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Title: Prognostic and monitoring value of tissue inhibitors of matrix metalloproteinases TIMP-1 and TIMP-2 in patients with colorectal cancer

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**Prognostic and monitoring value of tissue inhibitors of matrix metalloproteinases
TIMP-1 and TIMP-2 in patients with colorectal cancer**

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Abstract

The aim of this study was to analyze TIMP-1 and TIMP-2 serum levels in patients with colorectal cancer (CRC) and to correlate the results with the pathological stage of the disease and outcome in order to evaluate the role of TIMP-1 and TIMP-2 serum levels as prognostic markers.

The investigation has been made on 82 patients with operable CRC without distant metastases, who had undergone blood tests in order to determine the TIMP-1 and TIMP-2 serum levels in the following points of time: preoperatively, as well as 3, 6, 9 and 12 months postoperatively.

Significant differences were found between serum levels of TIMP-1 and TIMP-2 obtained preoperatively and postoperatively, as well as significant association of serum TIMP-1 levels obtained preoperatively in CRC patients in stage I and III, in the 3th and in the 6th month ($p < 0.001$) postoperatively as defined points of time with the outcome of CRC patients. Serum TIMP-2 levels obtained preoperatively was significantly associated with the outcome of the CRC patients. Analysis of the obtained TIMP-1 and TIMP-2 serum levels in CRC patients showed statistically significant differences with: disease progression, occurrence of liver metastasis, prior to and post chemotherapy treatment.

The results derived a conclusion that the serum levels of TIMP-1 and TIMP-2 could be indicators for occurrence and progression of CRC, as well as valuable and useful markers for following the effects of chemotherapy treatment.

Keywords: colorectal cancer, TIMP-1, TIMP-2, prognosis

Introduction

Colorectal cancer (CRC) prognosis predominantly depends on the disease stage, but new prognostic factors are being investigated in order to determine disease progression and outcome in patients as well as postsurgical pharmacology treatment (Ferlay et al., 2010).

The correct staging of each CRC patient is crucial in order to plan an optimal treatment regimen. It is widely recognised that prognostic information based on clinical and histopathological investigation may be insufficient, although tumour stage and lymph node involvement are the main prognostic tools in evaluating cancer specific survival. It is questionable to expose a large number of patients to adjuvant treatment with considerable side effects without indications that they will benefit from such treatment. Finding prognostic markers to better identify patients with higher risk for poor survival would be valuable in order to customise pre- and post-operative treatment as well as enabling closer follow-up for these patients (Graziano and Cascinu, 2003; Zlobec and Lugli, 2008).

Matrix metalloproteinases (MMPs) are a family of extracellular structurally related zinc-dependent endoproteases capable of degrading all the extracellular matrix (ECM) components. MMPs play an important role in the physiologic degradation of ECM and are associated with tumor progression including invasion, migration, angiogenesis and metastasis (Graziano and Cascinu, 2003).

Tissue inhibitors of matrix metalloproteinases (TIMPs) are a family of natural MMPs inhibitors that appear to affect many aspects of cancer biology. TIMPs role is not restricted only to MMPs inhibition but can modulate many cellular processes as cell growth, invasion, migration, metastasis, and angiogenesis and can be both anti- and protumorigenic (Makitalo, 2010; Visse and Nagase, 2003). TIMPs have similar structure in about 30 to 40% and inhibit MMPs proteolytic activity building 1:1 noncovalent stoichiometric complexes. Inhibiting MMPs TIMPs have a role of remodeling of extracellular matrix (ECM). There are 4 types of TIMPs: 1, 2, 3 and 4. TIMP-1, -2, and -4 are present in soluble form and TIMP-3 is present in ECM (Leco et al., 1994).

TIMP-1 (tissue inhibitor of metalloproteinases-1, human collagenase inhibitor, fibroblast collagenase inhibitor, EPA-erythroid potentiating activity) was first detected in the culture of fibroblasts and represents 28.5 KD secretory protein whose mRNA is found in macrophages, keratinocytes, endothelial cells and fibroblasts (DeClerck et al., 1992; Welgus et al., 1981).

