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N-acetyl-beta-D-glucosaminidase activity in patients with ovarian cancer and testicular embryonal carcinomas treated with cisplatin

Anna Wiela-Hojeńska[1], Emila Filipczyk-Cisarż[2], Krystyna Orzechowska-Juzwenko[1], Magdalena Hurkacz[1], Piotr Hudziec[3], Anna Ziemba[2], Katarzyna Pająk[2]

[1]Department of Clinical Pharmacology, Medical University, Bujwida 44, PL 50-345 Wrocław, Poland

[2]Lower Silesian Oncology Center, Chemotherapy Department, Hirszfelda 12, PL 53-413 Wrocław, Poland

[3]Department of Oncology and Gynaecological Oncology Clinic, Medical University, Hirszfelda 12, PL 53-413 Wrocław, Poland

Correspondence: Anna Wiela-Hojeńska, e-mail: wiela@lek.am.wroc.pl

Abstract:
The aim of our work was to evaluate the kidney function in patients with ovarian cancer and testicular embryonal carcinomas – nonseminomas and seminomas during anticancer chemotherapy containing cisplatin. The tubular function was studied by estimation the activity of N-acetyl-beta-D-glucosaminidase (NAG) in urine and glomerular function was studied by estimation the concentration of creatinine in urine, and creatinine, urea, uric acid, electrolytes in blood serum. On the basis of our study, we have shown the increase in NAG activity in urine in patients with organ neoplasms. We have also recorded the lack of enzyme activity normalization on the 20th day after the administration of cytostatic protocols containing cisplatin. These observations have shown that there is a necessity of detailed estimation of kidney excretory function before the beginning and after the end of anticancer chemotherapy in the patients suffering from the diseases mentioned above.

Key words:
kidney function, ovarian cancer, testicular embryonal carcinomas, cisplatin

Introduction

Modern anticancer chemotherapy, which depends on administration of high doses of cytostatics and other drugs, can become the cause of numerous adverse effects in the organism, whose functions had already been disturbed by the neoplastic process itself. Insufficiency of kidney function, which is the main organ responsible for drugs excretion, can diminish the possibility or even make impossible carrying out a complete treatment cycle [8, 15, 23].

Estimation of renal efficiency is based on determination of the degree of the excreting organ damage. It also enables monitoring of causal treatment efficiency. Standard determination of serum creatinine and urea concentration is most frequently applied. However, it should be taken into account that high concentrations of those compounds belong to late indicators of renal insufficiency. The glomerular filtration rate must be thus diminished to the half of normal values to make creatinine exceed the upper normal range. Recently, enzymatic examination of urine has

been suggested to constitute a valuable supplement of diagnostic methods used in renal insufficiency. An advantage of enzymuria examinations is their noninvasiveness with simultaneous possibility of making conclusions upon morphological state of renal parenchyma. The highest activity of the enzymes important for diagnosis has been proven to exist in renal tubules. The enzymes can be supposed to mainly originate from proximal renal tubules which contribute to over 42% of the kidney mass. The determination of enzymatic activity, especially of N-acetyl-beta-D-glucosaminidase can enable an early detection of damage in epithelial cells of proximal tubules, as well as it can be applied in monitoring of kidney state after exposure to different nephrotoxic compounds, especially cytostatic drugs [2, 16, 22, 28].

The aim of this work was to assess the effect of neoplastic process and late-phase toxicity of cytostatic protocols containing cisplatin on the excretory function of the kidney in patients with ovarian cancer, testicular embryonal carcinomas – nonseminomas and seminomas.

Materials and Methods

Prospective studies were carried out in 281 adult persons: 134 patients with ovarian cancer, 82 patients with testicular embryonal carcinomas and 65 healthy persons, as a control group. Patients' data are presented in Table 1.

