ORIGINAL PAPERS

Adv Clin Exp Med 2015, **24**, 1, 103–111
DOI: 10.17219/acem/38154

ISSN 1899–5276

Anna Wiela-Hojeńska[1, A, C–F], Teresa Kowalska[1, B–D], Emilia Filipczyk-Cisarż[2, B, C, F], Łukasz Łapiński[1, A, B, E, F], Karol Nartowski[1, B]

Evaluation of the Toxicity of Anticancer Chemotherapy in Patients with Colon Cancer

[1] Department of Clinical Pharmacology, Wroclaw Medical University, Poland
[2] Department of Chemotherapy, Lower Silesian Oncology Center, Wrocław, Poland

A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. Modern anticancer chemotherapy can cause numerous adverse effects in the organism, whose functioning has already been disrupted by the neoplastic process itself.
Objectives. The aim of the study was to evaluate and compare the frequency and severity of the toxicity of FOLFOX-4 and CLF-1 anticancer therapy in patients with colon cancer, and to analyze certain factors that might have increased the toxicity of the chemotherapy.
Material and Methods. The study involved 64 patients suffering from generalized colon cancer, including 48 patients treated according to the FOLFOX-4 regimen and 16 patients treated according to the CLF-1 regimen. The toxicity of each regimen was analyzed on the basis of a confidential questionnaire formulated by the authors and laboratory research according to the extended WHO toxicity criteria.
Results. The analysis of the symptoms of toxicity symptoms associated with the use of the FOLFOX-4 and CLF-1 therapeutic regimens revealed that the most common side effects included nausea and vomiting, despite ondansetron premedication, and neurotoxicity. Disruption of the functioning of the nervous system under the FOLFOX-4 regimen statistically significant exacerbation that increased with the number of chemotherapy cycles administered; this was more common and more severe in women. Paresthesia was also revealed to be a neurotoxic effect of the FOLFOX-4 regimen after termination of therapy. A statistically significant relationship was observed between the use of vitamin supplements and the incidence and severity of the toxicity of the FOLFOX-4 regimen.
Conclusions. The findings of the current study regarding the toxicity of the FOLFOX-4 and CLF-1 therapy regimens should be taken into consideration when monitoring chemotherapy safety in colon cancer. The patients' tolerance of the administered medication and the side effects reported by patients should be constantly evaluated, which will help prevent these side effects, apply appropriate therapy and contribute to the improvement of the patients' quality of life. The functioning of the central nervous system should be carefully evaluated when planning the anticancer therapy, especially if repeated administration of neurotoxic drugs is necessary in cases of a recurrence of the disease. Chemotherapy should be thoroughly monitored for safety, especially in women over 65 years of age suffering from coexisting diseases. Colon cancer patients and their families should be informed of the risks of nutritional supplements before the start of the anticancer chemotherapy, and may need to dispense with their use **(Adv Clin Exp Med 2015, 24, 1, 103–111)**.

Key words: FOLFOX-4, CLF-1, chemotherapy, toxicity, colon cancer.

Modern anticancer chemotherapy based on the administration of high doses of cytostatics can cause numerous adverse effects in the organism, whose functioning has already been disrupted by the neoplastic process itself. Therefore, such patients should be given special attention in order to improve the efficiency as well as the safety of pharmacological treatment. Their therapy should be individualized, enabling both early prediction of cytostatic toxicity and the treatment of possible unwanted effects [1–4].

The aim of the study was to evaluate the frequency and severity of the toxicity of anticancer therapy carried out according to the FOLFOX-4 and CLF-1 chemotherapy regimens in patients with colon cancer; compare the incidence and severity of the toxicity of selected chemotherapy regimens administered to the patients

investigated; and analyze certain factors, such as age, sex, associated morbidity, simultaneously administered treatments, and the use of dietary supplements and drugs of plant origin which might have increased the toxicity of the anticancer chemotherapy.

Material and Methods

The study involved 64 patients suffering from generalized colon cancer who were hospitalized in the Clinical Oncology/Chemotherapy Department of the Lower Silesian Oncology Center in Wrocław, Poland. The participants included 48 patients being treated according to the FOLFOX-4 regimen (oxaliplatin, folinic acid, fluorouracil) and 16 patients being treated according to the CLF-1 regimen (irinotekan, folinic acid, fluorouracil). Detailed descriptions of both groups of patients and the anticancer chemotherapy regimen administered are presented in Tables 1 and 2.

Taking the Histories

Each patient's history was taken using a confidential questionnaire formulated by the authors. Participation in the study was voluntary, and the patients were randomly selected. The questionnaire included questions providing information on personal data, which were next properly encoded. The clinical data given by patients were then complemented with information on diagnosis of the disease, the treatment administered (present and/or past), adverse effects reported, the regularity of the cycles and laboratory findings.

