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A retrospective analysis of haematological side effects of olaparib in excess-weight and normal BMI patients with ovarian cancer

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ABSTRACT

Background: Olaparib is the first poly(ADP-ribose) polymerase inhibitor approved in Europe for the treatment of platinum-sensitive patients with newly diagnosed or recurrent platinum-sensitive ovarian cancer with a confirmed BRCA mutation or homologous recombination deficiency (HRD). Epidemiological studies have shown an incompatible association between ovarian cancer and obesity, but there have also been scientific reports indicating that obesity, especially severe obesity, increases the risk of ovarian cancer. Olaparib has a wide range of side effects, especially anaemia and neutropenia, which may lead to dose reduction or therapy discontinuation. Therefore, therapeutic drug monitoring (TDM) is recommended. The aim of the study was a retrospective analysis of threshold value of the trough concentration of olaparib (C_{trough}) and haematological adverse reactions after olaparib treatment (300 mg/12 h) in excess-weight and normal body mass index (BMI) patients with ovarian cancer.

Materials and methods: The pilot study was conducted on 38 ovarian cancer patients who were divided into two groups: I — normal BMI patients (BMI = 18.5–24.9 kg/m^2; n = 14), II — excess-weight patients, i.e. overweight and obese patients (BMI ≥ 25 kg/m^2; n = 24). The severity of neutropenia and anaemia was graded according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0). The values of the mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), and red blood cell distribution width (RDW) parameters were also taken into account. HPLC-UV method (λ = 254 nm) was applied to measure olaparib plasma concentrations.

Results: There were no statistically significant differences in olaparib C_{trough} between the groups — 1602.86 *vs.* 1567.40 ng/mL (p = 0.9156). However, the overweight and obese patients had slightly higher dose/kg-adjusted olaparib C_{trough} — 204.17 *vs.* 159.32 ng/mL/mg/kg. The incidence of grade 1 anaemia in the groups was as follows: I — 42.86%, II — 41.67%. Grade 2 and 3 anaemia was observed only in group II — 4.17% and 8.33%, respectively. The incidence of neutropenia in the groups of patients was as follows: grade 1: group I — 21.43%, group II — 20.83%; grade 2: group I — 7.14%, group II — 4.17%.

Conclusions: The incidence of haematological adverse reactions to olaparib, such as neutropenia and grade 1 anaemia in the group of overweight and obese patients was the same as in the normal BMI group. The overweight and obese patients were characterised by higher severity of haematological adverse reactions to olaparib and slightly higher dose/kg-adjusted olaparib C_{trough}. After one month of treatment with olaparib the overweight and obese patients had significantly lower red blood cells (RBC) and haemoglobin (Hgb) levels than the patients with normal BMI, which may indicate that anaemia develops faster in this group of patients.

Key words: olaparib; overweight; obesity; anaemia; neutropenia; C_{trough}

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Introduction

The incidence of cancer is increasing worldwide. In Poland, it is the second most common cause of death after cardiovascular dysfunction. Although there is huge public awareness of cancer and a lot of preventive screening tests, it is still the most common cause of death worldwide [1]. Scientists have conducted numerous clinical trials to change the standard treatment of cancer. By standard, patients with ovarian cancer are administered platinum derivates, carboplatin or cisplatin combined with paclitaxel in 6 cycles every 3 weeks. High-risk patients are additionally administered bevacizumab. The patients who completed first-line chemotherapy with a complete or partial response, according to the RECIST 1.1 criteria, and with documented abnormalities in the BRCA1/2 gene, are treated with olaparib [2, 3]. This drug is the first poly(ADP-ribose) polymerase inhibitor (PARP) approved in Europe in 2014 under the trade name of Lynparza. Clinical trials (e.g. SOLO1, SOLO2, and STUDY-19) proved its effectiveness. Those studies showed that olaparib and drugs with an analogous mechanism of action extended the progression-free survival (PFS), time to 2nd progression (PFS2), and overall survival (OS) and they increased complete response (CR) and partial response (PR) in platinum-sensitive patients without significant deterioration of their quality of life [4–6]. Currently olaparib is indicated for patients with BRCA1/2 mutation or confirmed homologous recombination deficiency for the treatment of newly diagnosed platinum-sensitive FIGO (Fr. *Fédération Internationale de Gynécologie et d'Obstétrique)* stage 3 and 4 ovarian cancer, fallopian tube cancer, peritoneal cancer, and for the treatment of recurrent platinum-sensitive ovarian cancer [7]. A study conducted on a group of ovarian cancer patients who received one PARP inhibitor and at least two lines of platinum-based chemotherapy showed that maintenance olaparib rechallenge resulted in a statistically significant PFS improvement over a placebo, remaining progression-free for 1 year [7].