TIMP-1 inhibits activity of MMP-7, -14, -16, -19 and -24, but also has a role in the promotion and stimulation of cell growth by inhibiting apoptosis (Amour et al., 1998; Nagase et al., 2006). Elevated TIMP-1 levels in blood circulation was expected to be a useful prognostic indicator for cancer patients due to inhibitory effect on MMPs, but in a number of published studies claim otherwise because TIMP-1 inhibits the apoptosis.

Several previous studies of TIMPs role in various cancer diseases have shown contradictory results, and some of them have shown that serum levels of TIMPs may play important role as an indicator of occurring of CRC and its progression (Albini, 1991; DeClerck et al., 1992; Giaginis et al., 2009; Oberg et al., 2000).

In the present study we have measured TIMP-1 and TIMP-2 serum levels in patients with CRC and we correlated the results with the pathological stage of the disease and outcome in order to evaluate the role of TIMP-1 and TIMP-2 serum levels as a prognostic markers and markers that may indicate the changes in cancer disease progression.

Materials and methods

The study included a total of 82 previously untreated CRC patients, 30 females and 52 males (age range from 43 to 75 years, averaged 67.85) with operable CRC, without detectable distant metastases, who respected the medical instructions and were available for follow-up. All the patients underwent surgical resection of the primary neoplasm at the University Clinic for Abdominal Surgery in Skopje in the period of 2 years.

Blood samples from all the patients were drawn before surgical treatment, as well as 3, 6, 9, and 12 months postoperatively, in order to examine the TIMP-1 and TIMP-2 serum levels. None of the CRC patients had received chemotherapy before blood sample collection. To standardize clotting conditions, all serum samples were separated within 1 h after blood collection, aliquoted and stored at -80 °C until assayed.

Serum levels of TIMP-1 and TIMP-2 were determined using a quantitative solid phase sandwich enzyme-linked immunosorbent assay (ELISA) (R&D Systems, USA) according to the manufacturer's instructions. High concentrations of TIMP-1 and TIMP-2 were diluted with calibrator, to produce samples with values within the dynamic range of the assay.

The histopathological analysis of surgically removed operative material was made at the Institute of Pathology at the Faculty of Medicine, Skopje, where the pathological stage was defined for every patient according to the International Union Against Cancer (UICC-pTNM) and American Joint Committee on Cancer (AJCC), 2010.

Forty-three patients with Stage II B and III (A, B, C) received adjuvant chemotherapy, postoperatively at the Institute for Radiotherapy and Oncology in Skopje.

Correlations were made between the MMPs serum levels and the pathological parameters.

Statistical analysis

Descriptive statistics data are given according to normality of the distribution. Normality of the distribution was determined by Kolmogorov-Smirnov's test. Analysis of variance with Kruskal-Wallis test was used in the analysis of different sample types. In the case of significant results, the analyses were continued by pairing the variables and analyzing them with Mann-Whitney's U-test. Fisher's exact probability test and Pearson's Chi-Square test (r) were used for testing the association (linearity of the correlation of serum concentrations) between TIMPs and major prognostic variables in CRC, such as grade and stage. P-values less than 0.05 ($p < 0.05$) were considered as statistically significant.

Results

There have been 17 (20.73%) patients in stage I, 40 (48.78%) patients in stage II and 25 (30.48%) patients in stage III of the CRC. Lymph node metastases were substantiated in 25 (30.48%) patients and were not found in 57 (69.51%) patients with different pT category.

The majority of patients were with pT3N0M0 (26.82%), i.e. patients in stage II A of the disease, and the smallest number of patients were with pT4aN1M0 (4.87%), i.e. patients in stage III B of the CRC.

