ORIGINAL ARTICLE

Platinum-free interval affects efficacy of following treatment for platinum-refractory or -resistant ovarian cancer

Mayumi Kobayashi-Kato[1] · Mayu Yunokawa[2,3] · Seiko Bun[4] · Naoyuki Miyasaka[5] · Tomoyasu Kato[1] · Kenji Tamura[2]

Abstract

Background/objective Platinum-refractory or -resistant ovarian cancer (PRROC) is associated with poor prognosis and low response to further chemotherapy. We investigated predictors of effectiveness of following treatments for PRROC.

Patients and methods We included 380 patients diagnosed with stage I–IV ovarian, fallopian tube, or primary peritoneal cancer, who were treated at the National Cancer Center Hospital in Japan from January 2007 to December 2014 and recurred after initial treatment, who had a platinum-refractory or -resistant relapses and received chemotherapy, in this single-center, retrospective study. We investigated factors related to response to following treatment, and to progression-free survival (PFS).

Results Among 183 patients (48%) who suffered recurrences, 62 (34%) developed PRROC after chemotherapy. In multivariate analysis, platinum-free interval (PFI) < 3 months was independently associated with progressive disease (odds ratio [OR] 6.043, 95% confidence interval [CI] 1.485–24.595, $P = 0.012$). Median PFS was 139 days (95% CI 19.4–258) among patients with PFI > 3 months, but was 57 days (95% CI 34.7–79.2) among those with PFI < 3 months. In multivariate analysis, two factors, performance status (PS) 1–2 (HR 1.915, 95% CI 1.074–3.415, $P = 0.028$) and PFI < 3 months (HR 1.943, 95% CI 1.109–3.403, $P = 0.02$), were independently associated with worse PFS.

Conclusions PS 1–2 and PFI < 3 months were significant predictors of poor response to following treatment for PRROC. Risks and benefits of treatment should be frankly discussed with patients who have these characteristics.

Keywords Platinum-refractory ovarian cancer · Platinum-resistant ovarian cancer · Predictive marker · Prognostic marker · Chemotherapy · Platinum free interval

Introduction

Ovarian cancer (OC) is the seventh most frequently diagnosed cancer, and the eighth most common cause of cancer mortality, among women worldwide, with an estimated

✉ Mayu Yunokawa
mayu.yunokawa@jfcr.or.jp

1 Department of Gynecology, National Cancer Center Hospital, Tokyo, Japan

2 Breast and Medical Oncology, National Cancer Center Hospital, Tokyo, Japan

3 Department of Medical Oncology/Gynecologic Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, 3-8-31, Ariake, Koto, Tokyo 135-8550, Japan

4 Department of Pharmacy, National Cancer Center Hospital, Tokyo, Japan

5 Department of Perinatal and Women'S Medicine, Tokyo Medical and Dental University, Tokyo, Japan

21,000 new cases diagnosed, and more than 14,000 deaths, in 2015 [1, 2]. Although patients who receive platinum-based regimens as first-line treatment have a 70–80% response rate and, with approximately 50% response for patients with platinum-sensitive relapses [3–7]. Some patients are initially refractory or resistant to platinum-containing regimen and most patients including initially platinum-sensitive relapse will eventually become resistant to platinum.

Treatment options for patients with platinum-refractory or -resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer (PRROC) include single cytotoxic agents such as pegylated liposomal doxorubicin (PLD), gemcitabine (GEM), topotecan (NGT) and paclitaxel (PTX) [1]. However, a few clinical trials and real-world studies show low response rates to these chemotherapies (average 10–15%), with progression-free survival (PFS) of 3–4 months and median survival of about a year [8]. The effective survival in patients with PRROC is dismal and development of new treatment strategies for PRROC is crucial. Also, indications

for chemotherapy for patients with PRROC should be cautiously evaluated, with the equivocal efficacy of chemotherapy weighed against its likely effects on the patient's systemic condition and quality of life. Frequent hospitalizations from toxicities or complications have been reported for patients with PRROC because of poor general health or poor organ function caused by their disease or past treatments [1]. Few studies have evaluated predictors of chemotherapy response among patients with PRROC, although PFI is the strongest predictor for platinum retreatment response in platinum-sensitive recurrent OC [9, 10].

As it is therefore uncertain which patients with PRROC can benefit from these regimens, we investigated predictive factors for chemotherapy response in this setting.

