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ORIGINAL RESEARCH

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Trabectedin-pegylated liposomal doxorubicin compared to cisplatin desensitization regimen-paclitaxel in ovarian cancer patients

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Abstract

Treatment with trabectedin/pegylated liposomal doxorubicin (PLD) has shown effectiveness in patients with platinum-sensitive recurrent ovarian cancer (ROC). The study evaluates whether this chemotherapy combination may replace treatment with cisplatin desensitization regimen combined with paclitaxel in platinum-sensitive ROC patients when carboplatin is contraindicated. Thirty-nine ROC patients treated with multiple lines of chemotherapy who had developed hypersensitivity (84%, n = 32) or other adverse events (16%, n = 7) to carboplatin were included in this observational study (10 June 2009–31 May 2019). Two ROC cohorts were evaluated for clinical outcomes: Sixteen patients received trabectedin and PLD (T-cohort) and 23 patients received cisplatin desensitization regimen and paclitaxel (C-cohort). The primary diagnosis of ovarian cancer stage I–IV were from September 1986 to December 2016, last observation date was 31 December 2022. The response rate among the patients in the T-cohort was lower than in the C-cohort (63% *vs.* 92%, $p < 0.05$). Progression free survival (PFS) was 110 and 43 months in the T- and C-cohort, respectively ($p = 0.16$). In regards to adverse events, two patients in the C-cohort had life-threatening serious adverse events (SAE) compared to none in the T-cohort, whereas more patients in the T-cohort (56%, n = 9) had grade 3 SAE compared to patients in the C-cohort (22%, n = 5). Sixty-nine percent (n = 11) and 52% (n = 12) had fatigue in the respective cohorts. Thirty-eight and 37% of the patients had previous received more than two lines of chemotherapy, respectively. Five patients had crossed over to either the T- (n = 1) or the C-cohort (n = 4) in a later recurrence. Treatment with trabectedin and PLD is a good alternative to cisplatin desensitization regimen combined with paclitaxel in patients with platinum sensitive ROC when platinum is contraindicated.

Keywords

Gynecological cancer; Ovarian cancer; Chemotherapy; Adverse events; Platinum; Trabectedin; Pegylated liposomal doxorubicin; Carboplatin; Cisplatin desensitization; Paclitaxel

1. Introduction

Among gynecological malignancies, ovarian cancer (OC) is the most common cause of death, with a total of 207,252 deaths globally in 2020 [1]. The standard treatment is primary cytoreductive surgery followed by 6 cycles of chemotherapy with carboplatin and paclitaxel. When indicated, neoadjuvant chemotherapy is given initially followed by interval cytoreductive surgery and adjuvant chemotherapy. After completion of chemotherapy most patients now receive maintenance treatment with a PARP (poly adenosine diphosphate ribose polymerase) inhibitor ± bevazicumab [2–5] or bevacizumab monotherapy [6].

Most patients with OC present with metastatic disease at time of diagnosis and they will experience recurrence. As long as the disease is considered platinum sensitive, retreatment with platinum-based chemotherapy is recommended until resistance occurs [7].

Trabectedin, a DNA damaging agent like carboplatin, is a tetrahydroisoquinoline alkaloid that is produced synthetically. It acts by interfering with DNA transcription factors, DNA binding proteins and DNA repair pathways, which probably causes DNA double-strand breaks, resulting in cell cycle arrest and apoptosis. Trabectedin decreases the level of proangiogenic Vascular endothelial growth factor, chemokine (C-C motif) ligand 2 and interleukin-6 (IL-6), indicating that trabectedin is cytotoxic with immune regulatory effects. Trabectedin has shown additional effects on the tumor micro-environment,

especially on monocytes and macrophages [8]. Moreover, tumor infiltration of cluster of differentiation 8 and T cells has been associated with better survival in OC patients receiving trabectedin in combination with durvalumab [9].