Table 1

The mean TIMP-1 levels in patients in all stages of the disease decreased after tumor resection, whereas the mean serum values in stage III demonstrated most intensive changes, unlike the mean serum values in CRC patients in stage I and II which showed mild changes. All three groups of followed patients showed decreasing values postoperatively, where the decline was most evident in 3th month postoperatively in all CRC patients at all determined stages.

Table 2

Mean serum levels of TIMP-1 in CRC patients in stage II remained approximately at the same level in further defined points of time, with a slightly increase in 9th and 12th month postoperatively.

Mean TIMP-1 serum levels of CRC patients in stage I showed approximately the same movement, while the curve mean TIMP-1 serum levels of CRC patients in stage III showed a plateau values from 3th to 6th month postoperatively, then abruptly increases at 9th month and again achieves plateau up to 12 months postoperatively.

Fig. 1

Most evident decline in mean serum levels of CRC patients was observed at 6th month postoperatively in all determined stages, and the most pronounced increase in mean serum levels was observed in CRC patients in stage III, especially in the defined points from 6th to 9th months postoperatively.

The explanation of this condition would be identical as in previously displayed results of the other investigated parameters, i.e. due to the change of condition of the disease in patients most of the stage III, in which is shown the largest percentage of lethal outcomes.

In Table 3 are presented significant associations in TIMP-1 and TIMP-2 and outcome of the CRC patients, where it is shown that serum levels of TIMP-1 and TIMP-2 preoperatively, as well as the TIMP-2 serum levels in 3th and 6th month postoperatively, are in a significant correlation with the outcome of the CRC patients.

Table 3

There were significant differences between the mean serum levels of TIMP-1 before tumor resection and 3th and 6th month ($p < 0.001$) postoperatively in CRC patients in stage I and III, between 3th and 6th month and 9th and 12th month postoperatively in CRC patients in stage III ($p < 0.001$ among all) and between preoperative and postoperative levels during defined control points of time in CRC patients in stage II.

Regarding mean serum levels of TIMP-2 obtained prior to surgical intervention and 6th month in all CRC patients stages postoperatively we found statistically significant differences between mentioned features ($p < 0.001$), as well as between 3th and 6th month and 9th and 12th month postoperatively in CRC patients in stage III ($p < 0.001$ among all).

The CRC patients with different stages who received and who didn't receive chemotherapy treatment, and their outcome are shown in Table 4.

Table 4

In twenty patients that were particularly monitored to the appearance of liver metastasis and subsequently were administered first-line chemotherapy treatment (in patients with stage I and II A) and additional second-line chemotherapy treatment (in patients with stage II B and III).

The liver metastasis was substantiated by imaging techniques and liver biopsy with histological confirmation with the following distribution: in 2 patients of stage I, 3 patients of stage II A, 4 patients of stage II B, 8 patients of stage III B and in 3 patients of Stage III C.

In these patients' blood samples were drawn additionally for quantifying of TIMPs serum levels prior to and post chemotherapy treatment in order to determine variability of serum levels for their role as markers, which could indicate a change in the condition of the disease in CRC patients, that indicate possible progression and occurrence of metastases.

The mean serum levels of TIMP-1 and TIMP-2 in CRC patients obtained prior to chemotherapy treatment reached approximately the levels of the mean values of the group of CRC patients in stage IIIC in 12th month separately, while the mean serum levels abruptly decreased ($p < 0.001$) post chemotherapy treatment, i.e. similar values were obtained after resection of the primary neoplasm.

Table 5

Fig. 2

Discussion

TIMPs are also linked with a wide variety of other functions of cell growth and survival, and at least some of these functions seem to be independent of MMP inhibition. TIMP-1 and TIMP-2 were first identified as proteins potentiating the epo-effect on proliferation and differentiation of erythroid progenitor cell (Gasson et al., 1985).

Additionally, the cell-growth promoting effects of TIMP-1 and -2 have been shown in various normal and malignant cell lines (Hayakawa et al., 1998; Yamashita et al., 1996). There

is some evidence supporting the hypothesis that TIMPs' role as growth stimulators and MMP inhibitors is functionally as well as possibly structurally separated (Chesler et al., 1995).

