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Gemcitabine and vinorelbine: treatment option in recurrent platinum - resistant ovarian cancer

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Summary. *Background and aim of the work:* to evaluate the efficacy and toxicity of vinorelbine plus gemcitabine combination in patients who had recurrent platinum resistant ovarian cancer. *Patients and method:* twenty one patients with recurrent platinum resistant ovarian cancer were designated to receive vinorelbine 25 mg/m^2 plus gemcitabine 1 gm/m^2 on 1st and 8th day of each 21 – day cycle. *Results:* The Median age was 56 years (range 38-67). One patient (4.8%) achieved complete response and 5 patients (23.8%) had partial response with an overall response rate 28.57%. Median time to progression was 4 months and median overall survival was 11 months. Toxicity was modest and generally tolerated. Nine events (42.85%) of grade 3 hematological toxicity and only one event (4.57%) grade 3 non hematologic toxicity were observed. *Conclusion:* The combination of gemcitabine and vinorelbine is a moderately active regimen in recurrent platinum resistant ovarian cancer with an acceptable toxicity rating it as an option in treatment of such disease.

Key words: gemcitabine, vinorelbine, platinum resistant, recurrent ovarian cancer

Ovarian cancer (OC) is the fifth most frequently diagnosed malignant solid tumor in females and the leading cause of death among genital malignancies. Epithelial carcinoma constitutes about 85% to 90% of malignant ovarian tumors (1, 2).

In spite of recent evolution in cancer diagnosis, OC is commonly diagnosed in advanced stages and generally carries a dismal prognosis. Nevertheless, significant improvement in 5- year survival rates was reported in such patients treated with aggressive surgical cytoreduction and platinum- paclitaxel chemotherapy (3-5).

Although complete clinical response to first-line chemotherapy was achieved in 40%-60% of patients, relapse had been demonstrated in about 50% of these patients within 5 years (6, 7) and long-term remission was obtained in only 10%-15% of patients presenting with advanced stage OC (8). This high relapse rate is thought to be in part due to inherent or acquired resistance to chemotherapy (9-11).

Many factors were assumed to influence treatment strategies for recurrent OC including efficacy and toxicity of previous therapy, availability of drugs, financial support, patient compliance, and platinum sensitivity status being the most reliable factor commanding the treatment type (12, 13).

The length of disease free interval after platinum identified several categories of platinum sensitivity with different survival prognosis: platinum refractory defined as patients experiencing disease progression during or within one month after the end of therapy; platinum resistant disease as progression occurred through 6 months of therapy; and platinum sensitive as disease progression more than 6 months after the last platinum dose (14-16).

Currently, numerous platinum based chemotherapeutic regimens are available for treatment of recurrent platinum sensitive OC patients, and a greater chemotherapy regimens are also utilized as salvage treatment for recurrent platinum resistant OC patients, however

non of these regimens had been emerged as the standard therapy in this phase of the disease (17).

Gemcitabine is an active chemotherapeutic agent in treatment of OC. It has a convenient toxicity profile which suggest possible combinations with other active treatment (18-24). Vinorelbine is another active non platinum agent used in recurrent OC. Studies utilizing these agents reported response rates of 10%-30% in platinum resistant recurrent disease, and 30%-65% in platinum sensitive disease (25-29).

Giving the tolerability and convenience of administration of gemcitabine and vinorelbine and the only modest activity of each drug as a monotherapy in platinum resistant OC (25, 26), a combination of both drugs was tested to improve the dismal outcome of such disease (30-32).

This study was conducted to evaluate the efficacy and toxicity of vinorelbine plus gemcitabine combination in patients who had recurrent platinum resistant OC.

Patients and methods

This study was conducted in the Department of Clinical Oncology and Nuclear Medicine, Mansoura University Hospital, Egypt, on 21 patients.

