Cytokines levels in prostate adenocarcinomas

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Abstract

In this research, we determined the levels of IL-2, IL-6 and TNF-α at 60 patients with prostate adenocarcinomas situated in II, III and IV stages. The method used was ELISA quantitative. We observed that the IL-2 levels were normal in II stage, and the levels of IL-6 and TNF-α were lightly increased. In III and IV stages of prostate cancer the levels of IL-2 were very low and the levels of IL-6 and TNF-α were very increased. The high levels of pro-inflammatory cytokines are correlated with diseases evolution. The decrease of IL-2 levels in advanced prostate cancer goes to the decrease of immune response in prostate cancer.

Keywords: *cytokines, prostate cancer.*

Introduction

Prostate cancer is nowadays considered a world health problem, the most frequent cancer in men following the skin cancer and representing the second mortality cause by cancer. The rate of mortality by prostate cancer is variable at a world level; the highest of which was registered in Norway and Switzerland. At the end of 1980, the prostate cancer incidence rapidly increased in USA, that's probably due to the introduction of screening by PSA (Prostatic Specific Antigen) therefore allowing the earlier discovering of the disease and, as a consequence decreasing its incidence, during the last years in USA [1, 2].

In Asia countries this incidence, though for 10 times lower than in USA, rapidly increased, probably due to the larger and larger adaptation of the occidental style of life [1].

Prostate cancer is seldom diagnosed before the age of 50, its incidence significantly increasing between 60–80 years old. The immune system in its complexity comprises a series of components representing importance effectors of the body resistance towards the appearance and development of a tumor, the concept being known as the theory of the immune watching.

Anti-tumoral immunity is prevalently a cell-type one, the main components being the cytotoxic T-lymphocytes, NK cells, activated macrophages and also the diverse cytokines, some of which playing a regulatory part, and another ones having an antitumoral effect [3, 4].

In the tumor – immune system relation of the host, two main elements can intervene: the oncogene potential of the tumor and the existence of some deficiencies of the immune system, which are increased at the same time stages [5–7].

Objectives

Starting from the special role of the immune system, antitumoral protection and especially the cytokines role in molding the immune response and, as it is known that in neoplasias it has always existed an immune deficit which increases with the disease advancing, we proposed to determine a number of cytokines in a group of patients with prostate cancer in different stages of the disease.

Material and methods

We studied a group of 60 patients between 50–70 years old being clinically and anatomo-pathologically diagnosed with prostate adenocarcinoma; they were in the II, III and IV stages of the disease when discovered, before the specific treatment.

The patients were traced out in the Clinics of Urology and Oncology within the Emergency County Hospital of Craiova. As concerning the evolutional stage, a number of 21 patients were in the IInd stage, 14 in the IIIrd, and 25 in the IVth stage (metastasis).

Anatomo-pathologically, all the patients presented well and moderate differentiated adenocarcinomas showing different patterns of growing after Gleason. So, most of the patients in the IInd stage present very rare G_1 (Figure 1a) and G_2 Gleason score (Figure 1b); those in the IIIrd and IVth stages present the Gleason scores: G_2, G_3 (Figure 1c), and G_4 (Figure 1d).

The following cytokines were determined in these patients: IL-1, IL-6 and TNF-α.

We used the indirect ELISA technique of quantitative sandwich type. The normal values for each interleukin were the following: IL-6 <10 pg/ml; TNF-α <13 pg/ml; IL-2 = 5–15 pg/ml.

Results and discussions

IL-2

IL-2 is a glycoprotein with a molecular weight of 15–17 kD made up of 133 amino-acids and it is produced by Th1 lymphocytes but also by cytotoxic T-lymphocytes after antigenic stimulation with an effect on proliferation and activation some other

T-lymphocytes (with producing some other IL-4, IFN lymphokines) and also on NK cells, these latter having the capacity of lyses several types of cells including the tumoral ones.

IL-2 antitumoral effect was supposed to follow the generation of the macrophage-dependent suppression, neoprotein increasing, the level of IL-2 soluble receptors (sIL-2R) and the cortizol production [8, 9].

IL-2 values in the studied group were different according to the tumor stage compared to the control group. So, in the IInd stage patients, the values of IL-2 were about 25 pg/ml very closed to the control group.

In the IIIrd stage patients, the value were even more increased than the IInd stage patients with an average of 27 pg/ml, despite the fact that the clinical evolution is advanced for all that these patients presented a protective immune response.

The situation was totally different in the patients with metastasis prostate cancer (IVth stage) where IL-2 levels were much decreased compared to the control group, some of the patients having values even much under the inferior limit of normal. This is probably due to the immune system degradation during the advanced stages of disease (Figure 2).