Evaluating Toxicity

The toxicity of individual regimens was analyzed according to the extended WHO toxicity criteria. Evaluations of hematological toxicity, hepatotoxicity and nephrotoxicity were performed on the basis of available laboratory test findings. The activity of the hematopoietic system was evaluated on the basis of peripheral blood hemoglobin, WBC, granulocyte and thrombocyte count; the activity of the liver was evaluated on the basis of the levels of bilirubin and AspAT, AlAT and ALP activity. Renal function was assessed on the basis of serum creatinine and urea levels as well as the presence of proteinuria and hematuria. The tests were performed on a routine basis on the day of the patient's admission to the Chemotherapy Department, i.e. prior to the planned administration of a therapeutic cycle. The clinical symptoms of the toxicity to individual organs and systems were evaluated on the basis of the patient's own reports.

Table 1. Description of patients

Investigated group of patients with generalized colon cancer	Number of patients	Age (years)		Sex		Number of administered cycles	
			± SD	males	females		± SD
Patients treated with the FOLFOX-4 regimen	48	58.3	9.0	24	24	5.9	3.1
Patients treated with the CLF-1 regimen	16	61.1	9.1	8	8	4.9	4.0

Table 2. Anticancer chemotherapy regimens administered

Regimen, drugs	Daily dosage	Route (time) of drug administration	Days of drug administration	Interval between cycles
FOLFOX-4				
Oxaliplatin	85 mg/m^2 p.c.	*c.i.v.* (2 h)	1	14 days
Folinic acid	200 mg/m^2 p.c.	*c.i.v.* (2 h)	1–2	
Fluorouracil	400 mg/m^2 p.c.	*i.v.* (bolus)	1–2	
Fluorouracil	600 mg/m^2 p.c.	*c.i.v.* (22 h)	1–2	
CLF-1				
Irinotekan	180 mg/m^2 p.c.	*c.i.v.* (2 h)	1	14 days
Folinic acid	200 mg/m^2 p.c.	*c.i.v.* (2 h)	1–2	
Fluorouracil	400 mg/m^2 p.c.	*i.v.* (bolus)	1–2	
Fluorouracil	600 mg/m^2 p.c.	*c.i.v.* (22 h)	1–2	

i.v. – intravenous, *c.i.v.* – continuous intravenous infusion.

Statistical Analysis of Results

The study findings were analyzed statistically using EPIINFO (v. 3.4.3) software. Mean values ($\bar{\chi}$), medians (M) and standard deviations (SD) of the investigated continuous parameters were evaluated for both the groups. Due to the small number of cases, verification of the hypothesis of equality of the mean parameters in the groups was performed using a non-parametric Kruskal-Wallis analysis of variance by ranks. For discrete parameters, the frequency of traits in the groups was analyzed by means of a χ^2_{df} test with Yates' correction with an adequate number of freedom degrees, or, in cases in which the expected value was lower than 5, by means of Fisher's exact test. For selected pairs of parameters, a correlation analysis was performed and Spearman's correlation rank coefficient was calculated. Values $p \leq 0.05$ were considered statistically significant.

Results

The results present the incidence of severe and life-threatening adverse effects of anticancer chemotherapy (severity of toxicity 3/4); among hematological complications toxicity grades ≥ 2 were considered, as they preclude the administration of a subsequent chemotherapy cycle. The total results of the toxicity evaluation for individual therapeutic programs in numbers and percentages are presented in Tables 3 and 4.

The Toxicity of the FOLFOX-4 Regimen

The observed hematological complications did not prolong the intervals between consecutive chemotherapy cycles or lead to the discontinuation of

Table 3. An evaluation of the toxicity of the FOLFOX-4 regimen according to WHO criteria