The role of TIMPs in cancer is very complex, and acknowledging the fact that angiogenesis and ECM degradation are very crucial in tumor cell spreading and metastasis formation, it is obvious that TIMPs have a role of some importance in cancer. Previously the TIMPs' role as MMP inhibitors seemed most important, and there is clear evidence that downregulation of TIMP-1 and TIMP-2 expression is associated with increased invasiveness of tumors, while overexpression leads to reduced tumor growth and metastasis formation in tumors of various origins (Chesler et al., 1995).

In meta-analysis for determining plasma and serum levels TIMP-1 as predictors of the outcome of CRC patients, Lee et al. (2011) reported that the elevated TIMP-1 values obtained in blood samples, as well as expression of TIMP-1, are associated with shorter survival time.

Contemporary researches have been made in order to determine the significance of the serum TIMP-1 levels in patients of pre-invasive to invasive CRC, in order to diagnose the malignancies and to determine TIMP-1 influence on the disease's outcome (Pellegrini et al., 2000).

TIMP-2 (tissue inhibitor of metalloproteinases-2, CHIAMP-chondrocyte-derived inhibitor of angiogenesis and metalloproteinase activity, CSC-21K) could either promote the activity of MMP-2 through interaction with Mo1-MMP or to inhibit through direct action (Stetler-Stevenson, 2008). TIMP-2 can reduce proliferation of endothelial cells, fibroblasts and some tumor cell lines. In a mouse model, TIMP-2 could protect from CRC and reduce the growth of the existing metastasis (Baker et al., 1998; Brand et al., 2000; Stetler-Stevenson and Seo, 2005).

Some researchers investigated TIMP-1 and -2 serum levels in 97 CRC patients and discovered a significant correlation between elevated TIMP-1 serum levels and shorter survival time, which led them to the conclusion that the elevated TIMP-1 serum levels are an independent prognostic factor for survival in patients with CRC (Giaginis et al., 2009).

In the examination conducted by Oberg et al. (2000) on 158 CRC patients was confirmed that the elevated serum TIMP-1 levels are significantly higher in patients with an advanced stage of the disease, and that the increased values of TIMP-2 were in correlation with worse prognosis.

Conclusion

In the present study significant differences were found between serum levels of TIMP-1 and TIMP-2 obtained preoperatively and postoperatively, as well as significant association of serum TIMP-1 levels obtained preoperatively, in the 3th and in the 6th month as defined points of time with the outcome of CRC patients. Serum TIMP-2 levels obtained preoperatively was significantly associated with the outcome of the CRC patients.

Analysis of the obtained TIMP-1 and TIMP-2 serum levels in CRC patients showed statistically significant differences with: disease progression, occurrence of liver metastasis, prior to and post chemotherapy treatment.

The results derived a conclusion that the serum levels of TIMP-1 and TIMP-2 could be indicators for occurrence and progression of CRC, as well as valuable and useful markers for following the effects of chemotherapy treatment.

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Резиме

Прогностичко и мониторирачко значење на ткивните инхибитори на матрикс металопротеинази ТИМП-1 и ТИМП-2 кај пациенти со колоректален карцином

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Клучни зборови: колоректален карцином, ТИМП-1, ТИМП-2, прогноза

Целта на оваа студија беше да се анализираат серумските нивоа на ТИМП-1 и ТИМП-2 кај пациенти со колоректален карцином (КРК), да се корелираат резултатите со патолошкиот стадиум на болеста и со исходот, и притоа да се евалуира улогата на серумските нивоа на ТИМП-1 и ТИМП-2 како прогностички маркери.

Истражувањето беше направено на 82 пациенти со операбилен КРК без далечни метастази, од кои беа земени крвни примероци за одредување на серумските нивоа на ТИМП-1 и ТИМП-2 во следните временски точки: предоперативно, како и 3, 6, 9 и 12 месеци постоперативно.