PLD was the first approved nanomedicine globally in 1995. It has an outer phospholipid bilayer modified with polyethylene glycol and inner doxorubicin. PLD has a prolonged half-life in blood owing to its structural features unlike conventional doxorubicin, reducing the risk of severe adverse effects such as myelosuppression and cardiac toxicity and has also shown better therapeutic effects [10].

A phase III international multicentre study which included patients receiving second-line treatment of platinum-sensitive or -resistant recurrent ovarian cancer (ROC) showed an improved progression free survival and overall response rate in patients receiving trabectedin and PLD compared to PLD alone [11]. Furthermore, trabectedin in combination with durvalumab has shown effect on refractory ROC [9].

In a clinical setting, trabectedin can replace platinum in patients experiencing serious hypersensitivity reactions to carboplatin [11]. However, carboplatin has commonly been replaced by cisplatin desensitization regimen. Trabectedin is an alternative for patients having contraindications to cisplatin, including serious adverse events (SAE), kidney failure, hearing loss or neuropathy [11].

The aims of this single institution study were to compare oncologic outcomes and tolerance of trabectedin in combination with PLD to cisplatin desensitization regimen in combination with paclitaxel in patients with platinum-sensitive ROC.

2. Patients and methods

Efficacy and safety data of two cohorts of platinum-sensitive ROC patients treated with multiple lines of chemotherapy who had experienced hypersensitivity or other SAE to carboplatin were collected. Cohort 1 (T-cohort) received trabectedin 1.1 mg/m^2 and PLD 30 mg/m^2 every 3 weeks, whereas cohort 2 (C-cohort) received cisplatin desensitization regimen 50 mg/m^2 and paclitaxel 175 mg/m^2 every 3 weeks, **Supplementary Table 1**. Platinum hypersensitivity reaction was defined as a reaction with two or more of the following symptoms: urticaria, flushing, pruritus, abdominal cramping, diarrhea, back pain, bronchospasm, tachycardia, hypotension, hypertension or chest pain [12].

Progression free survival (PFS) was defined as survival from start of trabectedin or cisplatin based treatment until date of next progression, all assessed by computed tomography, except for six patients showing progression according to gynecologic cancer intergroup cancer antigen 125 (CA125) criteria [13]. Cancer specific survival (CSS) was defined as survival from primary diagnosis until death of OC. Furthermore, the effect on tumor size as well as adverse events of the two treatment regiments were recorded.

Clinical data was collected from the patients' electronic medical record (Distributed Information and Patient Data System in Hospitals, DIPS ver. 7.4.9.2). Receipt of chemotherapy was identified and collected from electronic chemotherapy dosage programs by a unique chemotherapy code for each drug (Cytodose ver. 2.3-07.10.2014 or Cyto Management Systems (CMS) ver. 3.0.9).

The study was registered in clinicaltrials.gov (NCT05512676-Clin.Trials gov).

2.1 Study design and patient population

This single institution cohort study included patients with platinum-sensitive ROC with hypersensitivity reactions (84%, n = 32) or other contraindications to carboplatin such as thrombocytopenia and neurotoxicity (16%, n = 7). Patients were treated with either trabectedin and PLD (T-cohort) or cisplatin desensitization regimen and paclitaxel (C-cohort) according to physician's choice. A previously described cisplatin desensitization protocol was used [14]. According to study protocol, the intention was to include 20 patients in each cohort. Patients were allocated to T- or C-cohort at first cycle, independent of later cross over, and there was no randomization to either treatment. The choice of drugs were made by the clinicians.

The patients had primary diagnosis from 19 September 1986 until 23 December 2016, and were enrolled from 10 June 2009 until 31 May 2019.

One patient was excluded because cisplatin was given without desensitization regimen. Four patients in the T-cohort had previously received cisplatin desensitization treatment, and these patients we allocated to the C-cohort. Finally, the T- and C-cohort consisted of 16 and 23 patients, respectively.

