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Gemcitabine and carboplatin treatment in Patients with relapsing ovarian cancer

J. SUFLIARSKY[1*], J. CHOVANEC[2], D. SVETLOVSKA[1], T. MINARIK[1], T. PACKAN[3], D. KROSLAKOVA[4], R. LALABOVA[5], L. HELPIANSKA[6], D. HORVATHOVA[7], L. SEVCIK[8], J. SPACEK[9], A. LALUHA[10], V. TKACOVA[11], V. MALEC[12], G. RAKICKA[12], D. MAGDIN[13], I. JANCOKOVA[13], A. DORR[5], M. STRESKO[4], V. HABETINEK[14], I. KOZA[1]

[1]National Cancer Institute Bratislava , 833 10 Bratislava, Slovakia, e-mail: jozef.sufliarsky@nou.sk , [2]Teaching Hospital Brno, [3]Eastern-Slovakian Institute of Oncology Košice, [4]Teaching Hospital Nitra, [5]Masaryk´s Institute of Oncology Brno, [6]St. Elizabeth´s Institute of Oncology Bratislava, [7]Teaching Hospital with an Outpatient Clinic Nové Zámky, [8]Teaching Hospital Ostrava, [9]Teaching Hospital Hradec Králové, [10]St. Lucas' Hospital with an Outpatient Clinic Galanta, [11]Teaching Hospital in Prešov, [12]Hospital with an Outpatient Clinic Banská Bystrica, [13]Hospital with an Outpatient Clinic Bojnice, [14]Eli Lilly Czech Republic, Prague.

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Despite progress in primary treatment of patients with advanced ovarian cancer, the majority develop recurrence of the disease. A platinum salt treatment, either as monotherapy or in combination with another cytostatic agent, is indicated for patients who have relapsed 6 or more months after primary treatment and thus have platinum-sensitive relapse. Because repeated use of paclitaxel treatment may lead to substantial neurotoxicity, the combination of gemcitabine with carboplatin represents a suitable treatment option, which is widely used in common clinical practice in the Czech Republic and Slovakia.

This non-interventional, prospective study observed the effectiveness and tolerability of second-line treatment with gemcitabine and carboplatin in patients with platinum-sensitive relapse of ovarian cancer in routine clinical practice. The primary endpoint was to evaluate the survival and secondary endpoints were to evaluate time to disease progression, objective tumor response rate, and treatment toxicity.

Patients were enrolled to planned second-line treatment with gemcitabine and carboplatin (gemcitabine 1000 mg/m^2 and carboplatin AUC 5 on Day 1, and gemcitabine 1000 mg/m^2 on Day 8 of a 21-day cycle) for platinum-sensitive relapse of ovarian cancer as a part of routine clinical practice and followed for 12 months. The events (death, tumor progression), tumor response, and maximal grades of toxicity were recorded according to common clinical practice. Survival time (using Kaplan-Meier analysis) and objective tumor response rate were calculated using data forms, and a subgroup analysis was performed using log rank tests for time-to-event endpoints; p-values were also calculated. Response rates were calculated for the whole population; for the subgroups, the Fisher's exact test was performed and only p-values were calculated.

Between January 2004 and June 2005, 53 patients were enrolled in the study. The median age was 57 years and 96% of patients had an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 and 1 at baseline. Approximately 91% of patients were originally diagnosed with stage III or IV; 60% of patients had disease free intervals (DFIs) of 12 or more months from previous therapy, and the additional 40% less than 12 months. The 1-year survival rate was 83%. Median survival time was not determined within the 12-month period following the start of the treatment study due to the limited duration of follow-up. Objective tumour response rate was 67.3%. Most common reasons for discontinuation of therapy were "Planned treatment completed" (53%) and "Tumor progression" (11%). Most common toxicities were leukopenia, anaemia, neutropenia, and thrombocytopenia; grades 3 and 4 of these toxicity types did not exceed 30%. Febrile neutropenia was recorded in two patients. Most common non-haematological toxicities were nausea and vomiting, fatigue, and neuropathy; grades 3 and 4 of these were below 6%. Results on time to disease progression are not published due to inconsistent statistical analysis of reported data.

Based on this observation from routine clinical practice, which corresponds with previously published results from controlled clinical trials, the gemcitabine and carboplatin combination seems to be a suitable therapeutic option for patients with platinum-sensitive relapse of ovarian cancer.