FOLFOX-4 regimen (number of patients n = 48)					
Symptoms of toxic effect	**lack of toxic symptoms**	**toxicity grades according to WHO criteria**			
		1	**2**	**3**	**4**
Anemia	45 (93.8%)	3(6.3%)	0	0	0
Leukopenia	37 (77.1%)	6 (12. 5%)	3 (6.3%)	2 (4.2%)	0
Granulocytopenia	38 (79.1%)	5 (10.4%)	4 (8.3%)	1 (2.1%)	0
Thrombocytopenia	47 (97.9%)	1 (2.1%)	0	0	0
Bleeding	33 (68.8%)	5 (10.4%)	10 (20.8%)	0	0
Elevated level of bilirubin*	22 (91.7%)	2 (8.3%)	0	0	0
Increased AST activity*	23 (95.8%)	1 (4.2%)	0	0	0
Increased ALT activity*	20 (87.5%)	4 (16.7%)	0	0	0
Increased ALP activity*	20 (87.5%)	3 (12.5%)	0	1 (4.2%)	0
Oral lesions	37 (77.1%)	8 (16.7%)	3 (6.3%)	0	0
Nausea/vomiting	16 (33.3%)	20 (41.7%)	3 (6.3%)	8 (16.7)	1 (2.1%)
Diarrhea	28 (58.3%)	13 (27.1)	2 (4.2%)	5 (10.4%)	0
Elevated urea level**	45 (100%)	0	0	0	0
Elevated creatinine level**	45 (100%)	0	0	0	0
Proteinuria**	44 (97.8%)	1 (2.2%)	0	0	0
Hematuria**	43 (97.8%)	2 (4.4%)	0	0	0
Pathological changes in respiratory function	43 (89.6%)	3 (6.3%)	1 (2.1%)	1 (2.1%)	0
Drug induced fever	41 (85.4%)	3 (6.3%)	3 (6.3%)	1 (2.1%)	0
Allergic reactions	42 (87.5%)	1 (2.1%)	4 (8.3%)	0	1 (2.1%)
Skin lesions	36 (75.0%)	5 (10.4%)	7 (14.6%)	0	0
Hair loss	32(66.6%)	12 (25.0%)	2 (4.2%)	2 (4.2%)	0
Infections	44 (91.7%)	3 (6.3%)	1 (2.1%)	0	0
Disturbed consciousness	33 (68.8%)	10 (20.8%)	1 (2.1%)	4 (8.3%)	0
Peripheral nervous system depression	12 (25.0%)	16 (33.3%)	16 (33.3%)	4 (8.3%)	0
Constipation	34 (70.8%)	6 (12.5%)	6 (12.5%)	2 (4.2%)	0
Pain	37 (77.1%)	4 (8.3%)	6 (12.5%)	1 (2.1%)	0

* – number of investigated patients n = 24, ** – number of investigated patients n = 45.

treatment in any of the patients (Table 3). Nausea and vomiting were the most commonly observed toxic effects of the FOLFOX-4 regimen affecting the gastrointestinal system. All the patients were premedicated with ondansetron – an antiemetic drug. Allergic reactions were observed in 12.5% of patients. In the most severe case they took the form of an anaphylactic reaction. According to the patient's records: "after the onset of oxaliplatin administration, with the first drops: sneezing, dyspnea, retrosternal pressure, redness of the skin, anxiety, generalized itching of the skin, pulse impalpable, BP dropped to 40/0, drenched in sweat". Among the investigated patients, hypersensitivity reactions occurred during the 5th through 8th courses and were relieved after the administration of glucocorticosteroids and antihistamine drugs.

The Toxicity of the CLF-1 Regimen

Leucopenia and granulocytopenia were the most common hematological side effects among the patients in the study (Table 4). An abnormal granulocyte count was observed in 26.7% of the patients, including 6.7% with a severity grade > 2, necessitating the administration of granulocyte growth factor (filgrastim). In order to prevent vomiting, all the patients were premedicated with ondansetrone. Half of the patients (50%) suffered from diarrhea, 18.8% of them with severity grade 3. All the patients were administered atropin prior to irinotecan, in order to prevent the early diarrhea associated with the cholinergic syndrome. Nervous system distress occurred in 75% of the patients.

Table 4. Evaluation of the toxicity of the CLF-1 regimen according to WHO criteria

CLF-1 regimen (number of patients n = 16)					
Symptoms of toxic effects	**lack of toxicity symptoms**	**toxicity grades according to WHO criteria**			
		1	**2**	**3**	**4**
Anemia*	13 (86.7%)	2 (13.3%)	0	0	0
Leukopenia*	10 (66.7%)	3 (20.0%)	1 (6.7%)	1 (6.7%)	0
Granulocytopenia*	11 (73.3%)	3 (20.0%)	0	1 (6.7%)	0
Thrombocytopenia*	14 (93.3%)	1 (6.7%)	0	0	0
Bleeding	11 (68.8%)	3 (18.8%)	2 (12.5%)	0	0
Elevated level of bilirubin**	14 (100%)	0	0	0	0
Increased AST activity**	14 (100%)	0	0	0	0
Increased ALT activity**	14 (100%)	0	0	0	0
Increased ALP activity**	14 (100%)	0	0	0	0
Oral lesions	12 (75.0%)	2 (12.5%)	1 (6.3%)	1 (6.3%)	0
Nausea/vomiting	5 (31.3%)	2 (12.5%)	3 (18.8%)	5 (31.2%)	1 (6.2%)
Diarrhea	8 (50.0%)	2 (12.5%)	3 (18.8%)	3 (18.8%)	0
Elevated urea level**	12 (85.7%)	2 (14.3%)	0	0	0
Elevated creatinine level**	13 (92.9%)	1 (7.1%)	0	0	0
Proteinuria**	13 (92.9%)	1 (7.1%)	0	0	0
Hematuria **	11 (78.6%)	1 (7.1%)	2 (14.3%)	0	0
Pathological changes in respiratory function	13 (81.3%)	0	2 (12.5%)	1 (6.2%)	0
Drug induced fever	11 (68.8%)	4 (25.0%)	1 (6.2%)	0	0
Allergic reactions	13 (81.3%)	1 (6.2%)	2 (12.5%)	0	0
Skin lesions	9 (56.2%)	3 (18.8%)	3 (18.8%)	1 (6.2%)	0
Hair loss	6 (37.5%)	3 (18.8%)	2 (12.5%)	5 (31.2%)	0
Infections	13 (81.3%)	0	1 (6.2%)	2 (12.5%)	0
Disturbed consciousness	8 (50.0%)	5 (31.3%)	2 (12.5%)	1 (6.2%)	0
Peripheral nervous system depression	4 (25.0%)	3 (18.7%)	7 (43.8%)	2 (12.5%)	0
Constipation	9 (56.3%)	1 (6.2%)	5 (31.3%)	1 (6.2%)	0
Pain	11 (68.8%)	0	4 (25.0%)	1 (6.2%)	0