The kidney function (NAG activity, creatinine concentration in urine, and serum concentration of creatinine, urea, uric acid, electrolytes) was evaluated before and 20 days after chemotherapy in patients with: ovarian cancer – after administration of each of 8 consecutive cycles of chemotherapeutic programs: CP (cisplatin 75 mg/m^2, 1. day, cyclophosphamide 600 mg/m^2, 1. day) or CAP (cisplatin 50 mg/m^2, 1. day, cyclophosphamide 500 mg/m^2, 1. day, epirubicin 50 mg/m^2, 1. day); testicular nonseminomas after administration of each of 4 consecutive cycles of BEP program (cisplatin 20 mg/m^2, 1–5 days, etoposide 120 mg/m^2, 1–3 days, bleomycin 30 mg/m^2, 2nd, 9th, 16th day and in patients with testicular seminomas after administration each of 3 consecutive cycles of PVB program (cisplatin 100 mg/m^2, 1. day, winblastin-10 mg/m^2, 1–2 days, bleomycin-30 mg/m^2, 2nd, 9th, 16th day). Cytostatics were given intravenously except for bleomycin, which was administered intramuscularly. Treatment cycles were repeated every 3 weeks. The patients received rescue therapy which included: hydration with 0.5 l of isotonic solution before cisplatin infusion, the cytostatic was given in 1.5 l of fluid (5% glucose or 0.9% physiological saline) and then diuresis was forced by 0.5 l of 5% glucose with 1 amp. of furosemide. In addition, renal function was closely monitored in all patients, the fluid balance was monitored within 48 h by control of urea and electrolytes. The fluid was supplemented with electrolytes when abnormal values were observed.

The activity of NAG, as an early factor of renal tubular efficiency, was determined in urine by the enzymatic method. The influence of diuresis volume on enzymatic activity was eliminated by scaling NAG activity in relation to creatinine concentration in urine [4, 29]. Creatinine concentrations in urine and blood were determined according to Jaffe's colorimetric method. Creatinine clearance was calculated according to the Cockroft and Gault equation.

Tab. 1. Data of healthy persons, as a control group and patients with cancer

Group	Number of subjects	Age (years)		Body weight (kg)	
		$\overline{X}$	± SD	$\overline{X}$	± SD
Healthy persons	65	36.2	8.9	63.2	8.5
Patients with ovarian cancer	134	48.6	8.6	62.2	10.8
Patients with testicular embryonal carcinomas – nonseminomas	55	31.0	8.3	75.2	13.9
Patients with testicular embryonal carcinomas – seminomas	27	34.8	7.2	70.6	11.6
Total	281	39.2	8.4	66.1	10.6

Statistical significance of differences between the means was calculated using one-way analysis of variance or the Wilcoxon signed rank test, if the variances in the groups were not homogeneous. Correlations between parameters were evaluated using Pearson's correlation coefficient test. Statistical analysis was performed using the Statistica Software Package. The protocol for the study was approved by the Ethics Committee of Wrocław Medical University.

Results

The comparison of the mean values of NAG activity between patient groups before anticancer chemotherapy and healthy persons is shown in Table 2. Statistically significant differences in the enzymatic activity between patients before treatment and healthy persons point to the decrease in the kidney tubular function under the influence of ovarian cancer, testicular embryonal carcinomas – nonseminomas and seminomas.

We have recorded the lack of differences in NAG activity in patients with ovarian cancer treated according CAP and CP protocols and, therefore, these patients were analyzed as one group.

The comparison of mean values of NAG activity between patients before anticancer treatment and after consecutive cycles of chemotherapy containing cisplatin is presented in Tables 3, 4 and 5. In patients with ovarian cancer, we have observed a statistically significant decrease in NAG activity on the 20th day after consecutive chemotherapy cycles (II–VIII) in comparison to its value before antineoplastic treatment. Similarly in patients with testicular embryonal carcinomas – nonseminomas and seminomas NAG activity after consecutive IV and III cycles was lower than its value before treatment. Explanation of that phenomenon could be very cautiously attributed to kidney rescue procedure.

In the examined groups of patients, the concentration of creatinine in urine did not differ significantly, between the values obtained before antineoplastic chemotherapy or after the consecutive cycles of treatment, when compared to this parameter in healthy persons (13.81 ± 6.54 mmol/l). Mean values of serum creatinine, urea, uric acid and electrolyte concentrations, as well as creatinine clearance also did not exceed the normal values.

Discussion

The present investigations are justified by the literature data, pointing out difficulties connected with the evaluation of kidney function in neoplastic diseases, especially during chemotherapy with potentially nephrotoxic antineoplastic drugs, including, first of all, cisplatin.