Inclusion criteria

Patients had to have histologically proven epithelial OC recurred or progressed during or through 6 months of last injection of platinum based regimen. A maximum of 2 prior chemotherapy recurrence regimens were allowed. Other criteria include: age above 18 years, performance status ≤2 according to Eastern Cooperative Oncology Group (ECOG) status, adequate hematological, hepatic, and renal functions, and patient's informed consent.

Exclusion criteria

Previous or concurrent malignancies, underlying serious medical co-morbidities or uncontrolled infection, and patients received more than 2 different chemotherapy regimens for disease recurrence.

Treatment plan

Study patients were designated to receive vinorelbine 25 mg/m^2 over 10 minutes iv infusion followed by iv infusion of gemcitabine 1 gm/m^2 over 30 minutes. Both drugs were given on 1st and 8th day of each 21 – day cycle.

Treatment was planned for 2 cycles at least and response was assessed every 2 cycles. Patients expressed objective response (complete response, partial response or stable disease) proceeded on the treatment regimen for a minimum of 2 cycles after maximal tumor response, disease progression, unacceptable toxicity, or patient refusal.

Toxic effects were graded based on the National Cancer Institute Common Toxicity Criteria and chemotherapy was prohibited if any of these toxicities were detected: ≥grade 3 non hematologic toxicities, grad 3 neutropenia with fever ≥38.5° and/or infection, grade 3 thrombocytopenia with bleeding, grade 4 neutropenia, and grade 4 thrombocytopenia. Chemotherapy was delayed till toxic effects resolved to grade 1 or less. Dose reduction was not permissible. The use of erythropoietine and granulocyte colony stimulating factor (GCSF) was allowed as appropriate.

Patient assessment

Pretreatment assessment

Full history, clinical examination, complete blood count (CBC), biochemistry profile including CA125. The size and extent of the disease were documented by CT and/or MRI of chest, abdomen, and pelvis.

Assessment of response and toxicity

Before each treatment cycle, each patient underwent complete physical examination, CBC and biochemical profile. Response to treatment had to be assessed every 2 cycles by the same imaging technique used at base line and by examining CA 125 level however, progression could not be considered by CA 125 elevation alone.

Toxicity of treatment was graded on the basis of National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0

Survival

Time to disease progression (TTP) was considered as the time between 1st treatment infusion and the 1st detection of tumor progression. Overall survival (OS) was considered as the time period between the 1st day of treatment and date of last follow up or death.

Statistical analysis

Analysis of data was accomplished by SPSS program version 20. Demographic data was expressed by descriptive statistics. Analysis of TTP and OS was done using Kaplan-Meir method

Results

Patients characteristics

Between December 2009 and July 2015, 25 patients with platinum resistant recurrent OC were enrolled in this study. Four patients were excluded after initial inclusion: two patients lost to follow up after 1st injection, one patient had uncontrolled fever, and the last one developed elevated liver enzymes requiring dose reduction and exclusion from the study.

Base line characteristics of 21 evaluable patients were listed in table 1. Median age was 56 years. The serous cell type was the most common histological subtype (52%) with grade 2 differentiation in 57% of tumors. The majority of recurrences were abdominal and 7 patients had ≥3 sites of recurrence.

All patients were previously treated with paclitaxel and carboplatin regimen in the post operative adjuvant setting and 3 patients received it as neoadjuvant therapy.

Treatment administration

Three patients had 1ry platinum resistant tumors, only one of them received gemcitabine - vinorelbine after 1st tumor recurrence. Nine patients received gemcitabine - vinorelbine regimen on 2nd recurrence, 7 patients received it after their 3rd tumor recurrence, and 4 on 4th recurrence. Previous chemotherapy of study patients was listed in table 2.

