.

Total TFPI, free TFPI, lipid-bound TFPI, D dimer and thrombomodulin were assayed via ELISA using the respective commercially available kits (Asserachrom; Diagnostica STAGO, France). APC res was tested via an assay based on clotting time (STA-Staclot APCR; Diagnostica STAGO). Clotting time was measured in the presence of factor V-poor plasma and APC. GFC was measured by a method that utilizes the capacity of plasma at 37°C to degrade fibrin in the presence of tissue plasminogen activator (tPA) (Global Fibrinolytic Capacity STA Liatest D-Di; Diagnostica STAGO). In this experiment, the concentration of D dimer, which is directly proportional to GFC, was measured after the incubation of a tablet of dry-frozen plasma in plasma sample from patient. Coagulation factors V, VII and X were analysed by assays (Diagnostica STAGO, France) that make use of factor-deficient plasma. Activated factor VII (VIIa) was determined by STA clot VIIa-rTF assay kit (Diagnostica STAGO), which utilizes a recombinant tissue factor (TF) that binds solely to activated factor VII and triggers the coagulation cascade.

Statistical analysis

Paired samples Student's *t*-test or Wilcoxon signed ranks test, depending on the distribution of studied parameters, were used for the analysis. Spearman analysis was employed for correlations. A P value <0.05 was considered as statistically significant. Statistical Package for Social Sciences (SPSS v10.0) software was used for statistical analyses.

Results

A total of 43 patients, mean age 52 ± 12 years (range 25–74), with hormone receptor-positive breast cancer receiving adjuvant TAM completed the study. Basic clinical characteristics of the patients are summarized in Table 1. No clinically evident thromboembolic events were encountered during the 6-month study period.

Table 1. Clinical characteristics of the study group ($n = 43$)

	n	%
Menopausal status		
Premenopausal	21	49
Postmenopausal	22	51
Stage (AJCCS 1997)		
I	7	16
IIA	13	30
IIB	13	30
IIIA	6	14
IIIB	4	10
Chemotherapy		
FAC/FEC	24	56
CMF	8	19
AC/EC	2	5
TEF	1	2.3
Local radiotherapy	27	63

AJCCS, American Joint Committee on Cancer Staging; FAC/FEC, fluorouracil, adriamycin/epirubicin, cyclophosphamide; CMF, cyclophosphamide, methotrexate, fluorouracil; AC/EC, adriamycin/epirubicin, cyclophosphamide; TEF, docetaxel, epirubicin, fluorouracil.

Following 6 months of TAM therapy, median total TFPI decreased significantly from 48.5 to 36.2 ng/ml ($P = 0.001$), free TFPI from 10 to 7.6 ng/ml ($P = 0.001$) and lipid-bound TFPI from 39.1 to 28.7 ng/ml ($P = 0.001$) (Figure 1). Furthermore, APC res was found to be significantly prolonged (162.1 versus 167.2 s; $P = 0.04$). However, this statistical significance vanished when five patients with hereditary APC res were excluded from the analysis (164.7 versus 169.0 s; $P = 0.14$).

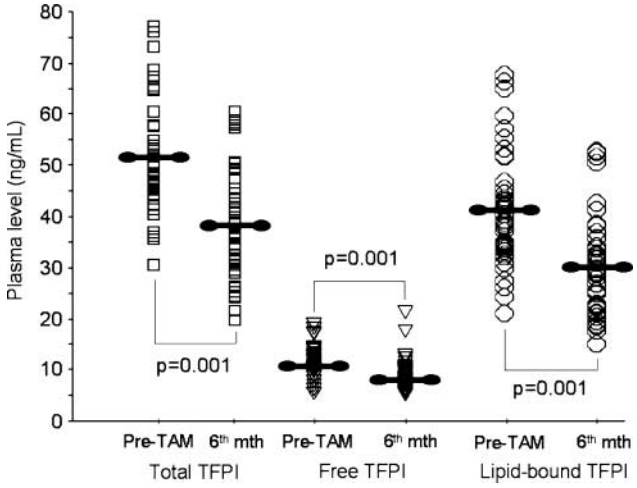

Figure 1. Pre- and posttreatment plasma levels of total, free and lipid-bound tissue factor pathway inhibitor (TFPI). For each pair, the left column represents the pre-tamoxifen and the right column represents the 6 month level. Dumb-bells indicate median values.

