Treosulfan in the Treatment of Advanced Ovarian Cancer - Results of a German Multicenter Non-interventional Study

RADOSLAV CHEKEROV[1], GABRIELE KALTENECKER[2], DIETMAR REICHERT[3], THOMAS GÖHLER[4], PETER KLARE[5], GÜLTEN OSKAY-ÖZCELIK[5], UWE SAUER[6], ARTHUR WISCHNIK[7], URSULA VEHLING-KAISER[8], MARTIN BECKER[9], ULRICH HUTZSCHENREUTER[6], ANDREAS AMMON[10], ELKE HEIDRICH-LORSBACH1[1] and JALID SEHOULI[1]

[1]*Department of Gynecology, European Competence Center for Ovarian Cancer, Campus Virchow Klinikum, Charité – Universitätsmedizin, Berlin, Germany;*
[2]*Department of Gynecology, Städtisches Klinikum Karlsruhe, Karlsruhe, Germany;*
[3]*Onkologische Gemeinschaftspraxis, Westerstede, Germany;*
[4]*Onkozentrum, Dresden, Germany;*
[5]*Praxiskliniken Krebsheilkunde für Frauen, Berlin, Germany;*
[6]*Hämatologisch-Onkologische Gemeinschaftspraxis, Nordhorn, Germany;*
[7]*Department of Gynecology, Klinikum Augsburg, Augsburg, Germany;*
[8]*H.O.T., Landshut, Germany;*
[9]*Onkologische Praxis, Minden, Germany;*
[10]*Hämatologisch-Onkologische Praxis, Göttingen, Germany;*
[11]*Alcedis GmbH, Giessen, Germany*

Abstract. *Background: Data on routine systemic treatment of patients with ovarian cancer are currently available only to a limited degree. The alkylating agent treosulfan is approved in oral (p.o.) and intravenous (i.v.) form for the treatment of ovarian carcinoma. The present non-interventional study analyzed the clinical use of treosulfan in Germany, evaluating the mode of application, toxicity, and response and survival rate. Patients and Methods: Two hundred and forty-eight ovarian cancer patients in 57 Centers, who received treosulfan mainly either i.v. (5,000-8,000 mg/m^2 d1, q21d or q28d) or p.o. (400-600 mg/m^2 d1-14 or 21, q28d) for at least one therapy cycle were evaluable and were included in the study. Results: With a median age of 70 years (range=36-92 years), predominantly elderly patients received treosulfan treatment. Most participants presented serous histology (131, 52.8%) and advanced-stage FIGO III (122, 49%) or IV (55, 22%) disease. Median ECOG status was 1 (range=0-2), whereas cardiac co-morbidity was common (31%). Treosulfan was usually administered as second- (26%), third- (21%) or fourth-line (17%) therapy. Two hundred and one patients received i.v. and 47 p.o. treatment. The most common reason for dose modifications was due to hematological toxicity (46%). The main reason for a therapy discontinuation was progressive disease (38.5%). Response was observed in 25.8% of participants, disease stabilization in 28.6 % and progress in 45.6%. The median progression-free and overall survival was 196 and 405 days, respectively. Conclusion: In predominantly elderly and heavily pre-treated patients with recurrent ovarian cancer, treosulfan featured a clinical relevant efficacy and well-manageable, mostly hematological, toxicity, which resulted in a positive therapeutic index.*

Correspondence to: Radoslav Chekerov, Department of Gynecology, European Competence Center for Ovarian Cancer, Campus Virchow Klinikum, Charité Universitätsmedizin, Augustenburger Platz 1, 13353 Berlin, Germany. Tel: +49 30450664399, Fax: +49 30450564952, e-mail: radoslav.chekerov@charite.de

Key Words: Treosulfan, ovarian cancer, elderly, non-interventional study.

Over 150,000 women worldwide die annually due to ovarian cancer . Ovarian cancer is the leading cause of death among all gynecologic malignancies (1). The majority of patients (70%) are diagnosed at an advanced FIGO stage (III/IV) (2). A 5-year survival rate applies to 15-25% of patients in this group. Despite improved surgical techniques and increasing evidence regarding effectiveness of adjuvant first-line chemotherapy, 65% of patients suffer from tumor progression or recurrence (2). Data regarding routine systemic treatment of patients with recurrent ovarian cancer are still limited. Since numerous studies focus on the treatment of platinum-

sensitive disease and the corresponding evidence influences the current clinical practice, the therapeutic options for the resistant recurrent situation remain a significant clinical challenge. One of the most controversial topics is how to manage elderly patients and to optimize and implement novel treatment strategies for this patient population (3, 4).

