TNF-α levels in cachectic cancer patients

K.E. Nenova,[1] D.E. Kovatchev[2]

[1]*Department of Propedeutics of Internal Medicine*
[2]*Department of Biology, Medical University, Varna, Bulgaria*

Επίπεδα TNF-α σε καχεκτικούς καρκινοπαθείς

Περίληψη στο τέλος του άρθρου

Key words: Advanced carcinoma, Cachexia, Cytostatic, TNF-α levels

TNF-α is a powerful stimulating cytokin which influences various types of cells. A surplus of TNF-α causes a dramatic change of endothelial cells and contributes to cachexia development.[1] Dezube at al[2] consider that the elevated TNF-α values found in 50% of cancer patients in the active stage of the disease can result in cachexia.

Published data reveal an obvious interest in the problem of finding a relationship between the endogenic TNF-α generating activity and its biological significance, its contribution to the pathogenic symptoms and to cancer ca-chexia, and its role in tumour genesis, features which define to a large extent the prognosis concerning the therapy and the survival of patients. Detailed results have been reported by Balkwill et al.[3]

The objective of this study was to investigate the serum levels of TNF-α cytokin in advanced carcinoma patients and to attempt an evaluation of its prognostic significance and its relation to cancer cachexia.

Submitted 27.7.2000
Accepted 23.11.2000

MATERIAL AND METHOD

The study included 71 patients with an average age of 53.6±1.8 years, 51 women and 20 men, with advanced carcinoma (stage IV) at various sites, as follows: 19 ovarian cancer, 24 histologically verified pulmonary cancer and 28 breast cancer. The distribution of patients depending on the site and the histological carcinoma variant is shown in table 1. All patients had chemotherapy under various schemes, depending on the neoplastic disease site (tabl. 2).

In 3 patients with pulmonary carcinoma the serum TNF-α levels were examined once, before starting the chemotherapy. For the remaining 68 patients measurements were made both before, and after the 3rd course of treatment.

The serum TNF-α levels were measured by enzyme-linked-immunosorbent-assay (ELISA) using the Human Tumor Necrosis Factor alpha ELISA kit by ENDOGEN, Inc, MA, USA. The microwell strips were pre-coated with TNF-α antigen. The tests were performed according to the instructions of the manufacturer.

All samples were tested in triplicate and the mean was calculated. The TNF-α reference plasma values were 0–4.9 pg/mL and the reference serum values were 0–0.5 pg/mL.

Table 1. Distribution of patients studies.

Sex	Men		20
	Women		51
Cancer site	Lung		24
	Breast		28
	Ovary		19
	Lung	Adenocarcinoma	2
		Non small cell	8
		Small cell	14
Histologic variant	Breast	Infiltrative lobular	19
		Papilliferous adenocarcinoma	9
	Ovary	Papilliferous adenocarcinoma	12
		Poorly differentiated adenocarcinoma	7
Local radiotherapy			3
Hormone-therapy			21
TGT			23

Table 2. Treatment of the patients studied with basic cytostatic therapy.

Treatment		
Operative	Mastectomy	26
	Laparohysterectomy	14
	Lobectomy	1
Chemotherapy	*Lung*	24
	Cylophosphamide	
	Etoposit	
	Epirubicin	
	Ovary	19
	Epirubicin	
	Cyclophosphamide	
	Carboplatina	
	Breast	28
	Epirubicin	
	Cyclophosphamide	
	5-Fluorouracil	

Estimations were made of the cancer cachexia progress and of the quality of life using the Karnofsky scale.

The control group included 16 clinically healthy persons of average age 54.6±1.8, with serum TNF-α levels of 0–0.2 pg/mL and average activity of 0.1 pg/mL. The results were analysed statistically by variation methods and correlation assays.

RESULTS AND COMMENT

Elevated serum TNF-α levels were found in 50 (70.42%) of the patients, examined with the ovarian carcinoma patients accounting for the highest relative share –15 (78.9%) with activity of from 1.5 to 28.7 pg/mL, average value 8.2 pg/mL, followed by the localized pulmonary carcinoma patients –18 (75%) with activity of from 0.8 to 32 pg/mL, average value 5.6 pg/mL. The breast cancer patients accounted for the lowest relative share –17 (60.7%) with activity of from 3.2 to 21.3 pg/mL, average activity 3.1 pg/mL.

