Assessment of the tumor-associated trypsin inhibitor (TATI) marker in patients with carcinoma of the uterine body 17 years after treatment

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Summary

On the basis of literature review, the structure of the tumor-associated trypsin inhibitor (TATI) marker and its usefulness in diagnosing and monitoring of various malignant neoplasms has been described. The authors' own experiences are presented stemming from evaluation of TATI levels in a group of 305 patients suffering from carcinoma of the uterine body, who were primarily operated and then subjected to supplementary therapy in the Center of Oncology in Warsaw, classified in accordance with the FIGO 1988 protocol in the years 1994-1995, and who were observed for 17 years after discontinuation of treatment. A statistical analysis of the level of the TATI marker was carried out in the group of patients with unfavorable prognostic factors, that is the presence of cancerous infiltration in the uterine body, also found in the parametrium, ovaries, as well as diagnosed metastases to the lymphatic nodes found on the basis of postoperative histopathological protocol. The marker was determined three to seven times in serum after each stage of supplementary treatment, and at the beginning of the follow-up. Strong significance and elevation of the TATI marker were affirmed for the mean of four initial collections in patients, who had a relapse or metastases within one month to 11 years after termination of therapy.

Key words: Neoplastic markers; TATI; PSTI; Prognostic factors; Endometrial carcinoma.

Introduction

Diagnostic process of neoplastic diseases relies on various diagnostic methods, which aim at proper end effective treatment. Since the mid-1960s markers have also been used for that purpose, since they are supposed to be highly sensitive and specific. As a reliable examination tool markers might facilitate diagnosis of disease, its recurrence, and would help determine prognosis.

The marker whose prognostic role in monitoring and early diagnosis of neoplasms is still being investigated is tumor-associated trypsin inhibitor (TATI) First reports of the marker TATI determination appeared about 30 years ago [1]. In 1982 Stenman et al. described structural and functional similarity of the TATI marker to the earlier identified pancreatic secretory trypsin inhibitor (PSTI) [1]. Increased concentration of PSTI is observed in inflammatory states of the pancreas. TATI is a protein produced in high amounts by the cells of ovarian tumor, and this inhibitor undergoes expression in cells of other solid tumors. The TATI marker was first isolated in urine from patients suffering from ovarian cancer. The elevated TATI level in serum or urine is usually caused by an inflammatory state of tissular damage. The primary function of TATI is protection of pancreatic cells against damages resulting from trypsinogen activation [1, 2]. TATI and PSTI are coded by the same single gene, and the cDNA sequences of both inhibitors are identical. The inhibitor is coded by the SPINK1 gene whose name originates from another peptide synonym – *serine protease inhibitor kazal-type 1*. It is acknowledged in the literature that the PSTI term refers to the pancreatic inhibitor, while TATI refers to the inhibitor, which undergoes expression in neoplastic cells [3, 4].

Characteristics of the neoplastic TATI marker

TATI is a protein whose mass is 6 kDa, produced in high concentrations filled with mucus ovarian cysts and by the mucous membrane of the digestive tract. A rise in its level accompanies many types of various neoplasms [2, 5].

The concentration of TATI as determined by immunofluorometric methods with the use of monoclonic and polyclonic antibodies is 6.9 μg/l in healthy individuals, the referential range being 3.1 to 16 μg/l. TATI serum levels between three and 21 μg/l, mean value 11.3 μg/l, in healthy persons are considered normal, while levels in urine considered normal are 5-50 μg/l, mean 25 μg/l. Higher concentrations are determined in the case of some malignant neoplasms of the ovary, the uterine cervix, as well as of the pancreas, stomach, liver, gall bladder, rectum, lungs, and breasts. Elevated values are also observed in pregnant females in their amniotic fluid between the 14 and 16 week of pregnancy [6, 7]. This inhibitor is also present in the human colostrum, the highest PSTI concentration, 150 ng/ml, is found during lactation [8]. The PSTI/TATI proteins and EGF (epidermal growth factor) are characterized

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Table 1. — *Mean TATI values in patients with negative prognostic features on consecutive seven collections (T1 - T7).*
Table of statistic sections of mean TATI values on consecutive seven collections