The alkylating agent treosulfan is approved in oral (*p.o.*) and intravenous (*i.v.*) form for the treatment of ovarian carcinoma (5, 6). Moreover, it is known for its favorable hematological and non-hematological toxicity (7, 8). Treosulfan therapy is known to have a good tolerability in elderly patients (9). Even combination with gemcitabine showed a relevant response in a heavily pre-treated group of patients with platinum-resistant epithelial ovarian cancer, combined with a favorable side-effect profile (8, 10).

In the present non-interventional study, we analyzed the use of treosulfan in designated cancer Centers and outpatient facilities in Germany and evaluated the mode of application, toxicity, and response and survival rates. Additionally, we evaluated the impact of age on all clinical-relevant treatment characteristics.

Patients and Methods

This non-interventional study (NIS) was conducted at 57 German Institutions (11 Hospitals and 46 Outpatient Facilities). The primary aim of the study was to explore the best response, PFS, OS, and toxicity of *p.o.* or *i.v.* treosulfan (Ovastat®) use in patients with mainly recurrent ovarian cancer.

Patients who received at least one therapy cycle of treosulfan were included in the study. However, a maximum number of 10 cycles of treosulfan per patient was included in the final evaluation. A sub-group analysis, according to the age of patients (≥70 years) was performed. Furthermore, we divided the enrolled patients into two groups. Those were, after a response to first line platinum-based therapy, the platinum-sensitive and platinum-resistant. The purpose was to evaluate the best response, PFS and OS. Discontinuation of treosulfan treatment was performed in patients with progressive disease, new diagnosis of second malignancy or severe toxicity related to treatment.

Treosulfan was applied either *i.v.* (5,000-8,000 mg/m^2 d1, q21 or 28d) or *p.o.* (400-600 mg/m^2 d1-28, q56d or 400-600 mg/m^2 d1-14 or 21, q28d) for ≥1 cycle in documented patients. No general pre-medication was defined, and participating Centers could apply their specific standards. Any forms of supportive therapy including granulocyte-colony-stimulating factor (G-CSF) were allowed. The concomitant use of food, especially milk, was recommended for all women receiving treosulfan as oral application.

Blood samples for hematology (hemoglobin, leukocytes, and platelets) and blood chemistry (creatinine, alkaline phosphatase, SGOT, SGPT, gamma-GT, LDH, total bilirubin, albumin, and total serum protein), as well as CA-125 were documented prior to each cycle, if collected. Toxicity was graded according to the classification of the National Cancer Institute ''Common Terminology Criteria for Adverse Events'' (CTCAE) version 2.0, at the end of every cycle. Safety was assessed by analysis of toxicity parameters (occurrence of adverse events, serious adverse events, and death).

Table I. *Patients' characteristics and distribution of clinical parameters according to age, n=248.*

Parameter per age group	<70 years (n=112)	≥70 years (n=117)	Age not documented (n=19)	All (n=248)
Age, median (range)	62 (36-69)	76 (70-92)	-	70 (36-92)
ECOG Status				
0	12 (11%)	10 (9%)	6 (32%)	28 (11%)
1	76 (68%)	68 (58%)	9 (47%)	153 (62%)
2	21 (19%)	30 (26%)	3 (16%)	54 (22%)
3	1 (1%)	2 (2%)	1 (5%)	4 (2%)
Not documented	2 (2%)	7 (27%)	-	9 (4%)
FIGO-Stage				
I	4 (4%)	10 (9%)	1 (5%)	15 (6%)
II	8 (7%)	9 (8%)	1 (5%)	18 (7%)
III	59 (53%)	50 (43%)	13 (69%)	122 (49%)
IV	20 (18%)	32 (27%)	3 (16%)	55 (22%)
Not documented	21 (19%)	16 (14%)	1 (5%)	38 (15%)
Histology				
Serous	58 (52%)	63 (48%)	10 (53%)	131 (53%)
Other	45 (40%)	45 (39%)	8 (42%)	98 (39%)
Not documented	9 (8%)	9 (8%)	1 (5%)	19 (8%)
Therapy situation				
First-line	8 (7%)	38 (33%)	4 (21%)	50 (20%)
Second-line	26 (23%)	33 (28%)	6 (32%)	65 (26%)
Third-line	31 (28%)	19 (16%)	2 (11%)	52 (21%)
Fourth-line	19 (17%)	18 (15%)	4 (21%)	41 (16%)
Fifth-line	13 (12%)	5 (4%)	3 (16%)	21 (9%)
>Fifth-line	15 (13%)	4 (3%)	-	19 (8%)
Number of previous systemic therapies				
Median (range)	2 (0-5)	1 (0-5)	1 (0-5)	2 (0-5)