Table 1. Baseline patients characteristics

Characteristics	N (%)
Age	
Median: 56	
Range: 38-67	
ECOG performance status	
0	5 (23.8)
1	13 (61.9)
2	3 (14.3)
Initial FIGO stage	
II	9 (42.85)
III	9 (42.85)
IV	3 (14.3)
Tumor histology	
Serous	11 (52.38)
Endometroid	5 (23.8)
Mucinous	3 (14.3)
Undifferantiated	2 (9.52)
Tumor grade	
Grade 1	1 (4.76)
Grade 2	12 (57.14)
Grade 3	8 (38.1)
Resistance to platinum	
1ry resistance	3 (14.3)
2ry resistance	16 (76.19)
2ry refractory	2 (9.52)
Site of recurrence	
Omental	5 (23.8)
Peritoneal	12 (57.14)
Lung	6 (28.57)
LN	6 (28.57)
Liver	4 (19.04)
Ascites	4 (19.04)
Pleural	2 (9.52)
Other	3 (14.3)
Involved sites	
One site	4 (19.04)
2 sites	9 (42.85)
≥3 sites	8 (38.09)

Gemcitabine - vinorelbine combination was given for a median of 6 cycles (range: 2-6). Treatment was delayed 1 week for 7 patients because of lack of hematological recovery. Hematological support was reported in 9 patients. No dose reduction was allowed.

Table 2. Details of chemotherapy

Chemotherapy	N (%)
Neoadjuvant chemotherapy	
Taxol/Carboplatin	3 (14.3)
Adjuvant chemotherapy	
Taxol/Carboplatin	21 (100)
1st recurrence chemotherapy	
Reinduction taxol/carboplarin	14 (65.75)
1st line	
Docetaxel/carboplatin	4 (19.04)
Docetaxel	2 (9.52)
Gemcitabin/Vinorelbin	1 (4.76)
2nd recurrence chemotherapy	
Reinduction taxol/carboplatin	4 (19.04)
1st line	
Docetaxel/Carboplatin	4 (19.04)
Docetaxel/Cisplatin	2 (9.52)
Docetaxel	2 (9.52)
Gemcitabin/Vinorelbin	2 (9.52)
2nd line	
Gemcitabin/Vinorelbin	4 (19.04)
Docetaxel	1 (4.76)
Paclitaxel	1 (4.76)
3rd recurrence chemotherapy	
1st line	
Docetaxel/Carboplatin	1 (4.76)
Docetaxel	3 (14.3)
2nd line	
Paclitaxel	4 (19.04)
Gemcitabin/Vinorelbin	4 (19.04)
3rd line	
Gemcitabin/Vinorelbin	2 (9.52)
4th recurrence chemotherapy	
2nd line	
Gemcitabin/Vinorelbin	4 (19.04)
3rd line	
Gemcitabin/Vinorelbin	4 (19.04)

Table 3. Response to treatment

Response	N (%)
Complete response	1 (4.76)
Partial response	5 (23.8)
Overall response	6 (28.57)
Stable disease	6 (28.57)
Progressive disease	9 (42.85)

Response

All 21 patients were evaluated for response (table 3). One patient achieved complete response (4.76%), 5 patients had partial response (23.8%), 6 patients (28.57%) had stable disease, and 9 patients (42.86%) had disease progression.

Survival

At time of final analysis, progressive disease had been reported in the entire patients, whereas 15 patients had died at different times over the study period.

Median TTP was 4 months (95% CI: 2.9-5.1 months) fig 1. Median OS was 11 months (95% CI: 6.5-15.5 months) fig 2.

Toxicity

Adverse events of treatment were listed in table 4. The study drugs were generally well tolerated with modest toxicity. Grade 3 neutropenia was observed in 5 patients (23.5%), 3 patients (14.4%) developed grade 3 anemia, and 1 patient had grade 3 thrombocytopenia. Except for 1 event of grade 3 diarrhea, mild to moderate (grade 1/2) non hematologic toxicities were reported including nausea and vomiting in 10 patients, constipation in 5 patients, phlebitis in 3 patients, fatigue in 8 patients, and peripheral neuropathy in 5 patients.