Patients and methods

Patients

We performed this single-center, retrospective study with approval from the National Cancer Center Institutional Review Board No. 2016-442), in accordance with guidelines on medical and epidemiological research in an epidemiologic study. After obtaining institutional review board approval, the OC database containing all patients treated at the National Cancer Center Hospital in Japan was used to identify all patients diagnosed with International Federation of Gynecology and Obstetrics FIGO) stage I–IV ovarian, fallopian tube, or primary peritoneal cancer treated from January 2007 to December 2014. We extracted data of patients who had a platinum-refractory or -resistant relapses and received chemotherapy. We defined "platinum-refractory relapse" as disease progression while receiving last-line platinum-based therapy or within 4 weeks of a patient's last platinum dose; and defined "platinum-resistant relapse" as disease for which progression-free interval was less than 6 months after the patient received her last-line platinum-based therapy [10]. Patients were categorized as "primary platinum-resistant" PPR) if they recurred within 6 months of the conclusion of primary platinum chemotherapy. Patients who acquired platinum-resistant disease in the course of platinum-containing chemotherapy also were included in this study as "acquired platinum-resistant" APR). We excluded patients who were lost to follow-up, were assigned to clinical trials, or received following platinum-based regimens Fig. 1.

Definition of therapy

We performed surgery and/or chemotherapy for all patients in our institute, according to their stage, histology, and grade. Primary debulking surgery or interval debulking
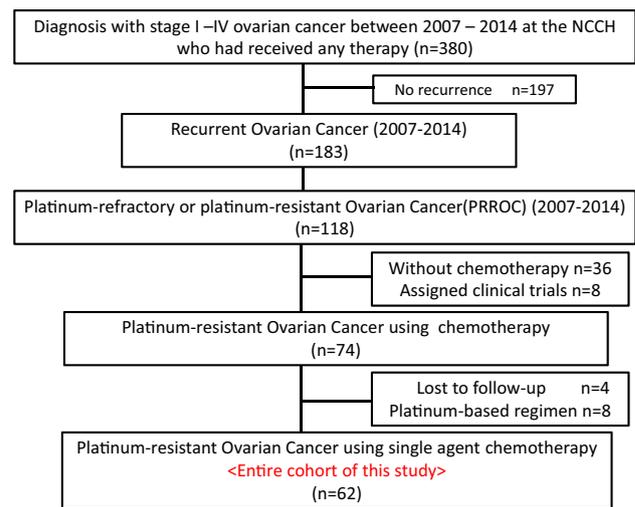

Figure1. Current study cohort

Fig. 1 Current study schematic

surgery was performed using maximal effort to achieve complete resections by a gynecologic oncologist, including metastases. All patients received platinum-containing regimens as first-line chemotherapies, according to patients' and doctors' choices, including conventional paclitaxel/carboplatin (TC), dose-dense TC, TC + bevacizumab, weekly TC, or docetaxel/carboplatin (DC). Each treatment was repeated for 6–8 cycles.

Patients with platinum-sensitive relapses also received platinum-containing regimens based on patients' and doctors' choices, including TC, GEM/carboplatin, DC, PLD/carboplatin, or weekly TC.

Patients with PRROC received single-agent regimens as patients' and doctors' choices, including PLD (50 mg/m^2 on Day 1) in a 28-day cycle; GEM (1000 mg/m^2 on days 1, 8, and 15) in a 28-day cycle; CPT-11 (irinotecan; 100 mg/m^2 on days 1, 8, and 15) in a 28-day cycle; NGT (1.5 mg/m^2 on days 1–5) in a 21-day cycle; and PTX (80 mg/m^2 on days 1, 8, and 15) in a 28-day cycle. For combination use of bevacizumab, doses were 10 mg/kg biweekly. Each treatment was repeated until progressive disease (PD) or severe adverse effect occurred.

Data collection

Detailed data were collected from patient records. Clinical characteristics included age; histological type; number of prior platinum-sensitive regimen; performance status (PS); PFI (defined as the interval between the date of the last platinum dose and the date of relapse); and types of regimen. We investigated which factors affected PFS and response to treatment. PFS was estimated from the date started of non-platinum chemotherapy to date of progression or death.