The patients received treatment and had follow-up visits at the study site. They were followed from date of first cycle of trabectedin and PLD or cisplatin desensitization regimen and paclitaxel until last observation 31 December 2022 or death. Date of death was obtained from the Norwegian Cause of Death Registry.

2.2 Response and safety assessments

Response evaluation with Computer Tomography (CT) scans were performed according to modified RECIST Criteria (NCI CTCAE V 5.0). SAEs were defined according to serious toxicity assessed as Common Terminology Criteria for Adverse Events (CTCAE) [15].

2.3 Statistics

All analyses were performed with IBM SPSS (Statistical Package for the Social Sciences, IBM, Chicago, IL, USA) for Windows version 25.0 and STATA version 16.0 (StataCorp, College Station, TX, USA). Pearson chi-square test were used to compare frequencies of different variables between the two cohorts in cross tables. Kaplan-Meier method was used to estimate PFS and CSS. To identify factors associated with CSS, we estimated hazard ratios from a multivariable Cox proportional hazards regression model with the following covariates: age and potential interactions between chemotherapy and other medication (**Supplementary Table 2**).

3. Results

3.1 Patient and treatment characteristics

Patient and tumor characteristics are shown in Table 1. All OC histologies were included. Two patients in the T-cohort

TABLE 1. Characteristics at primary diagnosis (n = 39).

Characteristics	All patients n = 39 (100%)	T-cohort[a] n = 16 (41%)	C-cohort[b] n = 23 (59%)	*p*-value[c]
5-years cancer specific survival (%)	100	100	100	
10-years cancer specific survival (%)	80	73	88	
15-years cancer specific survival (%)	41	29	70	
Age at primary diagnosis				
Median	54.4	55.3	54.4	
Mean	54.2	54.3	54.2	
Range	32.7–77.6	32.7–77.6	41.6–66.1	
Age at Trabectedin or Cisplatin treatment				
Median	60.9	61.1	60.9	
Mean	59.4	59.4	59.3	
Range	37.2–79.5	37.2–79.5	43.3–74.1	
Histology				
High grade serous	31 (80)	11 (69)	20 (87)	0.20
Low grade serous	2 (5)	2 (13)	0	
Endometroid	4 (10)	2 (13)	2 (9)	
Clear cell	1 (3)	0	1 (4)	
Other epithelial	1 (3)	1 (6)	0	
Germline-BRCA[d]				
Mutation	7 (18)	3 (19)	4 (17)	0.60
No-mutation	27 (69)	10 (63)	17 (74)	
Unknown	5 (13)	3 (19)	2 (9)	
Charlton risk score				
Low risk (0–2)	21 (54)	7 (44)	14 (61)	0.50
Medium risk (3–4)	17 (44)	8 (50)	9 (39)	
High risk (≥5)	1 (3)	1 (6)	0	
Primary surgery vs neoadjuvant chemotherapy				
Primary surgery	34 (87)	15 (94)	19 (83)	0.06
Neoadjuvant chemotherapy	5 (13)	1 (6)	4 (17)	
Primary residual disease (cm)[e]				
Median	0			
Mean	0.32			
0	23 (59)	11 (85)	12 (55)	0.03
0.1–0.9	8 (21)	0	8 (36)	
≥1	4 (10)	2 (15)	2 (9)	
No surgery	4 (10)	3 (19)	1 (4)	
FIGO[f]				
IA–C	3 (8)	3 (19)	0	0.20
IIA–IIIB	6 (15)	3 (19)	3 (13)	
IIIC	23 (59)	8 (56)	15 (65)	
IV	7 (18)	2 (13)	5 (22)	
Response primary treatment				
Complete response	30 (77)	13 (81)	17 (74)	0.04
Partial response	3 (8)	3 (19)	0	
Stationary disease	1 (3)	0	1 (3)	
Not evaluable disease	5 (13)	0	5 (13)	

