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Effect of the treatment stage on the serum levels of selected cytokines and antioxidant enzymes in patients with tumors of the reproductive organs

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Abstract. – OBJECTIVE: Chronic inflammation along with concomitant oxidative stress contributes to an increased risk of cancer development. The aim of this study was to analyze selected cytokines and antioxidant enzymes in patients with ovarian and endometrial cancers, taking into account the stage of oncological treatment.

PATIENTS AND METHODS: The study sample included 52 female patients with advanced endometrial cancer (n = 26.50%) and ovarian cancer (n = 26.50%), undergoing chemotherapy. Long-term observation at four time points was used in the subjects. Each of the women was blood sampled several times (before surgery, and then before the first, third, and sixth cycle of chemotherapy) in order to determine serum levels of pro- and anti-inflammatory cytokines and antioxidant enzymes.

RESULTS: The levels of catalase (CAT), glutathione reductase (GR), interleukin (IL)-10, IL-1α, IL-4 differed significantly depending on the stage of therapy and the type of cancer. The serum levels of IL-4 and IL-10 in patients with ovarian cancer were statistically significantly higher than those observed in patients with endometrial cancer. The activity of the tested antioxidant enzymes varied depending on the chemotherapy cycle. Their highest activity in most cases was observed before the third cycle of chemotherapy, and it decreased before the sixth cycle, irrespective of the type of cancer.

CONCLUSIONS: In the studied group of patients with ovarian and endometrial cancer, the applied chemotherapy significantly changed the concentration and activity of some interleukins and antioxidant enzymes. The type of tumor determined the levels of IL-4 and IL-10 before the treatment. Evaluation of inflammatory parameters and oxidative stress in women with cancer of the reproductive organ may help to understand physiological changes resulting from the applied therapy.

Key Words:
Antioxidant enzymes, Ovarian cancer, Endometrial cancer, Chemotherapy, Women's health.

Introduction

In Poland, malignant neoplasms of the reproductive organs continue to be a significant health problem. An increase in the number of cases is being observed in the population of younger and younger women, while late detection of these cancers contributes to high mortality rates. According to the National Cancer Registry[1] over 6,000 cases of uterine/endometrial cancer and over 3,700 cases of ovarian cancer are reported annually. Laboratory tests play a significant role in diagnosing cancer of the re-productive organs, and especially tumor marker tests are widely used in gynecological oncology. Analysis of the literature shows that cytokine testing can complement the therapeutic process, especially in terms of monitoring the course of treatment and detecting tumor recurrence[2-5]. The mechanism of neoplastic transformation has not yet been fully understood, although a special role of the increased risk of cancer development is attributed to chronic inflammation accompa-

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nied by concomitant oxidative stress. Therefore, research is conducted to assess the concentrations of cytokines and antioxidant enzymes, which may serve as diagnostic and prognostic markers. Cytokines are proteins responsible for the functioning of the immune system. They affect neutrophils, monocytes, lymphocytes, and eosinophils, and are involved in the regulation of immune and inflammatory processes. Currently, more than 200 cytokines are known. These proteins show an autocrine activity by affecting the cells that secrete them. They also have paracrine and endocrine effects, affecting nearby cells or cells of other organs[6]. Numerous scientific studies[6] indicate that the increased release of cytokines may be a factor associated with tumor progression. The importance of such interleukins as IL-1, IL-6, IL-8 is recognized in the diagnostics of ovarian malignancies[7-9], while in the case of uterine cancer, the usefulness of IL-2 and its soluble receptor (sIL-2Ra) and tumor necrosis factor (TNF-α) is indicated[10-12]. Research[13-16] in this field seems to be vital because it has been observed that some cytokines are sometimes notably elevated even at low stages of the disease, while tumor markers are still only slightly increased. According to current knowledge[17,18], cytokines contribute to the increased formation of reactive oxygen species (ROS). ROS play an important role in basic biological processes occurring in the human body in both health and disease. Higher levels of oxidative stress markers are observed in cancer patients. Numerous studies in literature have proven that ROS participate in the tumorigenesis process, as they can cause oxidation of fats, proteins, and DNA, thus contributing to tissue damage. Toxic products of oxidation reactions have a cytostatic effect on the cell, damaging cell membranes and leading to cell death by apoptosis or necrosis. Pro- and anti-oxidant balance is maintained by antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), glutathione-S-transferase (GST), glutathione peroxidase (GPx), and other antioxidants. Low activity of superoxide dismutase and catalase may lead to the initiation and progression of oxidative stress, resulting in DNA damage in cells. Numerous studies[19-22] indicate that excessive production of free radicals is a primary or secondary cause of cancer complications. Thus, the determination of these parameters may indicate the level of antioxidant depletion in the body and the desirability of taking measures to reduce oxidative stress in the body's cells, which may con-tribute to the clinical improvement of patients. The aim of this study was to analyze selected cytokines and antioxidant enzymes in patients with ovarian and endometrial cancers, taking into account the stage of oncological treatment.

Patients and Methods

Study Sample

The study involved 52 women treated in the Department of Gynecological Surgery and Gynecological Oncology of Adults and Adolescents, Pomeranian Medical University in Szczecin. They were patients with ovarian cancer and endometrial cancer undergoing first-line chemotherapy and systemic treatment for recurrent disease. Giving informed consent was a precondition for taking part in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Bioethical Committee (KB-0012/81/18).

Patients with ovarian cancer

Patients with primary ovarian tumors underwent surgery followed by chemotherapy, namely six cycles of chemotherapy based on platinum analogues and paclitaxel. In cases of incomplete surgical treatment, they received additional 18 administrations of bevacizumab. For recurrent disease, the choice of chemotherapy depended on the platinum sensitivity of the tumor.

Patients with endometrial cancer

Patients with advanced endometrial cancer underwent surgery, followed by chemotherapy and radiotherapy. The chemotherapy regimens were based on platinum analogues and paclitaxel given in six cycles. In relapse, doxorubicin regimens were used.

Study Design

The research procedure was divided into two parts, namely structured interview, and biochemical analysis of the tested parameters in blood serum.

First, the participants were asked about basic sociodemographic data (age, place of residence, employment status, education, marital status) as well as menstruation, family history of cancer, medications taken, and physical activity. Anthropometric measurements were taken on an empty stomach, in light clothes, without shoes, after

emptying the urinary bladder using an electronic scale with a height gauge. Based on the obtained data, the body mass index (BMI) was calculated – the range of 18.5-24.9 kg/m^2 was regarded as normal, overweight was defined as having a BMI in the range of 25.0-29.9 kg/m^2, and obesity as BMI of 30 kg/m^2 and more.