The study was performed according to ICH-GCP (International Conference on Harmonization - Good Clinical Practice) guidelines. An independent monitoring Institute was responsible for data control (Alcedis GmbH, Giessen, Germany). The statistical methods were mainly descriptive.

Comparison of two or more groups of discrete variables was performed by the Fisher's exact test or the χ^2 test, and continuous variables were tested by the appropriate methods (Wilcoxon test). The Kaplan-Meier method including a log-rank test was used to show PFS and OS.

Results

This NIS enrolled 248 patients with advanced or recurrent ovarian cancer who received at least one cycle of treosulfan.

The median age at the time of diagnosis was 70 years, whereas 47% of the patients were ≥70 years (median=76, range=36-69) and 45% younger than 70 years (median=62 years, range=70-92) of age. For 8% of patients age data are missing (Table I). The majority of all enrolled patients showed a good performance status with a median ECOG 1

Table II. *Current disease situation and number of administered treosulfan cycles.*

Parameters of treosulfan therapy per age group	<70 years (n=112)	≥70 years (n=117)	Age n.d.* (n=19)	All (n=248)
Type of application / Dose (n, %)				
Intravenous (*i.v.*) ≤7g/m^2, q28d	86 (77%)	86 (73%)	11 (58%)	183 (74%)
Intravenous (*i.v.*) >7g/m^2, q28d	8 (7%)	10 (9%)	-	18 (7%)
Oral, day 1-14/21, q21/28days	9 (8%)	8 (7%)	3 (16%)	20 (8%)
Oral, day 1-28, q56 days	9 (8%)	13 (11%)	5 (26%)	27 (11%)
Number of administered treosulfan cycles (median)				
Intravenous (*i.v.*) ≤7g/m^2	5	5	5	5
Intravenous (*i.v.*) >7g/m^2	5	5	-	5
Oral, day 1-14/21, q21/28days	4	6	6	6
Oral, day 1-28, q56 days	4	5	2	4
Number of cycles applied regularly (%)##				
Intravenous (*i.v.*) ≤7g/m^2				
Yes	66	67.0	62	66
No	33	30	33	32
N.d.*	1	3	5	2
Intravenous (*i.v.*) >7g/m^2				
Yes	71	55	-	62
No	26	43		36
N.d.*	3	2		2
Oral, d 1-14/21, q21/28d				
Yes	57	84	14	60
No	41	16	86	39
N.d.*	2	-	-	1
Oral, d 1-28, q56 d				
Yes	37	47	23	40
No	63	53	62	58
N.d.*	-	-	15	2
Main reasons for treatment alterations (%)				
Intravenous (*i.v.*) ≤7g/m^2				
Discontinue	2	3	7	3
Modulation	3	4	-	3
Delay	31	27	31	30
Intravenous (*i.v.*) >7g/m^2				
Discontinue	3	2	-	2
Modulation	3	4		4
Delay	23	43		35
Oral, d 1-14/21, q21/28d				
Discontinue	7	2	5	4
Modulation	3	4	-	5
Delay	34	12	86	77
Oral, d 1-28, q56d				
Discontinue	4	7	23	7
Modulation	4	11	-	7
Delay	59	56	54	55

##Data for 28 cycles were not documented. *N.d.: Not documented.

(range=0-2). Most of the tumors were diagnosed at advanced disease stage FIGO III (49%) or IV (22%), presenting predominantly serious histology (53%). With respect to age, we identified no significant differences in the distribution of the main clinicopathological characteristics at study entry.

