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Original Article

Clinical efficacy and prognosis of chemotherapy regimen of apatinib combined with paclitaxel in the treatment of advanced ovarian cancer

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Abstract: Objective: To explore and analyze the clinical efficacy and prognosis of a chemotherapy regimen of apatinib combined with paclitaxel in patients with advanced ovarian cancer. Methods: A total of 90 patients with advanced ovarian cancer having undergone and failed treatment with second-line chemotherapy who were admitted in our hospital from July 2014 to March 2016 were randomly selected and divided into a control group and a research group, 45 patients in each group. The control group was treated with apatinib alone, while the research group was treated with apatinib combined with paclitaxel. The two groups were compared in efficacy and adverse reactions after 6 cycles of treatment, and compared in their serum CA125 and CA199 levels before and after treatment, and then analyzed in prognosis and prognostic determinants. Results: The research group showed significantly higher total effective treatment rates than the control group ($P < 0.05$) and showed no significant difference with the control group in adverse reactions ($P>0.05$); before treatment, the two groups showed no significant difference in serum CA125 and CA199 levels (both $P>0.05$), while after treatment, the two groups showed significant decreased serum CA125 and CA199 levels (both $P < 0.05$) and the research group showed significantly lower serum CA125 and CA199 levels than the control group (both $P < 0.05$); the research group showed significantly higher 3-year survival rates and progression-free survival rates than the control group; multivariate cox analysis found that pathological stage, diabetes, hypertension and treatment method were all independent risk factors for poor prognosis of advanced ovarian cancer. Conclusion: Apatinib combined with paclitaxel is superior to apatinib alone for patients with advanced ovarian cancer in efficacy, because it can significantly improve serum CA125 and CA199, and survival rates and progression-free survival for patients. In addition, pathological stage, underlying disease and treatment method are independent risk factors for the prognosis of patients with ovarian cancer.

Keywords: Apatinib, paclitaxel, advanced ovarian cancer, clinical efficacy, prognosis

Introduction

Ovarian cancer, a common female reproductive system malignant tumor, shows increasing incidence and higher mortality with changes in social, environmental and living habits in recent years, causing a serious threat to the health of a large number of females [1, 2]. Ovarian cancer occurs without obvious symptom in the early stages, so most patients are already in advanced stage when diagnosed [3]. Patients with ovarian cancer are usually treated through surgical treatment, but because their cancer cells spread very quickly, it is usually necessary to additionally adopt chemotherapy [4]. In addition, ovarian cancer cells can easily develop resistance to chemotherapeutic drugs, which leads to relatively low remission rates for patients with ovarian cancer after first-line and second-line chemotherapy [5]. Therefore, it is of great clinical significance to seek out good treatment regimens for patients with advanced ovarian cancer and improving their prognosis.

With the development of molecular targeting technology, molecular targeted therapy has received more and more attention in the treat-

ment of cancer [6]. Angiogenesis plays a key role in tumor growth and metastasis, so anti-angiogenesis is one of the important directions of targeted therapy, which mainly inhibits tumor growth and metastasis by inhibiting tumor angiogenesis [7, 8]. Apatinib is an inhibitor for vascular endothelial growth factor, which can block downstream signaling by specific action on vascular endothelial growth factor receptor-2 (VEGFR-2) and ultimately inhibit tumor angiogenesis [9]. As a peroral small molecule antiangiogenic agent, apatinib performs well in advanced stage breast cancer and gastric cancer [10, 11].

Other studies pointed out that chemotherapy combined with apatinib has stronger anti-tumor effect, but there are relatively few studies on the efficacy of it in patients with advanced ovarian cancer [12]. Therefore, this study investigated the efficacy of chemotherapy combined with apatinib in patients with advanced ovarian cancer and its influence on the prognosis of patients.

Materials and methods

General materials

A total of 90 patients with advanced ovarian cancer having undergone failed second-line chemotherapy who were admitted in our hospital from July 2014 to March 2016 were selected, and those patients ((47.39±4.87) years old in mean age) consisted of 48 patients in stage III and 42 patients in stage IV in terms of pathological stage. They were divided into a research group (N = 45) and a control group (N = 45). The control group was treated with apatinib alone, while the research group was treated with apatinib combined with paclitaxel.