Беа најдени сигнификантни разлики помеѓу серумските нивоа на ТИМП-1 и ТИМП-2 предоперативно и постоперативно, исто така беше утврдена сигнификантна поврзаност на серумските нивоа на ТИМП-1 предоперативно кај пациентите со КРК во стадиум I и III, во 3-от и 6-от месец ($p < 0,001$) постоперативно. Серумските нивоа на ТИМП-2 добиени предоперативно беа сигнификантно поврзани со исходот на пациентите со КРК. Анализата на добиените ТИМП-1 и ТИМП-2 серумски нивоа кај пациентите со КРК покажа статистички значајни разлики со прогресијата на болеста, со вредностите пред и после хемотерапиското лекување.

Од резултатите се сугерира заклучок дека серумските нивоа на ТИМП-1 и ТИМП-2 би можеле да служат како индикатори за појавата и прогресијата на КРК, а

воедино може да бидат вредни и корисни маркери за следење на ефектите од хемотерапиското лекување.

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Table 1. Staging of CRC patients according to AJCC

Stage	pTNM	N (82)	Percent (%)
I	pT1N0 M0	8	9.75
I	pT2 N0 M0	9	10.97
II A	pT3 N0 M0	22	26.82
II B	pT4a N0 M0	18	21.95
III B	pT3 N1b M0	7	8.53
III B	pT3 N2a M0	9	10.97
III B	pT4a N1b M0	4	4.87
III C	pT4a N2b M0	5	6.09

Table 2. Mean serum TIMPs (ng/mL) values in terms of stages and defined points of time

Defined points in time	TIMP-1	TIMP-1	TIMP-1	TIMP-2	TIMP-2	TIMP-2
	Stage I	Stage II	Stage III	Stage I	Stage II	Stage III
Preoperat.	176.2	228.66	348.62	150.01	222.56	333.29
SD	46.87	66.11	102.97	31.35	65.11	97.24
Max	277.5	362.5	633	220.5	329.4	586
Min	115.4	89.5	175	102	65.5	162
3 months postop.	157.74	215.05	257.98	240.91	201.49	245.99
SD	54.82	215.05	50.98	48.3	65.53	50.49
Max	355	64.86	372.4	324.3	313.5	334.3
Min	137.5	50.6	176	136.4	58.5	126.7
6 months postop.	156.16	215.51	257.74	121.78	194.69	240.91
SD	34.3	64.19	54.82	28.83	64.86	48.3
Max	209	345.5	355	170.3	307.4	324.3
Min	95	55.5	137.5	79.8	29.2	136.4
9 months postop.	161.11	216.43	334.18	132.05	201.27	310.5
SD	40.45	59.54	109.13	30.61	62.44	104.8
Max	225	360	603	199	305.6	561
Min	82	100.5	150.2	80.8	70.4	135.6
12 months postop.	169.23	219.82	336.69	138.17	203.36	321.45
SD	44.88	60.05	102.09	28.82	58.57	96.02
Max	262	155.2	610	205	300.4	550.5
Min	110	110.5	165	92.5	90.7	147

Table 3. Significant correlations of serum levels of TIMPs (ng/mL) and CRC patients' outcome

Parameter	<i>p</i>	R
Stage	<0.001	0.635
pT	<0.005	0.331
pN	<0.005	0.618
TIMP-1 preoperatively	<0.001	4.0279
TIMP-1; 3 months postop.	<0.001	4.0595
TIMP-1; 6 months postop.	<0.001	4.6553
TIMP-1; 9 months postop.	NS	/
TIMP-1; 12 months postop.	NS	/
TIMP-2 preoperatively	<0.001	4.5372
TIMP-2; 3 months postop.	NS	/
TIMP-2; 6 months postop.	NS	5.1124
TIMP-2; 9 months postop.	NS	/
TIMP-2; 12 months postop.	NS	/

NS – not significant

Table 4. Distribution of the CRC patients according received and non-received chemotherapy treatment and outcome