We compared our present clinical data with a group of healthy volunteers. NAG activity in urine of 65 healthy persons (females and males jointly) did not differ from the values reported in the literature by other authors [25]. In our own study, similarly to Skinner et al., no sex effect on NAG activity was observed. The views concerning the effect of age on enzyme activity seem to be diversified. High value of NAG/creatinine ratio have been observed in younger children under 2 years of age and in persons older than 56 years of age, which is connected with lower values of muscle mass in those age groups and decreased creatinine excretion [21]. In the examined groups, age ranged from 15 to 56 years. Therefore,

Tab. 2. Activity of N-acetyl-beta-D-glucosaminidase in patients before the beginning of anticancer chemotherapy and in healthy persons as a control group

Group	Number of subjects	NAG activity (UI/g)	
		$\overline{X}$	SD
Patients with ovarian cancer	92	12.80**	15.60
Patients with testicular nonseminomas	36	9.58**	6.45
Patients with testicular seminomas	24	8.60*	5.43
Healthy persons	65	3.52	1.99

Statistically significant difference of the mean value of NAG activity between patients and healthy persons: * $p < 0.001$, ** $p < 0.0001$

Tab. 3. Activity of N-acetyl-beta-D-glucosaminidase in patients with ovarian cancer before the beginning of anticancer chemotherapy and after consecutive treatment cycles with cisplatin

Group		Number of subjects	NAG activity (UI/g)		Percent changes in NAG activity	Serum creatinine concentration (μmol/l)		Creatinine clearance (ml/min)	
			$\overline{X}$	SD		$\overline{X}$	SD	$\overline{X}$	SD
Patients with ovarian cancer before the beginning of anticancer chemotherapy		92	12.80	15.60		89.45	13.45	94.62	21.30
Patients with ovarian cancer after consecutive treatment cycles	I	86	9.69	9.55	–24.30	94.87	18.45	99.90	18.94
	II	73	7.61*	6.75	–40.55	87.35	22.18	105.32	23.05
	III	80	8.37*	7.56	–34.61	98.24	14.56	91.33	13.79
	IV	64	7.33*	7.34	–42.73	89.45	31.23	94.15	25.24
	V	53	8.57*	8.35	–33.05	97.53	25.43	97.94	22.95
	VI	38	8.33*	7.52	–34.92	79.24	27.41	85.67	13.35
	VII	10	5.98*	3.98	–53.28	89.35	14.11	86.78	9.12
	VIII	8	8.04*	6.96	–37.19	73.45	19.23	97.43	4.56

Statistically significant difference of the mean value of NAG activity between patients before cytostatic treatment and after consecutive treatment cycles: $p < 0.05$

Tab. 4. Activity of N-acetyl-beta-D-glucosaminidase in patients with testicular embryonal carcinomas-nonseminomas before the beginning of anticancer chemotherapy and after consecutive treatment cycles with cisplatin

Group		Number of subjects	NAG activity (UI/g)		Percent changes in NAG activity	Serum creatinine concentration (mol/l)		Creatinine clearance (ml/min)	
			$\overline{X}$	SD		$\overline{X}$	SD	$\overline{X}$	SD
Patients with testicular nonseminomas before the beginning of anticancer chemotherapy		36	9.58	6.45		91.34	16.45	103.24	28.45
Patients with testicular nonseminomas after consecutive treatment cycles	I	33	5.45	2.33	–43.11	85.32	19.43	113.11	14.23
	II	24	5.17	2.28	–46.03	87.43	17.43	119.56	15.13
	III	23	6.09	4.37	–36.43	86.73	12.32	121.32	14.41
	IV	17	6.61	3.91	–31.01	94.35	8.42	118.24	11.41

Tab. 5. Activity of N-acetyl-beta-D-glucosaminidase in patients with testicular embryonal carcinomas-seminomas before the beginning of anticancer chemotherapy and after consecutive treatment cycles with cisplatin