Cancer beyond the uterine body	Number of patients	T1	T2	T3	T4	T5	T6	T7
Uterine cervix	76	27.5394	27.1081	44.6379	41.0526	31.3333	33.0000	17.5000
Parametrium	40	27.6875	30.2500	46.1750	26.8750	7.2750	3.0750	1.2750
Ovaries	38	32.2105	38.9736	44.7105	32.2702	7.2702	2.2432	0.5675
Int. iliac lymphatic nodes	12	29.4100	29.2500	23.2500	32.0833	14.4166	5.2500	2.4166
Ext. iliac lymphatic nodes	10	33.5000	331.800	23.1000	27.4000	15.2000	5.6000	2.9000
Obturatory lymphatic nodes	8	35.0000	28.2500	20.7500	27.3750	16.5000	3.12500	1.25000
Vessel	71	31.8169	31.5197	40.2957	25.1875	4.7329	2.0704	0.8450
Number of negative features	255	30.0055	30.9181	41.0803	31.716	14.6731	11.7931	6.0022

by similar size and manifest great homology of amino acid sequences, which is connected with having similar biological effects such as stimulation of fibroblasts and epithelial cells growth [9].

The TATI concentration in serum within referential ranges given above is detected not only in healthy individuals, but also in patients after total pancreatomy (*pancreatomia totalis*). This effect means the majority of the inhibitor present in serum is not produced by the pancreatic gland, but derives from other organs [6, 9].

The chief function of the TATI inhibitor undergoing expression in neoplasms is protection of cancerous cells against trypsin. Trypsinogen undergoes hyper-expression in several types of cancerous cells, and after conversion into trypsin stimulates their growth and contributes to malignant transformation of tumors. Excessive production of proteinases also acts destructively on the proteins of the extracellular matrix, which may increase the migration of neoplastic cells and generate metastases [10-12].

The goal of the work was to assess the changes of the TATI marker level in patients affected by carcinoma of the uterine body who underwent surgical treatment in the case of poor prognostic signs having been found, and to determine the prognostic role of TATI in evaluation of the therapeutic result in patients with endometrial carcinoma who were primarily surgically treated.

Materials and Methods

The levels of TATI marker in 305 patients suffering from carcinoma of the uterine body, who were surgically treated in the years 1994-1995 and followed up for 17 years at the Center of Oncology in Warsaw are presented. All patients were referred to therapy at an oncological facility after removal of the reproductive organ, and in some cases after removal of lymphatic nodes in certain hospitals. The first TATI examination was performed at an oncological center on first patient's report, consecutive collections were carried out after each therapeutic stage, e.g. teletherapy, brachytherapy, and on the initial observation period after treatment. Three to seven blood collections from each examinee were recorded. Mean levels of the marker were analyzed only in patients with confirmed unfavorable prognostic factors (Table 1.) found on the basis of histopathological protocol, i.e. cancerous infiltration in the cervical canal of the uterine cervix present in 76 patients (25%), in the parametrium in 40 patients (13%), confirmed metastases to the ovaries in 38 patients (12%), to the internal iliac lymph nodes in 12 patients (4%), external iliac lymph nodes in ten (3%), obturatory lymph nodes in eight patients (3%), and cancer cells present in blood vessels in 71 examined patients (23%).

It has been agreed on that the referential range of concentration determined in serum of healthy individuals is up to 21 μg/l of the value recently assessed as elevated or abnormal.

Results

The yielded measurements of the levels of the TATI marker showed general tendency to rise on second and third collection (T2 and T3). The maximum was reached on the third collection (T3), and then the marker level progressively decreased to zero (Figure 1). The concentration observed in serum was 25-1,125 μg /l. In all patients with present poor prognostic features in comparison to patients free from such features the TATI marker levels were higher, especially on first four collections (Table 1.).

Therefore, as a new indicator of the TATI marker was assumed the mean of first four determinations of the marker level (T1-T4) in patients that histopathologically manifested all negative cancerous features. Values of that indicator were compared in groups of patients with present negative prognostic features with groups free of those features.

Significant differences of the mean TATI marker level were not found in the first four collections between groups with present neoplastic cells in the cervix, but neither in the parametrium nor in the ovaries and lymphatic nodes, compared to patients without these features. However, the occurrence of relapse and metastases highly-differentiated the levels of the TATI marker. Tables 2 and 3 show a comparison of the mean of the first four TATI marker collections in groups with relapse and metastases, respectively.

