



Serum Haptoglobin, CA 125 and Interleukin 6 Levels in Malignant and Non-Malignant Tumors of the Ovary

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Abstract. In sera of women with malignant and non-malignant ovarian tumors, concentrations of the following proteins were determined: haptoglobin, measured by the reactions either with hemoglobin (Hp-Hb) or with concanavalin A (Hp-Con A), CA 125 antigen and interleukin 6 (IL-6). Besides preoperative data, obtained from all the patients and the group of healthy women, in the patients with ovarian cancer (III/IV FIGO stages) effects of administration of cytostatics were measured by monitoring changes in the levels of the examined parameters through the course of the therapy. All the results were submitted to statistical evaluation which showed differences and correlations among definite groups (normal/non-malignant, normal/cancers, non-malignant/cancers). Similar results were obtained for Hp-Hb and CA 125 determination. Moreover, a correlation between haptoglobin level and age was found. Patterns of monitoring revealed a surprising absence of Hp-Con A interaction in some cases.

Key words: haptoglobin-hemoglobin; haptoglobin-concanavalin A; interleukin 6; CA 125; ovarian cancer.

Introduction

Of all gynecologic malignancies, ovarian cancer has the lowest overall survival time. Most patients have an advanced stage of the disease at the time of diagnosis. Therefore, numerous attempts have been undertaken to improve the preoperative diagnosis and prognosis by application of suitable tumor marker analysis. A variety of tumor markers have been analyzed in ovarian cancer (enzymes, hormones, cytokines, growth factors, oncogenes, oncofetal proteins, glycoconjugates, sialic acid etc.)^{3, 12, 35}. Some determinations have been shown to be of insufficient sensitivity or specificity regarding epithelial tumors. The management of patients with epithelial ovarian cancer, especially when establishing response to treatment or predicting clinical outcome can

be sometimes improved by combining detection of different serum markers.

Evaluation of laboratory tests for ovarian carcinoma has been a subject of our studies for several years^{11, 40-42}. Special interest has been directed to haptoglobin (Hp), a genetically determined α_2 -acid glycoprotein belonging to “acute phase” reactants, present in most body fluids. Haptoglobin is composed of two α (light) and two β (heavy) chains. Oligosaccharides, located on β chains, consist of N-acetyl-glucosamine, mannose, galactose, fucose and sialic acid; they are present as bi- and triantennary N-linked glycans¹⁰.

Haptoglobin forms a stable complex with hemoglobin (Hb), showing an activity of “true” peroxidase. This property has become a basis for some methods of Hp quantification²². On the other hand, oligosaccharide

chains of Hp enable to bind plant lectins. Such a complex with a mannose specific lectin concanavalin A (Con A), was applied in lectin-ELISA determination of Hp in body fluids^{23, 24}.

In the present work, parallelly to Hp, two other serum components CA 125 and interleukin 6 (IL-6), were studied. CA 125 is a high molecular weight glycoprotein identified by a murine monoclonal antibody raised against the serous ovarian cancer cell line OVCA 433¹. The Ca 125 assay has been the most widely used method for serum marker for epithelial ovarian cancer^{6, 14, 16, 18, 19, 32, 34, 36}. IL-6 may be a useful tumor marker in some patients with epithelial ovarian cancer, as it correlates with the tumor burden, clinical disease status, and survival⁴. On the other hand, IL-6 being present at very high levels in the ascites and serum of women with advanced stage epithelial cancer, shows increased levels in only about 66% of patients³.

IL-6 has been aptly called a “cytokine for gerontologists”. Levels of IL-6 in normal sera are low or undetectable in the absence of inflammation, while with age they become measurable even in the absence of inflammation³⁰. The age of ovarian cancer patients was also taken into account as one of the chosen laboratory parameters, in evaluation of chemotherapy effects.