Then, each of the enrolled women, after giving her consent to participate in the study, was blood sampled several times (before surgery, before the first, third, and sixth cycle of chemotherapy). Venous blood (a maximum of 5.5 ml) was collected fasting (at least eight hours after the last meal) using the Monovette closed system. After obtaining biological material, the blood was centrifuged, and the separated serum was frozen at -80°C until biochemical tests were performed. The data concerning the tested parameters were collected before surgery (25 patients), before the first cycle of chemotherapy (46 patients), before the third cycle of chemotherapy (48 patients), and before the sixth cycle of chemotherapy (38 patients).

Determination of Biochemical Parameters

Biochemical analysis was performed in a certified laboratory of the Pomeranian Medical University in Szczecin using commercial, standardized methods.

The serum obtained was used to perform the following analyses:

Panel I: cytokine determination and analysis of proinflammatory and anti-inflammatory factors: IL-1, IL-2, IL-6, TNF-α, IFN-γ, IL-4, IL-10, prostaglandin E2 (PGE2), and thromboxane B2 (TXB2). The cytokine analysis was performed using commercially available reagent kits (Abcam, Cambridge, UK), and the Bio-Tek ELx800 automated microplate reader (Winooski, VT, USA) at the wavelength recommended by the manufacturer (450 nm). Kits parameters: IL-1 (sensitivity: 5.64 pg/ml, range: 14.06 pg/ml-900 pg/ml, precision CV%: 4.8%), IL-2 (sensitivity: 32.1 pg/ml, range: 39 pg/ml-2,500 pg/ml, precision CV%: 3.2%), IL-6 (sensitivity: 1.6 pg/ml, range: 7.8 pg/ml-500 pg/ml, precision CV%: 2.1%), TNF-α (sensitivity: 4.32 pg/ml, range: 15.63 pg/ml-1,000 pg/ml, precision CV%: 2.3%), IFN-γ (sensitivity: 470 pg/ml, range: 0.468 ng/ml-30 ng/ml, precision CV%: 1.1%), IL-4 (sensitivity: 1.08 pg/ml, range: 6.25 pg/ml-400 pg/ml, precision CV%: 6%), IL-10 (sensitivity: 1.4 pg/ml, range: 9.4 pg/ml-3,000 pg/ml, precision CV%: 5.2%), PGE2 (sensitivity: 18.75 pg/ml, range: 31.25 pg/ml-2,000 pg/ml, precision CV%: < 8%), and TXB2 (sensitivity: 10.54 pg/ml, range: 13.7 pg/ml-10,000 pg/ml, precision CV%: 3.6%).

Panel II: antioxidant enzyme activity analysis: superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), oxidized form of glutathione (GSSG), catalase (CAT), paraoxonase-1 (PON1). Analysis of antioxidant enzymes activity was performed by spectrophotometric method using commercially available reagent kits Cayman Chemical (Ann Arbor, MI, USA) for SOD, GPx, GR, GSSG, CAT and Thermo Fisher Scientific (Waltham, MA, USA) for PON1. Measurements were performed on the Bio-Tek ELx800 automated microplate reader (Winooski, VT, USA) at the wavelength recommended by the manufacturer (540 nm for CAT, 450 nm for SOD, 405 for GSSG, 340 nm for GPx and GR). Kits parameters: SOD (range: 0.005-0.050 units/ml, precision CV%: 3.2%), GPx (range: 50-344 nmol/min/ml, precision CV%: 7.2%), GR (range: 20-255 nmol/min/ml, precision CV%: 3.7%), GSSG (range: 0-8 μM, precision CV%: 3.6%), CAT (range: 2-35 nmol/min/ml, precision CV%: 3.8%), PON1 (sensitivity: 0.2 ng/mL, range: 0.2-50 ng/mL).

Statistical Analysis

The MedCalc statistical software v. 20.014 (Ostend, Belgium) and R software (available at: https://www.R-project.org; accessed on 16 February 2022) were used for calculations. The Shapiro-Wilk test was used to assess whether variables were normally distributed. Accordingly, the data has been ranked for compliance with normality. However, measurements were presented in original scales separately to give the reader an overview of the data obtained. We performed repeated ANOVA measures with two corrections based upon the estimates of sphericity by Greenhouse and Geisser or Huynh and Feldt as appropriate. Next, we utilized linear mixed models followed by the maximum likelihood ratio test to deal with missing data and to search for the relationship between a group (cancer type) and the stage of therapy. Where necessary, Satterthwaite's method was used to obtain the *p*-values. The dependent variable was the log concentration of particular parameter tested, whilst the independent ones were the stage of therapy and the type of cancer (both fixed). The Patient ID was the only random

variable. Correlation analyses were performed using Pearson's method. Statistical significance was set as $p < 0.05$.

Results

Characteristics of the Study Sample

The study involved 52 women diagnosed with ovarian (n = 26, 50%) or endometrial (n = 26, 50%) cancer. The mean age of ovarian cancer patients was 57.11 ± 9.62, and that of subjects with endometrial cancer was 64.38 ± 8.11. The difference was statistically significant ($p < 0.0001$). The BMI of the participants remained stable over time ($p = 0.864$; surgery Median: 26.43; IQR: 23.17 - 32.00; 1st cycle Median 27.71; IQR: 15.5-32.98; 3rd cycle Median: 27.79; IQR: 24.40 - 32.98; 6th cycle Median: 27.88; IQR: 23.55 - 31.48). In terms of weight status in particular, study points there were no significant differences.

Data on education, place of residence, marital status, and employment status were collected from all participants (Table I). The data concerning the tested parameters were collected before surgery (25 patients), before the first cycle of chemotherapy (46 patients), before the third cycle of chemotherapy (48 patients), and before the sixth cycle of chemotherapy (38 patients). However, due to limited amount of serum, in some cases the biochemical parameters were evaluated in smaller number of samples.

The Levels of the Tested Parameters Before Surgery and During Chemotherapy

The basic descriptive statistics of the tested parameters are presented in Table II. By means of the independent *t*-test, we managed to demonstrate that the concentrations of CAT, GR, IL-10, IL-1α, IL-4 differed significantly depending on the stage of therapy and the type of cancer. The results are presented in Table III, and only significant ones in Figure 1.

The concentrations of the tested interleukins and antioxidant enzymes did not depend on the type of cancer (they did not differ between ovarian and endometrial cancer patients), except for the results obtained for IL-4 and IL-10 before surgery. Their serum levels in patients with ovarian cancer were statistically significantly different from those observed in patients with endometrial cancer – in both cases, higher concentrations were observed in the serum of patients with ovarian cancer ($p = 0.004$ for IL-4 and $p = 0.028$ for IL-10). Additionally, a statistically significant difference was found in serum IL-10 levels in patients before the sixth cycle of chemotherapy. Again, higher values were obtained for the group of patients with ovarian cancer ($p = 0.042$).

Table I. Sociodemographic data.