Only in the group of patients with confirmed follow-up relapse and without metastases or other neoplastic disease in comparison to patients without relapse and additional negative features differed significantly by mean TATI maker level in the first four determinations (Mann-Whitney U = 2806.000; Z = 5.20811; p = 0.00000). Similar re-

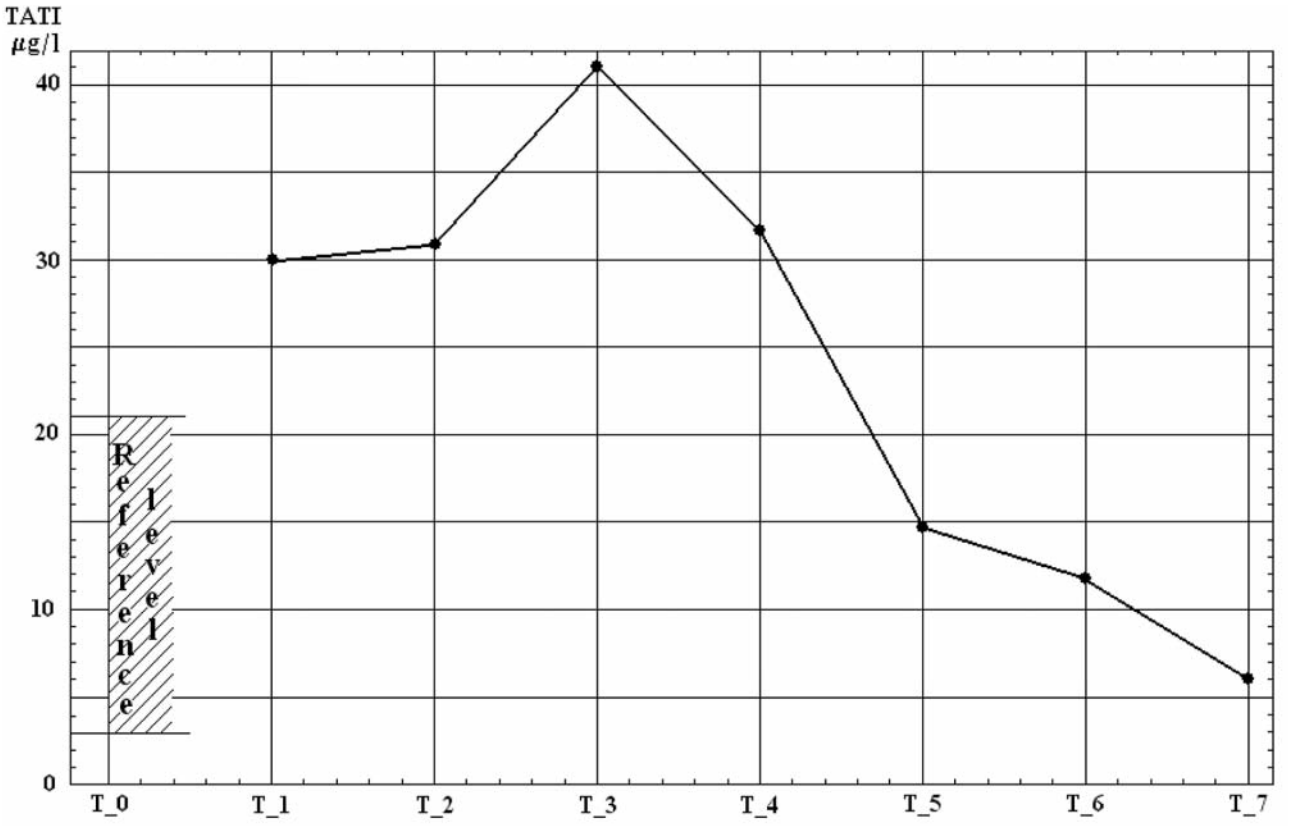

Figure 1. — Graphic representation of mean TATI levels for consecutive collections (T1-T7) of the marker in the tested group.