Materials and Methods

Sera samples. Control group (group I) consisted of sera from 21 healthy women (23–66 years old; mean value 43.0 ± 12.1 ; median 43.0 years). This could be divided into premenopausal subgroup Ia with 10 subjects (23–43 years; mean value 33.1 ± 7.0 years), and postmenopausal subgroup Ib with 11 subjects (43–66 years old; mean value 52.0 ± 7.8 years). Serum samples were chosen on the basis of routine laboratory tests (erythrocyte sedimentation rate, activity of aminotransferases and acid phosphatase, glucose concentration etc.). Pathological sera were collected from 87 women treated in the Second Clinic of Gynecology, University Medical School in Wrocław. To group II sera from 22 women (17–75 years old; mean value 42.6 ± 18.5 ; median 39.0 years) with non-malignant tumors of the ovaries (cystis simplex, cystadenoma mucinosum, cystadenofibroma serosum, endometriosis) were assigned. Blood was taken before surgery from the patients suspected to have ovarian cancer. Only patients diagnosed by surgical and histopathological criteria were included into definite groups. The patients with coexisting inflammation of different origin, as reflected by routine laboratory tests, were excluded from the study. After removing tumor mass, the extent of the disease stage

according to the FIGO classification, was determined²⁷. Non-hemolyzed serum samples were stored at -20°C until analysis. Sera from 45 patients, suffering from ovarian carcinoma, were assigned as group III. These were divided into subgroup IIIA (FIGO stages I and II). Because of small number of patients (5 women with stage I and 3 with stage II), they were classified together in subgroup A. These patients were 15–67 years old (43.1 ± 18.8 ; median 46.0 years). Subgroup IIIB (FIGO stage III) included 13 patients 44–81 years old (58.1 ± 11.1 ; median 55 years); subgroup IIIC (FIGO stage IV) – 24 patients 35–70 years old (58.0 ± 10.5 ; median 61.0), respectively. Classification of ovarian cancers according to histopathological types and FIGO stages is shown in Table 1.

Table 1. Number of patients with histopathological types and FIGO stages of ovarian cancers (group III)

Histopathological type	Disease stage			
	I	II	III	IV
Serous	4	–	4	5
Mucinous	–	–	–	3
Endometrioid	2	–	7	2
Undifferentiated	–	1	2	8
Clear cell	–	–	–	4
Others	–	1	–	2
Total	6	2	13	24

The patients with diagnosed ovarian cancer were treated once per month through 6 months with the following cytostatics. First day: Farmorubicin – 40 mg; second day: Farmorubicin – 40 mg, cis-Platinum – 100 mg, Endoxan – 1000 mg. This was preceded by the collection of blood samples.

Methods. Haptoglobin concentration was measured in g/l either by the method of JONES and MOULD²², using the specific reaction of haptoglobin with hemoglobin (Hp-Hb), or by the enzyme immunoassay with concanavalin A (Hp-Con A), described by KATNIK and DOBRYSZYCKA²³. The Hp-Hb/Hp-Con A ratio was also calculated.

CA 125 levels in serum samples were measured using a commercial luminiscent immunoassay (LIA) kit (Byk-Roland, Warszawa), according to the manufacturer's instruction.

IL-6 concentrations were determined by an enzyme immunoassay (EIA) PredictaTM Diagnostics kit (Genzyme Diagnostics, Cambridge, USA).

The average, median, standard deviations, and probability level among the examined groups were calculated by χ^2 , Kruskal-Wallis and Wilcoxon tests, according to different kind of comparison required. Correlations were calculated using the Spearman Rang test for unpaired samples.

Results

Table 2 summarizes results of Hp-Hb, Hp-Con A, IL-6 and CA 125 determinations in sera of healthy women (group I), non-malignant tumors (group II), and ovarian cancer patients (group III), respectively.