Key words: gemcitabine, carboplatin, relapsing ovarian cancer, second-line treatment

* Corresponding author

Ovarian cancer still represents a major problem among gynaecological malignancies. In 2003, 437 new cases were reported in the Slovak Republic, representing an incidence of 15.8 cases per 100,000 women, and resulting in a mortality rate of 9.6 per 100,000 women [1]. In 2002, the Czech Republic reported 1265 new cases of ovarian cancer (equivalent to 24.2 cases per 100,000 women), and reported 743 cases of mortality [2].

As shown in the GOG 111 study of patients with suboptimal debulking, the primary treatment of ovarian cancer achieved tumor response in up to 73% of cases, and complete response in 51%, with a median disease free interval (DFI) of 18 months and median survival of 36 months [3]. The pathological complete response rates in various studies varied between 10%-30%. Nevertheless, many patients succumb to a relapse and die within 5 years [4, 5]. Studies of second-line treatment of ovarian cancer relapse with platinum derivatives have identified two patient groups, platinum-resistant and platinum-sensitive, determined by whether the relapse occurred within 6 or more months of the primary treatment [6, 7]. Repeated administration of a platinum derivate has been the conventional therapy for those patients. Carboplatin treatment has become gradually more common due to its ease administration and satisfactory toxicity profile. In a recent phase III study, repeated administration of paclitaxel with carboplatin resulted in a prolongation of progession free survival (PFS) and median survival compared with patients only receiving carboplatin [8]. However, patients receiving the paclitaxel and platinum combination as primary treatment are at risk of severe cumulative neurotoxicity if this combination is used in platinum-sensitive relapse patients [9].

Gemcitabine is a pyrimidine analogue which is also efficacious on epithelial ovarian tumors. When used in monotherapy, objective response rates of about 20% and median survival of between 7 and 9 months have been reported in relapsing tumors [10–19]. Subsequent studies of the gemcitabine and platinum combination have been conducted; in primary treatment, gemcitabine with cisplatin in phase II studies have achieved objective tumour response rates of up to 80%, median time to progression of up to 10 or more months, and median survival of up to 2 or more years [20–25]. Gemcitabine and cisplatin combination treatments of relapsing ovarian cancers have resulted in objective responses of 40-50%, PFS of about 6 months, and overall survival of about 12 months, depending on the patients' previous treatment [26–29]. Evidence for the gemcitabine and carboplatin combination is less extensive, though in several phase II studies patients with relapsing tumors have achieved a response in 40%-70% of cases, time to progression of 7–10 months, and overall survival of up to 2 years [30–33]. Since 2000, the combination of gemcitabine and carboplatin is widely used within routine clinical practice in the Slovak and Czech Republics, and is currently registered in most European countries for the treatment of relapsing ovarian cancer based on the results of a phase III registrational trial [34].

The aim of this observational study was to describe the effectiveness and safety of gemcitabine and carboplatin in the second-line treatment of patients with relapsing platinum-sensitive ovarian cancer in routine medical practice. The primary objective of the study was to evaluate the survival of patients with ovarian cancer and secondary objectives included time to disease progression, objective tumor response rate, and toxicity.

Patients and methods

Patients with relapsing ovarian cancer and planned second-line treatment with a gemcitabine and carboplatin combination as part of normal clinical care (gemcitabine 1000 mg/m^2 and carboplatin AUC 5 on Day 1, and gemcitabine 1000 mg/m^2 on Day 8 of a 21-day cycle) were included in the study subject to the following inclusion criteria:

- histologically confirmed ovarian cancer;
- the first relapse occurring after previous surgical treatment and adjuvant chemotherapy containing platinum;
- a 6- to 24-month interval between previous chemotherapy and initiation of treatment with gemcitabine and carboplatin;
- no additional planned concomitant treatment for ovarian cancer with gemcitabine and carboplatin combination;
- no additional malignant diseases, with the exception of basal cell skin cancer, breast, or cervical carcinoma in situ;
- no signs of central nervous system metastases;
- no additional serious conditions which would significantly interfere with the expected survival of patients or with therapeutic strategy.

Patients were expected to have an adequate marrow reserve and function of kidneys, liver, and other organs which were considered sufficient by the treating physician to initiate treatment with the gemcitabine and carboplatin combination. Patients were included in the study if only they signed a consent to release their information.