Group		Number of subjects	NAG activity (UI/g)		Percent changes in NAG activity	Serum creatinine concentration (mol/l)		Creatinine clearance (ml/min)	
			$\overline{X}$	SD		$\overline{X}$	SD	$\overline{X}$	SD
Patients with testicular seminomas before the beginning of anticancer chemotherapy		24	8.60	5.43		89.21	19.06	111.23	16.32
Patients with testicular seminomas after consecutive treatment cycles	I	16	5.70	3.08	–33.72	93.21	11.04	121.23	11.29
	II	12	5.43	2.60	–36.86	87.45	17.11	108.45	15.43
	III	12	6.72	5.57	–21.86	94.54	7.32	126.43	9.43

age can be eliminated as a factor altering enzyme's activity. The above-mentioned activity can differ in various pathological states [27]. Since there are no sufficient literature data concerning the effect of neoplastic process on kidney function, especially on renal tubules, this paper presents investigation on the effect of neoplastic diseases: ovarian cancer and testicular embryonal carcinomas on NAG activity. The latter parameter has been considered to be an early indicator of renal tubular damage. The choice of group of patients, which included persons suffering from organ neoplasms was justified by the administered chemotherapy with cisplatin, an antineoplastic drug inducing nephrotoxic adverse effects, that have not been thoroughly explained.

Aiming to determine the effect of neoplastic process on NAG activity, examinations were done before treatment with cytostatics in 92 patients suffering from ovarian cancer, 36 patients with testicular embryonal carcinomas – nonseminomas and 24 patients with testicular embryonal carcinomas – seminomas. Those patients showed statistically significantly higher NAG activity in urine, in comparison to the control group of healthy persons. The obtained results are similar to those reported by other authors, who observed increased enzymatic activity in patients with gallbladder cancer, thyroid and lung cancers, as well as in patients suffering from acute myeloblastic leukemia [11, 27]. Neoplastic disease can cause both local and general functional disturbances of the whole organism. They result from different types of molecular changes in the cells. In the kidney, ultrastructural metabolic and biochemical changes can be most often observed in S3 segment of proximal tubules. A decrease in ATP quantity, increase in intracellular concentration of calcium, as well as activation of phospholipases have been observed in the cells with insufficient amount of oxygen. Those processes can lead to the damage of cellular membrane and release of different enzymes, including NAG, into the lumen of renal tubules. Another cause of the observed enzymuria can be the loss of integrity of cell-membrane in the renal tubules which results from peroxidation of membrane phospholipids through oxygen free radicals and the products of their oxidation, occurring at higher amount in the process of oncogenesis. Severini et al. observed an increased NAG activity in serum of patients with breast, stomach and liver cancers. The nature of that phenomenon has not been explained so far. Neoplastic process can increase NAG activity through the change in permeability of cellular membranes and the effect on the metabolism of their components, as well as through intensified processes of cell damage. It can also directly prolong the time of NAG presence in the circulatory system through diminishing its elimination. The latter process involves through endocytosis in Kupffer cells [12, 20]. The increased serum NAG activity can probably be accompanied by the increased activity of the enzyme in urine. Our examinations proved four-fold increase in enzyme activity in urine of women suffering from ovarian cancer as compared to healthy persons. That fact can be connected with late diagnosis of ovarian cancer in over 70% of patients showing the symptoms of advanced stages of that disease. The women participating in the study were diagnosed with II and IV clinical stage of neoplasms. In patients suffering from testicular nonseminomas and seminomas (II and III clinical stage), three- and two-fold increase in NAG activity was seen in comparison with the control group. Rapid development of testicular embryonal carcinomas results in earlier appearance of the disease, and, therefore, patients earlier visit a doctor. These patients remain in better clinical state than women with ovarian cancer.

Cisplatin is an antineoplastic drug causing a high risk of damage of convoluted renal tubules, proximal and distal, as well as collective tubules [1, 13]. Those changes can lead to hemodynamic disorders. They can be detected as early as within the first two days of the therapy and then continue even for a number of months after the drug had been withdrawn [7].

The detailed mechanism of cisplatin nephrotoxicity has not been understood so far. A view is held that cisplatin, when stimulating free oxygen radicals in renal tubule cells, simultaneously impairs their activity. Some hours after cytostatic had been administered, an increased enzyme excretion in urine was recorded, especially NAG excretion was more intensive [5, 10, 11, 13, 17–19, 24, 25].