The decision for a treatment with treosulfan depended strongly on former guidelines, patient's age and disease situation. At the time of trial initiation (2001), treosulfan was approved for the treatment of advanced ovarian cancer, and the current therapy standard of carboplatin and taxane was not yet recommended for the first-line application. Therefore in elderly patients, treosulfan was administered also as first-line therapy (33%), but predominantly as a treatment for recurrent disease mostly in the second (28%), third (16%) or fourth line (15%), and rarely in highly palliative ≥5 line situation (8%). Younger patients received treosulfan

Table III. *Type of adverse events (AEs) with respect to therapy regimen and age.*

		i.v. ≤7g/m^2 d1 q21d or q28d		*i.v.* >7 mg/m^{2}d1 q21 or g28d		*p.o.* d1-14/21 q28d		*p.o.* d1-28 q56d	
		Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Age	Adverse events (%)								
<70 years	Anemia	44.2	4.7	75	12.5	22.2	-	22.2	-
	Leukopenia	30.2	1.2	62.5	-	33.3	-	33.3	-
	Neutropenia	12.8	3.5	25	-	11.1	-	11.1	-
	Thrombocytopenia	30.2	2.3	50	-	11.1	-	11.1	-
	Emesis	10.5	-	25	12.5	-	-	11.1	-
	Constipation	12.8	3.5	25	-	-	-	11.1	-
	Vomiting	34.9	-	75	-	11.1	-	22.2	-
≥70 years	Anemia	53.5	2.3	70	10	62.5	-	76.9	-
	Leukopenia	31.4	5.8	50	20	25	-	53.8	7.7
	Neutropenia	15.1	3.5	30	-	12.5	-	30.8	-
	Thrombocytopenia	25.6	5.8	30	20	25	-	15.4	7.7
	Emesis	23.3	2.3	10	10	25	-	23.1	-
	Constipation	24.4	-	20	10	50	-	15.4	-
	Vomiting	33.7	2.3	60	10	75	-	30.8	-

predominantly in the second (23%), third (28%) or fourth (17%) recurrent line. Highly palliative treatment with treosulfan in the fifth and above lines was administered in only 25% of the younger population (Table I).

Following former treatment guidelines, most patients for whom treosulfan was recommended in the first line were older than 70 years (76%) and therapy was initiated before 2006. At the same time, elderly patients (>70 years) received treosulfan most often as palliative treatment: 60% in third-line, 46% in fourth-line, 62% in fifth-line and 79% in ≥5th-line of treatment.

By analyzing previous treatments, we identified that nine out of ten patients had undergone primary surgical tumor debulking. Out of patients who were not debulked, but recommended for primary systemic treatment, 69% were ≥70 years old. Platinum-based combinations were part of the adjuvant pre-treatment in 89% of the younger, but only 67% of the elderly participants, for whom the rate of therapy interruptions was higher (41% of elderly *vs.* 21% of younger patients). Management of recurrent disease consisted of established use of taxanes, topotecan, gemcitabine, anthracyclines (particularly formulated as PLD), where combinations of these agents with carboplatin were mostly part of the second-line treatment in the platinum-sensitive groups and monotherapy was predominantly recommended for the palliative, platinum-resistant disease. Younger patients received in median 2 previous systemic treatments, whereas the elderly woman had higher chance to receive only 1 treatment. The two age-cohorts did not differ in their main pretreatment characteristics.

Treosulfan was administered in both age groups as *i.v.* therapy, with 201 patients (81%) receiving the recommended dose of 7,000 mg/m^2, and a small group (n=18) for whom the administered dose was 7,000-8,000 mg/m^2 (Table II). An oral therapy was administered in 47 patients (19%) with large variation in the treatment mode. In addition to the classic 28-day oral treosulfan schedule, followed by a 4-week treatment-free interval (day 1-28/q56d), alternating schedules administered treosulfan either as a two-weekly (day 1-14/q21d) or three-weekly (day 1-21/q28d) regimen, followed by a therapy-free interval of 7 days.