[a] *Trabectedin and pegylated liposomal doxyrubicin (PLD).*
[b] *Cisplatin and paclitaxel.*
[c] *Pearson Chi-Square comparison between the chemotherapeutic groups.*
[d] *Breast Cancer gene (BRCA).*
[e] *Only primary operated patients.*
[f] *The International Federation of Gynecology and Obstetrics (FIGO, 2014).*

had low-grade serous histology, compared to none in the C-cohort. The patients received standard first line treatment with primary (n = 34) or interval cytoreductive surgery (n = 5) and totally 6 courses of carboplatin and paclitaxel, except for one receiving paclitaxel, epirubicine and carboplatin, one receiving paclitaxel, carboplatin and gemcitabine and one patient with FIGO (The International Federation of Gynecology and Obstetrics) stage IA (2014 revision) disease who did not receive adjuvant chemotherapy. There was a non-significant higher percentage who had undergone primary surgery (94%, n = 15) in the T-cohort compared to the C-cohort (83%, n = 19). More patients in the T-cohort had no residual disease after primary treatment (85%, n = 11), compared to the C-cohort (55%, n = 12). All patients in the T-cohort had either complete (n = 13) or partial response (n = 3), compared to 74% (n = 17) with complete response after primary treatment in the C-cohort (p = 0.04). Fewer patients had disease outside the abdominal cavity in the T-cohort compared to C-cohort (19% *vs.* 61%) at time of initiation of T- or C-therapy.

Chemotherapy lines prior inclusion to the study is shown in Table 2. Of the 16 patients included in the T-cohort, 2, 8, 5 and 1 patients were included after first, second, third and fourth line, respectively. Twenty-three patients were included in the C-cohort, and among these, 1, 13, 5 and 4 patients were included after first, second, third and fourth line, respectively.

Thirteen percent (n = 5) of the patients crossed over from cisplatin desensitization treatment to trabectedin (n = 4) or from trabectedin to cisplatin desensitization treatment (n = 1) (**Supplementary Table 3**). There was no difference between treatment free intervals before trabectedin or cisplatin treatment regimens.

A significantly lower proportion of patients in the T-cohort had an increased risk of potential drug-interactions between study-treatment and other prescribed drugs (n = 2) compared to patients in the C-cohort (n = 15), (13% *vs.* 65%, p = 0.01).

Nineteen percent of patients received antiestrogen after treatment in the T-cohort compared to 52% in the C-cohort. None of these patients had low-grade serous histology.

3.2 Adverse events

There was more neurotoxicity (moderate and serve) among the patients in the C-cohort (38%, n = 8) versus none in the T-cohort, whereas liver toxicity was more common in the T-cohort (44%, n = 7) compared to none in the C-cohort (**Supplementary Table 4**).

Sixty-nine percent (n = 11) of the patients had fatigue in T-cohort compared to 52% (n = 12) in the C-cohort. In the T-cohort, 13% (n = 2) changed treatment because of SAEs, compared to 17% (n = 4) in the C-cohort. Six percent (n = 1) received granulocyte colony stimulating factor in the T-cohort versus 14% (n = 3) in the C-cohort.

Two patients in the C-cohort had SAE. The first patient was hospitalized nine days after the third cycle of cisplatin, paclitaxel and bevazicumab, with a bleeding esophageal/gastric ulcer, platelet count of 9×10^9/L and hemoglobin 7.8 g/dL. She was treated with blood transfusions and pantoprazole for 8 weeks, and continued the remaining cycles as planned without bevazicumab. She was alive at last observation date. The second patient was hospitalized three days after the 6th cycle of cisplatin desensitization regimen with nausea, vomiting and a weight loss of 12.3% from start of cisplatin treatment. She was treated with IV nutrition. She died nine days after the 6th cycle of cisplatin. More patients in the T-cohort (39%, n = 9) had grade 3 SAEs compared to the C-cohort (22%, n = 5) (**Supplementary Table 4**).