Variable	Education				p
Cancer type	**Primary**	**Vocational**	**Secondary**	**Higher**	
Ovarian cancer	3	5	13	5	0.61
Endometrial cancer	1	8	13	4	
	Marital status				*p*
Cancer type	Unmarried	Married	Widowed	Divorced	
Ovarian cancer	3	10	11	2	0.37
Endometrial cancer	2	5	17	2	
	Employment status				*p*
Cancer type	Employed	Unemployed	Sickness pension	Pension	
Ovarian cancer	9	5	1	14	0.70
Endometrial cancer	6	4	2	14	
	Place of residence				*p*
Cancer type	Village	City with a population < 10 K	City with a population of 10 K-100 K	City with a population > 100 K	
Ovarian cancer	4	4	9	9	0.48
Endometrial cancer	4	8	8	6	

p: significance level.

Table II. Descriptive statistics of the tested parameters by the stage of therapy and the type of cancer.

Elements analyzed	Surgery					1st cycle					3rd cycle					6th cycle				
	n	M	Me	SD	25-75 P	n	M	Me	SD	25-75 P	n	M	Me	SD	25-75 P	n	M	Me	SD	25-75 P
Ovarian cancer																				
CAT [uM]	12	304.83	286.67	73.30	253.912-354.239	26	304.18	306.14	93.56	241.404-7 358.23	24	302.67	330.90	88.82	227.348-368.295	18	234.14	208.39	104.89	164.031-316.713
GPx [nM/min/ml]	12	101.24	92.45	41.51	77.172-120.724	26	160.20	107.23	114.56	80.992-230.241	24	81.88	80.23	25.88	61.890-97.802	18	99.50	90.67	75.35	66.220-98.311
GR [nM/min/ml]	12	20.55	19.61	13.49	11.715-23.686	26	24.53	16.30	28.52	11.716-22.413	24	27.42	18.34	35.11	15.537-22.922	18	31.04	16.05	41.36	11.716-24.960
GSSG [uM]	12	5.47	3.55	5.09	1.546-8.478	26	5.58	4.08	4.61	2.769-5.861	24	4.78	4.28	2.90	2.327-6.702	18	4.88	3.68	3.67	2.480-7.407
IFN-γ [pg/ml]	13	465.78	421.43	217.59	266.233-602.272	26	463.69	411.04	354.67	174.675-665.584	24	469.10	375.32	223.33	287.013-577.272	18	498.63	436.36	329.75	224.026-779.869
IL-10 [pg/ml]	13	45.06	39.02	31.75	25.571-54.150	26	36.61	33.71	20.76	19.908-51.407	24	39.83	40.26	15.66	28.756-49.637	18	52.15	37.78	35.41	28.402-67.687
IL-1α [pg/ml]	13	35.94	27.25	37.88	0.744-55.658	26	35.59	13.95	43.09	1.271-68.464	24	34.83	38.04	31.31	0.533-60.096	18	46.01	31.95	52.12	0.805-66.435
IL-1β [pg/ml]	13	67.18	43.86	75.45	17.712-77.379	26	55.39	28.43	68.80	11.808-52.292	24	61.16	27.01	84.27	22.350-77.650	18	47.11	30.79	47.81	21.086-45.545
IL-2 [pg/ml]	13	97.89	69.17	64.47	40.099-157.426	26	84.77	50.07	79.44	31.825-113.296	24	94.41	92.93	51.88	53.041-140.877	18	110.84	95.05	97.08	25.035-142.151
IL-4 [pg/ml]	13	136.11	122.94	53.01	101.033-162.685	26	124.87	105.46	60.68	85.034-150.995	24	155.40	133.77	86.14	95.864-196.773	18	134.78	134.51	48.05	96.356-168.715
IL-6 [pg/ml]	13	33.16	23.50	36.03	4.663-53.860	26	29.73	17.59	34.03	5.789-50.059	24	23.06	20.52	17.88	7.662-31.091	18	33.90	12.88	44.13	9.024-33.917
PGE2 pg/ml]	13	496.85	379.85	412.84	260.430-652.915	26	521.60	404.92	523.68	101.078-766.879	24	557.58	360.57	659.58	126.292-708.888	18	300.89	201.63	272.82	62.804-467.589
PON1 [pg/ml]	13	206.36	209.15	9.36	201.557-212.637	26	206.05	211.28	12.48	199.670-213.604	24	208.40	211.28	7.51	203.202-213.604	19	206.06	211.28	9.82	199.162-212.830
SOD [U/ml]	12	0.02	0.02	0.01	0.0120-0.0255	26	0.02	0.02	0.01	0.00900-0.0240	24	0.01	0.01	0.01	0.00450-0.0220	18	0.02	0.02	0.01	0.00200-0.0230
TNF-α [pg/ml]	13	13.17	14.31	4.63	9.443-15.915	26	14.04	13.13	5.09	9.970-15.048	24	14.05	15.11	4.43	10.156-16.844	19	14.76	12.70	7.13	9.537-8.763
TXB2 [pg/ml]	12	3300.51	1,106.82	4,547.40	337.521-5,156.692	26	2392.61	1,349.17	3,149.84	456.512-3,235.235	24	1,815.09	1,096.14	1,687.82	511.02-3,298.788	18	1,094.04	701.70	1,107.13	181.360-2,159.219

Continued

Table II *(Continued)*. Descriptive statistics of the tested parameters by the stage of therapy and the type of cancer.