Inclusion criteria and exclusion criteria

Inclusion criteria: Patients with ovarian cancer in stage III or stage IV confirmed based on pathological diagnosis [13] and patients having undergone failed first-line and second-line chemotherapy. Exclusion criteria: Patients having undergone molecular targeted therapy within 3 months before the experiment; patients with severe hepatic renal dysfunction or cardiocerebrovascular disease or other combined malignant tumors; patients with communication obstacles or cognitive impairment and patients unwilling to cooperate with the experiment. All patients and their families agreed to participate in the experiment and signed an informed consent form.

Treatment regimen

The control group was treated with apatinib (Jiangsu Hengrui Pharmaceutical Co., Ltd., H20140103) orally taken at an dose of 500 g/d, while the research group was treated with apatinib combined with paclitaxel where the apatinib was orally taken at an dose of 500 g/d and paclitaxel (Hanan Chuntch Pharmaceutical Co., Ltd., H20057065) was infused at 135-175 mg/m^2 based on intravenous drip (3 hours in each infusion, once every 2 weeks) for a total of 6 treatment cycles (3 weeks for 1 treatment cycle).

Observation indexes

The two groups were assessed in efficacy at the end of treatment based on RECIST1.1 [14]. The evaluation standard RECIST1.1 covers the following aspects: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD); objective remission rate (ORR) = (CR+PR)/the total of cases ×100%, disease control rate (DCR) = (CR+PR+SD)/the total of cases ×100%. (2) The two groups were recorded and compared in incidence of adverse reactions, including nausea and vomiting, leukopenia, diarrhea, alopecia and hypertension. (3) The two groups were measured in their serum CA125 (Shanghai Tellgen Life Science Co., Ltd., G.X.Z.Z.:20153401813) and CA199 (Shanghai Tellgen Life Science Co., Ltd., G.X.Z.Z.:20153401810) before and after treatment based on the electrochemiluminescence detection principle [15]. The electrochemiluminescence includes a test tube reaction and a machine test. The test tube reaction is performed by addition of [Ru(bpy)3]2+-labeled antibody, biotinylated antibody, and a sample in a test tube. The reaction was carried out for 10 min at 37°C, and then SA magnetic particles were added. The reaction was carried out for 10 min at 37°C, and then placed in a machine for inspection. (4) A 36-month follow-up was performed on patients to record and compare them in progression-free survival and 3-year survival rates. Progression-free survival refers to the period from definite diagnosis time to the time when the disease is confirmed with

Table 1. General information (n (%))

Factors	The research group n = 45	The control group n = 45	t/X^2	*P*
Age (Y)			0.044	0.833
≤47	23 (51.11)	24 (53.33)		
>47	22 (48.89)	21 (46.67)		
BMI (kg/m^2)			0.179	0.673
≤21	20 (55.14)	22 (52.46)		
>21	25 (44.86)	23 (47.54)		
Marital status			0.104	0.748
Married	39 (83.18)	40 (85.25)		
Unmarried	6 (16.82)	5 (14.75)		
Reproductive history			0.073	0.787
With child	36 (75.70)	37 (78.69)		
Without child	9 (24.30)	8 (21.31)		
Pathological type			0.182	0.980
Mucinous carcinoma	10 (22.22)	11 (24.44)		
Endometrioid carcinoma	11 (24.44)	12 (26.67)		
Clear cell carcinoma	12 (26.67)	11 (24.44)		
Serous carcinoma	11 (24.44)	10 (22.22)		
Pathological stage			0.179	0.673
Stage III	25 (44.86)	23 (47.54)		
Stage IV	20 (55.14)	22 (52.46)		
Underlying diseases				
Diabetes	15 (33.33)	16 (35.56)	0.049	0.824
Hypertension	12 (26.67)	11 (24.44)	0.058	0.809

Table 2. Comparison between the two groups in efficacy

Efficacy	The research group (n = 45)	The control group (n = 45)	X^2	P
CR	0	0	-	-
PR	21 (46.67)	13 (28.89)	3.025	0.082
SD	17 (37.78)	12 (26.67)	1.272	0.260
PD	7 (15.56)	20 (44.44)	8.942	0.003
ORR	21 (46.67)	13 (28.89)	3.025	0.082
DCR	38 (84.44)	25 (55.56)	8.942	0.003

CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, ORR: Overall response rate, DCR: Disease control rate.

no progress based on examination, clinical follow-up about serum CA125 and imaging examination meantime. (5) Multivariate analysis was performed on factors affecting the prognosis of patients with advanced ovarian cancer.