In all examined groups distribution of results of in-

correlations of the both forms of haptoglobin with age in sera of non-malignant tumors was found. Moreover, the ratio Hp-Hb/Hp-Con A showed negative correlation coefficient with age of healthy women and cancer IV^o patients. Hp-Hb was negatively correlated with IL-6 in sera from cancers I–III^o, and with CA 125 in sera from cancers I–II^o, respectively. The latter group was

Table 2. Preoperative levels of haptoglobin (Hp), interleukin 6 (IL-6), and CA 125 in sera of patients with non-malignant and malignant ovarian tumors

	Groups	Hp-Hb (g/l)	Hp-Con A (g/l)	Hp-Hb/Hp- -Con A ratio	IL-6 (pg/ml)	CA 125 (U/ml)
I	Normal sera	n = 21	n = 21	n = 21	n = 21	n = 20
	Mean value ± SD	1.24 ± 0.28	1.07 ± 0.35	0.88 ± 0.25	23.7 ± 35.7	19.2 ± 9.3
	Median	1.23	1.0	0.8	7.0	17.1
	Range of values	0.76–1.9	0.58–1.7	0.56–1.32	0–116.0	5.8–40.8
II	Non-malignant tumors	n = 17	n = 17	n = 17	n = 20	n = 21
	Mean value ± SD	2.27 ± 1.32	0.33 ± 0.43	0.12 ± 0.15	19.5 ± 22.1	54.6 ± 82.5
	Median	2.25	1.3	0.06	7.5	19.0
	Range of values	0.67–5.28	0–1.53	0–0.55	0–60.00	4–341.0
III Cancers	FIGO stages I and II	n = 5	n = 5	n = 5	n = 8	n = 7
	Mean value ± SD	4.18 ± 1.64	0.89 ± 1.24	0.17 ± 0.17	38.3 ± 29.5	400.3 ± 799.0
	Median	3.88	5.94	0.16	34.0	51.0
	Range of values	2.36–6.85	0–3.05	0–0.5	4.0–100.0	29.0–2184.0
	FIGO stage III	n = 6	n = 6	n = 6	n = 11	n = 9
	Mean value ± SD	3.58 ± 1.52	0.59 ± 0.47	0.14 ± 0.1	71.5 ± 103.2	698.6 ± 1040.7
	Median	4.04	0.63	0.15	30.0	64.0
	Range of values	1.58–5.46	0.02–1.13	0.01–0.27	0–336.0	18.0–3089.0
	FIGO stage IV	n = 15	n = 14	n = 14	n = 24	n = 18
	Mean value ± SD	4.80 ± 1.7	1.22 ± 1.13	0.23 ± 0.13	51.9 ± 62.7	472.6 ± 359.8
	Median	4.4	0.85	0.21	32.8	440.4
	Range of values	2.24–8.43	0–4.2	0–0.5	0–240.0	8.4–1245.8

SD – standard deviation.

Hp-Hb – haptoglobin concentration measured by the reaction with hemoglobin²¹.

Hp-Con A – haptoglobin concentration measured by the reaction with concanavalin A²².

IL-6 and CA 125 were measured by the commercial kits as in Materials and Methods.

dividual parameters as calculated by χ^2 and Kruskal-Wallis tests was found to be non-parametric at $p < 0.001$. One exception was IL-6 ($p < 0.05$). Comparisons among the groups, as calculated by the Wilcoxon test, are shown in Table 3.

Results from cancer sera (I–IV^o FIGO) differ in relation to those from normal sera in all examined parameters. Sera from non-malignant tumors differ in all parameters, when compared with cancer IV^o sera only, while cancer sera from I–III^o differ in Hp-Hb and CA 125. Level of CA 125 differentiates cancers I–II^o and IV^o, whereas Hp-Hb/Hp-Con A ratio distinguishes cancers III^o and cancers IV^o. Results obtained from normal and non-malignant sera differ only in Hp-Hb and the ratio Hp-Hb/Hp-Con A.

Relationships of Hp-Hb and Hp-Con A in all the groups was justifiable, but unexpectedly significant

Table 3. Dependence of the examined parameters and FIGO stages of ovarian cancers, according to Wilcoxon test. Only statistically significant results are shown

Groups	Hp-Hb	Hp- -Con A	Hp-Hb/ /Hp- -Con A ratio	IL-6	CA 125	Age
IIIA/IIIB						
IIIA/IIIC					+	++
IIIA/II	++				++	
IIIA/I	++	++	++	+	++	
IIIB/IIIC			+			
IIIB/II	+				++	++
IIIB/I	++	++	++	+	++	++
IIIC/II	++	++	++	+	++	++
IIIC/I	++	++	++	++	++	++
II/I	++		++			

++ statistical significance at $p < 0.05$;

+ statistical significance at $p < 0.1$.