3.3 Efficacy

The response rate (complete and partial) among the patients in the T-cohort was lower than in the C-cohort (63% *vs.* 92%, p = 0.04). PFS is shown in Fig. 1. The median time to subsequent recurrence/progression was 110 months in the T-cohort, and 43 months in the C-cohort (p = 0.16). The 5-year CSS was 100% in both cohorts. Furthermore, the 10-year CSS was 73% and 88% and the 15-year CSS 29% and 70% in the T- and C-cohort, respectively.

In univariate analyzes the hazard ratio (HR) for death was 0.59 (confidence interval (CI) 0.10–3.32) comparing the C-cohort to the T-cohort. When controlling for age and potential interactions the HRs were 0.30 and 0.31, respectively (CI 0.03–3.74). The potential interactions had no impact on HR. When omitting the two patients with low grade serous carcinoma (LGSC) and the five patients with later cross over to either trabectedin or cisplatin desensitization regimen from the analyses, the HR was 0.36 (CI 0.04–3.55), and when adjusted for age HR was 0.25 (CI 0.03–2.52).

4. Discussion

4.1 Summary of main results

Both trabectedin/PLD and cisplatin desensitization/paclitaxel regimens were well tolerated. There were two life threatening SAEs in the C-cohort, while more grade 3 SAEs in the T-cohort, fatigue being the most frequent AE in both cohorts. These heavily pretreated patients had a long CSS, 5-years of 100% in both cohorts, and median PFS was 110 and 43 months in T- and C-cohort, respectively [7]. These estimates should however be interpreted with caution due to few patients included.

4.2 Results in the context of published literature

In a study by Francis and coworkers analyzing data from the Caelyx in Platinum Sensitive Ovarian patients study (CALYPSO) [16], a decrease of vomiting, nausea and constipation after increasing number of carboplatin/paclitaxel or carboplatin/PLD cycles compared to the first cycle was found. However, there was an increase of neuropathy after each chemotherapy cycle and of alopecia in the use of paclitaxel. In the present study we do not have sufficient data to demonstrate this. However, 19% of the patients in the T-cohort was regarded as platinum resistant after the trabectedin treatment regimen, and any reduction of treatment related symptoms are of importance at this stage of disease.

We found that 54% (n = 21) developed hypersensitivity reaction to carboplatin in second line, and 38% in third and fourth

TABLE 2. Chemotherapy after primary- and before trabectedin or cisplatin treatment (n = 39).

Treatment	All patients n = 39 (%)	T-cohort n = 16	C-cohort n = 23	*p*-value[a]
First line (n = 39)				
Carboplatin and paclitaxel	37	15	22	
Carboplatin single	1	0	1	
No chemotherapy	1	1	0	
Changed to T- or C-cohort	3 (8)	2	1	0.4
Second line (n = 36)				
Carboplatin and paclitaxel	25	11	14	
Paclitaxel single per 3 weeks	2	1	1	
Carboplatin and Taxotere	1	1	0	
Carboplatin and PLD[b]	5	1	4	
PLD[b] single	1	0	1	
Paclitaxel weekly	1	0	1	
Paclitaxel weekly + Bevacizumab	1	1	0	
Changed to T- or C-cohort	21 (54)	8	13	0.5
Third line (n = 15)				
Paclitaxel weekly	7	5	2	
Paclitaxel and PLD[b]	5	0	5	
Paclitaxel per 3 months	1	0	1	
Docetaxel and PLD	2	0	2	
Changed to T- or C-cohort	10 (26)	5	5	0.4
Fourth line (n = 5)				
Carboplatin and paclitaxel	1	0	1	
Carboplatin and PLD[b]	1	0	1	
Paclitaxel and PLD[b]	2	0	2	
Gemcitabin and PLD	1	1	0	
Changed to T- or C-cohort	5 (13)	1	4	0.3

[a] *Pearson Chi-Square comparison between the chemotherapeutic cohorts.*
[b] *Pegylated Liposomal Doxorubicin (PLD).*

line which is in accordance with the study by Bergamini [12], who demonstrated that the risk of developing hypersensitivity to carboplatin increased with the number of carboplatin cycles.