Statistical methods

In the study, SPSS 20.0 software (Bizinsight (Beijing) Information Technology Co., Ltd.) was adopted for statistical analysis of experiment data; Count data were analyzed by chi-square test, and measurement data were expressed in mean ± standard deviation. Comparison between the two groups was tested by t test. The figure images were drawn using GraphPad Prism 6 software and analyzed in survival through Kaplan-Meier test. Cox multivariate regression analysis was adopted to analyze survival factors. $P < 0.05$ indicates statistical differences.

Results

No significant differences in baseline data of the two groups

There was no significant difference in age, body mass index (BMI) and pathological stage between the two groups (all $P>0.05$), which were comparable (**Table 1**).

Apatinib combined with paclitaxel showed more effective results

After treatment, the research group showed an ORR of 46.67% and DCR of 84.44%, with 0 patients, 21 patients, 17 patients and 7 patients in CR, SR, SD and PD, respectively; while the control group showed an ORR of 28.89% and DCR of 55.56%, with 0 patients, 13 patients, 12 patients and 20 patients in CR, SR, SD and PD, respectively; so the research group showed significantly higher ORR and DCR than the control group (both $P < 0.05$) (**Table 2**).

Apatinib combined with paclitaxel exhibited less adverse reactions

The research group showed an incidence of adverse reactions of 26.67%, with nausea and vomiting, leukopenia, diarrhea and alopecia in 3 patients, 2 patients, 3 patients and 4 patients, respectively; and the control group

Table 3. Comparison between the two groups in adverse reactions

Efficacy	The research group (n = 45)	The control group (n = 45)	X^2	P
Nausea and vomiting	3 (6.67)	4 (8.89)	0.155	0.694
Leukopenia	2 (4.44)	3 (6.67)	0.212	0.645
Diarrhea	3 (6.67)	4 (8.89)	0.155	0.694
Alopecia	4 (8.89)	3 (6.67)	0.155	0.694
Incidence of adverse reactions	12 (26.67)	14 (31.11)	0.216	0.612

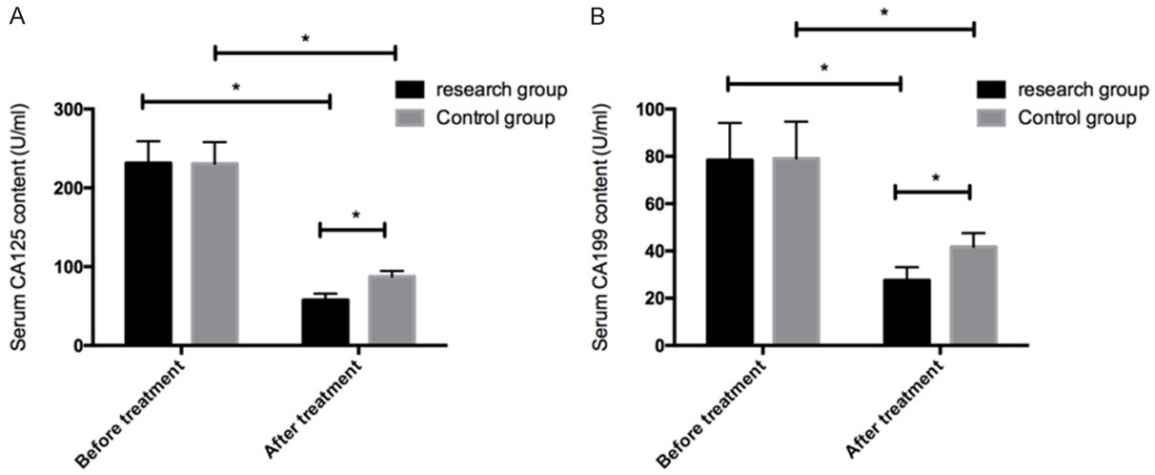

Figure 1. Serum CA125 and CA199 levels in the two groups before and after treatment. Note: * indicates P < 0.05.

showed an incidence of adverse reactions of 31.11%, with nausea and vomiting, leukopenia, diarrhea and alopecia in 4 patients, 3 patients, 4 patients and 4 patients, respectively; so the two groups have no significant difference in incidence of adverse reactions (P> 0.05). More details are shown in **Table 3**. All adverse reactions were relieved after termination of treatment.