* number of investigated patients n = 15; ** number of investigated patients n = 14.

All the patients who reported neurotoxicity symptoms had been treated previously, at different times, with the FOLFOX-4 regimen. All cases of allergic reactions were skin reactions. Other skin lesions were reported by 43.7% of the patients; only one of them had severity grade 3. Hair loss affected 62.6% of patients; in 31.3% of them the hair loss was complete but reversible (severity grade 3).

Comparison of the Incidence and Severity of Toxic Effects in Patients Suffering from Colon Cancer Treated According to FOLFOX-4 and CLF-1 Regimens

The analysis of the toxicity of the administered anticancer chemotherapy regimens with respect to individual systems evaluated on the basis of mean values of individual biochemical laboratory assessments and clinical symptoms revealed a statistically significant increase in renal distress in patients treated according to the CLF-1 regimen in comparison to those on FOLFOX-4 ($p < 0.0003$).

Comparing the incidence of toxicity symptoms in patients suffering from advanced colon cancer treated according to the FOLFOX-4 and CLF-1 regimens revealed that the only statistically significant difference is hair loss: In patients treated with the FOLFOX-4 regimen, hair loss was significantly more common than in patients undergoing the CLF-1 regimen ($p < 0.02$).

However, no statistically significant differences were found in the incidence of severe adverse effects (life-threating adverse effects, severity grade 3/4) during the treatment of advanced colon cancer with the FOLFOX-4 and CLF-1 regimens.

Analysis of Factors that Might Potentially Affect the Toxicity of the FOLFOX-4 Regimen

Factors that might potentially affect the toxicity of anticancer chemotherapy were analyzed; the analysis involved patients who were treated with the FOLFOX-4 regimen since that group was more numerous. Factors that were considered in this context included age, sex, coexisting diseases and the use of pharmacotherapy other than colon cancer chemotherapy, as well as the use of vitamin supplements and preparations of plant origin. The questionnaire also included questions on the use of stimulants and dietary habits. However these factors were not taken into account in the analysis, as only a few patients gave positive responses.

A statistically significant correlation was demonstrated between the patient's age and the incidence of some of the side effects of the FOLFOX-4 regimen. Toxicity symptoms in elderly patients were manifested as excretory system distress ($r = 0.33$, $p = 0.0255$), including hematuria ($r = 0.33$, $p = 0.0252$) and constipation ($r = 0.30$, $p = 0.0358$).

The analysis of the relationship between the patients' sex and the incidence of toxicity symptoms of the FOLFOX-4 regimen demonstrated that women showed a significantly higher incidence and increased severity of bleeding ($r = 0.30$, $p = 0.0379$), elevated ALT activity ($r = 0.45$, $p = 0.0284$) and peripheral nervous system depression ($r = 0.32$, $p = 0.0258$).

In the investigated group of patients suffering from colon cancer and being treated with the FOLFOX-4 regimen, 24 patients (50.0%) were also being treated for coexisting diseases. The incidence and kind of diseases coexisting with the neoplastic process is presented in Fig. 1. The analysis of the correlations between coexisting diseases and elevated FOLFOX-4 toxicity revealed that the comorbidity exerts a statistically significant effect on the incidence and severity of nervous system depression ($r = 0.29$, $p = 0.0447$), including disturbed consciousness ($r = 0.40$, $p = 0.0231$), infections ($r = 0.33$, $p = 0.0231$) and skin lesions ($r = 0.29$, $p = 0.0420$).

The effects on the toxicity of the FOLFOX-4 regimen of drugs other than cytostatic and adjuvant anticancer drugs, of vitamin supplements and of preparations of plant origin were also analyzed.