Olaparib has a wide range of side effects, but there have been no studies showing whether the patient's body weight may increase the risk of haematological complications. Therefore, the aim of the study was a retrospective analysis of threshold value of the trough concentration of olaparib (C_{trough}) and haematological adverse reactions to olaparib in excess-weight and normal body mass index (BMI) patients with ovarian cancer. As epidemiological studies have shown an incompatible association between ovarian cancer and indicated that obesity and severe obesity increase the risk of ovarian cancer [8]. Even though it is found that the effectiveness of different dietary strategies in the management of obesity and obesity-related complications have shown heterogeneous findings, none of our patients was on diet [9].

Materials and methods

Reagents

High-performance liquid chromatography with UV detection was used to determine plasma olaparib concentrations. The standard of olaparib was purchased from LGC Standards (Łomianki, Poland). Acetaminophen was used as an internal standard, which was provided by Sigma Aldrich. The mobile phase consisted of a mixture of methanol and glacial acetic acid purchased from Merck. The extractive mixture contained methyl tert-butyl ether (Sigma Aldrich).

All patients qualified for the study were administered Lynparza® in tablets (batch: 70818, RN192, RT576, and RV411). The drug was manufactured by AstraZeneca Pharma Poland Sp. z o.o.

Subjects

All the regulations were prepared due to Declaration of Helsinki Rules: the planning stage, acts during the investigation and planning dissemination of the obtained results. Authors obtained approval of the appropriate bioethical committee [10].

The study was conducted at the Department of Gynaecological Oncology and the Department of Clinical Pharmacy and Biopharmacy, Poznań University of Medical Sciences, Poland, with the approval from the Bioethics Committee, Poznań University of Medical Sciences, Poland (697/20). The ClinicalTrials.gov ID NCT05081765. The study was conducted on patients with ovarian cancer who received olaparib between January 2021 and March 2022.

All the medical data were obtained thanks to the General Data Protection Regulation (GDPR)

becoming directly applicable in the EU member states in 2018 for better protection of patients' personal data. This regulation was welcomed by the public, partly due to reports on the theft of customer data from banks and other institutions in the media. It is unquestionable that the information about one's health should be kept private and not disclosed to others unless lawfully permitted [11]. Olaparib was administered in tablets of 150 mg; dosing 300 mg twice a day. The patients were included in the study if they met the following criteria: treatment with olaparib longer than four days, age > 18 years; no history of allergy to olaparib. The chief exclusion criteria were: allergy to olaparib, age under 18 years, the state which did not allow the patient to continue the study. All the patients provided their written consent before participating in the study.

Drug dosage and blood sampling

The patients with ovarian cancer (n = 38) were treated with olaparib tablets at a dose of 300 mg/12 h. The samples were obtained at steady state just before the administration of the drug. 2 mL blood samples were collected. They were transferred into heparinised tubes and centrifuged (2880 g for 10 min at 4°C). The plasma was placed in propylene tubes and stored in a freezer at –20°C until analysis. Each C_{trough} measurement was taken after the first cycle of olaparib treatment, i.e. 28 days after starting the olaparib treatment.

Assays

High-performance liquid chromatography (HPLC) with ultraviolet (UV) detection was applied to assay the concentrations of olaparib in the plasma. Acetaminophen was used as the internal standard (IS). The samples were analysed on Alliance 2695 HPLC UV-Vis system with the Empower 1154 Software (Waters Corporation, USA). The gradient method was used for separation. Phase A was 0.2% acetic acid in water, phase C was ultrapure water, phase D was methanol. The gradient started at 100% C and decreased linearly to 11% C, 1% A and then increased to 88% D in 17 min, then changed to 1% D, 98% C and after 25 min it returned to the starting condition for column equilibration. The flow rate was 1 mL/min. The HPLC process was conducted on Waters Symmetry C8, 5 µm, 4.6 mm x 250 mm analytical column. The column temperature was maintained at 25°C, the UV detection wavelength was set at 254 nm and the injection volume was 20 µL. The method was validated according to the guidelines of the European Medicines Agency [12]. The method had a linear range of 100.0–4,000 ng/mL (r = 0.9994) and good precision (CV < 15%). The accuracy ranged from 92.3% to 115.0%.