Apatinib combined with paclitaxel significantly reduced CA125 and CA199 levels

The serum CA125 level of the research group before and after treatment was (231.45± 27.57) U/ml and (57.66±8.29) U/ml, respectively; and serum CA199 level of the research group before and after treatment was (231.45± 27.57) U/ml and (27.57±5.59) U/ml, respectively. The serum CA125 level of the control group before and after treatment was (78.35± 15.75) U/ml and (87.25±7.33) U/ml, respectively; and serum CA199 level of the control group before and after treatment was (79.03±15.69) U/ml and (41.71±5.83) U/ml, respectively. So the two groups showed no significant difference in serum CA125 and CA199 levels before treatment (both P>0.05), but showed significantly decreased serum CA125 and CA199 levels after treatment (both P < 0.05), and the research group showed significantly lower serum CA125 and CA199 levels than the control group (both P < 0.05) (**Figure 1**).

Apatinib combined with paclitaxel showed higher progression-free survival and 3-year survival rates

The research group showed a progression-free survival rate of 33.33% with 30 patients having disease progression and a 3-year survival rate of 53.33% with 21 patients dead within 3 years; and the control group showed a progression-free survival rate of 4.44% with 43 patients having disease progression and a 3-year survival rate of 35.56% with 29 patients dead within 3 years. So the research group showed significantly higher progression-free survival rates and 3-year survival rates than the control group (both P < 0.05) (**Table 4** and **Figure 2**).

Univariate analysis for the prognosis of patients with advanced ovarian cancer

The patients were divided into a survival group (40 patients) and a death group (50 patients)

Table 4. Comparison between the two groups in progression-free survival and 3-year survival rate

Item	The research group (n = 45)	The control group (n = 45)	t/X^2	P
Progression-free survival rate	15 (33.33)	2 (4.44)	12.26	< 0.001
3-year survival rate	24 (53.33)	16 (35.56)	23.98	< 0.001

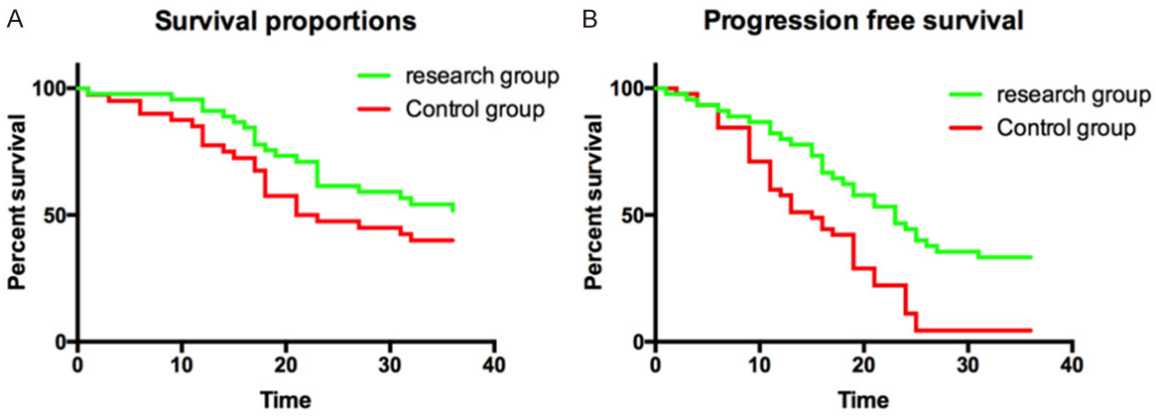

Figure 2. Comparison between the two groups in progression-free survival and 3-year survival rate.