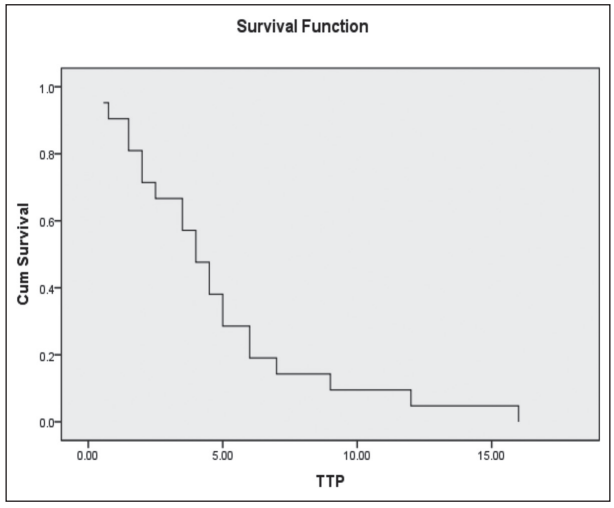

Figure 1. Time to progression of evaluable patients

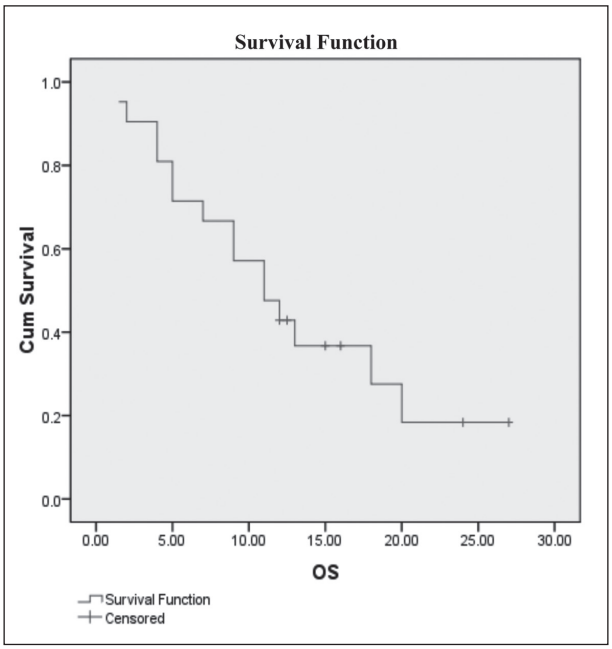

Figure 2. Overall survival of evaluable patients

Table 4. Toxicity of chemotherapy

Toxicity	G1/2 N (%)	G 3/4 N (%)
Hematological		
Anemia	12 (57.1)	3 (14.3)
Neutropenia	8 (38)	5 (23.8)
Thrombocytopenia	3 (14.3)	1 (4.76)
Non hematological		
Nausea	6 (28.6)	-
Vomiting	4 (19)	-
Diarrhea	1 (4.8)	1 (4.76)
Cramps	4 (19)	-
Constipation	5 (23.8)	-
Stomatitis	3 (14.3)	-
Phlebitis	3 (14)	-
Peripheral neuropathy	5 (23.8)	-
Fatigue	8 (38)	-

Discussion

Although OC is considered as one of the most chemo-sensitive tumors at initial diagnosis, tumor recurrence is expected in more than 80% of patients who had advanced disease with possible emergence of drug resistance. The principal chemotherapy regimens used for platinum sensitive recurrent OC are platinum based drugs. Conversely, in platinum resistant setting, several non platinum chemotherapy regimens are utilized. Gemcitabine and vinorelbine are non platinum chemotherapeutic agents with modest activity in OC.

In the present study, we evaluate both efficacy and safety of this doublet in treatment of recurrent platinum resistant OC patients.

Our study reported a response rate of 28.57% (one complete and 4 partial responses) and a disease control rate 52.38% . We also determined median TTP and median OS 4 months and 11 months respectively. These results were consistent with reports of different gemcitabine combination in recurrent platinum and taxane resistant ovarian cancer (31-34) and better than rates reported with either single gemctabine or single vinorelbine (24-26, 35). Chanpanitkitchot et al demonstrated lower response rate (5%) among platinum resistant patients who received gemcitabine alone or as combination therapy. They explained this by the poor inclusion criteria of their patients (36).