Table 2. Coagulation factor levels prior to and after 6 months of tamoxifen therapy

	Pre-tamoxifen	6th Month	*P*
Total TFPI (ng/ml)	51.5 ± 1.7	38.2 ± 1.7	0.001
Free TFPI (ng/ml)	10.4 ± 0.4	7.97 ± 0.4	0.001
Lipid soluble TFPI (ng/ml)	41.0 ± 1.7	30.3 ± 1.6	0.001
Thrombomodulin (ng/ml)	17.2 ± 2.6	13.3 ± 2.0	0.01
Factor II (%)	93.4 ± 2.0	85.9 ± 2.8	0.03
Factor V (%)	87.9 ± 2.6	77.4 ± 2.5	0.001
Factor VII (%)	112.5 ± 2.9	106.7 ± 3.5	NS
Factor VIIa (%)	172.0 ± 54.7	211.9 ± 72.3	NS
Factor X (%)	96.8 ± 2.8	98.4 ± 2.8	NS

Values are expressed as mean ± SEM.
TFPI, tissue factor pathway inhibitor; NS, not significant.

Table 3. Changes in the components of the fibrinolytic system prior to and after 6 months of tamoxifen treatment

	Pre-tamoxifen	6 months	*P*
D dimer (μg/ml)	0.6 ± 0.1	0.4 ± 0.0	0.001
GFC (μg/ml)	3.2 ± 0.4	4.2 ± 0.7	NS
APC res (s)	154.6 ± 4.3	159.7 ± 0.0	0.04

Values are expressed as mean ± SEM.
GFC, global fibrinolytic capacity; APC res, activated protein C resistance; NS, not significant.

The decreases in the median D dimer levels from 0.35 to 0.27 μg/ml ($P = 0.001$), and the median thrombomodulin concentration from 11.66 to 9.27 ng/ml ($P = 0.011$) were also significant. GFC did not change ($P = 0.21$) following the use of TAM.

Significant changes were also observed in the levels of the coagulation cascade proteins. TAM therapy resulted in a decrease from 95% to 88% in median factor II ($P = 0.03$) and from 87% to 76% in median factor V ($P = 0.001$). The decrease in median factor VII from 116% to 104% was just below the level of statistical significance ($P = 0.06$). However, the levels of factor VIIa and factor X remained unchanged ($P = 0.70$ and $P = 0.43$, respectively). The alterations in the levels of hemostatic molecules in association with 6 months of TAM therapy are given in Tables 2 and 3.

Pre-TAM levels of total TFPI were found to be significantly correlated to D dimer ($r = 0.30$, $P = 0.04$) and factor X ($r = 0.34$, $P = 0.03$) levels. Similarly, pre-TAM free TFPI was correlated to thrombomodulin ($r = 0.42$, $P = 0.004$), GFC ($r = -0.38$, $P = 0.016$) and factor X ($r = 0.32$, $P = 0.042$). However, none of these correlations was maintained after 6 months of TAM treatment.

Discussion

Cancer patients represent a complex model for the study of hemostatic processes, due to confounding factors like the malignancy itself and associated chemotherapy and/or radiotherapy. However, our study comprises only patients whose tumors were completely removed by surgery and who remained in clinical complete remission during the study period. Though the presence of microscopic foci cannot be ruled out, their effect on the hemostatic system may be neglected. Furthermore, blood samples were taken at least 14 days after the last day of local (surgery and/or radiotherapy) and systemic (chemotherapy) treatment in order to minimize their potential confounding effect on the studied hemostatic parameters [5, 12, 13].

The most striking observations of our study are the significant declines in the levels of total TFPI, free TFPI and lipid-bound TFPI (Figure 1). The levels of thrombomodulin, coagulation factor II, factor V, D dimer and APC res were also significantly altered. However, these changes remained at the subclinical level and during the 6-month follow-up period no vascular thrombosis was observed in any patient. On the other hand, there were no changes in the levels of GFC, factor X or factor VIIa (Tables 2 and 3).

TFPI modulates the activation of coagulation cascade by antagonizing the effects of TF to a great extent [14, 15], and is altered in several disease states associated with thrombosis, such as systemic lupus erythematosus, Behçet's disease and cirrhosis [16–18]. Hormone replacement therapy may decrease TFPI level by 30% to 50%, which leads to substantial increments in the markers of coagulation activation [19]. A recent study demonstrated that TFPI can be 50% lower in patients using oral contraceptives and that the thrombotic risk significantly increases when it is below the 2nd percentile [20]. In this study, mean free TFPI level in oral contraceptive users was 6.2 ng/ml, while it was 11 ng/ml in non-users, 14.5 ng/ml in postmenopausal women and 15 ng/ml in men. Mean total TFPI levels were 50.1, 63.2, 74.5 and 73.7 ng/ml, respectively. Other studies have also shown that exogenous oral contraceptives significantly lower TFPI levels [21, 22]. Our findings are consistent with those in oral contraceptive users in the study of Dahm et al. [20]. We may therefore assume that TAM has an effect similar to oral contraceptives on TFPI. To our knowledge, our study is the first to indicate decreased TFPI concentrations associated with TAM use. However, it must be noted that we have measured TFPI levels only in antigen concentrations and simultaneous functional activity assays could have provided invaluable information.