In the present study two doublet chemotherapy regimens were compared, since single agent treatment has been demonstrated to be inferior to double agents in platinum-sensitive ROC [11, 17]. Some authors have hypothesized that prolongation of the platinum free interval with a non-platinum regimen will improve overall survival if the patients later have a platinum regimen [11]. We cannot confirm this, however, we show that patients receiving trabectedin and PLD have a longer PFS, but shorter CSS, than patients receiving cisplatin desensitization regimen and paclitaxel. This is in accordance with the International, Randomized Study in Patients With Ovarian Cancer (INOVAYTON) study [18].

In this observational study, one to four lines of chemotherapy were given before trabectedin or cisplatin desensitization regimens with a median of 2.4 lines, and mean 3.1 lines. On average, these patients had 1.2 lines of chemotherapy after trabectedin or cisplatin treatment regimens. Kessous and coworkers have demonstrated partial response for some patients up to seven lines of chemotherapy. The only factor that predicted response was the time interval from the previous line of chemotherapy [19].

In line with other authors, we demonstrated an acceptable toxicity in the T- and C-cohorts. However, in the latter cohort there were two life threatening SAEs to cisplatin [20]. This is not in line with a most recent study comparing single-agent trabectedin with physician's choice of chemotherapy where trabectedin showed a worse safety profile [21].

The INOVATYON study did not demonstrate a significant difference in survival for treatment with trabectedin and PLD compared to carboplatin and PLD in patients with platinum-sensitive ROC. In the present study, efficacy comparison between the two regimens is not possible due to low number of study participants. Moreover, the patients included in this study were heavily pretreated with platinum, as 38% and 39% in the T- and C-cohort, respectively had received more than