Data from clinical trials utilizing other combination chemotherapy in recurrent platinum resistant OC revealed similar moderate results. A combination of oral etoposide and intravenous irenotecan displayed an overall response rate 21.7%, TTP 4.1 months and OS 11.9 months (37). Mutch et al reported a non significant difference between gemcitabine and liposomal doxorubicin in response rates (6% vs 8% respectively), TTP (4 months vs 3 months respectively), and OS (13 months vs 14 months respectively) (12). The low response rates in this trial were due to the high proportion of platinum refractory patients.

Sehouli et al studied the advantage of adding either etoposide or gemcitabine to topotecan in treatment of recurrent ovarian cancer. They found no significant difference in response rates (36.3%, 36%, and 31.6%), TTP (7 months, 7.8 months, and 6.3 months) and OS (17.2 months, 17.8 months, 15.2 months) between treatment groups: topotecan monotherapy, topotecan plus etoposide, and topotecan plus gemcitabine (38). The high figures observed in this study were due to inclusion of patients with recurrent platinum sensitive disease.

Regarding the adverse events of gemcitabine – vinorelbine regimen used in this study, we illustrated a high tolerability and safety profile of this regimen, re-

flecting the acceptable and non overlapping toxicities of its individual drugs. We reported 9 events (43%) of hematological toxicities consistent with studies using gemcitabine combination (30, 32-34) and higher than the biweekly regimen used by Xenidis et al, because of its low dose threshold (31) and those reported with either drug (25, 26, 35, 39). Non hematologic toxicities were generally mild and rare which were also compatible with other reports (26, 30, 31, 34-36).

The outcome of traditional chemotherapeutic regimens in recurrent platinum resistant OC was still dismal. Response rates less than 30% had been reported. Novel strategies to overcome drug resistance and improve outcome have been emerged. The most currently studied in this phase are inhibitors of angiogenesis particularly bevacizumab. This is a humanized monoclonal antibody that attaches to vascular endothelial growth factor, inactivates it and thus blocks angiogenesis and inhibits tumor growth and metastases (40-42). Furthermore, the cytotoxic effect of chemotherapeutic agents is deemed to be enhanced by bevacizumab through normalizing tumor vascularity that improves oxygenation leading to better delivery and response to chemotherapy (43, 44).