Figure 2 presents the percentage of patients who were taking drugs other than cytostatic and

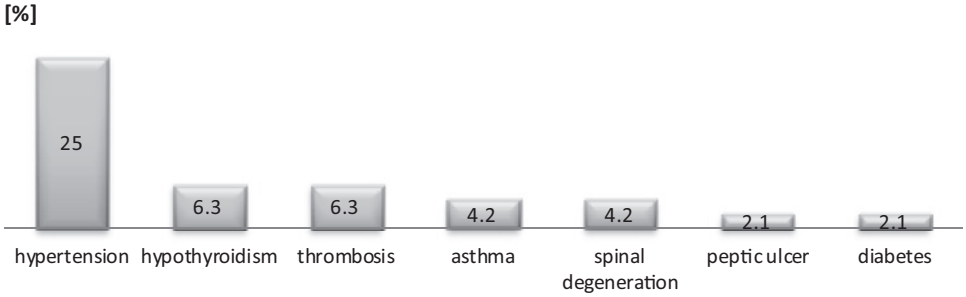

Fig. 1. Percentage of colon cancer patients being treated with the FOLFOX-4 regimen and suffering from coexisting diseases

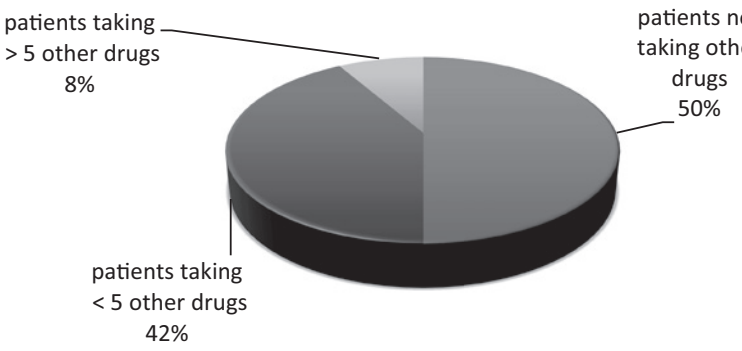

Fig. 2. Percentage of colon cancer patients being treated with the FOLFOX-4 regimen who were taking drugs than anticancer and adjuvant drugs

adjuvant anticancer drugs. It was found that the administration of other drugs than those used in anticancer therapy may significantly increase the incidence and severity of the toxic effects of chemotherapy according to the FOLFOX-4 regimen. This especially concerned skin lesions ($r = 0.31$, $p = 0.0308$), hair loss ($r = 0.30$, $p = 0.0404$) and disturbed consciousness ($r = 0.34$, $p = 0.0177$).

In the FOLFOX-4 group, 45.8% of the patients reported taking vitamin supplements. The analysis of the relationship between their use and increased toxicity of the FOLFOX-4 regimen revealed statistically significantly increases in the incidence and severity of bleeding ($r = 0.36$, $p = 0.0127$), oral lesions ($r = 0.29$, $p = 0.0470$), infections ($r = 0.33$, $p = 0.0231$), pain ($r = 0.29$, $p = 0.0427$) and constipation ($r = 0.34$, $p = 0.183$).

Herbal preparations were taken by 18.8% of the patients in the FOLFOX-4 group. A statistically significant relationship was found between their use and the incidence and severity of bleeding ($r = 0.31$, $p = 0.0307$).

Discussion

Anticancer chemotherapy is a branch of medicine that is developing very dynamically. The evolution of therapeutic methods is an ongoing process and it includes the introduction of new anticancer drugs to therapy, as well as the modification of dosage regimens and routes of administration of cytostatic drugs that are already in use. The significance and role of adjunctive therapy in oncology is growing in parallel to the development of anticancer chemotherapy. This supportive therapy is aimed at preventing and treating complications of cancer as well as preventing and ameliorating complications associated with toxicity of the medication administered [2].

The authors' own observations and conversations with patients indicate how important it is to consider the adverse effects of anticancer therapy in order to prevent them. Continuous assessment of patients' tolerance to the administered therapy, considering side effects reported by patients and diagnosing them in order to prevent their incidence and to administer adequate therapy is indispensable. Such measures may contribute to improvement of the patients' quality of life [1, 2].

In the present study the toxicity of anticancer chemotherapy was assessed on basis of laboratory findings and side effects reported by the patients. The obtained results are therefore likely to be biased and laden with errors. The patients' responses might have been affected by numerous factors, such as individual personality traits, interpretations, motivations and expectations. This fact was emphasized in the observations by Gotay et al. [5]. Bash et al. and Ruhstaller et al. noticed that patients reported more adverse effects than were noticed by physicians. However, new reports demonstrate that despite differences in the reporting of adverse effects by patients and by attending physicians, the perspectives are mutually complementary and provide full clinical information on the course of the disease and its therapy [6–8].

The current study assessed the toxicity of the FOLFOX-4 and CLF-1 regimens administered in the therapy of advanced colon cancer. Hematological side effects included granulocytopenia with a severity ≥ 2 (granulocyte count $< 1.5 \times 10^9$/L), observed in 10.4% of patients treated with the FOLFOX-4 regimen (oxaliplatin, fluorouracil, calcium folinate). Thrombocytopenia at this severity level (thrombocyte count $< 50 \times 10^{-9}$) was not found among the investigated patients. Among the patients treated with the CLF-1 regimen (irinotecan, fluorouracil, calcium folinate), granulocytopenia with a severity ≥ 2 was observed in 6.7% patients. The statistical analysis did not reveal any significant differences in the hematological toxicity of the two investigated therapeutic regimens. However, in a randomized GERCOR study Tornigand et al. showed that the CLF-1 regimen evokes neutropenia with a severity grade 3/4 significantly much more often than the FOLFOX-4 regimen [9].