Also, overall survival (OS) was estimated from the initial date of non-platinum chemotherapy to date of death. Treatment responses were evaluated based on Response Evaluation Criteria in Solid Tumors (RECIST) guideline ver 1.1 [11].

Statistical analysis

We performed univariate and multivariate analyses with patients' data, and considered histology type (serous/ endometrioid, clear/ mucinous/ other), number of prior platinum-sensitive regimen (1 vs 2–4), Eastern Cooperative Oncology Group PS (0 vs 1–2), PFI (< 3 months vs ≥ 3 months), types of regimen (PLD, GEM/ CPT-11/ NGT/ weekly PTX/ others). We divided the histology type with considering sensitivity of chemotherapy. The PFI were separated into two terms, that is, < 3 months and ≥ 3 months because the 3 months of PFI is sometimes used for stratification in PRROC trial including the AURELIA trial and several reports, which showed that sensitivity of chemotherapy was different by 3 months of PFI in patients with platinum-sensitive relapse [12–14]. Independent prognostic factors for PFS were determined using Cox proportional hazards regression models. In multivariate analyses, we included variables for which $P < 0.05$ in univariate analyses. Independent prognostic factors for response to following treatment were determined using logistic regression analysis. All statistical tests were two-sided; $P < 0.05$ was considered significant. We used SPSS version 17.0 (Chicago, IL, USA) for all analyses.

Results

Patient characteristics

A schematic of our study cohort is shown in Fig. 1. Among 380 patients who were diagnosed with FIGO stage I–IV ovarian, fallopian tube, or primary peritoneal cancer from January 2007 to December 2014 at our hospital, 183 patients (48%) who had received any treatment suffered recurrences; of these 183 patients, 62 (34%) had PRROC and were treated with single-agent chemotherapy; these 62 patients met the inclusion criteria for this study.

Their characteristics are shown in Table 1. Their median age was 57 years (range 36–76 years). Their performance scores were PS 0: $n = 44$, PS 1: $n = 16$, and PS 2: $n = 2$ (patients with PS3 or 4 received no chemotherapy). Of the 62 patients, 26 patients were PPR, 36 patients were APR. Among APR patients, 27 had two prior platinum-sensitive regimens, 7 had three regimens, 1 had four regimens and 1 had five regimens. Forty-one patients had PFIs of 3–6 months and 21 patients had PFIs < 3 months. Fifty % of patients choose Doxil regimen for the schedule in a

Table 1 Patients clinicopathological characteristics

	N (%)
Median age (range)	57 (36–76)
Operation	
PDS	29 (47)
IDS	28 (45)
None	5 (8)
The residual tumor volume	
Complete surgery	17 (27)
Optimal surgery	26 (42)
Suboptimal surgery	14 (23)
None	5 (8)
Histological type	
Serous	51 (82)
Clear	8 (13)
Endometrioid	1 (2)
Mucinous	1 (2)
Other	1 (2)
The number of prior platinum-sensitive regimen	
PPR	
1	26 (42)
APR	
2	27 (44)
3	7 (11)
4	1 (2)
5	1 (2)
PS	
0	44 (71)
1	16 (26)
2	2 (3)
PFI (months)	
≥ 3	41 (66)
< 3	21 (34)
Regimen	
PLD[a]	31 (50)
GEM	19 (31)
CPT-11	6 (10)
NGT	2 (3)
wPTX	1 (2)
Others	3 (5)

PDS primary debulking surgery, *IDS* interval debulking surgery, *PFI* platinum-free interval, *PPR* primary platinum resistant, *APR* acquired platinum resistant; *CPT-11* irinotecan, *GEM* gemcitabine, *NGT* topotecan, *PLD* pegylated liposomal doxorubicin, *wPTX* weekly paclitaxel

[a] Among the PLD group ($n = 31$) is 1 patient who received a combined PLD + bevacizumab regimen

28-day cycle as patients' and doctors' choices. There was no information of breast cancer susceptibility gene (*BRCA*) status in our cohort.

Efficacy of single-agent regimens

Of the 62 patients on single-agent regimens, 7 (11%) showed partial response (PR), 18 (29%) showed stable disease (SD); 37 (60%) showed progressive disease (PD) during the study period, and 0 showed complete response CR; Table 2. Median PFS among all patients was 75 days (95% CI 0–673 days), and median OS was 9.7 months (95% CI 1.5–44.5 months).