Conclusion

The combination of gemcitabine and vinorelbine is a moderately active regimen in recurrent platinum resistant OC with an acceptable toxicity rating it as an option in treatment of such disease. However, further studies are needed for identification of ideal schedule and doses along with inclusion of potential active molecular targeted agents hoping to increase response rates, and improve both patients' survival and quality of life.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer Statistics. CA Cancer J Clin 2014; 64: 9-29.
2. Jayson G, Kohn E, Kitchener H, et al. Ovarian cancer. Lancet 2014; 384: 1376-1388.
3. Kim A, Ueda Y, Naka T, et al. Therapeutic strategies in epithelial ovarian cancer. J Exp Clin Cancer Res 2012; 31: 14.
4. Holschneider C, Berek J. Ovarian cancer: epidemiology, biology, and prognostic factors. Semin Surg Oncol 2000; 19: 3-10.
5. Ozols R. Management of advanced ovarian cancer consensus summary. Advanced Ovarian Cancer Consensus Faculty. Semin Oncol 2000; 27(Suppl 7): 47-49.
6. Li M, Yin J, Mao N, et al. Upregulation of phosphorylated cofilin 1 correlates with taxol resistance in human ovarian cancer in vitro and in vivo. Oncology Rep 2013; 29(1): 58-66.
7. Rubin S, Randall T, Armstrong K, et al. Ten-year follow-up of ovarian cancer patients after second-look laparotomy with negative findings. Obstet Gynecol 1999; 93(1): 21-24.
8. Armstrong D. Relapsed ovarian cancer: challenges and management strategies for a chronic disease. The Oncologist 2002; 7(Supplement 5): 20-28.
9. Di Nicolantonio F, Mercer S, Knight L, et al. Cancer cell adaptation to chemotherapy. BMC Cancer 2005; 5(1): 78.
10. Goff B. Advanced ovarian cancer: what should be the standard of care? J Gynecol Oncol 2013; 24(1): 83-91.
11. Winter W, Maxwell G, Tian C, et al.Prognostic factors for stage iii epithelial ovarian cancer: a gynecologic oncology group study. J Clin Oncol 2007; 25(24): 3621-3627.
12. Mutch D, Orlando M, Goss T, et al. Randomized Phase III Trial of Gemcitabine Compared With Pegylated Liposomal Doxorubicin in Patients With Platinum-Resistant Ovarian Cancer J Clin Oncol 2007; 25: 2811-2818.
13. Luvero D, Milani A, Ledermann J. Treatment options in recurrent ovarian cancer: latest evidence and clinical potential. Ther Adv Med Oncol 2014; 6(5): 229-239.
14. Colombo N, Gore M: Treatment of recurrent ovarian cancer relapsing 6-12 months post platinum based chemotherapy. Crit Rev Oncol Hematol 2007; 64: 129-138.
15. Friedlander M, Trimble E, Tinker A, et al. Clinical trials in recurrent ovarian cancer. Int J Gynecol Cancer 2011; 21: 771-775.
16. Stuart G, Kitchener H, Bacon M, et al. 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 2011; 21: 750-755.
17. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Ovarian cancer: including fallopian tube cancer and primary peritoneal cancer. Version 3; 2014.
18. Greggi S, Salerno MG, D'Agostino G, et al. Topotecan and gemcitabine in platinum/paclitaxel-resistant ovarian cancer. Oncology 2001; 60: 19-23.
19. D'Agostino G, Amant F, Berteloot P, et al. Phase II study of gemcitabine in recurrent platinum-and paclitaxel-resistant ovarian cancer. Gynecol Oncol 2003; 88: 266-269.
20. Garcia A, O'Meara A, Bahador A, et al. Phase II study of gemcitabine and weekly paclitaxel in recurrent platinum-resistant ovarian cancer. Gynecol Oncol 2004; 93: 493-498.
21. Ferrandina G, Paris I, Ludovisi M, et al. Gemcitabine and liposomal doxorubicin in the salvage treatment of ovarian