The following equation was used to calculate dose/kg-adjusted olaparib concentrations (ng/mL/mg/kg): olaparib concentration (ng/mL)/olaparib daily dose per body mass kilogram (mg/kg/day).

The Common Terminology Criteria for Adverse Events (CTCAE v5.0) was used to assess the severity of neutropenia and anaemia [13].

The grade of anaemia was determined by the haemoglobin level and G1, G2, G3, G4 mean LLN — 10.0 g/dL, 10.0–8.0 g/dL, < 8.0 g/dL, transfusion indicated and life-threatening consequences and urgent intervention indicated, respectively.

The grade of neutropenia was determined according to the count of neutrophils in blood samples and G1, G2, G3, G4 mean LLN — 1,500/µL, 1,500–1,000/µL, 1,000–500/µL, G4: < 500/µL, respectively [12].

Statistical analysis

The Shapiro-Wilk test showed that the quantitative data did not always have normal distribution, so they were presented not only as means ± standard deviation (mean ± SD), but also as medians with interquartile range [Median (Q1–Q3)]. The data in two independent groups, i.e. those with normal BMIs and the least overweight patients were compared with the Mann-Whitney test or unpaired t-test, depending on the normality of distribution and homogeneity of variance. The changes occurring over time were compared with the paired t-test or Wicoxon rank sum test, depending on the flatness of the assumptions for using these tests. A significance level of $\alpha = 0.05$ was assumed. The PQStat v1.8.6 statistical package was used for statistical analysis.

Results

The study was conducted on 38 patients between January 2021 and March 2022. The patients were divided into two groups according to their

BMI: I — normal BMI patients (BMI = 18.5–24.9 kg/m^2; n = 14), II — overweight and obese patients (BMI > 25 kg/m^2; n = 24). The mean age of the patients in the normal-weight group was 63.21 (±13.37) years. The youngest patient was 41 years old; the oldest patient was 83 years old. The mean age of the patients in the excess-weight group was 58.58 (±9.67) years. The youngest patient was 40 years old; the oldest patient was 83 years old.

Table 1 shows the biochemical parameters of all groups of patients.

The olaparib concentration was 1,602.86 ± 1,593.50 ng/mL in group I and 1,567.40 ± 1,134.94 ng/mL (p = 0.9156) in group II. The dose/kg-adjusted olaparib concentrations in these groups were: I — 159.32 ± 150.82 ng/mL/mg/kg and II — 204.17 ± 172.10 ng/mL/mg/kg (p = 0.372012).

Anaemia was observed in 19 patients (50.00%). There were 6 normal weight patients (42.86%) with G1 anaemia. There were 10 patients (41.67%) with G1 anaemia, 1 patient with G2 anaemia (4.17%), and 2 patients (8.33%) with G3 anaemia

Table 1. The comparison of selected parameters between the patients with normal (n = 14) and abnormal body mass index (BMI) (n = 24) before the olaparib therapy and after one month of the therapy