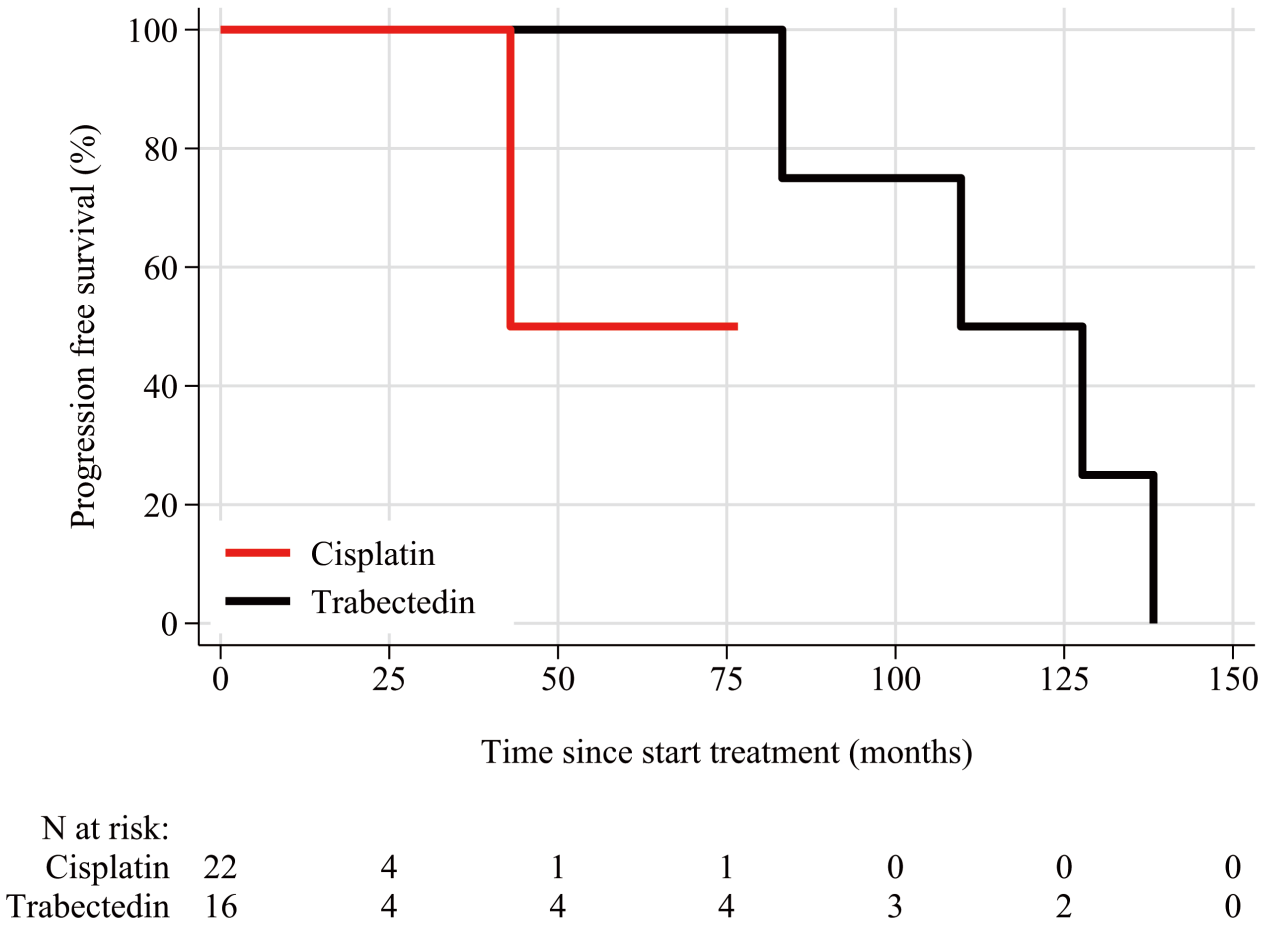

FIGURE 1. Progression free survival (PFS) after treatment with trabectedin and pegylated liposomal doxorubicin (PLD) compared to cisplatin desensitization and paclitaxel regimen in ovarian cancer patients.

2 lines of platinum-based treatment compared to 30% in the INOVATYON study [18].

In accordance with other authors, we confirm that the Breast Cancer (BRCA) mutation carriers among the ROC patients have more frequent carboplatin reactions compared to non-carriers. More patients in the present cohorts had BRCA mutations (18%) compared to Norwegian OC patients in general (7.9%) [12, 22]. We cannot confirm that carboplatin and PLD compared to carboplatin and paclitaxel have less frequent carboplatin hypersensitivity reactions; because only six patients in the present study were treated with carboplatin and PLD before they had a hypersensitivity reaction to carboplatin [12].

The 5-year CSS in the present two cohorts is higher compared to the relative 5-year survival in the Norwegian OC population with all FIGO stages included. Between 2018 and 2020, the relative 5-year survival was 50.6% in Norway [23]. However, the two cohorts in the present study consists of few patients that were highly selected with high tolerance and response to chemotherapy. The maximum tolerated dose used in this study is in accordance with a recent published study where trabectedin 1.1 mg/m^2, and was tolerated well by the majority of the patients [24].

Many factors might explain the difference in PFS found between the two regimens; the median PFS in the T- and C-cohort being 110 and 43 months, respectively (p = 0.16). In a Cochrane review looking at trabectedin treatment for recurrent ovarian cancer, one of the main conclusions was that combination of PLD with other chemotherapies compared to compounds without PLD increased PFS, but did not improve CSS. Possibly, PLD may contribute the most to the increased PFS [25]. We hypothesize that the initial effect of trabectedin may be better than cisplatin, but with rapid development of resistance in the next treatment line. Several patients with BRCA mutations as well as the two patients with LGSC in the T-group might have contributed to a longer PFS in this cohort. More patients in the T-group had high and medium Charlton comorbidity scores, compared to the C-group (56% *vs.* 39%). This could explain the better PFS as well as the inferior CSS in the T-group. Furthermore, more patients in the C-group were treated with a PARP inhibitor (PARPi), 26% versus 19% in the T-group, which might also improve CSS in the C-group.