In terms of non-hematological side effects, oral lesions did not constitute a significant percentage among other adverse effects of the therapies,

despite the recognized mucotoxic effect of fluorouracil, which is a constituent of both regimens. However, in patients treated with the CLF-1 regimen the lesions were more severe.

Nausea and vomiting occurred in both groups of patients despite premedication with ondansetrone. However, these symptoms were very rarely resistant to treatment and had a severity grade 4 in only 2.1% of the FOLFOX-4 regimen patients and in 6.3% of the patients on CLF-1.

Diarrhea, alongside neutropenia, is a significant side effect that necessitates a reduction of the dose of irinotecan during the CLF-1 regimen. However, the present study did not reveal an increased incidence of this symptom in patients on the CLF-1 regimen in comparison with those treated with the FOLFOX-4 regimen; in fact, it was more common in the latter patients. Similarly, a higher risk of acute diarrhea associated with the FOLFOX-4 regimen in comparison to CLF-1 was noted by Dranitsaris et al. [10]. On the other hand, Tornigand et al. did not observe any differences between the two regimens in the incidence of acute diarrhea with a CTCAE severity grade of 3/4 [9].

Renal distress was rarely observed during chemotherapy according to the FOLFOX-4 and CLF-1 regimens. However the CLF-1 regimen, which includes irinotecan, caused nephrotoxicity statistically significantly more often.

Hypersensitivity reactions were observed in 12.5% of patients; in 2.1% of them these reactions took the form of anaphylactic reaction (severity grade 4). As shown by other authors, allergic reactions constitute a serious problem in the management of patients treated according to the FOLFOX regimen; they are difficult to predict, and they may occur during any cycle of drug administration [11, 12]. Among the patients in the present study they were observed during the 5^{th}–8^{th} chemotherapy cycle. In a study by Shibat et al. the incidence of allergic reaction reached 17%, out of which patients with acute hypersensitivity reaction with a CTCAE severity grade of 3 constituted 4% [13].

The present study did not reveal any significant differences in the incidence of allergic reactions between the regimen containing oxaliplatin (FOLFOX-4) and the one containing irinotecan (CLF-1). However, it should be emphasized that during CLF-1 therapy there were no cases with a general systemic hypersensitivity reaction (anaphylactic shock), and such a case did occur during therapy with oxaliplatin.

Skin lesions were observed in 25.0% of patients being treated with the FOLFOX-4 regimen. The reported skin reactions included dry desquamation, blisters, itching (severity grade 2) and erythema (severity grade 1). Their incidence might have been associated with hypersensitivity reaction, which was not reported by the patients probably due to difficulties in interpreting the WHO criteria. In case of the CLF-1 regimen, skin lesions were observed in 43.8% of patients. No significant differences in the intensity and severity of skin lesions were found between the two regimens.

On the other hand, there was a statistically significant difference between the two regimens in terms of hair loss ($p = 0.0245$). It was observed in only 33.3% of the patients on the FOLFOX-4 regimen, while the CLF-1 regimen was associated with hair loss in 62.5% of patients; in half of them it was complete and reversible. A similar effect was observed by Tournigand et al. [9].

Peripheral nervous system toxicity is a well-known adverse effect of oxaliplatin, which limits its applicability. In the present study it affected 75.0% of the investigated patients, among whom 8.3% developed unbearable paraesthesia and/or significant loss of muscle strength (severity grade 3). The symptoms were significantly more severe in patients who were administered more cycles of the FOLFOX-4 regimen ($p = 0.00396$). Petroli et al. reported the incidence of peripheral neuropathy in 93.8% of patients, including 18.7% with CTCAE severity grade 3. According to those authors, prolonging oxaliplatin infusion time from 2 h (the routine duration of administration in the FOLFOX-4 regimen) to 6 h significantly diminishes the incidence of neurotoxicity with severity grade ≥ 2 ($p = 0.02$) [12]. Numerous reports in the literature state that the neuropathy associated with oxaliplatin has a transient character and is relieved upon the cessation of therapy [1, 14]. In their neurotoxicity study, Petroli et al. included patients who had terminated therapy from 1 to 12 months previously. After a month, manifestations of neurotoxicity had a severity grade ≥ 2 in 25% of the patients, while after 12 months only 3% of the patients still had symptoms with severity grade 2 [15]. In a study by Tournigand et al. the incidence of neuropathy reached 88%; however, the patients were treated with the FOLFOX-6 regimen, in which the dose of oxaliplatin was increased to 100 mg/m^2 p.c. In that study, significant differences were found between the FOLFOX-6 and CLF-1 regimens in terms of the incidence of neurotoxicity in the treatment of the first episode of advanced colon cancer ($p < 0.001$). It reached CTCAE severity grade 3 during the administration of the FOLFOX-6 regimen in 31% of the patients, while none of the patients treated according to the CLF-1 regimen experienced this adverse effect at a severity grade higher than 1. On the other hand, when the CLF-1 regimen was administered as a therapy for the second relapse of the disease