No correlation was established between high cytokin levels and the histological carcinoma variant irrespective of its localization, although some authors report more frequently elevated TNF-α levels in patients with planocellular pulmonary carcinoma.[4]

In three pulmonary carcinoma patients (tabl. 3) at stage IV with the highest TNF-α levels, 26.1, 29.6 and 32 pg/mL respectively, average activity 29.2 pg/mL, a correlation (r=+0.48) was established between the activity of the serum TNF-α levels and the stage of malignancy. These patients were in a severe general condition, with pronounced cancer cachexia and functional activity of 30 points on the Karnofsky scale. They could not undergo a dynamic TNF-α test, as they died in the course of the study. Similar results were reported by Chiczewska et al,[5] who found high TNF-α and IL-6 concentrations in 20 patients with advanced planocellular pulmonary cancer, correlated with serious general condition of the patients.

Correlation was found between the degree of cancer cachexia and the activity of the serum TNF-α levels (r=+0.53). Of the patients studied with the highest initial TNF-α levels, 4.5 to 28.7 pg/mL and average activity 15.8 pg/mL (tabl. 3), 32 had a significant weight loss

Table 3. Dynamics of the serum TNF-α levels before and during treatment with basic cytostatic therapy.

Group		Control group n=16	Patients with death issue n=3	Patients with unsatisfactory effect from the therapy n=32	Patients with relatively good effects from the therapy
Serum TNF-α levels, pg/mL	Initial	0–0.2	26.1–32	4.5–28.7	0.8–3.7
	Sx	0.1±0.1	29.2±2.9	15.8±8.8	2.6±1.0
	In the course of treatment			15.5–41.9	0.1–0.3
	Sx			28.6±9.4	0.2±0.1
	P			<0.001	<0.001
Body weight, kg	Expected		78–85	65–89	59–84
	Sx		83.3±4.7	76±8.1	71.5±8.3
	Initial		56–64	62+82	58–81
	Sx		60.7±4.1	70.7±9.2	70.0±7.6
	In the course of treatment			52–74	60.5–82.5
	Sx			63.1±7.1	72.0±7.3
Functional activity points	Initial		30	40–60	50–70
	Sx		30±0.0	50±10.0	60±10.0
	In the course of treatment			20–50	60–90
	Sx			30±11.2	80±9.25

of on average 5 kg, and a functional activity of on average 50 points according to the Karnofsky scale. A dynamic follow-up of TNF-α values indicated enhancement after the third course of treatment of from 15.5 to 41.9 pg/mL, average 28.6 pg/mL ($P<0.001$), while at the same time the patients lost up to 11% of their initial body weight and their functional activity decreased by an average of 20 points. For these patients, irrespective of the site of the neoplastic process, an unsatisfactory effect was reported from the basic cytostatic therapy, since the X-ray examination of the pulmonary carcinoma patients showed progressive tumor process, while the mammography and ultrasound examination of the breast and ovarian cancer patients respectively, demonstrated recurrent tumor process. X-ray examination revealed occurrence of pulmonary metastases in 7 patients, computer tomography showed cerebral metastases in 2 pa-tients, and ultrasound examination demonstrated hepatic metastases in 8 patients.

At the same time 15 patients (21.12%) (tabl. 3), 4 with pulmonary, 8 with breast and 3 with ovarian carcinoma, had initial TNF-α levels of 0.8 to 3.7 pg/mL, with average activity 2.6 pg/mL, low-degree weight reduction and functional activity defining the quality of life on the average 60 points. These patients had relatively good effects from the cytostatic therapy as estimated by X-ray, mammography, computer tomography and sonography which showed stationary tumor process and lack of metastases. Following cytostatic therapy in these 15 patients the cytokin levels decreased considerably to 0.2 pg/mL ($P<0.001$), their functional activity went up to an average of 80 points, and their weight increased by 2 kg on the average (tabl. 3).

Four ovarian carcinoma, 11 breast carcinoma and 3 pulmonary carcinoma patients with a relatively good effect from the therapy, namely stationary tumor process with no occurrence of further hematogenous metastases and no cancer cachexia progress, and with preservation of their initial functional activity of average 70 points, had normal initial and dynamically followed serum TNF-α levels.