Description of the groups as in Table 2.

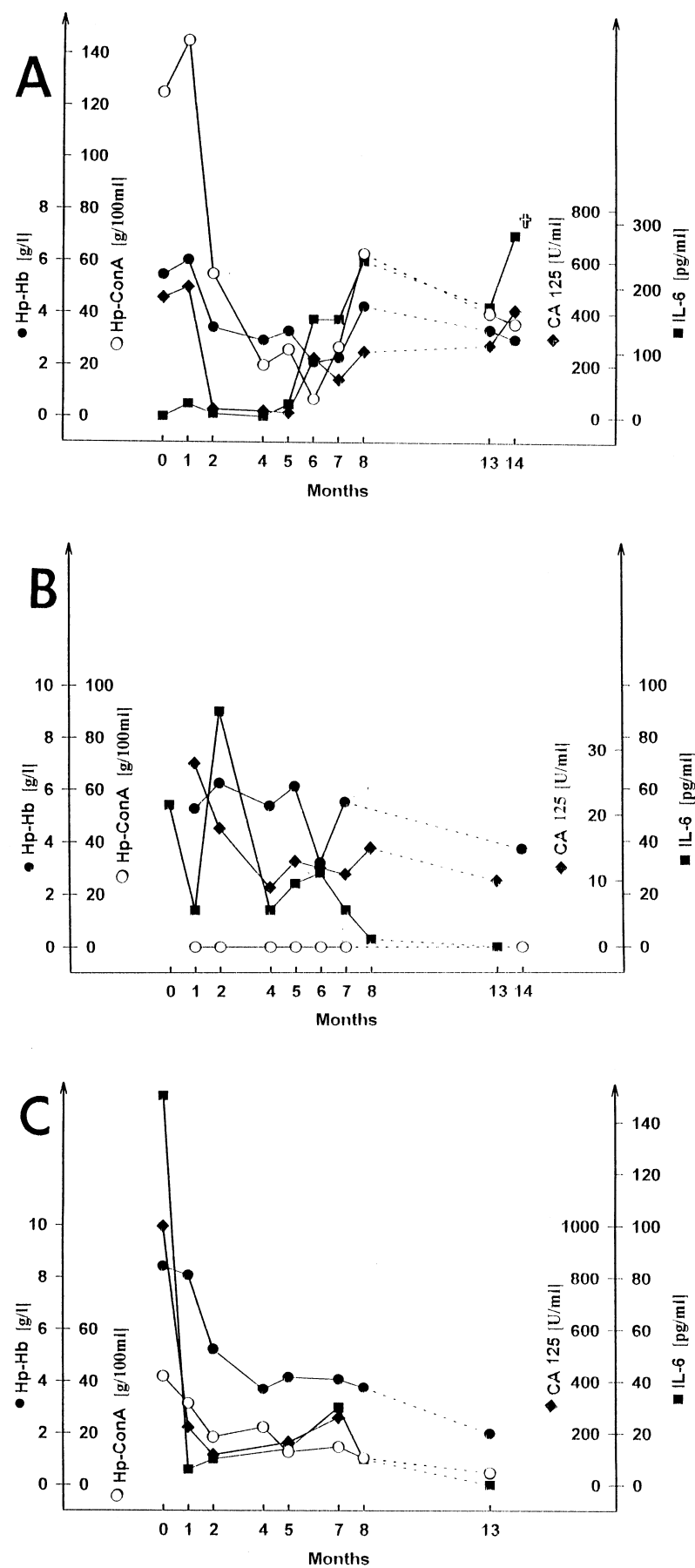


Fig. 1. Concentrations of haptoglobin (measured by the reaction with Hb or with Con A), IL-6 and CA 125 in sera of patients: A, B, C with ovarian cancers (IV FIGO stage) during the course of chemotherapy with: cis-Platinum, Endoxan and Farmorubicin