cancer: updated results and long-term survival. Gynecol Oncol 2005; 98: 267-273.
22. Bozas G, Bamias A, Koutsoukou V, et al. Biweekly gemcitabine and cisplatin in platinum-resistant/refractory, paclitaxel-pretreated, ovarian and peritoneal carcinoma. Gynecol Oncol 2007; 104: 580-585.
23. Watanabe Y, Koike E, Nakai H, et al. Phase II study of single-agent gemcitabine in heavily pretreated Japanese patients with recurrent ovarian cancer. Int J Clin Oncol 2008; 13: 345-348.
24. Yoshino K, Hiramatsu K, Enomoto T, et al. Salvage chemotherapy using gemcitabine for taxane/platinum-resistant recurrent ovarian cancer: a single institutional experience. Anticancer Res 2012; 32: 4029-4033.
25. Sorensen P, Hoyer M, Jakobsen A, et al. Phase II study of vinorelbine in the treatment of platinum-resistant ovarian carcinoma. Gynecol Oncol 2001; 81: 58-62.
26. Markman M, Webster K, Zanotti K, et al. Phase II trial of single-agent gemcitabine in platinum paclitaxel refractory ovarian cancer. Gynecol Oncol 2003; 90: 593-596.
27. Kucukoner M, Isikdogan A, Yaman S, et al. Oral etoposide for platinum-resistant and recurrent epithelial ovarian cancer: a study by the anatolian society of medical oncology. Asian Pac J Cancer Prev 2012; 13: 3973-3976.
28. Suprasert P, Manopunya M, Cheewakriangkrai C. Outcomes with single agent LIPO-DOX in platinum-resistant ovarian and fallopian tube cancers and primary peritoneal adenocarcinoma - Chiang Mai University Hospital experience. Asian Pac J Cancer Prev 2014; 15: 1145-1148.
29. Berek J, Friedlander M, Hacker N. Epithelial ovarian, fallopian tube, and peritoneal cancer. In: Berek JS, Friedlander M, Hacker NF (eds) Berek & Hacker's Gynecologic oncology. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins. 2010; 484-508.
30. Ferrero A, Logrippo V, Spanu P.G, et al, Gemcitabine and vinorelbine combination in platinum-sensitive recurrent ovarian cancer. Int J Gynecol Cancer 2009;19:1529-1534.
31. Xenidis N, Neanidis K, Amarantidis K, et al. Biweekly vinorelbine and gemcitabine as second-line and beyond treatment in ovarian cancer. Cancer Chemother Pharmacol 2011; 67: 69-73
32. Hong S, Lee S, Kim H, et al. Pahse II study of gemcitabine and vinorelbine as second - or third- line therapy in patients with primary refractory or platinum-resistant recurrent ovarian and primary peritoneal cancer by the Korean Cancer Study Group (KCSG)_KCSG GY10-10. Gyneccol Oncol 2015; 136(2): 212-217.
33. Goff B, Thompson T, Greer B, et al. Treatment of recurrent platinum resistant ovarian or peritoneal cancer with gemcitabine and doxorubicin: A phase I/II trial of the Puget Sound Oncology Consortium (PSOC 1602). Am J Obstet Gynecol 2003; 188: 1556-1562.
34. Raspagliesi F, Zanaboni F, Vecchione F, et al. Gemcitabine combined with oxaliplatin in patients with advanced ovarian cancer refractory or resistant to platinum and taxane. Oncology 2004; 67(5-6): 376-381.
35. Suprasert P, Cheewakriangkrai C, Manopunya M. Outcome of single agent generic gemcitabine in platinum-resistant ovarian cancer, fallopian tube cancer and primary peritoneal adenocarcinoma. Asian Pac J Cancer Prev 2012; 13: 517-520.
36. Chanpanitkitchot S, Tangjitgamol S, Khunnarong J, et al. Treatment Outcomes of Gemcitabine in Refractory or Recurrent Epithelial Ovarian Cancer Patients. Asian Pac J Cancer Prev 2o14; 15: 5215-5221.
37. Matsumoto K, Katsumata N, Shibata T, et al. Pase II trial of oral etoposide plus intravenous irenotecan in patients with platinum-resistant and taxane pretreated ovarian cancer (JCOG0503). Gynecol Oncol 2015; 136(2): 218-223.
38. Sehouli J, Stengel D, Oskay-Oezcelik G, et al. Non platinum Topotecan Combinations Versus Topotecan Alone for Recurrent Ovarian Cancer: Results of a Phase III Study of the North-Eastern German Society of Gynecological Oncology Ovarian Cancer Study Group. J Clin Oncol 2008; 26: 3176-3182.
39. Ferrandina G, Ludovisi M, Lorusso D, et al. Phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in progressive or recurrent ovarian cancer. J Clin Oncol 2008; 26: 890-896.
40. Ellis L, Hicklin D. VEGF-targeted therapy: mechanisms of anti-tumour activity. Nat Rev Cancer 2008; 8: 579-591.
41. Burger R. Overview of anti-angiogenic agents in development for ovarian cancer. Gynecol Oncol 2011; 121: 230-238.
42. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. J Clin Oncol 2014; 32: 1302-1308.
43. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science 2005; 307: 58-62.
44. Lin Y, Ren Z, Xu S, et al. Low-dose-intensity bevacizumab with weekly irenotecan for platinum- and taxanes resistant epithelial ovarian cancer. Cancer Chemother Pharmacol 2015; 75: 645-651.

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