Parameter Mean ± SD Median [Q1, Q3]	Before olaparib treatment			After 1 month of olaparib treatment		
	Normal BMI 18.5–24.9 [kg/m^2]	Overweight and obesity BMI ≥ 25 [kg/m^2]	p-value	Normal BMI 18.5–24.9 [kg/m^2]	Overweight and obesity BMI ≥ 25 [kg/m^2]	p-value
WBC	5.58 ± 2.06 4.85 [4.38; 6.47]	5.92 ± 1.56 5.6 [4.63; 6.93]	0.3328[1]	5.06 ± 1.95 4.99 [3.42; 5.58]	5.57 ± 1.94 4.94 [4.39;6.13]	0.4959[1]
NEUT	3.15 ± 1.45 2.58 [2.37; 3.31]	3.15 ± 1.13 2.86 [2.31; 3.63]	0.6717[2]	2.90 ± 1.24 2.78 [1.86; 3.69]	3.27 ± 1.77 2.86 [2.10; 3.79]	0.7737[2]
MCV	97.64 ± 5.49 97.5 [92.75; 101.50]	100 ± 6.43 99.5 [96.75; 100.25]	0.3233[2]	97.29 ± 5.38 96.5 [93.50; 98.75]	99.63 ± 6.09 98.5 [95.75; 101.25]	0.1768[2]
MCH	2.03 ± 0.10 2.05 [1.96; 2.08]	2.08 ± 0.17 2.09 [1.98; 2.16]	0.3025[1]	2.06 ± 0.15 2.06 [2.00; 2.14]	2.08 ± 0.15 2.06 [2.00; 2.15]	0.7559[1]
MCHC	20.79 ± 0.46 20.93 [20.48; 21.13]	20.73 ± 0.75 20.49 [20.23; 21.19]	0.7871[1]	21.17 ± 0.77 21.11 [20.64; 21.76]	20.88 ± 0.87 20.81 [20.49; 21.33]	0.3070[1]
RDW	13.74 ± 1.38 13.6 [12.8; 14.35]	15.54 ± 1.83 15.65 [13.93; 16.83]	0.0031[1]	15.51 ± 1.44 15.6 [14.55; 16.20]	16.63 ± 1.96 16.60 [15.45; 17.35]	0.0724[1]
RBC	3.81 ± 0.35 3.81 [3.63; 3.93]	3.69 ± 0.45 3.66 [3.49; 3.85]	0.4045[1]	3.78 ± 0.36 3.75 [3.58; 4.01]	3.50 ± 0.59 3.55 [3.25; 3.80]	0.1096[1]
HGB	7.69 ± 0.68 7.50 [7.23; 7.90]	7.60 ± 0.60 7.65 [7.28; 7.90]	0.7026[1]	7.68 ± 0.57 7.65 [7.33; 8.08]	7.21 ± 1.07 7.40 [6.93; 7.80]	0.2081[1]
HCT	0.37 ± 0.03 0.37 [0.35; 0.38]	0.37 ± 0.03 0.36 [0.35; 0.39]	0.7913[1]	0.37 ± 0.03 0.37 [0.35; 0.39]	0.42 ± 0.30 0.36 [0.35; 0.38]	0.8429[1]
PLT	212.21 ± 52.66 200.5 [173.75; 238.00]	243.83 ± 122.33 25.50 [188.75; 257.75]	0.3883[2]	224.43 ± 45.27 211.50 [201.00; 241.00]	196.08 ± 63.58 192.50 [142.50; 229.00]	0.1524[2]
ALAT	22.50 ± 8.39 22.00 [18.00; 26.75]	27.75 ± 10.56 26.00 [21.50; 30.25]	0.1336[2]	18.93 ± 8.24 18.00 [13.50; 23.25]	22.04 ± 8.58 19.50 [16.75; 24.25]	0.3320[2]
ASPAT	23.93 ± 5.30 23.50 [22.25; 27.50]	25.58 ± 10.38 22.50 [21.00; 27.00]	0.6709[2]	22.93 ± 4.78 22.50 [18.50; 26.75]	22.96 ± 6.85 21.50 [19.00; 23.25]	0.7496[2]
BIL	7.14 ± 3.17 8.00 [5.03; 9.00]	7.20 ± 4.24 7.35 [4.00; 9.00]	0.9654[1]	7.84 ± 4.22 8.00 [3.75; 10.00]	7.97 ± 4.19 8.00 [3.80; 10.75]	1.000[1]
CREAT	70.86 ± 13.68 68.00 [64.50; 73.24]	69.04 ± 10.69 66.50 [60.00; 75.00]	0.6713[2]	81.57 ± 22.15 79.50 [67.50; 86.00]	79.96 ± 17.67 77.50 [70.50; 85.25]	0.9396[2]