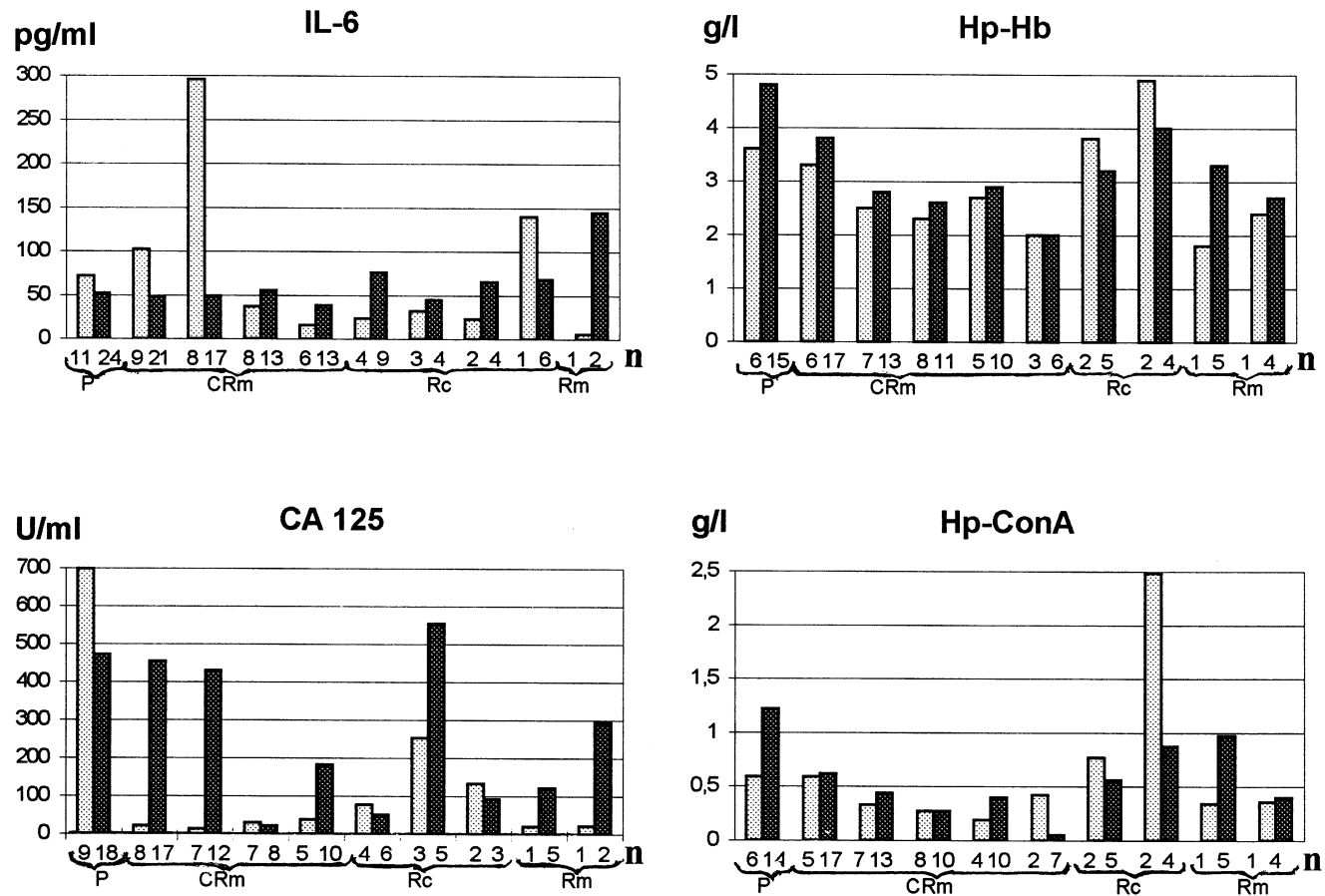


Fig. 2. Consecutive determinations of Hp-Hb, Hp-Con A, IL-6 and CA 125 in sera of patients with ovarian cancers of III stage (group IIIB), and of IV stage (group IIIC). Mean values are given with respective number of determinations (n). P – preoperative values, C – chemotherapy, Rm – remission, Rc – recurrence of malignancy

characterized by the negative correlation of CA 125 in relation to IL-6.