Stadium n=82	With		Without		Poor	
	chemo-therapy	%	chemo-therapy	%	outcome	%
Stadium I	/	/	17	20.73	6	7.31
Stadium IIA	/	/	22	26.82	8	9.75
Stadium IIB	18	21.95	/	/	11	13.41
Stadium IIIB	20	24.39	/	/	15	18.29
Stadium IIIC	5	6.09	/	/	3	3.65
Total	43	52.43	39	47.56	43	52.43

Table 5. Mean serum levels of TIMP-1 and TIMP-2 in 20 patients prior to and post chemotherapy treatment

Time	TIMP-1 (ng/mL)	TIMP-2 (ng/mL)
Prior to chemotherapy	329.03	386.19
Postchemotherapy	164.62	271.24

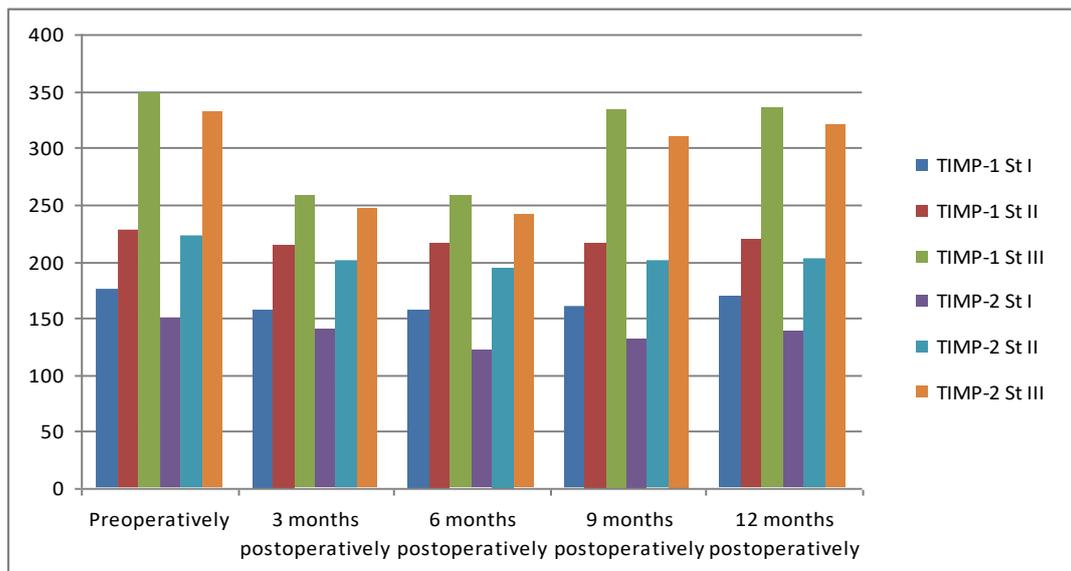


Fig. 1. Mean serum TIMP-1 (ng/mL) and TIMP-2 (ng/mL) levels in terms of stage and time.

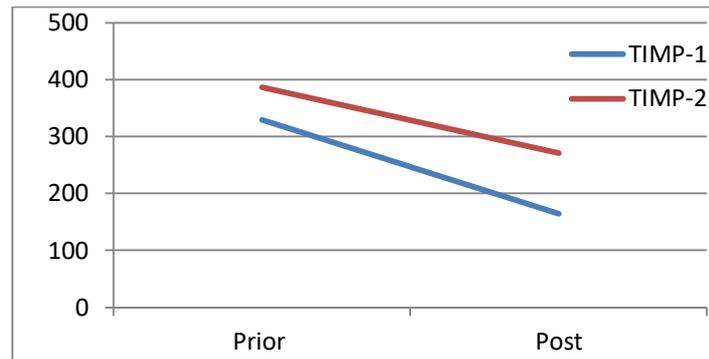


Fig. 2. Mean serum TIMP-1 (ng/mL) and TIMP-2 (ng/mL) levels prior to and post-chemotherapy treatment.