Table 5. Univariate analysis for the prognosis of patients with advanced ovarian cancer

Clinicopathological parameters	n	The survival group n = 40	The death group n = 50	X^2	P
Age (Y)				0.002	0.962
≤47	47	21 (52.50)	26 (52.00)		
>47	43	19 (47.50)	24 (48.00)		
Pathological type				0.683	0.896
Mucinous carcinoma	21	10 (25.00)	11 (27.50)		
Endometrioid carcinoma	23	11 (27.50	12 (24.00		
Clear cell carcinoma	23	11 (27.50)	12 (24.00)		
Serous carcinoma	21	8 (20.00)	13 (26.00)		
Pathological stage				10.63	0.001
Stage III	48	29 (72.50)	19 (38.00)		
Stage IV	42	11 (27.50)	31 (62.00)		
Treatment method				8.820	0.003
Apatinib alone	45	13 (32.50)	32 (64.00)		
Chemotherapy combined with apatinib	45	27 (67.50)	18 (36.00)		
Diabetes	31	9 (25.00)	22 (42.00)	3.905	0.048
Hypertension	23	6 (15.00)	17 (34.00)	4.217	0.040
Reproductive history				0.058	0.809
With child	73	32 (80.00)	41 (82.00)		
Without child	17	8 (20.00)	9 (18.00)		

based if the patient died or not. Univariate analysis found that the prognosis of patients with advanced ovarian cancer was not significantly related to age, pathological type and reproductive history (all P>0.05), but was related to pathological stage, treatment method and combined underlying diseases (all P < 0.05) (**Table 5**).

Multivariate analysis for the prognosis of patients with advanced ovarian cancer

Indexes with differences in univariate analysis were done with valuation (**Table 6**), and independent risk factors about patients' prognosis were analyzed using multivariate cox analysis, indicating that pathological stage (RR: 6.097,

Table 6. Valuation

Item	Valuation
Pathological stage	Stage III = 1, stage IV = 2
Treatment method	Chemotherapy combined with apatinib = 1, apatinib along = 0
Hypertension	Yes = 1, No = 0
Diabetes	Yes = 1, No = 0

Table 7. Multivariate analysis

Factor	B	S.E	Wald	RR	95% CI	P
Pathological stage	1.769	0.243	49.671	6.097	3.693-648.264	< 0.01
Hypertension	0.829	0.213	12.763	2.310	1.414-3.769	< 0.01
Diabetes	0.665	0.185	10.375	1.979	1.279-2.881	< 0.01
Treatment method	0.357	0.241	2.315	1.432	1.729-6.127	< 0.01

95% CI: 3.693-648.264), combined with diabetes (RR: 1.979, 95% CI: 1.279-2.881), combined with hypertension (RR: 2.310, 95% CI: 1.279-2.881) and treatment method (RR: 1.432, 95% CI: 1.729-6.127) and were all independent risk factors for poor prognosis in patients with advanced ovarian cancer (**Table 7**).

Discussion

Ovarian cancer, a common female reproductive system malignant tumor, ranks at the top in incidence and mortality among gynecologic malignant tumors [16]. At present, ovarian cancer is mostly treated with traditional laparotomy or comprehensive treatment regimen such as radiotherapy and chemotherapy, but patients with advanced ovarian cancer usually have missed the surgery opportunity and also cannot obtain good radiotherapy and chemotherapy efficacy, so it is very important to seek for an effective treatment regimen for patients with advanced ovarian cancer [17, 18].

In our experiment, apatinib alone and apatinib combined with paclitaxel (a chemotherapeutic drug) were adopted to treat patients and compare the efficacy and prognosis of patients. As a small molecule targeted anti-tumor drug, apatinib has clear anti-tumor effects in malignant tumors such as gastric cancer, lung cancer and thyroid cancer. The treatment regimen includes apatinib alone and chemotherapy combined with apatinib [19, 20]. In this study, paclitaxel was selected as a chemotherapeutic drug for combined use due to its role in the initial treatment of advanced reproductive tumors [21]. It turned out that the research group showed significantly higher effective rates than the control group, which indicates that apatinib combined with paclitaxel has higher efficacy than apatinib alone. In addition, the comparison between the two groups in adverse reactions showed that apatinib combined with paclitaxel did not increase the incidence of adverse reactions, which indicates that apatinib combined with paclitaxel has relatively high safety. A previous study also reported that chemotherapy combined with apatinib has good efficacy on patients with ovarian cancer who have undergone failed second-line treatment, which is consistent with our conclusions [22].