Elements analyzed	Surgery					1st cycle					3rd cycle					6th cycle				
	n	M	Me	SD	25-75 P	n	M	Me	SD	25-75 P	n	M	Me	SD	25-75 P	n	M	Me	SD	25-75 P
Endometrial cancer																				
CAT [uM]	13	244.36	224.12	84.23	191.240-285.635	20	273.81	281.64	103.34	231.216-327.288	243	223.94	224.90	123.25	101.488-19.421	16	240.73	247.98	101.32	153.714-304.850
GPx [nM/min/ml]	13	127.19	105.44	101.18	64.819-137.406	20	130.05	100.86	88.93	73.861-149.758	24	90.46	80.23	55.28	62.655-99.075	16	92.20	73.10	68.67	55.778-94.236
GR [nM/min/ml]	13	30.64	17.83	38.22	7.004-37.057	20	26.56	15.03	30.11	8.660-36.166	24	20.21	11.72	35.68	7.895-18.337	16	31.36	21.14	30.30	12.735-42.024
GSSG [uM]	13	4.34	3.79	3.56	1.618-	20	6.42	4.10	5.53	3.296-8.274	24	5.80	3.70	5.42	1.733-8.919	16	6.78	4.81	5.72	2.471-9.701
IFN-γ [pg/ml]	14	421.34	434.42	264.55	204.545-513.636	21	407.89	347.40	236.21	213.636-669.155	23	423.01	416.23	269.09	199.025-640.584	17	416.16	370.78	310.05	167.207-550.649
IL-10 [pg/ml]	14	25.32	21.86	12.72	14.953-39.374	21	27.78	24.51	12.87	18.050-36.897	23	35.90	28.76	21.65	23.624-45.656	17	29.38	23.45	18.60	15.219-36.365
IL-1A [pg/ml]	14	14.62	4.59	21.89	0.241-18.764	21	14.49	0.88	20.22	0.526-19.905	23	19.54	3.36	26.32	0.371-40.825	17	15.55	2.54	20.28	0.403-36.768
IL-1B [pg/ml]	14	67.67	64.36	46.64	20.242-108.085	21	62.87	39.64	58.73	22.772-92.425	23	69.75	31.93	90.88	19.136-62.162	17	60.97	31.21	95.06	11.054-56.126
IL-2 [pg/ml]	14	65.47	51.77	44.75	40.311-90.382	21	65.45	56.44	39.38	37.765-90.171	23	72.82	52.19	55.84	28.217-108.204	17	66.67	53.89	67.84	22.914-85.502
IL-4 [pg/ml]	14	87.00	91.19	22.32	72.236-103.247	21	106.90	106.20	32.90	89.219-127.367	23	117.27	112.11	49.53	95.618-142.380	17	117.61	121.95	42.89	90.203-151.733
IL-6 [pg/ml]	14	17.78	10.47	15.76	6.909-19.471	21	17.38	11.58	20.16	7.023-16.958	23	14.55	8.79	11.89	7.055-19.538	17	12.29	6.91	11.47	4.725-17.068
PGE2 pg/ml]	14	600.74	390.18	464.42	217.075-1,053.698	21	431.56	209.15	576.51	82.756-520.036	23	493.89	258.08	544.32	127.117-648.982	17	370.77	343.86	307.96	88.112-532.821
PON1 [pg/ml]	14	203.87	204.75	8.62	196.961-211.282	20	206.04	210.56	9.83	199.718-213.217	23	206.02	209.06	9.57	199.453-212.056	17	205.36	210.61	12.51	203.517-213.411
SOD [U/ml]	12	0.01	0.01	0.01	0.00450-0.0205	20	0.02	0.02	0.01	0.0130-0.0240	24	0.01	0.01	0.01	0.00250-0.0225	6	0.01	0.01	0.01	0.00250-10.0205
TNF-α [pg/ml]	14	15.28	14.18	7.11	11.704-15.048	20	13.95	13.07	5.31	11.209-14.553	23	14.21	12.57	7.55	9.413-17.586	7	14.71	14.31	7.90	10.713-115.698
TXB2 [pg/ml]	13	2,154.33	1,553.96	2,134.21	598.937-2,985.898	20	1,593.04	1,072.70	1,345.36	572.348-2,379.573	24	1,858.81	556.43	3,523.03	382.908-1,576.956	16	1,797.38	681.25	3,194.95	298.432-1,940.944

M: mean; Me: median; SD: standard deviation; P: percentyl, CAT: catalase, GR: glutathione reductase, IL: interleukin, SOD: superoxide dismutase, GPx: glutathione peroxidase, GSSG: oxidized form of glutathione, PON1: paraoxonase-1, PGE2: prostaglandin E2, TXB2: thromboxane B2, total GSH: total glutathione, TNF-α: tumor necrosis factor.

Table III. Parameters by the stage of therapy and the type of cancer.

Parameter	Stage of therapy	Ovarian cancer			Endometrial cancer					
		n	Mean	SD	n	Mean	SD	Difference	95% CI	p
CAT [uM]	Surgery	12	15.83	6.21	13	10.38	7.59	-5.45	-11.2140 - 0.3166	0.0628
	1st cycle	26	24.96	13.40	20	21.60	13.56	-3.36	-11.4334 - 4.7103	0.4058
	3rd cycle	24	29.08	12.04	24	19.92	14.55	-9.17	-16.9266 - -1.4068	0.0216
	6th cycle	18	17.00	10.07	16	18.06	10.13	1.06	-6.0047 - 8.1297	0.7614
GPx [nM/min/ml]	Surgery	12	12.92	6.20	13	13.08	8.55	0.16	-6.0653 - 6.3858	0.9580
	1st cycle	26	24.52	14.10	20	22.18	12.73	-2.34	-10.4495 - 5.7610	0.5629
	3rd cycle	24	24.02	14.40	24	24.98	13.88	0.96	-7.2579 - 9.1746	0.8154
	6th cycle	18	19.28	9.41	16	15.50	10.47	-3.78	-10.7223 - 3.1667	0.2761
GR [nM/min/ml]	Surgery	12	13.13	6.59	13	12.88	8.27	-0.24	-6.4595 - 5.9787	0.9370
	1st cycle	26	24.27	12.24	20	22.50	15.08	-1.77	-9.8834 - 6.3449	0.6625
	3rd cycle	24	29.81	11.95	24	19.19	14.08	-10.63	-18.2138 - -3.0362	0.0071
	6th cycle	18	16.31	10.31	16	18.84	9.69	2.54	-4.4758 - 9.5522	0.4664
GSSG [uM]	Surgery	12	13.46	8.39	13	12.58	6.59	-0.88	-7.0945 - 5.3317	0.7718
	1st cycle	26	22.88	12.90	20	24.30	14.37	1.42	-6.7094 - 9.5402	0.7272
	3rd cycle	24	24.65	12.11	24	24.35	15.93	-0.29	-8.5140 - 7.9306	0.9434
	6th cycle	18	16.33	9.08	16	18.81	11.01	2.48	-4.5408 - 9.4991	0.4771
IFN-γ [pg/ml]	Surgery	13	15.77	7.72	14	12.36	8.06	-3.41	-9.6754 - 2.8512	0.2725
	1st cycle	26	23.85	14.78	21	24.19	12.62	0.34	-7.8465 - 8.5351	0.9329
	3rd cycle	24	25.96	11.55	23	21.96	15.65	-4.00	-12.0600 - 4.0564	0.3225
	6th cycle	18	19.33	10.09	17	16.59	10.53	-2.75	-9.8349 - 4.3447	0.4365
IL10 [pg/ml]	Surgery	13	17.42	7.10	14	10.82	7.52	-6.60	-12.4119 - -0.7914	0.0276
	1st cycle	26	26.44	14.44	21	20.98	12.41	-5.47	-13.4908 - 2.5585	0.1769
	3rd cycle	24	26.42	12.66	23	21.48	14.56	-4.94	-12.9444 - 3.0675	0.2205
	6th cycle	18	21.39	9.70	17	14.41	9.82	-6.98	-13.6937 - -0.2606	0.0422
IL1α [pg/ml]	Surgery	13	16.19	8.74	14	11.96	6.80	-4.23	-10.4073 - 1.9513	0.1711
	1st cycle	26	27.58	13.75	21	19.57	12.60	-8.01	-15.8344 - -0.1766	0.0453
	3rd cycle	24	26.85	14.35	23	21.02	12.63	-5.83	-13.7878 - 2.1230	0.1467
	6th cycle	18	20.86	11.14	17	14.97	8.50	-5.89	-12.7332 - 0.9522	0.0892
IL1β [pg/ml]	Surgery	13	12.73	8.47	14	15.18	7.52	2.45	-3.8906 - 8.7862	0.4339
	1st cycle	26	22.02	14.15	21	26.45	13.05	4.43	-3.6475 - 12.5138	0.2750
	3rd cycle	24	23.96	12.67	23	24.04	15.00	0.09	-8.0600 - 8.2303	0.9833
	6th cycle	18	19.03	8.65	17	16.91	11.87	-2.12	-9.2303 - 4.9983	0.5492
IL2 [pg/ml]	Surgery	13	15.38	8.62	14	12.71	7.32	-2.67	-8.9924 - 3.6518	0.3926
	1st cycle	26	24.21	15.06	21	23.74	12.19	-0.47	-8.6627 - 7.7158	0.9078
	3rd cycle	24	26.69	12.67	23	21.20	14.45	-5.49	-13.4686 - 2.4849	0.1724
	6th cycle	18	20.56	10.66	17	15.29	9.33	-5.26	-12.1692 - 1.6463	0.1308