[1]t-test; [2]Mann-Whitney test; Mean — arithmetic mean; SD — standard deviation; Q1–Q3 — Quartile; BMI — body mass index; WBC — white blood cells; neut — neutrophils; RBC — red blood cells; HBG — haemoglobin; HCT — haematocrit; MCV — mean corpuscular volume; MCH — mean corpuscular haemoglobin; MCHC — mean corpuscular haemoglobin concentration; RDW — red blood cell distribution width; PLT — platelet count; ALT — alanine transaminase; AST — aspartate transaminase; BIL — bilirubin; CREAT — creatinine

Table 2. The comparison of selected parameters within the groups of patients with normal (n = 14) and abnormal body mass index (BMI) (n = 24) before the olaparib therapy and after one month of the therapy

Parameter Mean ± SD Median [Q1, Q3]	Normal BMI 18.5–24.9 [kg/m^2]			Overweight and obesity BMI ≥ 25 [kg/m^2]		
	Before olaparib treatment	After 1 month of olaparib treatment	p-value	Before olaparib treatment	After 1 month of olaparib treatment	p-value
WBC	5.58 ± 2.06 4.85 [4.38; 6.47]	5.06 ± 1.95 4.99 [3.42; 5.58]	0.1771[2]	5.92 ± 1.56 5.6 [4.63;6.93]	5.57 ± 1.94 4.94 [4.39;6.13]	0.3065[2]
NEUT	3.15 ± 1.45 2.58 [2.37; 3.31]	2.90 ± 1.24 2.78 [1.86; 3.69]	0.3003[2]	3.15 ± 1.13 2.86 [2.31; 3.63]	3.27 ± 1.77 2.86 [2.10; 3.79]	0.3986[2]
MCV	97.64 ± 5.49 97.5 [92.75; 101.50]	97.29 ± 5.38 96.5 [93.50; 98.75]	0.8249[1]	100 ± 6.43 99.5 [96.75; 100.25]	99.63 ± 6.09 98.5 [95.75; 101.25]	0.3657[2]
MCH	2.03 ± 0.10 2.05 [1.96; 2.08]	2.06 ± 0.15 2.06 [2.00; 2.14]	0.3567[1]	2.08 ± 0.17 2.09 [1.98; 2.16]	2.08 ± 0.15 2.06 [2.00; 2.15]	0.9685[1]
MCHC	20.79 ± 0.46 20.93 [20.48; 21.13]	21.17 ± 0.77 21.11 [20.64; 21.76]	0.0501[1]	20.73 ± 0.75 20.49 [20.23; 21.19]	20.88 ± 0.87 20.81 [20.49; 21.33]	0.4313[1]
RDW	13.74 ± 1.38 13.6 [12.8; 14.35]	15.51 ± 1.44 15.6 [14.55; 16.20]	0.0038[1]	15.54 ± 1.83 15.65 [13.93; 16.83]	16.63 ± 1.96 16.60 [15.45; 17.35]	0.0036[1]
RBC	3.81 ± 0.35 3.81 [3.63; 3.93]	3.78 ± 0.36 3.75 [3.58; 4.01]	0.8581[1]	3.69 ± 0.45 3.66 [3.49; 3.85]	3.50 ± 0.59 3.55 [3.25; 3.80]	0.0107[1]
HGB	7.69 ± 0.68 7.50 [7.23; 7.90]	7.68 ± 0.57 7.65 [7.33; 8.08]	0.9650[1]	7.60 ± 0.60 7.65 [7.28; 7.90]	7.21 ± 1.07 7.40 [6.93; 7.80]	0.0043[2]
HCT	0.37 ± 0.03 0.37 [0.35; 0.38]	0.37 ± 0.03 0.37 [0.35; 0.39]	0.5304[1]	0.37 ± 0.03 0.36 [0.35; 0.39]	0.42 ± 0.30 0.36 [0.35; 0.38]	0.0982[2]
PLT	212.21 ± 52.66 200.5 [173.75; 238.00]	224.43 ± 45.27 211.50 [201.00; 241.00]	0.30261	243.83 ± 122.33 25.50 [188.75; 257.75]	196.08 ± 63.58 192.50 [142.50; 229.00]	0.0553[2]
ALAT	22.50 ± 8.39 22.00 [18.00; 26.75]	18.93 ± 8.24 18.00 [13.50; 23.25]	0.1089[1]	27.75 ± 10.56 26.00 [21.50; 30.25]	22.04 ± 8.58 19.50 [16.75; 24.25]	0.0005[2]
ASPAT	23.93 ± 5.30 23.50 [22.25; 27.50]	22.93 ± 4.78 22.50 [18.50; 26.75]	0.5358[1]	25.58 ± 10.38 22.50 [21.00; 27.00]	22.96 ± 6.85 21.50 [19.00; 23.25]	0.0415[2]
BIL	7.14 ± 3.17 8.00 [5.03; 9.00]	7.84 ± 4.22 8.00 [3.75; 10.00]	0.5179[1]	7.67 ± 4.11 7.85 [4.20; 9.00]	7.97 ± 4.19 8.00 [3.80; 10.75]	0.5610[1]
CREAT	70.86 ± 13.68 68.00 [64.50; 73.24]	81.57 ± 22.15 79.50 [67.50; 86.00]	0.0131[2]	69.04 ± 10.69 66.50 [60.00; 75.00]	79.96 ± 17.67 77.50 [70.50; 85.25]	0.0001[2]