4.3 Strengths and weaknesses

To our knowledge, this is the first study comparing trabectedin and PLD with cisplatin desensitization regimen and paclitaxel in platinum-sensitive ROC patients with hypersensitivity, intolerable SAEs or other contraindications to carboplatin. The two cohorts have a follow-up of more than 15 years from

primary diagnosis with detailed information on clinical data, and no patients were lost to follow up. The follow-up of the T- and C-cohorts were more than 3.5 years after trabectedin or cisplatin desensitization treatment regimens.

In the present study, data on all lines of treatments was collected. This represents strength of the study.

Weaknesses of the present study include lack of randomization, few study participants and possible selection bias. We cannot conclude which of the two regimens should be preferred for patients with contraindications to carboplatin. It is likely not possible to estimate a difference in efficacy between trabectedin and cisplatin regimens in an observational, small study design like this. Potential confounding factors such as histology, primary resection rate, primary response rate, BRCA mutational status, previous lines of chemotherapy and cross over cannot be assessed in this small dataset. Therefore, results presented herein must be interpreted with this in mind.

4.4 Implications for practice and future research

The use of trabectedin and cisplatin regimens among ROC patients with contraindications to carboplatin are well tolerated with acceptable efficacy. For patients experiencing serious anaphylaxis to carboplatin or have hypersensitivity reactions or other contraindications to cisplatin desensitization regimen, trabectedin and PLD may be the preferred drug in platinum-sensitive ROC.

In the present study cross over from cisplatin to trabectedin regimen was an adequate strategy in patients with intolerant SAEs to cisplatin, and should be considered in clinical practice.

Baert and coworkers found that patients after second line receiving maintenance treatment with a PARPi after second line chemotherapy had lower response to platinum-based third line treatment compared to patients not receiving a PARPi [26]. This could be explained by an overlapping mechanism of drug resistance for platinum and PARPis [27]. Therefore, an interesting treatment alternative to platinum could be trabectedin, possibly delaying platinum-resistance. Still, patients progressing on a PARPi often retain sensitivity to platinum [27] and a retrospective multicenter study uncovered a three months shorter PFS among patients treated with trabectedin and PLD compared to platinum-based treatment, previously treated with PARPi [28]. In this study, no patients had PARPi treatment before trabectedin and cisplatin regimens.

5. Conclusions

The present study shows that trabectedin and PLD is a good alternative to cisplatin desensitization regimen combined with paclitaxel in platinum-sensitive ROC patients having contraindications to carboplatin, including serious anaphylaxis to carboplatin or other contraindications to cisplatin desensitization regimen. Treatment with trabectedin and PLD is well tolerated and with acceptable efficacy.

AVAILABILITY OF DATA AND MATERIALS

Raw data are available upon request.

AUTHOR CONTRIBUTIONS

TP—collected data from the medical records. TP, BV, AB, TÅM, AD and AGZE—wrote the manuscript. TÅM and TP—contributed to the statistical analyses. All authors read and commented on the manuscript and approved the final version.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Regional Ethical Committee approved the present study on 06 January 2016 for Health Research, (2015/2167 REK Sør-Øst B). Patients that were alive by inclusion signed an informed consent. The patients were included prospectively with informed consent from 07 March 2016 to 20 May 2019, apart from twelve patients who had received one of the two treatment regimens prior to study initiation and were included retrospectively before 07 March 2016.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.ejgo.net/files/article/1867406494722342912/attachment/Supplementary%20material.docx.

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