Continued

Table III ***(Continued).*** Parameters by the stage of therapy and the type of cancer.

Parameter	Stage of therapy	Ovarian cancer			Endometrial cancer					
		n	Mean	SD	n	Mean	SD	Difference	95% CI	*p*
IL4 [pg/ml]	Surgery	13	18.31	7.64	14	10.00	6.02	-8.31	-13.7385 - -2.8769	0.0042
	1st cycle	26	24.96	15.05	21	22.81	12.11	-2.15	-10.3168 - 6.0127	0.5981
	3rd cycle	24	26.90	14.36	23	20.98	12.60	-5.92	-13.8683 - 2.0331	0.1408
	6th cycle	18	19.67	10.51	17	16.24	9.96	-3.43	-10.4826 - 3.6198	0.3293
IL6 [pg/ml]	Surgery	13	14.58	9.82	14	13.46	6.01	-1.11	-7.5143 - 5.2890	0.7234
	1st cycle	26	25.31	15.42	21	22.38	11.41	-2.93	-11.0704 - 5.2170	0.4729
	3rd cycle	24	26.88	14.89	23	21.00	11.94	-5.88	-13.8281 - 2.0781	0.1438
	6th cycle	18	20.28	10.81	17	15.59	9.31	-4.69	-11.6477 - 2.2687	0.1796
PGE2 [pg/ml]	Surgery	13	13.38	7.87	14	14.57	8.25	1.19	-5.2146 - 7.5882	0.7058
	1st cycle	26	26.27	13.21	21	21.19	14.12	-5.08	-13.1265 - 2.9690	0.2102
	3rd cycle	24	24.71	13.78	23	23.26	13.90	-1.45	-9.5827 - 6.6877	0.7217
	6th cycle	18	16.86	10.43	17	19.21	10.22	2.34	-4.7631 - 9.4526	0.5068
PON1 [pg/ml]	Surgery	13	15.42	7.89	14	12.68	8.01	-2.74	-9.0562 - 3.5672	0.3790
	1st cycle	26	24.12	14.12	20	22.70	12.67	-1.42	-9.5161 - 6.6853	0.7264
	3rd cycle	24	25.75	13.45	23	22.17	14.00	-3.58	-11.6404 - 4.4882	0.3765
	6th cycle	19	18.29	10.54	17	18.74	10.79	0.45	-6.7876 - 7.6793	0.9011
SOD [U/ml]	Surgery	12	14.25	7.34	12	10.75	6.63	-3.50	-9.4211 - 2.4211	0.2332
	1st cycle	26	22.83	14.06	20	24.38	12.85	1.55	-6.5740 - 9.6702	0.7027
	3rd cycle	24	24.77	13.32	24	24.23	14.92	-0.54	-8.7622 - 7.6788	0.8951
	6th cycle	18	18.81	10.92	16	16.03	8.86	-2.77	-9.7783 - 4.2297	0.4257
TXB2 [pg/ml]	Surgery	13	12.88	9.01	14	15.04	6.96	2.15	-4.2015 - 8.5037	0.4920
	1st cycle	26	23.54	14.13	20	23.45	12.78	-0.09	-8.2196 - 8.0427	0.9826
	3rd cycle	19	14.76	7.13	17	14.71	7.90	-0.05	-5.1389 - 5.0422	0.9847
	6th cycle	19	18.47	11.81	17	18.53	9.26	0.06	-7.1929 - 7.3044	0.9876
TNF-α [pg/ml]	Surgery	12	13.46	8.39	13	12.58	6.59	-0.88	-7.0945 - 5.3317	0.7718
	1st cycle	26	22.88	12.90	20	24.30	14.37	1.42	-6.7094 - 9.5402	0.7272
	3rd cycle	24	24.65	12.11	24	24.35	15.93	-0.29	-8.5140 - 7.9306	0.9434
	6th cycle	18	16.33	9.08	16	18.81	11.01	2.48	-4.5408 - 9.4991	0.4771
Total GSH [pg/ml]	Surgery	12	13.04	8.50	13	12.96	6.49	-0.08	-6.3048 - 6.1445	0.9790
	1st cycle	26	23.69	14.80	20	23.25	11.77	-0.44	-8.5774 - 7.6928	0.9132
	3rd cycle	24	26.98	14.09	24	22.02	13.75	-4.96	-13.0481 - 3.1314	0.2236
	6th cycle	18	16.67	10.81	16	18.44	9.16	1.77	-5.2774 - 8.8191	0.6123

M: mean; Me: median; SD: standard deviation; p: significance level, CAT: catalase, GR: glutathione reductase, IL: interleukin, SOD: superoxide dismutase, GPx: glutathione peroxidase, GSSG: oxidized form of glutathione, PON1: paraoxonase-1, PGE2: prostaglandin E2, TXB2: thromboxane B2, total GSH: total glutathione, TNF-α: tumor necrosis factor.