The group I (healthy women) was divided into two subgroups: premenopausal (n=10, mean age 33.1 years), and menopausal (n=11, mean age 52.0 years) ones. Taking into consideration the latter, significant correlations (age vs Hp-Hb/Hp-Con A ratio included) were similar as in the whole group I. The ratio in premenopausal women was approximately 1.0 (in menopausal 0.8), IL-6 concentrations were 20 pg/ml as related to the older subgroup 38.7 pg/ml. However, because of wide range of values the latter result did not achieve statistical significance. Effects of administration of cytostatics to patients with ovarian cancers were monitored by changes in concentrations of the investigated parameters.

In Fig. 1 examples of serial analyses of Hp-Hb, Hp-Con A, IL-6 and CA 125 in patients with ovarian carcinoma (IV FIGO stage), treated by cytostatics, are presented.

Results of parallel determinations in serum of the patient (Fig. 1A) clearly indicate 5–6 month remission, followed after second-look laparotomy in increase of levels of 4 parameters, leading to death. Proper results of the therapy are shown in Fig. 1C, whereas in Fig. 1B the patterns of IL-6 and CA 125 suggest remission, whereas Hp-Hb level indicates occult disease and progression of malignancy, verified subsequently by other clinical and biochemical data. A surprising absence of Hp-Con A may be observed.

Data obtained from patients with cancers of III and IV FIGO stages, during the course of chemotherapy, are summarized in Fig. 2. They show results of Hp-Hb, Hp-Con A, IL-6, and CA 125 measurements.

Periods of remission during administration of cytostatics and recurrence of malignancy in patients with ovarian cancer III and IV FIGO stages, shown in Fig. 2, are fairly separated in measurements of Hp-Hb, Hp-Con A. The pattern of IL-6 is better visible in cancers III°, while that of CA 125 in stage IV° does not show any regularity.

Observation of changes in Hp-Con A level during the course of chemotherapy revealed 3 patients with cancers of stage IV and 1 with stage III, lacking completely this form of haptoglobin in spite of parallel high values of Hp-Hb. Similar zero values of Hp-Con A were found in the group of I–II^o cancers (1/6) and in non-malignant tumors (6/17). Mean values of the ratio Hp-Hb/Hp-Con A in all the pathological groups were very low (0–0.55), whereas in the group of healthy women the ratio was 0.88, resulting from the similar values of both forms of haptoglobin (see Table 2).

Discussion

Serum tumor markers include oncofetal proteins, hormones and ectopic hormones, enzymes, immunoglobulins, acute phase reactants, and miscellaneous markers. Very few of them fulfil criteria of an ideal tumor marker, which in the broadest sense might be considered a laboratory measurement of a substance or a process that provides clinically useful information with regard to tumor diagnosis and patient management^{25, 28, 37}. Though serum markers are of limited value in screening the general population for ovarian cancer, they can be used to assist the general gynecologist in avoiding potentially difficult oncologic surgery. Therefore, it is important to discriminate non-malignant vs malignant tumors and to define the extent of ovarian cancer in patients clinically free of disease after initial surgery and chemotherapy. Haptoglobin belongs to acute phase glycoproteins but was shown in our laboratory to be useful in monitoring chemotherapy in ovarian cancer patients¹¹. On the contrary, according to EMERICH et al.¹⁵, Hp determinations were of no use in follow-up of women with ovarian cancer. In the present work both forms of haptoglobin (Hb- or Con A-bound) were used, because results of our previous work suggested that the ratio of Hp-Hb/Hp-Con A might be used as a biomarker²⁵.

Consecutive determinations of both forms of Hp and CA 125 (Fig. 2) reflect satisfactorily duration of remission following chemotherapy and/or recurrence of malignancy. Moreover, discrimination between cancers and normal sera or cancers and non-malignant tumors was achieved by use of the above parameters, while determinations of IL-6 were relatively less valuable.