Overall 959 cycles of treosulfan <7,000 mg/m^2 and 84 cycles >7,000 mg/m^2 were administered intravenously. The oral treatment included 239 cycles. There was no statistical difference in the median number of administered treosulfan cycles according to age, although the median of oral therapy was lower than for the *i.v.* cohorts. The regular treatment was administered as scheduled in 61.0% of all therapy cycles (range=40.3%-66.0%), where 37.4% of cycles (range=31.6%-58.1%) were subject to change of the planned therapy mode (1.6% no data; Table III). Negative influence on completion of treatment was observed for the prolonged 28-day *p.o.* therapy and also for the high-dose *i.v.* application (>7g/m2), especially in elderly participants. The highest rate of successfully completed treosulfan treatment (83.7%) was observed for the short two- and three-weekly oral schedules and in the elderly cohort. The most common reasons for treatment alterations were extension of therapy interval due to toxicity (82.2%), dose modification (9.5%) or therapy discontinuation (8.3%). The main reason for dose modifications (45.8%) in both age cohorts and both drug applications was cumulative hematological toxicity. Prolongation of therapy interval was mostly associated with

Table IV. *Response rates according to application form and age cohort.*

Response to treosulfan regimen		*i.v.*	Oral	All patients
Age	Best response (%)			
<70 years	CR	8.5	5.6	8
	PR	13.8	16.7	14.3
	SD	20.2	27.8	20.5
	PD	42.6	38.9	42
	Not documented	14.9	11.1	14.3
≥70 years	CR	9.4	9.5	9.4
	PR	17.7	14.3	17.1
	SD	21.9	38.9	23.9
	PD	36.5	38.1	36.8
	Not documented	10.6	4.8	9.4

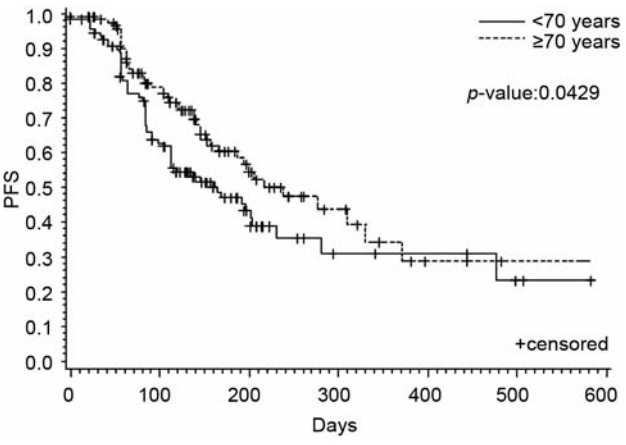

Figure 1. *Progression-free survival.*

patient's preference or organisational reasons (59.5%), followed by hematological events (15.2%). Non-hematological toxicity was identified as causing 6.3% of all dose modifications and 3.9% of treatment delays. Analyzing these factors, we observed oral administration of treosulfan to be associated with increased need of therapy modification or discontinuation, but this effect was not associated with age.

In total, 2,351 adverse events of NCI-CTCAE v2.0 grade 1-4 were evaluated in the present trial. AEs were predominantly of grade 1 (69.0%), grade 2 (24.6%), grade 3 (5.7%) and grade 4 (0.7%). Forty-three percent of the AEs were registered in the <70 years age cohort, while elderly participants developed 47.6% of AEs, and 8.8% of AEs were in the group without documented age. Hematological side-effects occurred most commonly, predominantly in a moderate form at any age (Table III). We observed that a high *i.v.* dose >7,000 mg/m^2 and dose-intensive oral therapy such as a 28-day application rhythm increased the risk of hematological AEs. Interestingly, oral treosulfan was very well tolerated in patients <70 years, but its toxicity doubled in the elderly population. Most common non-hematological events were vomiting, constipation and emesis, where toxicity effects were stronger and of prolonged duration in elderly participants. However, a general trend of increased toxicity was associated with the elderly population and with patients who received their oral therapy as a 28-day application. About half of patients discontinued therapy due to progressive disease. Elderly participants preferred most commonly to discontinue treatment and presented slightly more cumulative toxicity than the younger population.

Evaluation of treatment response identified an overall response rate of 25.8%, stable disease of 28.6% and progressive disease in 45.6% of all individuals (Table IV). For 31 participants, response data were not documented. Median progression-free survival of participants older 70 years was significantly higher than of the younger patients (median=219 days resp161 days, p=0.0429). This finding probably resulted due to the large number of participants who received treosulfan as adjuvant treatment, but was not reproducible for overall survival (Figure 1). The median progression-free survival was 196 days (95%CI=112-333 days) and median overall survival 405 (95%CI 261-not reached) days. In the sub-group analysis there were no relevant age-dependent differences in efficacy and survival rate.