In this prospective, 12-month, observational, multicenter study, all care provided to patients was entirely at the discretion of the treating physician. All patients were monitored equally and were not offered addidional visits, procedures, or investigations above the framework of routine clinical practice. As a part of routine clinical practice, the following investigations were carried out before treatment, during treatment, and within follow-up period after treatment completion: CBC (complete blood count), complete biochemistry, CA 125 level assessment, gynaecological examination with transvaginal ultrasonography, chest X-ray, abdominal and pelvic CT, and MRI and PET (in selected cases only). Therapeutic effectiveness was always assessed with the same method. Data on patients, their disease, treatment, and results were recorded in data forms upon the patients entry to the study, at the end of the treatment, and 12 months after initiating study treatment. Data were collected anonymously, which prevented identification of patients from the data forms. The planned enrollment

period was 18 months and the precise sample size was not determined at the outset.

Survival time, time to disease progression (using Kaplan-Meier analysis) and objective tumor response rates were calculated. The analysis censored patients whose data forms did not include date of death or disease progression. For missing information on date of last contact with patients surviving 12 months, the data were censored at 12 months from start of the treatment, for unknown date of death in patients not surviving 12 months, the data were censored at last date of contact with the patient. The relative changes in levels of Ca 125 marker, were calculated as relative changes in medians of values before and after treatment according to the different response types. The toxicity was calculated as percentage of patients reporting toxicity by type and grade and as the percentage of patients with ommited or reduced doses due to toxicity.

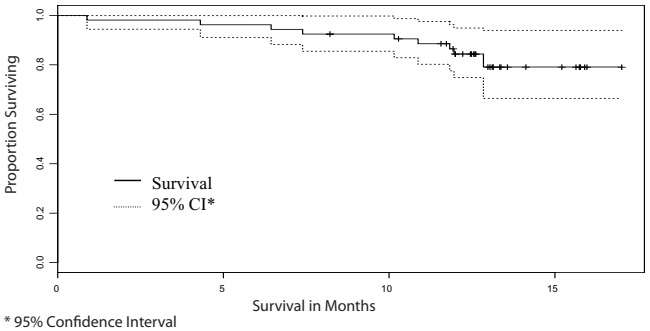
As a part of the explorative analyses to evaluate possible prognostic factors for further validation in other studies, post-hoc analyses were performed with subgroups according to the Eastern Cooperative Oncology Group Performance Status (ECOG-PS), the original International Federation of Gynecology and Obstetrics (FIGO) stage, presence of liver metastases in FIGO stage IV, age, weight loss, presence of symptoms, and duration of disease free intervals (DFIs) from previous therapy. Log rank tests were used to exploratively evaluate possible correlation of pre-specified factors with survival and p-values were calculated. Individual response rates were calculated for the respective subgroups, tests of independence were performed, and p-values were calculated using Fisher´s test. However, level of significance for any of those explorative analyses was not pre-specified in the statistical analysis plan. Due to the observational nature of the study, the strength of the statistical tests employed was not calculated. A sample size of 50 observed patients was estimated, based on the entry criteria and planned 18-month enrollment period.

Results

Between January 2004 and June 2005, 53 patients (median age of 57 years and 96% of patients with an ECOG-PS of 0 and 1; Table 1) from 13 centers in the Slovak and Czech Republics were included in this study. The majority of patients, 77% had a serous tumor, 66% of patients had grade 2 and 3 and a FIGO stage of IIIC and IV (74%) (Table 2). Six patients deviated from eligibility criteria: two patients concluded previous therapy approximately 1 month before the study and were therefore platinum-refractory and 4 patients were more than 24 months post previous chemotherapy.

The majority of patients (43; 81.1%) received more than 4 study treatment cycles, two patients (3.1%) received 2 cycles only. In total, 28 patients (52.8%) completed planned treatment. Reasons for premature discontinuation of study treatment are presented in Table 3.

A 1-year overall survival rate was achieved by 44 (83%) patients (see Figure 1). Overall median survival time was not determined within the 12-month follow-up period after start of the study treatment. Objective tumor response rates in the overall population of patients are displayed in Table 4. The relative changes in levels of Ca 125 marker correlated relatively well with the objective tumor response to treatment in both parameters of median and arithmetic mean difference in the marker values, as presented in Table 5.