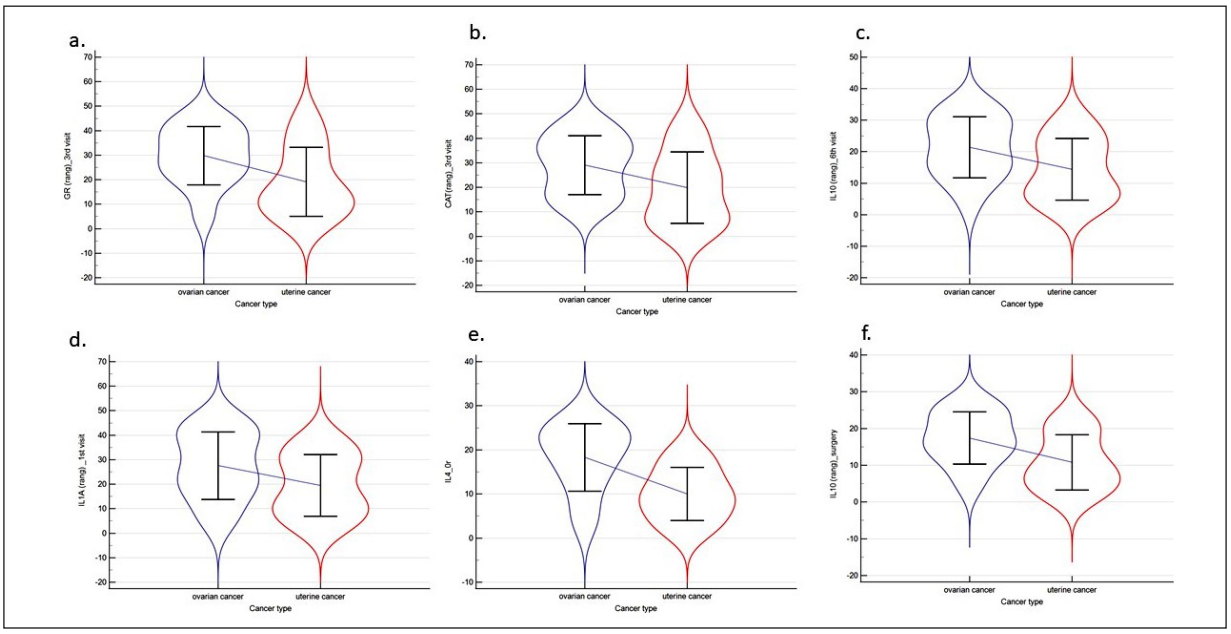

Figure 1. Significant changes in GR (**a**), CAT (**b**), IL-10 (**c**), IL1-a (**d**), IL4 (**e**) and IL-10 (**f**) by the type of cancer and the stage of therapy.

Analysis of the dynamics of changes in serum concentrations of certain parameters in patients, depending on the cycle of chemotherapy, shows that the applied treatment protocols contributed not only to the change in interleukin concentrations. The activity of the antioxidant enzymes varied depending on the cycle of chemotherapy, regardless of the type of cancer. The highest activity in most cases was observed in blood serum before the third cycle of chemotherapy, and it decreased before the sixth cycle. Similar observations were made for the level of total glutathione (total GSH), which is a substrate/product of the activity of selected enzymes. The differences, however, were not statistically significant (Table III).

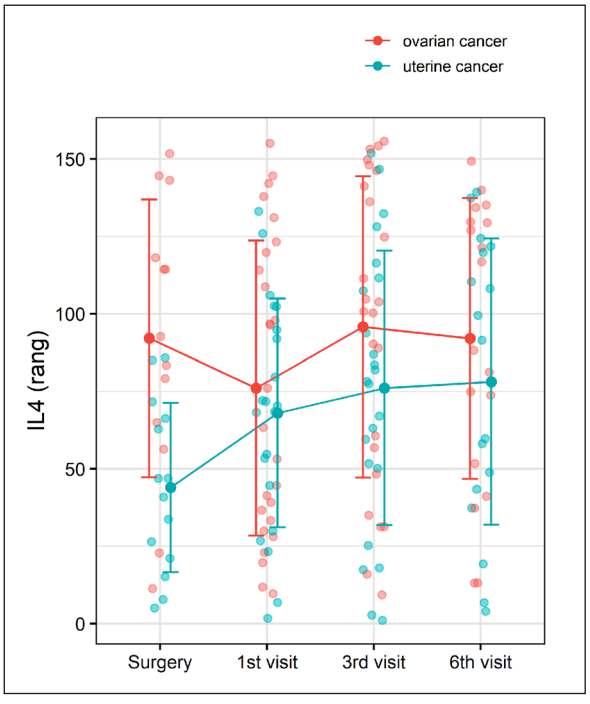

Figure 2. Changes for IL-4 concentration (ranked) by the stage of therapy and the type of cancer.

The Levels of the Tested Parameters by the Stage of Therapy and the Type of Cancer

After the analysis with the use of the linear mixed model, statistically significant differences in the change in serum levels between the groups (ovarian cancer *vs.* endometrial cancer) were only found for IL-4 (Figure 2). Details are presented in Table IV.

Discussion

The role of chronic inflammatory response in the pathogenesis of cancer is increasingly recognized. Cytokines are involved in initiating inflammation to alert immune cells to the presence

Table IV. Relationship between the groups and the stage of therapy for the tested parameters.

Parameter	*p*	Q
CAT	0.229	0.792
GPx	0.823	0.874
GR	0.151	0.792
GSSG	0.689	0.792
IFN-γ	0.902	0.902
IL-10	0.328	0.792
IL-1α	0.699	0.792
IL-1β	0.448	0.792
IL-2	0.565	0.792
IL-4	0.033	0.562
IL-6	0.682	0.792
PGE2	0.371	0.792
PON1	0.620	0.792
SOD	0.410	0.792
TNF-α	0.550	0.792
TOTAL GSH	0.689	0.792
TXB2	0.395	0.792

p: significance level, CAT: catalase, GR: glutathione reductase, IL: interleukin, SOD: superoxide dismutase, GPx: glutathione peroxidase, GSSG: oxidized form of glutathione, PON1: paraoxonase-1, PGE2: prostaglandin E2, TXB2: thromboxane B2, total GSH: total glutathione, TNF-α: tumor necrosis factor.

of infection or tissue damage. The production of cytokines stimulated by the immune system leads to chronic inflammation, which promotes cancer development[23]. Inflammatory cells and inflammatory mediators are present in the microenvironment of most tumors[24]. The ever-increasing knowledge of the function of cytokines indicates that they are significantly involved in cancer progression at all stages of tumorigenesis. It has been shown[25] that with the development and progression of cancer, the production of some cytokines becomes disturbed.

Chronic inflammation also occurs as a result of excessive accumulation of body fat, which contributes to the abnormal production of cytokines and the activation of pro-inflammatory signals. Adipose tissue is responsible for internal secretion of inflammatory (TNF-α, IL-6) and anti-inflammatory (adiponectin, IL-1, IL-10) substances. In obesity, cancer cells are constantly stimulated by proinflammatory cytokines, therefore there is a relationship between the high BMI and the risk of chronic diseases such as ovarian and endometrial cancers[26,27]. Our study, however, does not provide data on significant incidence of overweight and obesity regarding cancer type and over time.

Neoplastic cells are characterized by the ability to synthesize and release many cytokines[6], which form a network of interrelationships involved in different stages of cancer development. Cytokines can support the tumor microenvironment immunologically by suppressing antitumor cellular immunity, which directly contributes to tumor growth and metastasis[3].