Discussion

The management of advanced metastatic and recurrent ovarian cancer remains a clinical challenge. Tumor control and quality of life based on low toxicity are key landmarks of all treatment strategies. Treatment of the elderly in particular represents a significant challenge for gynecological oncologists (3, 4). The alkylating agent treosulfan characterized with low toxicity is still known, with its wide use, as an effective therapy option in recurrent ovarian cancer since the late 1990s (11, 12). Most available data demonstrated relevant clinical efficacy of the drug, especially in elderly and heavily pre-treated ovarian cancer patients (9, 10). Treosulfan has been approved for palliative therapy alone or in combination for advanced stage disease after failure of platinum-containing regimens (13). Even in the era of emerging implementation of new targeted agents, prospective reports of the clinical use and treatment management of treosulfan are still limited.

The results of this non-interventional study demonstrate good anti-tumor activity and a moderate toxicity of *p.o.* or *i.v.* treosulfan in patients with ovarian cancer. Treatment options with treosulfan are well-known in large oncological Centers (9,

13), and still have strong impact in the clinical management of recurrent ovarian cancer in the outpatient sector in Germany. Compared to previous data we identified partly higher efficacy for treosulfan in our cohort of 248 patients. Thus, we confirmed treosulfan as a useful agent for palliative management with favorable clinical impact independent of age, but of particular importance for the elderly ovarian cancer population. Meier *et al*. reported a phase III trial on the single-agent activity of topotecan and treosulfan in 274 patients either with platinum-resistant or platinum-refractory disease. The authors showed a favorable hematological toxicity profile for treosulfan, whereas non-hematological toxicity was similar for both regimens (13). Meier *et al*. favored topotecan due to its overall response (27.5%) and improved efficacy with regard to overall (55 *vs*. 41 weeks) and progression-free (23 *vs*. 13 weeks) survival. Herein we report a comparable overall response rate to previous published data of topotecan, whereas overall and disease-free survival showed improved results. This could probably be due to the propulsive effect of the sub-group of patients in the adjuvant setting. In this context it must be noted again that the recommendation for carboplatin/paclitaxel was not implemented as first-line standard treatment at the beginning of our study in 2003.

Mahner *et al*. reported preliminary results of a prospective trial of treosulfan in heavily pre-treated elderly patients. Most of participants were included with concomitant cardiovascular diseases or orthopedic problems. In median, 5 concomitant diseases were reported, and the median of concomitant medications was four at the time of enrollment. During the study most observed treatment hematological and non-hematological toxicities were of grade 1 or 2, therefore the therapy with treosulfan was reported as generally well-tolerated in this elderly population. In our study the majority of participants were in the third- and higher-treatment line, with median of two previous systemic therapies. In both age groups we observed similar tolerable hematological toxicity profiles for treosulfan. The slightly higher incidence of AEs correlates to age >70 years, higher *i.v.* dose than the recommended 7,000 mg/m^2 and continuous 28-day oral application, but none of this seemed to influence negative clinical outcome. In our opinion patients recommended for modified or more prolonged drug administration schedules should be selected more carefully and observed intensively. Our results underline treosulfan as a safe and feasible treatment option for any age group with both the *i.v.* and the oral formulation.

Reed *et al*. compared treosulfan and carboplatin as monotherapy in older and/or frail patients with advanced ovarian cancer (11). We observed comparable hematological toxicities in our collective, although Reed's cohort included patients without prior chemotherapy (11). Reed reported nearly twice as high a frequency of leucopenia in the carboplatin arm, where leucopenia and neutropenia were the most reported toxicities in our evaluation.

Regarding management of palliative strategies in recurrent ovarian cancer the impact of treosulfan is still not definitely determined. As the role of quality of life and patient reported outcomes in long-term survivals has recently become more important, we currently have only limited experience of the practical aspects of the use of systemic agents in clinical routine (8, 14). In this context, our data provide a realistic view of the clinical implementation of treosulfan as a feasible therapy alternative with a moderate toxicity profile in the palliative management of ovarian cancer. In particular, elderly and most heavily pre-treated individuals could benefit regarding efficacy and toxicity aspects with favoured therapeutic index, but precise patient selection is necessary. Additionally, we identified that age is not a negative factor with respect to impact on therapy procedures, and has no significant negative influence on outcome in ovarian cancer. The support and optimization of systemic treatment could improve outcomes even in this poor-prognosis population of patients with relapsed ovarian cancer.