Table 2. — *Assessment of the influence of the 4 TATI collections mean in the relapse group.*

Variable	Mann-Whitney U Test (Data T without zer.sta) relative variable relapse Highlighted results are significant, $p < 0.05000$								
	Sum.rang NO	Sum.rang YES	U	Z	*p*	Z Correct.	*p*	N signific. no	N signific. yes
Mean 1-4	41,032.00	9,371.000	2,806.000	-5.20811	0.000000	- 5.20849	0.000000	270	35

Relapse	N	Mean	Std. Deviation
0	270	18.61	32.40
1	35	44.32	51.94
Total	305		

Table 3. — *Assessment of the influence of the mean of four TATI collections in the metastases group.*

Variable	Mann-Whitney U Test (Data T without zer.sta) relative variable Metastases 1 Y/N Highlighted values are significant, $p < 0.05000$								
	Sum.rang NO	Sum.rang YES	U	Z	*p*	Z Correct.	*p*	N signific. no	N signific. yes
Mean 1-4	36,082.00	14,321.00	5,206.000	- 4.97475	0.000001	- 4.97512	0.000001	242	63

META1	N	Mean	Std. Deviation
0	242	19.58	30.33
1	63	37.61	56.38
Total	305		

lations were found in a group of patients with existing metastases and sans metastases, in whom the TATI levels differ greatly by significant mean marker level in the first four determinations (Mann-Whitney U = 5206,000; Z = - 4,97475; $p = 0.000001$). Thus an assessment of marker level after termination of therapy is quite essential. Significant elevation of TATI after treatment should be associated with negative prognosis due to relapse and metastases. Failures, that is metastases, were found in 63 (21%) patients, relapses in 35 (11%) patients, diagnosed one month to 11 years after treatment.

Discussion

There are several reports in the accessible literature regarding uses of TATI in prognosis of the courses of various neoplasms. Most numerous reports refer to the role of this marker in diagnosis of ovarian mucosa carcinoma. It was found that the level of TATI concentration rose evidently in the first stages of disease, later the tempo decreased and was correlated with the progress of disease. In the case of neoplasms of the reproductive organ, high concentration of TATI was observed both in urine and in serum. Austrian scientists conducted a study assessing the sensitivity of the TATI marker in women with endometriosis [13]. The results indicate that in the early stages the marker demonstrated little sensitivity, which gradually increased at the higher stages of disease. Some authors recommend the increased diagnostic sensitivity of the TATI marker connect its assessment with assessment of other marker, for example CA 125 [14]. In the case of pulmonary carcinoma, apart from TATI a determination of carcinoembryonic antigen (CEA) is recommended – the sensitivity of determination of both markers increases to about 74 per cent [15].

It was found that in the case of breast neoplasm the TATI level rises along with the stage of disease progress, but determination of TATI alone is not a sufficient prognostic indicator, and connecting it with other markers is clinically useless [15, 16].

Paju *et al.* in their study of patients suffering from prostate carcinoma observed that TATI expression increases along with the stage of cancerous progression and malignancy. It was demonstrated that high concentrations similarly to other types of tumor occur most frequently in the cases of malignant neoplasms, and sustained high concentrations may contribute to invasion and metastasizing [17]. In diagnosis of urine bladder carcinoma, TATI resulted out to be more useful than other commonly determined in serum markers, that is tissue polypeptide antigen (TPA), CEA, or the antigen of squamous cell carcinoma (SCC-AG). Depending on the progression stage, increased concentrations occur in 20% to 70% of patients suffering from urine bladder carcinoma, which indicates an essential role of TATI in monitoring the therapeutic process and in the assessment of its efficacy [18].

Studies indicating a significant prognostic value of the TATI marker in the diagnosis of ovarian carcinoma, of neoplasms of the urine bladder, and in postoperative observation of patients with renal carcinoma prompted researchers to analyze the clinical effectiveness of this marker [19-21]. Solakidi *et al.* found that TATI may have great clinical utility as supplementation of biomarkers in diagnosis and monitoring of malignant neoplasms of the digestive tract indicating its higher sensitivity than s-CEA [22].

The present study demonstrated that determination of the TATI level in patients with carcinoma of the uterine body accompanied by negative prognostic factors, defined on the basis of histopathological evaluation, does not show characteristic fluctuation of levels in relation to patients without those negative features. It has been found however, that the values of TATI in the group of patients with present negative factors are higher in relation to patients without negative features. It has been observed in the course of 17-year long follow-up that the elevations of the TATI marker level, which were determined on first check-up after finished therapy, correlated in a statistically highly significant manner ($p = 0.000000$) with cancer relapse and distant metastases ($p = 0.000001$), even in the cases where therapeutic failure occurred many years before its termination. Therefore, the authors suggest that assessment of the TATI marker immediately after termination of treatment is in prognostic terms the most important feature, which defines the probability of therapeutic failure in the cases of patients treated for carcinoma of the uterine body.

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