CA125, a recognized tumor marker for ovarian cancer, is the peptide epitope in the tandem repeat domain of the high molecular weight transmembrane glycoprotein MUC16, which can not only promote proliferation of tumor cells, but also inhibit anti-tumor immune responses [23, 24]. CA199 was adopted in the diagnosis of gastrointestinal tumors initially, but it was found to be highly expressed in ovarian cancer and closely related to the occurrence and development of ovarian cancer in some follow-up studies [25].

The two groups were measured and compared in serum CA125 and CA199, and it turned out that the two groups showed significantly improved serum CA125 and CA199, but the research group showed an improvement more significant than the control group, which indicates that combined treatment can improve patient's condition through effectively improving serum CA125 and CA199 levels. A previous study found that serum CA125 can be monitored and detected to predict efficacy in patients with ovarian cancer, which is the reason for CA125 detection in this study [26]. In follow-up studies, we will further explore the clinical significance of CA125 and CA199 in patients with ovarian cancer.

In addition, the prognosis of the two groups and factors with influence on prognosis were analyzed, finding that the research group showed significantly higher progression-free survival rates and 3-year survival rates than the control group. A study has found that pazopanib combined with paclitaxel can effectively prolong the survival of patients with advanced ovarian cancer [27]. Pazopanib is a molecular targeted agent with function similar to apatinib, so it also verifies our conclusions. Finally, in order further analyze the prognosis of patients, prognostic factors of patients were analyzed. Univariate analysis showed that pathological stage, underlying disease and treatment method had an impact on the prognosis of patients, and multivariate analysis showed that pathological stage, combined diabetes, combined hypertension and treatment method were all independent risk factors of poor prognosis of patients with advanced ovarian cancer, which is of great clinical significance in other factors to control besides treatment for patients with ovarian cancer. Previous data showed that patients with ovarian cancer in stage III had significantly different 3-year survival rates than the patients with ovarian cancer in stage IV, which suggests that clinical pathological stage is an important factor affecting the prognosis of patients with advanced ovarian cancer [28]. However, there are also studies indicating that patients in stage III with large metastases and patients in stage IV with less extensive metastases showed no significant difference in prognosis, which needs more study [29]. What's more, there were also studies indicating that patients with ovarian cancer and underlying diseases such as cardio-cerebrovascular disease showed poorer prognosis than those without underlying diseases [30]. There were studies about the prognosis analysis of ovarian cancer clearly indicating that timely and standardized treatment for patients with ovarian cancer was one of the important factors affecting the prognosis of patients [31], which confirmed our conclusions.

In summary, apatinib combined with paclitaxel is superior to apatinib monotherapy in patients with advanced ovarian cancer, which can significantly improve serum CA125 and CA199 levels, treatment efficacy, prolong survival and progression-free survival periods. Pathological staging, underlying disease, and treatment are independent risk factors for prognosis in patients with ovarian cancer.

However, there are certain deficiencies in this study. For example, apatinib combined with paclitaxel was not compared with other treatment regimens, which makes our conclusions still arguable. We will improve it in future experiments.

Disclosure of conflict of interest

None.

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References

[1] Reid BM, Permuth JB and Sellers TA. Epidemiology of ovarian cancer: a review. Cancer Biol Med 2017; 14: 9-32.

[2] Coburn SB, Bray F, Sherman ME and Trabert B. International patterns and trends in ovarian cancer incidence, overall and by histologic subtype. Int J Cancer 2017; 140: 2451-2460.

[3] Li J, Condello S, Thomes-Pepin J, Ma X, Xia Y, Hurley TD, Matei D and Cheng JX. Lipid desaturation is a metabolic marker and therapeutic target of ovarian cancer stem cells. Cell Stem Cell 2017; 20: 303-314.

[4] Torrey H, Butterworth J, Mera T, Okubo Y, Wang L, Baum D, Defusco A, Plager S, Warden S, Huang D, Vanamee E, Foster R and Faustman DL. Targeting TNFR2 with antagonistic antibodies inhibits proliferation of ovarian cancer cells and tumor-associated Tregs. Sci Signal 2017; 10.

[5] Coleman RL, Brady MF, Herzog TJ, Sabbatini P, Armstrong DK, Walker JL, Kim BG, Fujiwara K, Tewari KS, O'Malley DM, Davidson SA, Rubin SC, DiSilvestro P, Basen-Engquist K, Huang H, Chan JK, Spirtos NM, Ashfaq R and Mannel RS. Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2017; 18: 779-791.