Factors that affected response to chemotherapy

In univariate analysis, PS 1–2 ($P = 0.022$), and PFI < 3 months ($P = 0.005$) were significantly associated with worse response, including PD, whereas age, histological type, number of prior platinum-sensitive regimens, and types of regimen were not associated with chemotherapy response. Multivariate logistic regression analysis found only one factor, PFI < 3 months (OR 6.043; 95%

CI 1.485–24.595; $P = 0.012$) to be independently associated with PD. PS 1–2 tended to be associated with worse response, but not significantly so (OR 4.141, 95% CI 0.979–17.506, $P = 0.053$; Table 3.

Table 2 shows response percentages by PFI. Among the 21 patients with PFI < 3 months, 18 (86%) suffered PD, compared with the 41 patients in the PFI ≥ 3 months group, of whom 22 (54%) had CR, PR or SD. Among the 18 patients with PS 1–2, 15 (83%) had PD, compared with the 44 PS 0 patients, of whom 22 (50%) had CR, PR or SD.

Factors that affected PFS

In univariate analysis, PS 1–2 ($P = 0.036$), and PFI < 3 months ($P = 0.026$) were significantly associated with worse PFS, whereas age, histological type, number of prior platinum-sensitive regimen, and types of regimen were not associated with PFS Table 4. The multivariate Cox proportional hazards regression model showed that of the two factors, PS 1–2 (HR 1.915, 95% CI 1.074–3.415, $P = 0.028$) and PFI < 3 months (HR 1.943, 95% CI 1.109–3.403, $P = 0.02$) were independently associated with worse PFS; Table 4. Among patients with PS 0, median PFS with initial platinum-refractory or platinum-resistant treatment was 105 days (95% CI 36.7–173), compared with the PS 1–2 group median PFS: 48 days, (95% CI 10.1–85.8); Fig. 2. Among patients with PFI ≥ 3 months, median PFS was 139 days 95% CI 19.4–258, compared with the PFI < 3 months patients at 57 days (95% CI 34.7–79.2); Fig. 3.

Table 2 Response percentages for chemotherapy according to platinum-free interval (PFI)

Response for chemotherapy	Platinum-free interval		Total N (%)
	More than 3 months	Less than 3 months	
CR	0 (0)	0 (0)	0 (0)
PR	6 (15)	1 (5)	7 (11.3)
SD	16 (39)	2 (10)	18 (29.0)
PD	19 (46)	18 (86)	37 (59.7)

CR complete response, *PD* progressive disease, *PR* partial response, *SD* stable disease

Table 3 Uni- and multivariate analyses of factors thought to affect response to chemotherapy among patients with platinum-resistant disease

Variable	Category	N	Univariate analysis (p value)	Multivariate analysis		
				OR	95% CI	p Value
Age	< Median age	32	0.279			
	> Median age	30				
Histological type	Serous/endometrioid	52	0.982			
	Clear/mucinous/others	10				
The number of prior platinum-sensitive regimen	PPR	26	0.8			
	APR	36				
PS	0	44	0.022	1		
	1–2	18		4.141	0.98–17.51	0.053
PFI (months)	≧ 3	41	0.005	1		
	< 3	21		6.043	1.49–24.60	0.012
Regimen	PLD	31	0.279			
	Others	31				

PPR primary platinum resistant, *APR* acquired platinum resistant, *PFI* platinum-free interval, *PLD* pegylated liposomal doxorubicin

Table 4 Uni- and multivariate analyses of factors thought to affect progression-free survival among patients with platinum-resistant disease

Variable	Category	N	Univariate analysis (p value)	Multivariate analysis		
				HR	95% CI	p Value
Age	< median age	32	0.926			
	> median age	30				
Histological type	Serous/endometrioid	52	0.567			
	Clear/mucinous/others	10				
The number of prior platinum-sensitive regimen	PPR	26	0.64			
	APR	36				
PS	0	44	0.036	1		
	1–2	18		1.92	1.07–3.42	0.028
PFI (months)	≧ 3	41	0.026	1		
	< 3	21		1.94	1.11–3.40	0.02
Regimen	PLD	31	0.144			
	Others	31				

PPR primary platinum resistant, *APR* acquired platinum resistant, *PFI* platinum-free interval, *PLD* pegylated liposomal doxorubicin