* 95% Confidence Interval

Figure 1. Kaplan-Meier analysis of survival in the overall patient population

For the post-hoc subgroup analyses data on 1-year survival and overall median survival are displayed in Table 6. The data suggest that age, weight loss and presence of symptoms may be useful prognostic indicators. The objective tumour response rate for the subgroup analysis is presented in Table 7. However, none of the tested parameters seemed to have a significant effect. Calculations of level of significance for above mentioned subgroup analyses were not defined in the statistical analysis plan.

Table 1. Baseline patient characteristics

Characteristics	**N = 53 n (%)**
Age (years)	
median	57
min-max	39 - 80
Disease characteristics	
Performance status (ECOG-PS)	
0+1	51 (96.2)
2	2 (3.8)
Patients with >10% weight loss during previous 6 months	4 (7.5)
Disease-related symptoms	
Overall	25 (47.2)
Abdominal pain	12 (22.6)
Bloating	0 (0.0)
Abdominal discomfort	15 (28.3)
Other GIT symptoms	6 (11.3)
Vaginal bleeding	0 (0.0)
Urinary tract symptoms	2 (3.8)

N = total population size; n = number of patients; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; GIT = Gastrointestinal

Table 2. Baseline patient disease characteristics

Characteristics	(N = 53) n (%)
Histological types of tumours	
Serous	41 (77.4%)
Mucinous	1 (1.9%)
Endometroid	6 (11.3%)
Non-differentiated	3 (5.7%)
Other	2 (3.8%)
Grade	
1	7 (13.2%)
2	20 (37.7%)
3	15 (28.3%)
4	1 (1.9%)
FIGO stage (at diagnosis)	
NA	10 (18.9%)
IC	1 (1.9%)
IIA	1 (1.9%)
IIB	2 (3.8%)
IIC	1 (1.9%)
IIIA	1 (1.9%)
IIIB	8 (15.1%)
IIIC	28 (52.8%)
Liver metastases in FIGO IV[1]	7 (63.6%)
Lung x-ray	
Examined	49
Positive findings	5 (10.2%)
Time from previous chemotherapy (months)	
median	12
min – max	1 – 43
n (6 ≤ 12)[2]	23 (43.4%)
n (12 ≤ 24)[3]	24 (45.3%)

1. *Relative frequency is related to the number of subjects with FIGO IV;*
2. *Number of patients in the category between 6 and 12 months;*
3. *Number of patients in the category between 12 and 24 months.*

N = total population size; n = number of patients; FIGO = International Federation of Gynecology and Obstetrics

Table 3. Reasons for premature treatment discontinuation

	Number of Patients	
Reason for premature treatment discontinuation	**N = 53 n**	**(100) (%)**
Tumour progression	6	(11.3)
Unacceptable toxicity by physician´s judgement	3	(5.7)
Satisfactory therapeutic response according to physician/patient	3	(5.7)
Other	3	(5.7)
Secondary progression after response achievement, or stabilization	2	(3.8)
Unacceptable toxicity according to physician and patient	2	(3.8)
Satisfactory response (assessed by physician)	2	(3.8)
Tumour-related death	1	(1.9)
Other-cause death	1	(1.9)
Unsatisfactory effectiveness (assessed by physician and patient)	1	(1.9)
Unacceptable toxicity by patient´s judgement	1	(1.9)

N = total population size; n = number of patients

Table 4. Objective tumour response rates

	N=52 n	(100%) (%)
CR	17	(32.7)
PR	18	(34.6)
SD	8	(15.4)
PD	9	(17.3)
ORR	35	(67.3)
NA	1	(0.0)*

**Therapeutic response was not assessed in 1 patient as she died of ictus 3 weeks after initiation of the study treatment.*

N = total population size; n = number of patients; CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease; ORR = objective tumour response rate; NA = not applicable

Table 5. Relative change in Ca 125 levels compared to baseline (by type of response)

Heading	**PD**	**SD**	**PR**	**CR**	**Overall**
Minimum	-95.4%	-96.8%	-99.3%	-99.1%	-99.3%
1st quartile	-65.8%	-91.6%	-96.0%	-95.1%	-94.5%
Mean	19.2%	-29.4%	-78.1%	-87.3%	-55.3%
Median	-34.8%	-61.0%	-91.2%	-89.3%	-86.7%
3rd quartile	57.6%	-19.1%	-81.0%	-85.5%	-61.8%
Maximum	346.7%	162.1%	47.8%	-64.0%	346.7%
n	9	8	18	17	53
NA	0	0	1	0	1
SD*	135.9%	90.6%	38.2%	9.6%	78.5%