Cytokines determine the type of immune response, and the profile of secreted cytokines may predispose to or protect against the development of autoimmunity. There are two main groups of cytokines. Th1-type cytokines (IL-2, IL-12, IFN-γ, TNF-α) are responsible for inducing proinflammatory cellular response and IgG production and predispose to autoimmune reactions. Th2-type cytokines (IL-4, IL-5, IL-10, IL-13) have an anti-inflammatory effect, promote humoral response and IgE production[28]. However, the division into Th1 and Th2 cytokines is not so clear-cut, as some T cells release a combination of Th1/Th2 cytokines that have immunosuppressive effects. Such cells have been termed Th3 (TGFβ, IL-4, IL-10)[29].

The phenomenon of progressive impairment of the immune system function in cancer patients is well-documented[30,31] and is associated with an imbalance between the number of Th1 and Th2 cells, and consequently the levels of cytokines they secrete. In these patients, as the tumor progresses, the Th2 cell response prevails, which, according to Clerici et al[32], allows tumor cells to evade immune surveillance and promotes tumorigenesis. However, the results obtained by Hao at al[33] in their study with patients with ovarian cancer before treatment, showed higher levels of cytokines produced by Th2 cells (IL-4, IL-6, IL-10), indicating a shift in the Th1/Th2 balance towards antitumor activity. This is supported by our findings showing that serum levels of selected cytokines (IL-4, IL-6, IL-10) in patients with ovarian cancer were significantly high before treatment. Interestingly, their serum levels decreased after cytoreduction and/or chemotherapy. In patients with endometrial cancer, the cytokines analyzed, except for IL-4, were at a visibly lower level, although the difference was statistically insignificant.

Interleukin-6 is recognized as a cytokine involved in the development and progression of ovarian cancer and is often used as a marker in the diagnosis of this cancer[34-37]. It regulates immune and inflammatory responses, but recent reports[34,38,39] suggest that it is involved in the reg-

ulation of tumor growth and metastasis. At the same time, it is indicated that in ovarian cancer, the progression of inflammation in the tumor microenvironment, manifested, among others, by an increase in IL-6 levels, is associated with poorer prognosis[3,40,41] and the development of chemoresistance[41-43]. However, various inflammatory factors may differently modulate the response of ovarian cancer cells to chemotherapy[44]. The main inducers of IL-6 expression and secretion are local inflammatory cytokines, such as IL-1β and TNF-α[41,45], whose high levels have been detected in the serum of patients with advanced ovarian cancer[37,38,41,46,47]. Clendenen et al[48] provided evidence that higher levels of IL-2, IL-4 and IL-6 are also associated with the risk and development of this cancer. In 1990, Ding et al[49] observed that paclitaxel, an anti-cancer drug, induces gene expression of some cytokines, including TNF-α, IL-1β, IL-6, which was later confirmed by Lee et al[50]. Yigit et al[47], on the other hand, noted significantly lower serum IL-6 levels in patients with ovarian cancer after neoadjuvant chemotherapy, which was also confirmed by Lambeck et al[51]. The same results were obtained in our study, which demonstrated a decrease in IL-6 levels after the first and third cycle of chemotherapy, while TNF-α levels did not change throughout the treatment period, regardless of the chemotherapy cycle.

In the tumor environment, the source of cytokines are not only immune cells, but also tumor cells, which can affect the surrounding tissues. This contributes to the modulation of the immune response and the creation of an environment conducive to tumor cell proliferation. Mielczarek-Palacz et al[52] reported that ovarian cancer cells exhibit proinflammatory activity, which is manifested by the secretion of IL-1β and IL-6, with IL-1β being considered one of the most important cytokines involved in both immune and inflammatory responses. In cancer cells, IL-1 promotes angiogenesis, tumor growth, and metastasis. Its elevated levels are observed in many types of cancer, which is often associated with their metastasis[53,54]. In our study, IL-1α levels were significantly different in particular treatment time intervals depending on the type of cancer, with higher levels observed in the serum of patients with ovarian cancer, which may suggest that this cancer is more aggressive.

Being part of the tumor environment, cytokines are important factors affecting the tumor by modulating inflammation and contributing to the development of resistance to therapy. In ovarian cancer, the balance of cytokine secretion is disturbed, which is manifested by a decrease in serum IL-2 levels and an increase in the levels of IL-4 and IL-10[52,55,56]. Despite numerous studies[57-59], the relationship between IL-10 and cancer development is still very controversial. It is indicated that IL-10, produced in the tumor microenvironment, promotes its growth. Overexpression of IL-10 is often observed in cancer, which manifests itself in the protection of neoplastic cells against the immune system[60-63], and is associated with poor prognosis in ovarian cancer patients[38,64-66]. At the same time, it is more and more often hypothesized that under certain circumstances this cytokine may support the immune system by acting immunosuppressively and immunostimulatory against tumor cells[67-69], and stimulating the secretion of IL-2 and IFN-γ[70,71]. The role of IL-10 in the invasion of tumor cells is also unclear. Perceived as an anti-inflammatory cytokine, in the specific microenvironment of ovarian tumor, it may exacerbate chronic inflammatory process and increase the invasiveness of tumor cells[65]. This may explain the results obtained in our investigation, showing an upward trend in IL-10 serum levels in women with ovarian cancer during chemotherapy (after the first, third, and sixth chemotherapy cycle) and suggest a worse prognosis in this group of patients. Chen et al[72] findings suggest that ovarian cancer cells show the ability to produce more IL-10 and IL-4. This was confirmed in our study, in which the levels of these two interleukins were significantly higher before surgery compared to those after chemotherapy. It seems that the role of IL-4 in cancer differs from its role in other diseases, as it has somewhat contradictory effects (pro- or anti-cancer) depending on the tumor and tissue type[73], which is in line with our findings (statistically significantly higher serum IL-4 levels in women with ovarian cancer compared to those with endometrial cancer). This is probably due to the fact that cytokines often have either synergistic or antagonistic effect, as with IL-4, which can induce Th2 cells to secrete IL-10. IL-4 and IL-10, on the other hand, when act together, modulate the anti-inflammatory function of TGF-β (transforming growth factor β)[72]. In addition, IL-4 may have a feedback inhibitory effect on the secretion of proinflammatory mediators by macrophages, i.e., IL-1, TNF-α, ROS, and reactive nitrogen species (RNS)[74,75].

The search for biomarkers of endometrial cancer has been carried out for some time. The determination of serum TNF-α, IL-1, and IL-6 levels

has raised high hopes among researchers due to the role of these pro-inflammatory cytokines in the development of endometriosis[76] and endometrial carcinogenesis[4]. The literature confirms that IL-6, as an inflammatory factor, promotes cancer cell proliferation in several cancers, including uterine cancer metastasis[77,78]. High serum IL-6 levels in patients with endometrial cancer are associated with both endometrial carcinogenesis[79-81] and cancer progression[79]. Many researchers[82] hold a view that inflammation underlies the initiation and progression of endometrial cancer. Chronic inflammation predisposes to cancer development by generating ROS, and synthesizing pro-inflammatory derivatives of fatty acid metabolism, including PGE2, which in turn can damage DNA and induce cell proliferation, thus initiating and promoting neoplastic transformation. Significantly elevated levels of PGE2 in malignant endometrial epithelial cells were observed by Tamura et al[83], and according to Sales and Jabbour[84], increased levels of PGE2 may account for the transformation of normal endometrium into neoplastic tissue, by stimulating the production of cytokines (including IL-6) and growth factors that are necessary for cancer development[85].