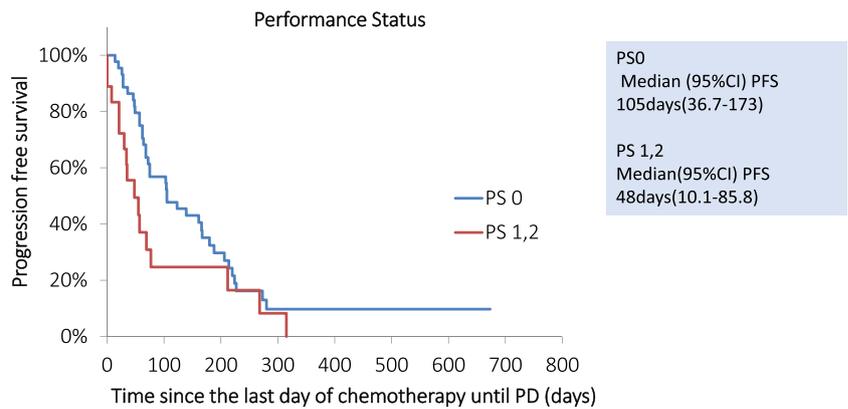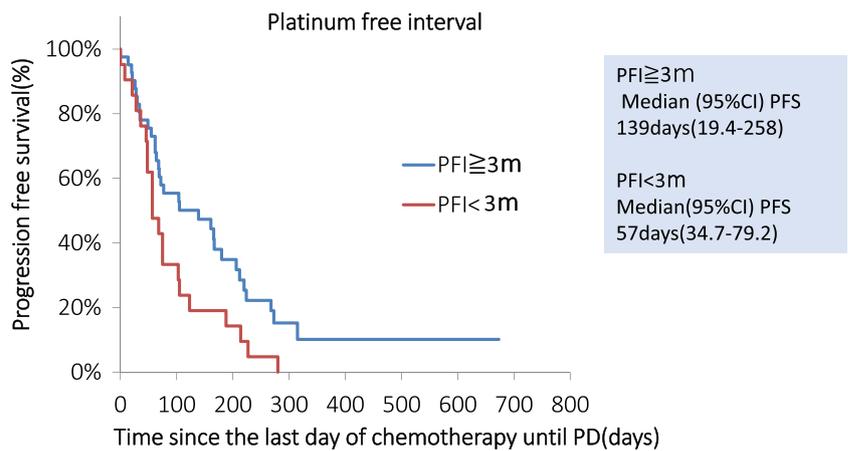**Fig. 2** Kaplan−Meier curve for progression-free survival (PFS) by performance status (PS)

Fig. 3 Kaplan−Meier curve for progression-free survival (PFS) by platinum-free interval (PFI)

Discussion

This study found that PFI < 3 months was a significant predictor of both poor PFS and poor response to chemotherapy, and PS 1–2 was also a significant poor predictive factor of PFS.

Median PFS for all patients was 2.5 months and median OS was 9.7 months in our study, which were consistent with median PFS and OS in published phase 3 clinical trials with single agents (median PFS: 3.7 [95% CI 2.1–7.2] months; median OS: 12.7 [95% CI 7.3–19] months) [15–17]. However, we found median PFS in patients with PS 1–2 or PFI < 3 months both less than only 2 months; and that percentages of PD following treatment were approximately 85% in patients with PS 1–2 or PFI < 3 months, compared with approximately 50% among all patients, which are also consistent with a prior study [15]. Moreover, response rates in patients with PS 1–2 or PFI < 3 months were 4–5%. PRROC patients are not homogeneous and parameters such as PS and PFI may help guide clinical decisions. Our study suggests that patients in these setting are unlikely to benefit from further chemotherapy and best supportive care may be the optimal choice for these patients.

In 2014, the AURELIA open-label randomized phase III trial showed PFS was prolonged from 3.4 to 6.7 months, and RR was increased from 11.8 to 27.3%, when bevacizumab was combined with non-platinum single-agent chemotherapy in patients with PRROC. However, median OS did not significantly differ (13.3 vs 16.6 months, respectively; OR 0.85, 95% CI 0.66–1.08; *P* < 0.174) [9, 12]. Single-agent and bevacizumab combination therapies are recognized as options for patients with PRROC, although we did not consider bevacizumab combination therapy to be the only standard therapy. Among patients with PRROC, 73% had cancer-related symptoms such as pain, dyspnea, fatigue, depression and so on, and 26% had symptomatic ascites in the GCIG Symptom Benefit trial [18]. For patients with cancer-related symptoms, good response or longer PFS is necessary for palliation and good quality of life. Actually, the bevacizumab combination regimen increased the percentage of patients who reported improvement in abdominal/gastrointestinal symptoms during chemotherapy in AURERIA trial to 15% [12]. In our results, response rates and PFS with single-agent chemotherapy were limited in patients with PS 1–2 or PFI < 3 months. These results suggest that the bevacizumab combination regimen is better for patients with cancer-related symptoms, especially those with PS 1–2 or PFI < 3 months.