TNF-α

TNF-α is a 17 kD protein secreted by cells such as: monocytes / macrophages, T, B and NK lymphocytes, neutrophiles, astrocytes, endothelial cells, smooth muscle cells; the protein proved to be an important antitumoral agent with cytotoxic, cytostatic and immuno-modulating effects. TNF-α is an acute phase reactant by participating into the vascular phases of the inflammation.

TNF-α produces tumoral necrosis; its action is not due to the direct cytotoxic effect on the malign cell but to both the hemorrhage hypoxia at the level of the tumor. It happened by destroying the capillary endothelium, releasing the local coagulation, fibrin forming and sanguine vessels stopping up [10–12].

The values of TNF-α for the group studied by us presented significant variations according to the tumor stage. So that, if the values were situated between normal limits during the IInd stage, and in the IIIrd stage they are slightly over normal (average 18 pg/ml), in the IVth stage the average is 10 pg/ml, the TNF-α values were increased compared to the control group and with normal accepted values (<18 pg/ml) with an average of 38.5 pg/ml (Figure 3).

TNF-α significant increasing in the IVth stage of prostate cancer do not translate an antitumoral benefic effect of that cytokine but an increased of the latter from peritumoral inflammatory area which is a source of TNF-α; all those increasements stressed the denutrition secondary effects such as anorexia and weakening, effects quickening the end of the disease.

IL-6

IL-6 is a protein having a molecular weight between 21–45 kD made up of 184 amino-acids synthesized into the body by several cells: fibroblasts, monocytes, macrophages, T- and B-lymphocytes, osteoblasts, hepatocytes, mesangial cells, tumoral clones – sarcoma, glyoblastoma, melanoma, renal carcinoma and urinary gallbladder [13]

Together with IL-2 and IFMγ it activates T-lymphocytes and changes the MK into the LAK lymphocytes. It also has the capacity to induce the acute phase reactants of the inflammation being considered an acute phase protein just like TNF-α.

IL-6 variations were also presented according to the evolutional stage of the prostate cancer with normal values in the IInd stage (9.21 pg/ml) slightly increased in the IIIrd stage (16.6 pg/ml) and very increased in the IVth stage (average 70.88 pg/ml) (Figure 4).

The increased values in the metastasis stage of the prostate cancer may probably be explained by the fact that tumoral cells can synthesize IL-6 [14].

Conclusions

In the later stages of prostate adenocarcinomas does not exist an emphasized immune deficiency especially.

IL-2 as a cytokine modulating the immune response present much decreased values in the IVth advanced stage.

TNF-α presents increased values in the advanced prostate cancer stages, which emphasize the already increased immune deficiency in this stage thus quickening the end of the disease.

In the metastasis prostate cancer, in the future, it is possible for IL-2 to be used as a therapy; it was already tested in the metastasis renal cancer where it proved his efficiency, being associated to interferon (IFN) and TNF. Therapy with TNF becomes a matter of future for the prostate cancer, its efficiency being proved by intratumoral administration in gallbladder cancer.