TNF-α is one of the most important cytokines in inflammatory and immune response. As one of the most potent pro-inflammatory cytokines, it is produced by activated macrophages and other cells in response to tissue damage or chronic inflammation. By affecting the immune system, it causes the release of many cytokines, including INF-γ from lymphocytes, and IL-1, IL-6 and INFβ from macrophages. Many studies[86-89] indicate that this cytokine is pro-tumorigenic, and that it inhibits apoptosis of tumor cells[86], and stimulates proliferation, migration and angiogenesis, which contributes to tumor growth and metastasis[87-89]. ROS, generated as a result of the pro-inflammatory effects of TNF-α, also play an important role in this process, causing DNA damage and inhibiting its repair[90]. Researchers[47,86,91] have long pointed to elevated serum levels of TNF-α in patients with ovarian cancer, especially to a strong correlation between the expression of this protein and increased tumor progression[47,91], shorter median survival time, and increased expression of IL- 6[86,92].

Free oxygen radicals – ROS – which arise as a result of metabolic processes in the body, such as aerobic respiration and inflammatory processes, play an important role in the proper functioning of cells. They participate in the regulation of many processes, among them, the secretion of hormones, the functioning of the immune system, and the removal of drugs from the body. However, when produced in excess, they have a negative effect on cell metabolism[93]. The ROS activity is balanced by antioxidant systems, which include antioxidant enzymes and other antioxidants[94]. A disturbed balance between the production of ROS and the efficiency of antioxidant systems leads to the development of oxidative stress[93]. The enzymatic antioxidant system includes: SOD, CAT, GPx, GSSG as well as GR and glucose-6-phosphate dehydrogenase (G6PD). These enzymes play a very important role in protecting the body's cells against the effects of ROS. Inhibition of their activity seems to be a decisive factor in reducing the ability of cells to defend themselves against increased ROS concentrations[22].

The available literature data indicate a strong oxidative stress in neoplastic cells, manifested by a high level of ROS, which in these cells may be responsible for the rapid rate of cell division, subsequent mutations in DNA, and genome instability, and lead to resistance to certain groups of drugs used in anticancer therapy. Potential mechanisms responsible for increased ROS formation in cancer cells include inflammation and cytokine activity, as well as increased metabolism resulting from continuous proliferation, mutations in mitochondrial DNA, and related dysfunctions[95,96]. Ongoing inflammation activates phagocytes, which secrete pro-inflammatory cytokines (IL-1, -6, -8, TNF-α, IFN-γ, etc.) at the site of damage. In turn, in activated phagocytes, the activity of enzymes increases, resulting in 'respiratory burst' and the release of large amounts of ROS, which, in addition to destroying pathogens, induce changes in cells leading to neoplastic transformation. In tumor cells, an imbalance of the redox system occurs, and the available research results indicate an increase in the levels of oxidative stress markers in the serum of patients diagnosed with cancer[97,98]. One of such markers is SOD, whose overexpression may enhance cancer cell proliferation and metastasis, and whose increased activity has been observed[99] in the serum of ovarian cancer patients. Research results[100] have also confirmed a worse prognosis in patients with various types of cancer, including ovarian cancer. Interestingly, numerous studies[42,101] have confirmed that inhibition of SOD activity in cancer cells leads to their increased apoptosis, inhibition of proliferation, and increased sensitivity to the applied anticancer therapy (also in ovarian cancer).

Increased ROS production in cancer cells, on the one hand, inhibits the activity of SOD and CAT, and on the other, increases the activity of GSH-dependent antioxidant enzymes. Researchers[102] suggest that cells with low SOD and CAT activity and increased GSSG activity (with variable GPx and GR activity) contribute to cancer formation. This was confirmed in studies[103-105] with patients with benign and malignant ovarian neoplasms, who had higher serum GSH-dependent enzyme activity[103,104], which significantly decreased after chemotherapy[105]. Also, the results of our study indicate that the activity of the analyzed antioxidant enzymes decreased after subsequent cycles of chemotherapy. Thus, the effective interaction of antioxidant enzymes in normal cells depends on the balance between the expression and activity of these proteins[106].

The ability of ROS to induce cell damage, ultimately leading to cell death, provides new opportunities to exploit the phenomenon of targeted ROS production in cancer cells in anticancer treatment. Cancer cells characterized by elevated intrinsic ROS levels are probably more sensitive to the applied chemotherapeutic agents, and many anticancer drugs generate ROS directly or indirectly and showing therapeutic selectivity preferentially lead to cancer cell death[96,107].

Conclusions

The studied interleukins and antioxidant factors act in the same way during systemic treatment, regardless of the type of cancer analyzed. The use of chemotherapy has a significant effect on the protein concentrations. In the groups of patients with ovarian and endometrial cancer, the applied chemotherapy significantly changed the concentration and activity of some interleukins and antioxidant enzymes. The type of tumor determined the levels of IL-4 and IL-10 before the treatment. Their serum levels in patients with ovarian cancer were statistically significantly higher than those observed in patients with endometrial cancer. Moreover, serum IL-10 levels in patients with ovarian cancer before the sixth cycle of chemotherapy were higher than those in the group of patients with endometrial cancer. The antioxidant enzyme activity in serum varied depending on the cycle of chemotherapy, regardless of the type of cancer. In most cases, the highest activity was observed in blood serum before the third cycle of chemotherapy. Evaluation of inflammatory parameters and oxidative stress in women with cancer of the reproductive organ may help to understand physiological changes resulting from the applied therapy.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contribution

Conceptualization: S.W.-H. and A.J.; methodology: S.W.-H., I.G. and A.Ch.-G.; software: S.W.-H.; validation: S.W.-H. and A.J.; formal analysis: S.W.-H.; investigation: S.W.-H., I.G., and A.Ch.-G.; resources: S.W.-H.; data curation: S.W.-H.; writing-original draft preparation: S.W.-H.; writing-review and editing: S.W.-H., I.G., and A.Ch.-G; visualization: A.J.; supervision: I.G. and A.Ch.-G.; project administration: A.J. and B.K.; funding acquisition: A.J. and B.K. All authors have read and agreed to the published version of the manuscript.

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Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Bioethical Commission of Pomeranian Medical University in Szczecin (Approval No. KB-0012/81/18 and date of approval 18.06.2018).

Informed Consent

Informed consent was obtained from all subjects involved in the study.

Availability of Data and Materials

The data presented in this study are available on request to the first author.

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