Acknowledgements

This non-intervention study was sponsored by medac GmbH, Wedel (Germany).

Furthermore, the Authors would like to thank all participating Institutions and all North-Easthern Society of Gynecological Oncology (NOGGO) centers for their contribution to this study.

References

1 Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D and Bray F: Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer *136(5)*: E359-386, 2015.

2 Heintz AP, Odicino F, Maisonneuve P, Quinn MA, Benedet JL, Creasman WT, Ngan HY, Pecorelli S and Beller U: Carcinoma of the ovary. FIGO 6th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet *95*: 161-192, 2006.

3 Courtney-Brooks M, Tellawi AR, Scalici J, Duska LR, Jazaeri AA, Modesitt SC and Cantrell LA: Frailty: an outcome predictor for elderly gynecologic oncology patients. Gynecol Oncol *126*: 20-24, 2012.

4 Trillsch F, Woelber L, Eulenburg C, Braicu I, Lambrechts S, Chekerov R, van Nieuwenhuysen E, Speiser P, Zeimet A, Castillo-Tong DC, Concin N, Zeillinger R, Vergote I, Mahner S and Sehouli J: Treatment reality in elderly patients with advanced ovarian cancer: a prospective analysis of the OVCAD consortium. J Ovarian Res *6(1)*: 42, 2013.

5 Gropp M, Meier W and Hepp H: Treosulfan as an effective second-line therapy in ovarian cancer. Gynecol Oncol *71*: 94-98, 1998.

6 Hilger RA, Jacek G, Oberhoff C, Kredtke S, Baumgart J, Seeber S and Scheulen ME: Investigation of bioavailability and pharmacokinetics of treosulfan capsules in patients with relapsed ovarian cancer. Cancer Chemother Pharmacol *45*: 483-488, 2000.

7 Breitbach GP, Meden H, Schmid H, Kühn W, Sass G, Schach S, Schmidt-Rohde P and Bastert G: Treosulfan in the treatment of advanced ovarian cancer: a randomised co-operative multicentre phase III-study. Anticancer Res *22(5)*: 2923-2932, 2002.
8 Markman M: Chemotherapy: Topotecan or treosulfan--that is the question. Nat Rev Clin Oncol *6(10)*: 559-560, 2009.
9 Mahner S, Oskay-Özcelik G, Heidrich-Lorsbach E, Fuxius S, Sommer H, Klare P, Belau A, Ruhmland B, Heuser T, Kölbl H, Markmann S and Sehouli J: A prospective multicenter study of treosulfan in elderly patients with recurrent ovarian cancer: results of a planned safety analysis. J Cancer Res Clin Oncol *138(8)*: 1413-1419, 2012.
10 Hilman S, Koh PK, Collins S and Allerton R: The use of treosulfan and gemcitabine in the treatment of platinum-resistant ovarian cancer. Oncol Lett *1(1)*: 209-213, 2010.
11 Reed NS, Poole CJ, Coleman R, Parkin D, Graham JD, Kaye SB, Ostrowski J, Duncan I, Paul J and Hay A: A randomised comparison of treosulfan and carboplatin in patients with ovarian cancer: a study by the Scottish Gynaecological Cancer Trials Group (SGCTG). Eur J Cancer *42(2)*: 179-185, 2006.
12 Keldsen N, Madsen EL, Havsteen H, Kamby C, Laursen L and Sandberg E: Oral treosulfan as second-line treatment in platinum-resistant ovarian cancer: a phase II study. The Danish Ovarian Cancer Study Group. Gynecol Oncol *69(2)*: 100-102, 1998.
13 Meier W, du Bois A, Reuss A, Kuhn W, Olbricht S, Gropp M, Richter B, Lück HJ, Kimmig R and Pfisterer J: Topotecan versus treosulfan, an alkylating agent, in patients with epithelial ovarian cancer and relapse within 12 months following 1st-line platinum/paclitaxel chemotherapy. A prospectively randomized phase III trial by the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group (AGO-OVAR). Gynecol Oncol *114(2)*: 199-205, 209.
14 Mahner S and Burges A: Quality of life as a primary endpoint in ovarian cancer trials. Lancet Oncol *15(4)*: 363-364, 2014.

Received September 13, 2015
Revised October 13, 2015
Accepted October 19, 2015