Trillsch et al. explored prognostic and predictive effects of primary versus acquired platinum resistance for PRROC in the AURELIA trial [19]. Their results showed no significant difference in PFS between the two groups in the chemotherapy-alone group (median PFS: 3.7 vs 2.3 months in PPR patients; *P* = 0.27). These data were consistent with our study; we did not find prior platinum sensitivity to be a significant predictor of effectiveness of following treatment for PRROC.

Limitations of this study include its retrospective design and small sample size. We also performed no biological analyses for predictive markers. The mechanism that causes platinum resistance in OC clearly warrants further study.

In conclusion, PS 1–2 and PFI < 3 months were significant predictors of poor response to following treatment for PRROC. Risks and benefits of treatment should be frankly discussed with patients who have these characteristics. However, these findings also emphasize the continued need for new treatment approaches that prolong survival without deteriorating quality of life.

Compliance with ethical standards

Conflict of interest There is no conflict of interest.

References

1. Parikh R, Kurosky SK, Udall M, Chang J, Cappelleri JC, Doherty JP, Kaye JA (2018) Treatment patterns and health outcomes in platinum-refractory or platinum-resistant ovarian cancer: a retrospective medical record review. Int J Gynecol Cancer 28(4):738–748. https://doi.org/10.1097/IGC.0000000000001222

2. Slaughter K, Holman LL, Thomas EL, Gunderson CC, Lauer JK, Ding K, McMeekin DS, Moore KM (2016) Primary and acquired platinum-resistance among women with high grade serous ovarian cancer. Gynecol Oncol 142(2):225–230. https://doi.org/10.1016/j.ygyno.2016.05.020

3. Katsumata N, Yasuda M, Takahashi F, Isonishi S, Jobo T, Aoki D, Tsuda H, Sugiyama T, Kodama S, Kimura E, Ochiai K, Noda K, Japanese Gynecologic Oncology G (2009) Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. Lancet 374(9698):1331–1338. https://doi.org/10.1016/S0140-6736(09)61157-0

4. Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, Mannel RS, Homesley HD, Fowler J, Greer BE, Boente M, Birrer MJ, Liang SX, Gynecologic Oncology G (2011) Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 365(26):2473–2483. https://doi.org/10.1056/NEJMoa1104390

5. Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, Carey MS, Beale P, Cervantes A, Kurzeder C, du Bois A, Sehouli J, Kimmig R, Stahle A, Collinson F, Essapen S, Gourley C, Lortholary A, Selle F, Mirza MR, Leminen A, Plante M, Stark D, Qian W, Parmar MK, Oza AM, Investigators I (2011) A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 365(26):2484–2496. https://doi.org/10.1056/NEJMoa1103799

6. Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, Gebski V, Heywood M, Vasey PA, Volgger B, Vergote I, Pignata S, Ferrero A, Sehouli J, Lortholary A, Kristensen G, Jackisch C, Joly F, Brown C, Le Fur N, du Bois A (2010) Pegylated liposomal Doxorubicin and Carboplatin compared with Paclitaxel and Carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. J Clin Oncol 28(20):3323–3329. https://doi.org/10.1200/JCO.2009.25.7519

7. Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A, Sovak MA, Yi J, Nycum LR (2012) OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol 30(17):2039–2045. https://doi.org/10.1200/JCO.2012.42.0505

8. Davis A, Tinker AV, Friedlander M (2014) "Platinum resistant" ovarian cancer: what is it, who to treat and how to measure benefit? Gynecol Oncol 133(3):624–631. https://doi.org/10.1016/j.ygyno.2014.02.038