[6] Zhang L, Shi M, Huang C, Liu X, Lt, Xiong JP, Chen G, Liu W, Liu W, Zhang Y and Li K. A phase II, multicenter, placebo-controlled trial of apatinib in patients with advanced nonsquamous non-small cell lung cancer (NSCLC) after two previous treatment regimens. Asco. Org 2012; 30.

[7] Kou P, Zhang Y, Shao W, Zhu H, Zhang J, Wang H, Kong L and Yu J. Significant efficacy and well

safety of apatinib in an advanced liver cancer patient: a case report and literature review. Oncotarget 2017; 8: 20510-20515.
[8] Song Z, Yu X, Lou G, Shi X and Zhang Y. Salvage treatment with apatinib for advanced non-small-cell lung cancer. Onco Targets Ther 2017; 10: 1821-1825.
[9] Hu X, Cao J, Hu W, Wu C, Pan Y, Cai L, Tong Z, Wang S, Li J, Wang Z, Wang B, Chen X and Yu H. Multicenter phase II study of apatinib in non-triple-negative metastatic breast cancer. BMC Cancer 2014; 14: 820.
[10] Lin Y, Wu Z, Zhang J, Hu X, Wang Z, Wang B, Cao J and Wang L. Apatinib for metastatic breast cancer in non-clinical trial setting: satisfying efficacy regardless of previous anti-angiogenic treatment. Tumour Biol 2017; 39: 1010428317711033.
[11] Wu D, Liang L, Nie L, Nie J, Dai L, Hu W, Zhang J, Chen X, Han J, Ma X, Tian G, Han S, Long J, Wang Y, Zhang Z, Xin T and Fang J. Efficacy, safety and predictive indicators of apatinib after multilines treatment in advanced nonsquamous nonsmall cell lung cancer: apatinib treatment in nonsquamous NSCLC. Asia Pac J Clin Oncol 2018; 14: 446-452.
[12] Li J, Qin S, Xu J, Xiong J, Wu C, Bai Y, Liu W, Tong J, Liu Y, Xu R, Wang Z, Wang Q, Ouyang X, Yang Y, Ba Y, Liang J, Lin X, Luo D, Zheng R, Wang X, Sun G, Wang L, Zheng L, Guo H, Wu J, Xu N, Yang J, Zhang H, Cheng Y, Wang N, Chen L, Fan Z, Sun P and Yu H. Randomized, double-blind, placebo-controlled phase III Trial of apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. J Clin Oncol 2016; 34: 1448-1454.
[13] Berliner JL, Fay AM, Cummings SA, Burnett B and Tillmanns T. NSGC practice guideline: risk assessment and genetic counseling for hereditary breast and ovarian cancer. J Genet Couns 2013; 22: 155-163.
[14] Baratto L, Davidzon GA, Moghbel M, Hatami N, Iagaru A and Mittra ES. Comparison between different PET and CT-based imaging interpretation criteria at interim imaging in patients with diffuse large B-cell lymphoma. Clin Nucl Med 2017; 43: 1-8.
[15] Michel PE, Rooij NFD, Koudelka-Hep M, Fähnrich KA, O'Sullivan CK and Guilbault GG. Redox-cycling type electrochemiluminescence in aqueous medium. A new principle for the detection of proteins labeled with a ruthenium chelate. J Electroanal Chem 1999; 474: 192-194.
[16] Nakamura K, Peng Y, Utsumi F, Tanaka H, Mizuno M, Toyokuni S, Hori M, Kikkawa F and Kajiyama H. Novel intraperitoneal treatment with non-thermal plasma-activated medium inhibits metastatic potential of ovarian cancer cells. Sci Rep 2017; 7: 6085.
[17] Zhu X, Ji M, Han Y, Guo Y, Zhu W, Gao F, Yang X and Zhang C. PGRMC1-dependent autophagy by hyperoside induces apoptosis and sensitizes ovarian cancer cells to cisplatin treatment. Int J Oncol 2017; 50: 835.
[18] Heinzelmann-Schwarz V, Knipprath Mészaros A, Stadlmann S, Jacob F, Schoetzau A, Russell K, Friedlander M, Singer G and Vetter M. Letrozole may be a valuable maintenance treatment in high-grade serous ovarian cancer patients. Gynecol Oncol 2018; 148: 79-85.
[19] Kong Y, Lin S, Hou Z, Zhang Y, Ping C, Cui Y, Zhu X, Song T, Qiang L and Li H. Apatinib is effective for treatment of advanced hepatocellular carcinoma. Oncotarget 2017; 8: 105596-105605.
[20] Xu J, Liu X, Yang S, Zhang X and Shi Y. Apatinib plus icotinib in treating advanced non-small cell lung cancer after icotinib treatment failure: a retrospective study. Onco Targets Ther 2017; 10: 4989-4995.
[21] Koh WJ, Greer BE, Abu-Rustum NR, Apte SM, Campos SM, Chan J, Cho KR, Cohn D, Crispens MA, Dupont N, Eifel PJ, Fader AN, Fisher CM, Gaffney DK, George S, Han E, Huh WK, Lurain JR 3rd, Martin L, Mutch D, Remmenga SW, Reynolds RK, Small W Jr, Teng N, Tillmanns T, Valea FA, McMillian N and Hughes M. Uterine neoplasms, version 1.2014. J Natl Compr Canc Netw 2014; 12: 248-280.
[22] Deng L, Wang Y, Lu W, Liu Q, Wu J and Jin J. Apatinib treatment combined with chemotherapy for advanced epithelial ovarian cancer: a case report. Onco Targets Ther 2017; 10: 1521-1525.
[23] Babic A, Cramer DW, Kelemen LE, Köbel M, Steed H, Webb PM, Johnatty SE, deFazio A, Lambrechts D, Goodman MT, Heitz F, Matsuo K, Hosono S, Karlan BY, Jensen A, Kjær SK, Goode EL, Pejovic T, Moffitt M, Høgdall E, Høgdall C, McNeish I and Terry KL. Predictors of pretreatment CA125 at ovarian cancer diagnosis: a pooled analysis in the Ovarian Cancer Association Consortium. Cancer Causes Control 2017; 28: 459-468.
[24] Hellstrom I and Hellstrom KE. Two new biomarkers, mesothelin and HE4, for diagnosis of ovarian carcinoma. Expert Opin Med Diagn 2011; 5: 227-240.
[25] Guo J, Yu J, Song X and Mi H. Serum CA125, CA199 and CEA combined detection for epithelial ovarian cancer diagnosis: a meta-analysis. Open Med (Wars) 2017; 12: 131-137.
[26] Zwakman N, Van dLR, Van GT, Zusterzeel PL, Snijders MP, Ferreira I, Massuger LF and Kruitwagen RF. Perioperative changes in serum CA125 levels: a prognostic factor for disease-specific survival in patients with ovarian cancer. J Gynecol Oncol 2017; 28: e7.