[1]t-test; [2]Wilcoxon test; mean — arithmetic mean; SD — standard deviation; Q1–Q3 — Quartile; BMI — body mass index, WBC — white blood cells; neut — neutrophils; RBC - red blood cells; HBG — haemoglobin; HCT — haematocrit; MCV — mean corpuscular volume; MCH — mean corpuscular haemoglobin; MCHC — mean corpuscular haemoglobin concentration; RDW — red blood cell distribution width; PLT — platelet count; ALT — alanine transaminase; AST — aspartate transaminase; BIL — bilirubin; CREAT — creatinine

in the obese and overweight group. There were no cases of G4 or G5 anaemia in either group (Tab. 3).

Neutropenia was diagnosed in 10 patients (26.32%), including G1 neutropenia in 3 normal weight patients (21.43%) and 5 excess weight patients (20.83%). Neutropenia G2 was diagnosed in 1 normal weight patient (7.14%) and in 1 (4.17%) obese/overweight patient. Neither G3 nor G4 toxicity was observed (Tab. 3).

Apart from the red blood cell distribution width (RDW), there were no statistically significant differences between the groups in the parameters under analysis before or after one month of the therapy (Tab. 1). There were significant differences in the RDW, RBC, and HGB in the group of excess-weight patients before and after one month of olaparib therapy. In the group of patients with the normal BMI there were significant differences only in the RDW (Tab. 2).

Table 3. Haematological adverse effect, threshold value of the trough concentration of olaparib (C_{trough}) and dose/kg-adjusted olaparib C_{trough}

Adverse effect	CTCAE scale	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anaemia	Body weight	C_{trough} [ng/mL] Mean ± SD (CV%)				
	Normal weight	1,567.82 ± 543.39 (35)	-	-	-	-
		n = 6	n = 0	n = 0	n = 0	n = 0
	Overweight and obesity	1,355.54 ± 538.76 (40)	1,166.30	2,462.22 ± 924.10 (37)		
		n = 10	n = 1	n = 2	n = 0	n = 0
	Body weight	dose/kg-adjusted olaparib concentrations [ng/mL/mg/kg] Mean ± SD (CV%)				
	Normal weight	157.30 ± 60.91 (39)	–	–	–	–
		n = 6	n = 0	n = 0	n = 0	n = 0
	Overweight and obesity	169.27 ± 71.55 (42)	149.67	354.48 ± 148.59 (42)	–	–
		n = 10	n = 1	n = 2	n = 0	n = 0
Neutropenia	Body weight	C_{trough} [ng/mL] Mean ± SD (CV%)				
	Normal weight	1,943.08±536.42 (28)	244.38	-	-	-
		n=3	n=1	n=0	n = 0	n = 0
	Overweight and obesity	1,162.38±469.09 (40)	1205	-	-	-
		n=5	n=1	n=0	n = 0	n = 0
	Body weight	dose/kg-adjusted olaparib concentrations [ng/mL/mg/kg] Mean ± SD (CV%)				
	Normal weight	204.99±58.23 (28)	24.03	-	-	-
		n=3	n=1	n=0	n = 0	n = 0
	Overweight and obesity	137.39±62.58 (45)	148.62	-	-	-
		n=5	n=1	n=0	n = 0	n = 0