Complex metabolic processes occurring in cancer include changes in structure and composition of the oligosaccharide chains of glycoproteins (increase/decrease of the content of specific carbohydrates, changes of antennae number). These phenomena are very clinically relevant³⁹. Taking into consideration reaction of

haptoglobin with Con A, zero values of Hp-Con A in some patients with ovarian cancers have been of interest. Phenotypical changes in glycosylation are of importance for processes like adhesion, invasion and metastasis²⁶. Antimetabolites do have the potency to affect cellular glycosylation. Different cytostatics influence glycosyltransferase activity, lectin binding, incorporation of sugars (glucosamine, fucose, mannose, galactose). In chemotherapy with antimetabolites many target and nontarget cells are exposed^{8, 20}.

Our patients with ovarian cancer were treated with Farmorubicin, cis-Platinum and Endoxan. Farmorubicin (4'-epi-doxorubicin) in combination with other drugs is known to give synergistic effects in chemotherapy of advanced ovarian cancer^{5, 13}. This substance, due to epimerization at position 4', may bind sugars. It looks like changes in glycosylation, induced by cancer and Farmorubicin (with cis-Platinum, Endoxan), have influenced reaction of carbohydrate moiety of Hp with Con A. However, the question why some patients with non-malignant tumors reveal similar changes (6/17 zero values of Hp-Con A, mean value of Hp-Hb/Hp-Con A ratio 0.12), awaits response. It should be pointed out that absence of Hp-Con A and very low ratios have never been found in normal sera.

Clinical utility of CA 125 measurements in sera of ovarian cancer patients has been controversial. For example, according to NAGELE et al.²⁹, CA 125 is the most powerful independent prognostic factor in patients with stage I epithelial ovarian cancer. On the contrary, the problems of poor sensitivity of CA 125 in small volume disease and elevation in some patients with benign conditions (uterine fibroids, pregnancy and endometriosis, hepatitis, pancreatitis, pelvic inflammatory disease or a host of other conditions) have been pointed out^{9, 19}. Results of our present study indicate striking similarity of CA 125 and Hp-Hb levels as well as in their use in monitoring effects of chemotherapy (Fig. 1, Table 3). Moreover, Hp-Hb determinations discriminate non-malignant tumors from normal sera, while CA 125 levels discriminate cancers of FIGO stages I and II from stage IV, respectively. It is interesting that only Hp-Hb/Hp-Con A ratio discriminates cancers stage III and IV, however with $p < 0.1$.

IL-6 is a pleiotropic cytokine involved in the regulation of immune response, induction of acute phase proteins by hepatocytes (Hp included) and hematopoiesis (induction of B cell and cytotoxic T cell differentiation), and can act as an autocrine growth factor in malignancy^{2, 4, 17, 21, 33, 38}. Circulating IL-6 may be used as a useful marker for predicting postoperative complications³¹. According to GASTL et al.¹⁷ serum IL-6

levels in patients with ovarian cancer were significantly higher than in patients with non-malignant ovarian conditions. In our work IL-6 test was shown to display relatively weaker links between non-malignant tumors and cancers (only with stage IV). IL-6 levels were negatively correlated with CA 125 in cancers of stage I–II as well as with Hp-Hb in cancers of stages I–III.

Statistical connections of both forms of Hp with age (Tables 3, 4) have been compatible in some sense with results of CASWELL et al.⁷, who found that some acute phase parameters (erythrocyte sedimentation rate, fibrinogen level, C-reactive protein level) rose in women aged between 65 and 74 years. On the other hand, because of small number of samples, we could not confirm the opinion of NARAYANAN³⁰ who found that in elderly adults IL-6 levels in serum are elevated, apparently owing to a loss in regulation of cytokines (development of autoimmunity, increased B cell proliferation, osteoporosis).

Similar results obtained from the use of the estimations, especially haptoglobin and CA 125, suggests a possibility of substitution of one test by another. Therefore, such features as rapidity and ease of performance, as well as **last but not least**, high prices of commercial tests, should be taken into consideration. The latter factor is of great importance in a choice of suitable tests in routine laboratory practice.

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