**Standard Deviation*

PD = progressive disease; SD = stable disease, PR = partial response, CR = complete response, n = number of patients; NA = not applicable

Clinical benefit represented by overall response rate (complete response [CR] and partial response [PR]) and stable disease (SD) was achieved in 100% of patients without liver metastases, whereas in patients with liver metastases it was only achieved in less than 43%. Objective tumor response or disease stabilization (clinical benefit) was more frequently reported in patients aged less than 60 years and tumor progression occurred more frequently in patients with DFIs of less than 12 months.

A summary of study treatment toxicity based on the maximum reported levels of specific types of toxicity in individual patients is presented in Table 8. Grades 3 and 4 haematological toxicities did not exceed 21%. High grades of non-haematological toxicities did not exceed 6%. Out of 53 patients, 20 (37.7%) had their dose of the study drug withdrawn due to toxicity during the treatment at least in one cycle. In 12 patients (22.6%) the dose was ommited due to toxicity in more than one cycle. Seventeen patients (32.7%) reduced the study drug dose due to toxicity at least in one cycle.

Table 6. One-year survival and median survival time of overall and subgroup population

		One-year survival				Median survival time		
		n	/	N	(%)	N	Median (months)	p-value
Overall		44	/	53	(83.0)	53	NA	
ECOG-PS	0+1	44	/	51	(86.3)	51	NA	0.0000
	2	0	/	2	(0.0)	2	2.60	
FIGO stage	I/II	4	/	5	(80.0)	5	NA	0.8266
	III/IV	40	/	48	(83.3)	48	NA	
Liver metastases in FIGO IV	Present	6	/	7	(85.7)	7	NA	0.4497
	Absent	4	/	4	(100.0)	4	NA	
Age [years]	60 and above	13	/	20	(65.0)	20	NA	0.0048
	less than 60	31	/	33	(93.9)	33	NA	
Weight loss >10%	Yes	2	/	4	(50.0)	4	8.26	0.0029
	No	41	/	48	(85.4)	48	NA	
Symptoms	Present	18	/	25	(72.0)	25	NA	0.0352
	Absent	26	/	28	(92.9)	28	NA	
Disease free interval from previous chemotherapy (months)	6-11	17	/	23	(73.9)	23	NA	0.0540
	12 and more	26	/	28	(92.9)	28	NA	

n = number of patients; N = total population size in this group; NA = not applicable; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; FIGO = International Federation of Gynecology and Obstetrics

Table 7. Objective tumour response rates in individual subgroups (N=52)

		n	/	N	(%)	p-value
ECOG-PS	0+1	35	/	51	(68.6)	0.3269
	2	0	/	1	(0.0)	
FIGO stage	I/II	3	/	5	(60.0)	1.0000
	III/IV	32	/	47	(68.1)	
Liver metastases in FIGO IV	Present	2	/	7	(28.6)	0.5758
	Absent	2	/	4	(50.0)	
Age [years]	60 and above	11	/	19	(57.9)	0.3602
	less than 60	24	/	33	(72.7)	
Weight loss >10%	Yes	1	/	3	(33.3)	0.2286
	No	34	/	48	(70.8)	
Symptoms	Present	18	/	24	(75.0)	0.3764
	Absent	17	/	28	(60.7)	
Disease-free intervals from previous therapy [months]	6-11	17	/	23	(73.9)	0.7582
	12 and more	18	/	27	(66.7)	

n = number of patients; N = total population size in this group; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; FIGO = International Federation of Gynecology and Obstetrics

Data on treatment of patients following study treatment completion are presented in Table 9. Nineteen patients (35.8%) remained without further treatment, 31 (58.5%) used subsequent monotherapy and 3 (5.7%) patients continued with combination treatment. One patient continued with combination of etoposide and vinorelbine, the other patient used as subsequent treatment combination of etoposide and weekly paclitaxel, and the third patient received combination of weekly paclitaxel and radiotherapy.