Verplanke et al. proved the increased NAG activity on the third, fourth and fifth day after cisplatin therapy in patients with ovarian, uterine cervix and urinary bladder cancer, in comparison with enzyme activity before chemotherapy [26]. Hayashi et al. observed gradual increase in enzyme activity in urine after administration of cisplatin to the patients suffering from ovarian and uterine cervix cancer. The highest NAG activity was recorded between the sixth and eighth day after chemotherapy had been completed [6]. Takeda et al. reported significantly increased

NAG excretion in patients with testicular cancer within the first and the second week of treatment according to PVEB scheme (cisplatin, vinblastin, etoposide, bleomycin) or PE scheme (cisplatin, etoposide), in comparison to the value of that parameter before therapy. After two weeks, NAG excretion returned to the initial values [25].

In contrast to previously known nephrotoxicity of cisplatin, professional literature presents only a few records on late effect of cisplatin on the activity of renal tubules. Besides, investigations by other authors were carried out on scanty and non-homogenous groups of sick people [3, 6, 26]. Our observations were carried out on 135 patients suffering from organ neoplasms before the administration of consecutive cycles of treatment with cytostatics including cisplatin. The purpose was to determine if the patients with ovarian cancer could safely undergo long-term administration of a potentially nephrotoxic drug. We recorded considerable increase in NAG activity on the 20th day after eight consecutive cycles of chemotherapy as compared to the enzyme activity in healthy persons, as well as significant decrease in enzyme activity in comparison with its value before antineoplastic treatment. Similar observations were made in patients suffering from testicular embryonal neoplasms – nonseminomas and seminomas. In this group, NAG activity was also higher on the 20th day after consecutive four and three cycles of the therapy than that in healthy people and was lower than its initial value before treatment. We did not record any significant changes in NAG activity in the patients' urine between consecutive cycles of anticancer treatment. Such stability of enzyme activity can indicate that in spite of impaired function of renal tubules under the influence of different factors mentioned above, the procedure aiming at protecting the patients against nephrotoxicity was carried out in a proper way.

The results of the examinations of the effect of cisplatin on renal glomerules cited in the literature are not univocal. Administration of cytostatics can cause an increase in NAG activity without significant differences in serum creatinine concentration [9]. In the majority of examined patients, we could record that the values of creatinine concentration in urine, and urea and uric acid levels in serum did not exceed the normal range. Creatinine clearance was diminished only in patients with ovarian cancer. Before the onset of chemotherapy, it amounted to 77.5% of normal value and after eight consecutive cycles of therapy, it averaged, 76.3% of the value accepted as normal. Brillet et al. indicated a significant increase in serum creatinine concentration and decrease in creatinine clearance 3 months after the therapy had been completed. Their investigation was conducted in the patients suffering from different types of organ neoplasms who underwent from 2 to 7 cisplatin cycles. NAG activity in urine did not differ in those persons from the value of that parameter in healthy persons [3]. Decreased glomerular filtration was also observed after 16 and even after 52 months since chemotherapy with cisplatin had been completed [14]. Because of so diversified results, it seems reasonable to determine jointly the values of parameters characterizing the activity of renal glomerules, as well as proximate and distal renal tubules.

Therapy with cisplatin can also evoke electrolyte disorders. Meyer et al. observed a decreased serum concentration of calcium, magnesium and potassium in children receiving cisplatin at cumulative doses from 310 to 1710 mg/m^2 [13]. In our investigations carried out in adults, we did not notice any changes in serum electrolyte concentration.

It should be stressed that the patients examined by us were treated according to protocols involving different antineoplastic drugs. Permanent components of each therapeutic program were, apart from cisplatin, cyclophosphamide or bleomycin. Those drugs belong to the group of cytostatics increasing the amount of oxygen free radicals in the tissues [18]. Therefore, their combined disadvantageous effect on renal tubules cannot be excluded.

Concluding, it should be stated that renal insufficiency in patients suffering from ovarian cancer and testicular embryonal carcinomas – nonseminomas and seminomas is manifested mainly through the impaired renal tubular function. Analysis of different factors responsible for the observed increase in N-acetyl-beta-D-glucosaminidase activity in urine suggests that neoplastic process itself most significantly affects renal tubules. Early diagnosed of neoplasms, especially when traditional indicators of kidney function remain within the normal range, is very important. Detection of an increased NAG activity in urine can be helpful in identification of the groups of patients endangered by renal insufficiency, especially impairment of renal tubules, which will enable their protection and ensure further satisfactory and safe therapy.

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