[27] Richardson DL, Sill MW, Coleman RL, Sood AK, Pearl ML, Kehoe SM, Carney ME, Hanjani P, Van LL and Zhou XC. Paclitaxel with and without pazopanib for persistent or recurrent ovarian cancer: a randomized clinical trial. JAMA Oncol 2017; 4: 196-202.

[28] Ojamaa K, Veerus P, Baburin A, Everaus H and Innos K. Time trends in ovarian cancer survival in estonia by age and stage. Int J Gynecol Cancer 2016; 27: 44-49.

[29] van Meurs HS, Tajik P, Hof MH, Vergote I, Kenter GG, Mol BW, Buist MR and Bossuyt PM. Which patients benefit most from primary surgery or neoadjuvant chemotherapy in stage IIIC or IV ovarian cancer? An exploratory analysis of the European Organisation for Research and Treatment of Cancer 55971 randomised trial. Eur J Cancer 2013; 49: 3191-3201.

[30] Wei W, Li N, Sun Y, Li B, Xu L and Wu L. Clinical outcome and prognostic factors of patients with early-stage epithelial ovarian cancer. Oncotarget 2017; 8: 23862-23870.

[31] Suidan RS, Zhou Q, Iasonos A, O'Cearbhaill RE, Chi DS, Long Roche KC, Tanner EJ, Denesopolis J, Barakat RR and Zivanovic O. Prognostic significance of the number of postoperative intraperitoneal chemotherapy cycles for patients with advanced epithelial ovarian cancer. Int J Gynecol Cancer 2015; 25: 599-606.