CTCAE — Common Terminology Criteria for Adverse Events; Mean — arithmetic mean; SD — standard deviation CV% — coefficient of variation

Discussion and Conclusions

Ovarian cancer has a poor prognosis, because most patients are diagnosed at late stages of the disease which develops without characteristic symptoms. Patients often underestimate ailments or explain them by temporary problems in their digestive or urinary systems. The standard treatment is a combination of cytoreductive surgery with subsequent chemotherapy based on paclitaxel, a platinum derivative (carboplatin or cisplatin), whereas high-risk patients are treated with bevacizumab [14, 15]. The prognosis for patients with BRCA1 and 2 gene mutations and confirmed homologous recombination deficiency has improved considerably. Therefore, it is necessary to apply genetic diagnostic tests to each patient with ovarian cancer. If mutation or homologous recombination deficiency is confirmed and if the patient responds to treatment with platinum derivatives, she is qualified for maintenance therapy with PARP inhibitors, including olaparib [3, 14].

The olaparib monotherapy usually caused mild or moderate adverse drug reactions (CTCAE grade 1 or 2), which did not require the treatment to be discontinued but some time off was necessary. Various clinical trials involving a olaparib monotherapy showed that the most common adverse reactions (≥ 10%) observed in the patients receiving the drug were: nausea, vomiting, diarrhoea, indigestion, fatigue, headache, dysgeusia, decreased appetite, dizziness, cough, dyspnoea, anaemia, neutropenia, thrombocytopenia, and leukopenia. Grade ≥ 3 adverse reactions were observed in more than 2% of the patients and included: anaemia (16%), neutropenia (6%), fatigue/asthenia (5%), leukopenia (3%), thrombocytopenia (3%), and vomiting (2%). Increasing fatigue may have

been mostly caused by the therapy the patients were undergoing as they complained of impaired cognitive functions, including concentration and memory problems [1]. The most common adverse reactions observed in the clinical trials, which usually led to interruption of the therapy and/or dose reduction, were: anaemia (16.2%), vomiting (6.8%), nausea (6.2%), neutropenia (6.2%), and fatigue/asthenia (6.0%). The most common adverse reactions which usually led to discontinuation of the therapy were: anaemia (1.8%), nausea (0.7%), fatigue/asthenia (0.7%), and thrombocytopenia (0.7%). However, the olaparib therapy is usually discontinued or the dose of the drug is reduced due to adverse reactions such as: nausea (73%), fatigue (5%), vomiting (36%), diarrhoea (30%), and anaemia (26%) [2].

The need to discontinue using the drug reduces the beneficial effects of the therapy. Therefore, it is so important to determine the dependence between the occurrence of adverse reactions and other factors. Therapeutic drug monitoring (TDM) is a practical tool facilitating safe therapy when the intensity of an adverse reaction depends on the concentration of the drug in the blood. However, olaparib is a relatively new drug and no therapeutic concentrations have been recommended yet, although Velev et al. postulated a C_{trough} of 2,500 ng/mL [16]. The patient's weight may also be a factor predisposing them to adverse reactions. Obesity is associated with numerous pathophysiological changes which may affect the pharmacokinetics (PK) and effect of the drug. Obese people are at higher risk of cardiomyopathy and atherosclerosis, alterations in pulmonary function, changes in large airway anatomy associated with obstructive sleep apnoea, increased rate of daytime hypoxemia, altered volume of distribution of lipophilic drugs, and altered drug metabolism due to enzyme levels and activity [12]. As olaparib is metabolised by CYP3A4, the lower activity of the enzyme in obese patients [17,18] may lead to higher drug concentrations despite the higher body weight, which translates into a greater volume of distribution of the drug.

In our study the C_{trough} of olaparib was assessed in individual groups of patients. The patients initially received the drug at a dose of 2 × 300 mg daily. After 28 days, i.e. after the first treatment cycle, the tolerance of the oncological treatment was assessed in laboratory investigations. There were no statistically significant differences in the steady-state trough concentrations of olaparib in patients in individual groups ($p = 0.9156$). There was a higher dose/kg-adjusted olaparib C_{trough} in the group of overweight and obese patients, i.e. 204.17 ± 172.10 ng/mL/mg/kg, as compared with 159.32 ± 150.82 ng/mL/mg/kg in the group of patients with normal BMI, but the difference was not statistically significant ($p = 0.3720$).