– after FOLFOX-6 regimen – 19% of the patients maintained grade 3 neurotoxicity, which they had developed during the first line therapy with oxaliplatin [9]. The present study revealed the incidence of toxicity affecting the peripheral nervous system in 3/4 of the patients on the CLF-1 therapy. In 87.5% of them it was second line treatment after previous therapy according to the FOLFOX-4 regimen. In the context of the above-quoted observations of other authors, it may be assumed that the patients sustained the cumulative toxic effect of both the consecutively administered therapeutic regimens.

In the current study, factors that might have contributed to increasing the toxicity of the administered anticancer therapy were analyzed. In patients suffering from colon cancer treated according to the FOLFOX-4 regimen, a significant relationship was found between the age of the patients and the incidence and severity of nephrotoxicity and constipation. These observations are associated with well-known facts concerning the effect of age-related processes on the renal function, which may undergo exacerbation under the influence of anticancer chemotherapy. The risk factors for constipation in elderly patients include, among other things, improper diet, decreased intake of fluids, decreased physical activity, stress associated with hospitalization, and the use of drugs [16]. The OPTIMOX studies on the safety of the FOLFOX-4 regimen in elderly patients (> 75 years of age) revealed a significantly elevated incidence of neutropenia and peripheral neuropathy of severity grade 3–4 in comparison to patients ≤ 75 years of age [17]. The current study did not confirm such a relationship.

The present authors' analysis demonstrated a statistically significant positive correlation between the female gender and increases in the incidence and severity of bleeding, elevated ALT activity and neurotoxicity. Gamelin et al. observed only an increased incidence of neuropathy in women [18].

In the present study a statistically significant relationship was observed between the severity of certain toxicity symptoms and the incidence of co-morbidities and the use of additional pharmacotherapy. Moreover, a statistically significant relationship was found between the use of vitamin supplements and increases in the intensity and severity of drug-associated side effects in colon cancer patients treated according to the FOLFOX-4 regimen.

The current assessment of the toxicity of anticancer chemotherapy in patients suffering from colon cancer provided the following conclusions:

The analysis of toxicity symptoms associated with the use of the FOLFOX-4 and CLF-1 therapeutic regimens in patients suffering from colon cancer revealed that the most common side effects include nausea and vomiting (despite premedication with ondansetron) and neurotoxicity. These observations should be taken into consideration when monitoring the safety of chemotherapy for colon cancer. The patient's tolerance of the medication administered, considering the side effects reported by patient, should be constantly evaluated, which will not only help prevent them and ensure that adequate therapy is applied, but may also contribute to improving the patient's quality of life.

Under the influence of the FOLFOX-4 regimen, nervous system depression underwent statistically significant exacerbations, increasing with the number of chemotherapy cycles administered. Nervous system depression was also more common and more severe in women. Paraesthesia as a neurotoxic effect of the FOLFOX-4 regimen was also noted in patients after the termination of therapy. These observations should be taken into consideration when planning anticancer therapy, especially if there is a necessity for repeated administration of neurotoxic drugs in case of a recurrence of the disease.

Statistically significant differences in the toxicity of the two therapeutic regimens investigated concerned increased hair loss in patients treated according to the CLF-1 regimen in comparison to the FOLFOX-4 regimen. This points to the comparable safety of the two therapeutic regimens in patients with colon cancer. However, the differences should be taken into consideration when planning anticancer therapy, especially for patients susceptible to this adverse effect.

A statistically significant relationship was found between the age of patients treated according to the FOLFOX-4 regimen and the incidence of constipation and renal dysfunction, and between their gender and the incidence and severity of bleeding, elevated ALT activity and nervous system depression, which suggests that the anticancer chemotherapy administered should be thoroughly monitored for safety, especially in women older than 65 years of age who are also suffering from coexisting diseases. Such monitoring may help in the early identification of patients with a high risk for drug side effects who should be given special medical care.

A statistically significant relationship was noted between the use of vitamin supplements and the incidence and severity of the toxicity of the FOLFOX-4 regimen, suggesting that prior to starting anticancer chemotherapy, colon cancer patients and their families should be informed of the risks of using vitamin supplements and possibly should dispense with their use.