The exact mechanism of the effect of TAM on TFPI remains to be elucidated. However, it is now known that 17β-estradiol can decrease the release of TFPI from human umbilical vein endothelial cells [23] and it is possible that TAM exerts a similar action. Furthermore, TAM use results in increased generation of thrombin, which in turn inhibits the synthesis of TFPI. Excess thrombin may also result in degradation of TFPI. Either by inhibition of synthesis or by degradation of TFPI, increased thrombin levels associated with TAM could result in the depletion of TFPI [23, 24].

The reduction of TFPI levels could lead to coagulation activation and affect the extrinsic pathway-driven coagulation.

However, it is difficult to predict the absolute direction of changes in the concentrations of all coagulation cascade elements. The TF–factor VIIa complex activates factor IX, which in turn activates factor X. Inhibition of the extrinsic pathway by TFPI might affect the concentrations of these two coagulation factors. In our present study, factor X levels were correlated with total TFPI ($r = 0.344$, $P = 0.03$) and free TFPI ($r = 0.323$, $P = 0.042$) prior to TAM therapy, which did not persist after 6 months of therapy. Therefore, reduction in levels of TFPI by TAM may actually shift the hemostatic system into a prothrombotic state. Furthermore, median factor V (87% versus 76%; $P = 0.03$) and factor II (94% versus 88%; $P = 0.03$) levels were also diminished after 6 months of TAM therapy, a finding that may also reflect the prothrombotic effects of the drug.

Previous studies analyzing TAM-induced thrombophilia focused on the inhibitors of coagulation [10, 11, 25, 26] and almost all showed decreased antithrombin III and protein C levels. Protein S, the cofactor of protein C was also decreased [11]. These findings together with results of our present study indicate that the fine balance of coagulation–anticoagulation is shifted by TAM in favor of over-coagulation, thus representing a prethrombotic state.

The most important inherited mechanism for APC res is the presence of factor V Leiden mutation [27]. Increased levels of factors VIII, XI and XI [28], oral contraceptives [29], liver transplantation [30], pregnancy [31], antiphospholipid syndrome [32], and many malignancies including breast cancer [33, 34] may result in acquired APC res. TAM has a partial agonistic effect on estrogen receptors and might have the potential to induce an acquired APC res state. In our study, APC res measurement was prolonged from 162.1 to 167.2 s ($P = 0.04$) by TAM therapy. However, there was no statistical difference when five patients who had APC res before TAM therapy were excluded ($P = 0.138$). This suggests that the possibility of clinically manifesting thrombotic events could be increased preferentially in individuals with pretherapy APC res [35].

Although the changes in prothrombin, factor V levels and APC resistance are consistent and statistically significant, the observed differences between pre- and posttreatment values are relatively small. It is therefore difficult to determine the clinical significance of these findings in the pathophysiology of hypercoagulability associated with TAM treatment.

Thrombomodulin limits coagulation in confines of damaged endothelial areas by capturing thrombin molecules that migrate away. Thrombin captured by thrombomodulin turns into an anticoagulant protein. It activates protein C, which then inactivates activated factor V and activated factor VIII, finally blocking the coagulation cascade. Protein S further supports protein C activation. In our study, TAM lowered soluble thrombomodulin levels from 11.66 to 9.27 ng/ml ($P = 0.01$) (Table 2). This finding may indicate a defect in the confinement of coagulation within focal areas of vascular endothelium in TAM-induced thrombophilia.

Fibrinolysis and coagulation processes have close pathobiological relations. Studies focusing on TAM-associated fibrinolysis indicated that plasminogen level [36], plasminogen activity [25], tPA level [25, 26] and fibrin degradation products [26] were increased; while α-2 antiplasmin level [36] was decreased. GFC may be considered more reliable than measuring each fibrinolytic system element individually, since it measures the activity as a whole in a dynamic fashion. Six months of TAM therapy did not change GFC, and D dimer was not increased, despite the apparent activation of coagulation in association with TAM, as mentioned above. On the contrary, D dimer decreased significantly in our study. It is known that, in healthy individuals, D dimer level is not affected by TAM [37]. In breast cancer patients, however, it is increased [38], and decreases with TAM therapy [39].

We conclude that TAM works in favor of coagulation by two major mechanisms: (i) it activates the extrinsic TF-driven coagulation pathway by inactivating TFPI; and (ii) it inhibits other coagulation inhibitors to alleviate hemostatic suppression. Moreover, TAM inhibits the counter-balancing fibrinolytic system, which normally functions to remove fibrin from the vasculature. In order to draw more definitive conclusions, these novel but still preliminary results need to be verified by further long-term trials designed to elucidate a causal relation between TAM-induced changes in TFPI levels and clinical thrombotic events.

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