In the 50 (70.42%) advanced carcinoma patients the serum TNF-α levels were considerably higher ($P<0.001$) than in the healthy control group (tabl. 3) and that they increased dynamically with the development of metastases and the tumor progress, irrespective of the site of carcinoma. Patients with elevated TNF-α levels had an average loss of body weight of 5 kg and a correlation $r=+0.53$ was found between the plasma cytokin activity and the cancer cachexia stage.

The 15 (21.12%) patients who responded positively to chemotherapy had a considerable ($P<0.001$) decrease of the TNF-α levels as compared to their initial levels.

These results provide the grounds for considering that elevated serum TNF-α levels on the one hand could have a prognostic value for pulmonary, ovarian and breast carcinoma patients, and on the other hand they could serve as evaluation criteria for the effectiveness of cytostatic therapy.

In conclusion elevated serum TNF-α activity can have a prognostic significance for advanced cancer patients in relation both to the faster progress of the tumour process and their survival, and to the therapeutic effect of cytostatic treatment on the disease.

ACKNOWLEDGEMENT

We thank Dr Sophia A. Bonanou-Tzedaki, Associate Professor of Biochemistry at the University of Thessaly, Larissa, Greece, for advice and critical reviewing of the manuscript of this paper.

ΠΕΡΙΛΗΨΗ

Επίπεδα TNF-α σε καχεκτικούς καρκινοπαθείς

K.E. NENOVA,[1] D.E. KOVATCHEV[2]

[1]Department of Propedeutics of Internal Medicine, [2]Department of Biology, Medical University, Varna, Bulgaria

Αρχεία Ελληνικής Ιατρικής 2000, 17(6):619–622

Μελετήθηκαν τα επίπεδα του TNF-α στον ορό 71 ασθενών (51 άνδρες και 20 γυναίκες, ηλικίας 53,6±1,8 ετών) με καρκίνο σταδίου IV διαφόρων εντοπίσεων, πριν και κατά τη διάρκεια της θεραπείας, καθώς και σε 16 υγιείς μάρτυρες. Ο προσδιορισμός των επιπέδων του TNF-α έγινε με ELISA. Σε 50/71 (70,4%) ασθενείς, τα πριν από τη θεραπεία επίπεδα TNF-α βρέθηκαν σημαντικά αυξημένα ($P<0,001$). Σε 32/71 (45%) ασθενείς παρατηρήθηκε συσχέτιση ($r=0,53$) των επιπέδων του TNF-α με το βαθμό της καρκινικής καχεξίας. Σε 15/71 ασθενείς, οι οποίοι παρουσίασαν καλή ανταπόκριση στην κυτταροστατική θεραπεία, παρατηρήθηκε, κατά τη διάρκειά της, σημαντική ($P<0,001$) ελάττωση των επιπέδων του TNF-α (από 2,6 σε 0,2 pg/mL).

Λέξεις ευρετηρίου: Καρκίνος, Καχεξία, Κυτταροστατικά, TNF-α

References

1. TRACEY KJ. Cachectin (TNF–tumour necrosis factor). *Lancet* 1989, i:1112–1115
2. DEZUBE BJ, SHERMAN LM, FRIDOVICH-KEIL JL. The use of oral pentoxifylline in cancer cachexia. *Cancer Res* 1990, 50:6806–6810
3. BALKWILL F, BURKE F, TALBOT D. Evidence for tumor necrosis factor (cachectin) production in cancer. *Lancet* 1987, ii:1229–1232
4. YAMAGUCHI T, YAMAMOTO Y, YOKOTA S, NAKAGAWA M. Involvement of interleukin-6 in the elevation of plasma fibrinogen levels in lung cancer patients. *Jpn J Clin Oncol* 1998, 28:740–744
5. CHYCZEWSKA E, MROZ MR, KOWAL E. TNF-alpha, IL-1 and IL-6 concentration in bronchoalveolar lavage fluid (BALF) of non-small cell lung cancer (NSCLC). *Rocz Akad Med Bialymst* 1997, 42: 123–125

Corresponding author:

D.E. Kovatchev, Medical University, Department of Biology, 55 Marin Drinov street, 9002 Varna, Bulgaria