Discussion

Treatment of relapsing ovarian cancer is problematic in all patients with this situation of the disease. Gemcitabine has an advantageous toxicity profile, justifying its application as second-line chemotherapy. In patients with platinum-sensitive relapse, a 62.5% objective response rate was achieved in a population of 40 patients (15% CR and 47.5% PR), whereas the effect was also reported in the group of patients whose

Table 8. Summary of treatment toxicities by type and grade (N=53)

Toxicities	GRADE / n (%)									
	1		2		3		4		Total	
Anaemia	11	(20.8)	14	(26.4)	11	(20.8)	0	(0.0)	36	(67.9)
Leukopenia	7	(13.2)	22	(41.5)	11	(20.8)	0	(0.0)	40	(75.5)
Neutropenia	9	(17.0)	14	(26.4)	9	(17.0)	3	(5.7)	35	(66.0)
Thrombocytopenia	8	(15.1)	7	(13.2)	5	(9.4)	9	(17.0)	29	(54.7)
Febrile neutropenia	0	(0.0)	2	(3.8)	0	(0.0)	0	(0.0)	2	(3.8)
Hepatic toxicity	5	(9.4)	0	(0.0)	1	(1.9)	0	(0.0)	6	(11.3)
Renal toxicity	3	(5.7)	1	(1.9)	0	(0.0)	0	(0.0)	4	(7.5)
Sensor. neurotoxicity	7	(13.2)	0	(0.0)	1	(1.9)	0	(0.0)	8	(15.1)
Motor. neurotoxicity	4	(7.5)	1	(1.9)	0	(0.0)	0	(0.0)	5	(9.4)
Nausea and vomiting	26	(49.1)	12	(22.6)	3	(5.7)	0	(0.0)	41	(77.4)
Flu-like syndrome	3	(5.7)	1	(1.9)	0	(0.0)	0	(0.0)	4	(7.5)
Pulmonary toxicity	0	(0.0)	0	(0.0)	1	(1.9)	0	(0.0)	1	(1.9)
Fatigue	9	(17.0)	4	(7.5)	1	(1.9)	0	(0.0)	14	(26.4)
Other	3	(5.7)	3	(5.7)	0	(0.0)	0	(0.0)	6	(11.3)

N = total population size; n = number of patients

Table 9. Numbers of patients by type of subsequent treatment

Subsequent treatment	n	(%)
Docetaxel	1	(1.9)
Paclitaxel	8	(15.1)
Platinum monotherapy	2	(3.8)
Topotecan	9	(17.0)
Etoposide	9	(17.0)
Ifosfamide	0	(0.0)
Palliative radiation	2	(3.8)
Other	6	(11.3)

n = number of patients

primary treatment was completed 6–12 months ago [31]. Median time-to-treatment failure was 9.3 months. When the gemcitabine and carboplatin AUC 4 combination was used in a population of 26 patients, objective response was achieved in 62% of patients, survival without disease progression averaged 10 months, and overall survival was greater than 18 months in the median follow-up of 23 months [33].

In the randomized studies AGO-OVAR, NCIC CTG and EORTC, significantly better progression-free survival was achieved in the treatment of relapse with the combination of gemcitabine and carboplatin as compared to carboplatin monotherapy (8.6 vs. 5.8 months). The objective response was reported in 47.2% vs. 30.9% patients respectively, though the overall survival was not significantly prolonged as the study lacked power to demonstrate such a difference [34].

The assessment of objective tumor response was not as exact as in the randomized study, and assessment by individual expert committee was not used. Moreover, assessment of therapeutic effectiveness in relapse of ovarian cancer is problematic even when computer tomography or magnetic resonance imaging is used. We achieved response rate higher than reported in above mentioned studies. Treatment toxicity was comparable to that presented in the available literature, despite the higher carboplatin dose of AUC 5 used. Median overall survival was not achieved in this observational study due to the limited duration of follow-up (12 months). The results on time to disease progression obtained in this observational study are not published in this report due to inconsistent method of statistical analysis used for evaluation of this parameter.

In conclusion, results of this multicenter, prospective, observational study of routine clinical practice confirmed previous clinical observations of the effectiveness and safety of the gemcitabine and carboplatin combination in the second-line treatment of relapsing platinum-sensitive ovarian cancer. This combination is a suitable therapeutic option in the treatment of patients with relapsing platinum-sensitive ovarian cancer within routine clinical practice.

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