9. Tomao F, Marchetti C, Romito A, Di Pinto A, Di Donato V, Capri O, Palaia I, Monti M, Muzii L, Benedetti Panici P (2017) Overcoming platinum resistance in ovarian cancer treatment: from clinical practice to emerging chemical therapies. Expert Opin Pharmacother 18(14):1443–1455. https://doi.org/10.1080/14656566.2017.1328055

10. Stuart GC, Kitchener H, Bacon M, duBois A, Friedlander M, Ledermann J, Marth C, Thigpen T, Trimble E, Participants of 4th Ovarian Cancer Consensus C, Gynecologic Cancer I (2011) 2010 Gynecologic Cancer InterGroup (GCIG) consensus statement on clinical trials in ovarian cancer: report from the Fourth Ovarian Cancer Consensus Conference. Int J Gynecol Cancer 21(4):750–755. https://doi.org/10.1097/IGC.0b013e31821b2568

11. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45(2):228–247. https://doi.org/10.1016/j.ejca.2008.10.026

12. Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, Sorio R, Vergote I, Witteveen P, Bamias A, Pereira D, Wimberger P, Oaknin A, Mirza MR, Follana P, Bollag D, Ray-Coquard I (2014) Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol 32(13):1302–1308. https://doi.org/10.1200/JCO.2013.51.4489

13. Champer M, Huang Y, Hou JY, Tergas AI, Burke WM, Hillyer GC, Ananth CV, Neugut AI, Hershman DL, Wright JD (2018) Adherence to treatment recommendations and outcomes for women with ovarian cancer at first recurrence. Gynecol Oncol 148(1):19–27. https://doi.org/10.1016/j.ygyno.2017.11.008

14. Lindemann K, Gao B, Mapagu C, Fereday S, Emmanuel C, Alsop K, Traficante N, Australian Ovarian Cancer Study G, Harnett PR, Bowtell DDL, deFazio A (2018) Response rates to second-line platinum-based therapy in ovarian cancer patients challenge the clinical definition of platinum resistance. Gynecol Oncol 150(2):239–246. https://doi.org/10.1016/j.ygyno.2018.05.020

15. Lacave ANGJTFDGDEPMEGAJ (2001) Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin. J Clin Oncol 15:20–28

16. Monk BJ, Poveda A, Vergote I, Raspagliesi F, Fujiwara K, Bae DS, Oaknin A, Ray-Coquard I, Provencher DM, Karlan BY, Lhomme C, Richardson G, Rincon DG, Coleman RL, Marth C, Brize A, Fabbro M, Redondo A, Bamias A, Ma H, Vogl FD, Bach BA, Oza AM (2016) Final results of a phase 3 study of trebananib plus weekly paclitaxel in recurrent ovarian cancer (TRINOVA-1): Long-term survival, impact of ascites, and progression-free survival-2. Gynecol Oncol 143(1):27–34. https://doi.org/10.1016/j.ygyno.2016.07.112

17. Meier W, du Bois A, Reuss A, Kuhn W, Olbricht S, Gropp M, Richter B, Luck HJ, Kimmig R, Pfisterer J (2009) 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 (AGOOVAR). Gynecol Oncol 114(2):199–205. https://doi.org/10.1016/j.ygyno.2009.04.026

18. Roncolato FT, Berton-Rigaud D, O'Connell R, Lanceley A, Sehouli J, Buizen L, Okamoto A, Aotani E, Lorusso D, Donnellan P, Oza A, Avall-Lundqvist E, Berek J, Hilpert F, Ledermann JA, Kaminsky MC, Stockler MR, King MT, Friedlander M (2018) Validation of the modified Glasgow Prognostic Score (mGPS) in recurrent ovarian cancer (ROC) - Analysis of patients enrolled in the GCIG Symptom Benefit Study (SBS). Gynecol Oncol 148(1):36–41. https://doi.org/10.1016/j.ygyno.2017.10.019

19. Trillsch F, Mahner S, Hilpert F, Davies L, Garcia-Martinez E, Kristensen G, Savarese A, Vuylsteke P, Los M, Zagouri F, Gladieff L, Sehouli J, Khoon Lee C, Gebski V, Pujade-Lauraine E (2016) Prognostic and predictive effects of primary versus secondary platinum resistance for bevacizumab treatment for platinum-resistant ovarian cancer in the AURELIA trial. Ann Oncol 27(9):1733–1739. https://doi.org/10.1093/annonc/mdw236