References

[1] **Orzechowska-Juzwenko K:** Zarys chemioterapii nowotworów narządowych i układowych. Volumed, Wrocław, 2000.
[2] **Krzemieniecki K:** Leczenie wspomagające w onkologii, Termedia Wydawnictwa Medyczne, Poznań 2008.
[3] **Cleeland CS, Allen JD, Roberts SA, Brell JM, Giralt SA, Khakoo AY, Kirch RA, Kwitkowski VE, Liao Z, Skillings J:** Reducing the toxicity of cancer therapy: recognizing needs, taking action. Nat Rev Clin Oncol 2012, 9, 471–478.
[4] **Ramesh A:** Toxicities of anticancer drugs and its managment. Int J Basic Clin Pharmacol 2012, 1, 2–12.
[5] **Gotay C, Kawamoto CT, Bottomley A, Efficace F:** The prognostic significance of patient-reported outcomesin cancer clinical trials. J Clin Oncol 2008, 26, 1355–1363.
[6] **Bash E, Artz D, Dulko D, Schrag D:** Patient online self-reporting of toxicity symptoms during chemotherapy. J Clin Oncol 2005, 23, 3552–3561.
[7] **Ruhstaller T, von Moos R, Rufibach K, Ribi K, Glaus A, Spaeti B, Koeberle D, Mueller U, Hoefliger M, Hess D, Boehme C, Thuerlimann B:** Breast cancer patients on endocrine therapy reveal more symptoms when self-reporting than in pivotal trials: An outcome research study. Oncology 2009, 76, 142–148.
[8] **Basch E, Iasonos A, Bar A, Culkin A, Kris MG, Artz D, Fearn P, Speakman J, Farquhar R, Scher HI, Mc Cabe M, Schrag D:** Long-term toxicity monitoring via electronic patient-reported outcomes in patients receiving chemotherapy. J Clin Oncol 2007, 25, 5374–5380.
[9] **Tournigand C, Andre T, Achille E, Ledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A:** FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004, 22, 229–237.
[10] **Dranitsaris G, Shah A, Spirovski B, Vincent M:** Severe diarrhea in patients with advanced-stage colorectal cancer receiving FOLFOX or FOLFIRI chemotherapy: the development of a risk prediction tool. Clin Colorectal Cancer 2007, 6, 367–373.
[11] **Porębski G, Woroń J, Krzemieniecki K:** Reakcje nadwrażliwości i desensytyzacja na leki w onkologii. Onkol Prakt Klin 2009, 5, 244–249.
[12] **Skif W, Roy S, Ledbetter L, Madison J, Syrigos K:** Fever as the only manifestation of hypersensitivity reactions associated with oxaliplatin in a patient with colonorectal cancer. Oxaliplatin-induced hypersensitivity reaction. World J Gastroenterol 2007, 13, 5277–5281.
[13] **Shibata Y, Ariyama H, Baba E, Takii Y, Esaki T, Mitsugi K, Tsuchiya T, Kusaba H, Akashi K, Nakano S:** Oxaliplatin-induced allergic reaction in patients with colorectal cancer. Int J Clin Oncol 2009, 14, 397–401.
[14] **Hidebrand J:** Neurological complications of cancer chemotherapy. Curr Opin Oncol 2006, 18, 321–324.
[15] **Petrioli R, Pascucci A, Francini E, Marsili S, Sciandivasci A, Tassi R, Civitelli S, Tanzini G, Lorenzi M, Francini G:** Neurotoxicity of FOLFOX-4 as adjuvant treatment for patients with colon and gastric cancer: a randomized study of two different schedule of oxaliplatin. Cancer Chemother Pharmacol 2008, 61, 105–111.
[16] **Sokol KC, Knudsen JF:** Polypharmacy in older oncology patients and the need for interdisciplinary approach to side-effect managment. J Clin Pharm Ther 2007, 32, 169–175.
[17] **Figer A, Perez-Staub N, Carola E, Tournigrand C, Lledo G, Flesch M, Barcelo R, Cervantes A, Andre T, Colin P, Louvet C, de Gramont A:** FOLFOX in patients aged between 76 and 80 years with metastatic colorectal cancer: an exploratory cohort of the OPTIMOX 1 study. Cancer 2007, 110, 2666–2671.
[18] **Gamelin L, Boisdron-Celle M, Delva R, Gue'rin-Meyer V, Ifrah N, Morel A, Gamelan A:** Prevention of oxaliplatin-related neurotoxicity by calcium and magnesium infusions: a retrospective study of 161 patients receiving oxaliplatin combined with 5-fluorouracil and leucovorin for advanced colorectal cancer. Clin Cancer Res 2004, 10, 4055–4061.

Address for correspondence:

Łukasz Łapiński
Department of Clinical Pharmacology
Wroclaw Medical University
Borowska 211a
50-556 Wrocław
Poland
Tel: +48 600 825 837
E-mail: lukasz.lapinski@umed.wroc.pl

Conflict of interest: None declared

Received: 13.11.2013
Revised: 29.04.2014
Accepted: 12.01.2015