Drug plasma concentrations in obese patients are usually lower due to the greater volume of distribution, but it is not always so. For example, Robert et al. observed a higher concentration of tacrolimus in obese patients than in those with a normal BMI [19]. The higher dose/kg-adjusted olaparib C_{trough} in the group of patients with excess weight may have been caused by the fact that CYP3A4 exhibits lower activity in obesity [12]. It also noteworthy that olaparib is a substrate for P-glycoprotein [16]. Vandelbo et al. found that a higher BMI was associated with reduced expression of P-glycoprotein in the human brain. It cannot be ruled out that a similar effect on P-gp can be observed in other tissues, such as the intestine or kidney. This would mean an increase in the concentration of drugs which are P-gp substrates [20]. Experiments on rats showed that in comparison with animals with normal body mass the expression levels of P-gp in the small intestine of obese animals were significantly reduced [21].

The $C_{through}$ and dose/kg-adjusted olaparib $C_{through}$ were not significantly higher at increasing grades of anaemia and neutropenia. The comparison of the group of patients with the normal BMI with the group of patients with the elevated BMI according to the CTCAE toxicity grade did not reveal any differences in the $C_{through}$ and dose/kg-adjusted olaparib $C_{through}$ values. According to Velev [16], during olaparib treatment toxicity occurs more frequently when $C_{through}$ is above 2,500 ng/mL. In our study, this concentration was measured in two patients with anaemia (including two patients with increased BMI) and in one patient with neutropenia and normal body weight.

There were 38 patients in our study. Anaemia was observed in 19 concentration measurements (50.0%, n = 19 samples, Tab. 3).

Additionally, the following parameters were assessed: mean corpuscular volume (MCV),

MCH, mean corpuscular haemoglobin concentration (MCHC), and red blood cell distribution (RDW) in the group of patients with the normal BMI and those with excess weight. There were significant differences in the RDW values between the groups (Tab. 2). In the morphology blood test, the RDW, i.e. the coefficient of variation of the erythrocyte volume distribution, determines the differences between the sizes of these blood cells. This parameter is used in the diagnosis of anaemia of various origins because it shows how different the red blood cells of a particular patient are. However, this result should not be interpreted individually and the parameters describing the red blood cell structure, i.e. MCV, MCH, and MCHC should also be taken into account.

After one month of treatment with olaparib at a dose of 2 × 300 mg/24 h the RBC and Hgb values in the group of overweight and obese patients were significantly lower than in the group of patients with the normal BMI (Tab. 2). This means that anaemia, which is one of the most common complications of olaparib treatment, develops faster in this group of patients, especially in the first months of therapy. The values of the RDW coefficient were statistically significantly higher in both groups of patients (Tab. 2). The statistically significant differences in both groups after one month of treatment with olaparib clearly proved that the drug changed the distribution of the red cell lineage already during the therapy and was directly related to the occurrence of anaemia.

Neutropenia means a decrease in the count of neutrophils below the lower limit of normal. However, from the clinical point of view, neutropenia grades 3 and 4 are significant [13]. A low level of neutrophils is conducive to the occurrence of febrile neutropenia and bacterial and viral infections. Grade 1 and 2 neutropenia was diagnosed in 10 patients (26.32%). It is noteworthy that olaparib not only affects the red blood cell lineage, but also the white blood cell lineage, which may increase the risk of serious infections.

Toxicity manifested by anaemia and neutropenia was noticed in most of the patients as early as after one month of the treatment. Therefore, as soon as the therapy is implemented, it is important to prepare patients for its possible side effects and their consequences.

The study was limited by small groups. Therefore, it should be continued on a larger number of patients.

Conclusions

The haematological adverse reactions to olaparib, such as neutropenia and grade 1 anaemia, were observed equally often in the overweight and obese patients and in those with the normal BMI. The haematological adverse reactions to olaparib in the overweight and obese patients were more severe, whereas the dose/kg-adjusted olaparib C_{trough} was slightly higher. After one month of treatment with olaparib the RBC and Hgb levels in the group of overweight and obese patients were significantly lower than in the patients with normal BMI, which may indicate that anaemia develops faster in this group of patients.

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