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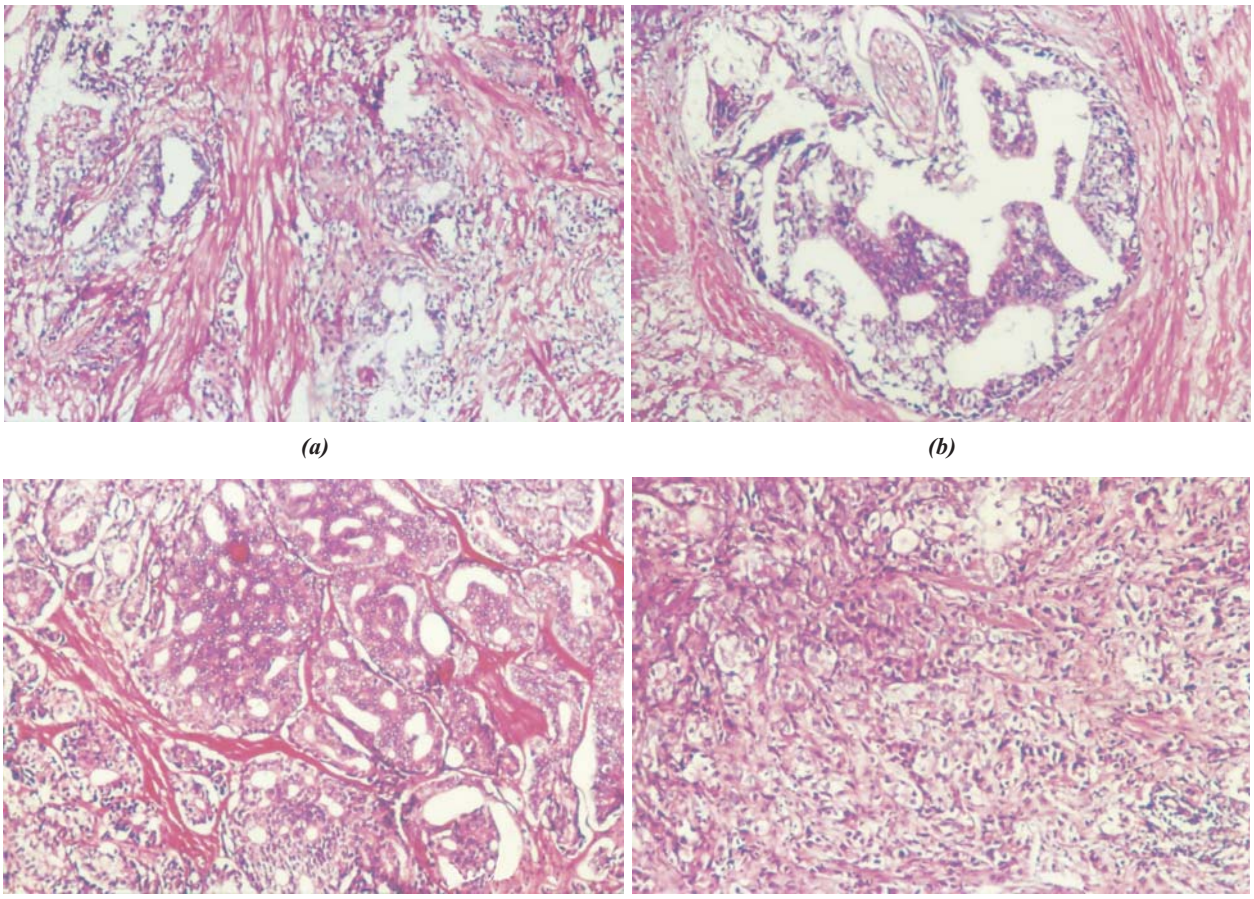

(a) *(b)*

(c) *(d)*

Figure 1 – *Well and moderate differentiated prostate adenocarcinomas showing different Gleason (G) scores: (a) – G_1, IInd stage (very rare); (b) – G_2, IInd stage; (c) – G_2, G_3, IIIrd and IVth stage; (d) – G_4, IIIrd and IVth stage*

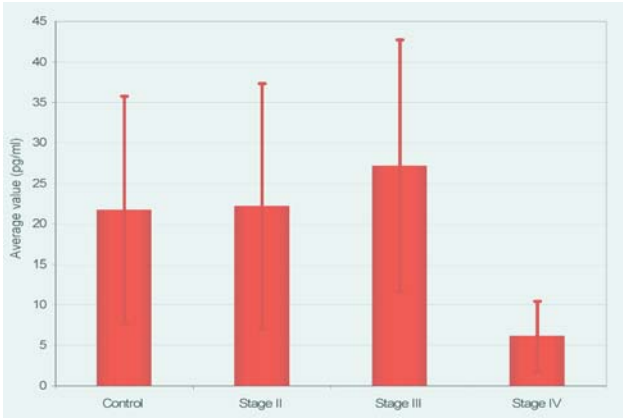

Figure 2 – *Average values and IL-2 standard deviation in the control group and three stages*

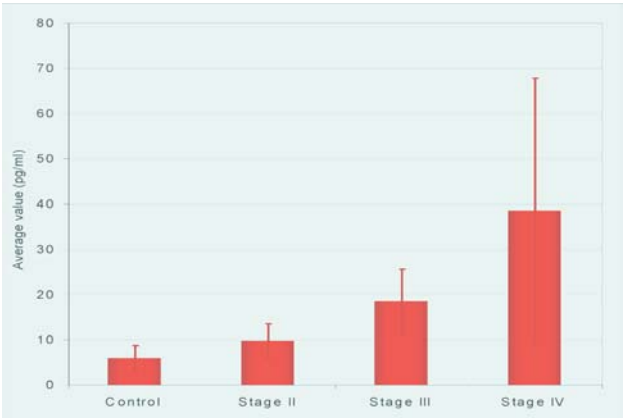

Figure 3 – *Average values and TNF-α standard deviation in the control group and three stages*

Figure 4 – *Average values and IL-6 standard deviation in the control group and three stages*

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