Original Article

Bevacizumab and Capecitabine in Relapsed Platinum-Resistant Epithelial Carcinoma of Ovary: A Retrospective Study

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Abstract

Background: Relapsed platinum-resistant epithelial carcinoma of the ovary is a disease with a dismal prognosis. Bevacizumab and capecitabine have been used in carcinoma of ovary both as a single agent and with other chemotherapeutic medicine. A retrospective study has been performed to assess the efficacy of bevacizumab + capecitabine in relapsed platinum-resistant epithelial carcinoma of the ovary. **Materials and Methods:** Patients who suffered from relapsed platinum-resistant epithelial carcinoma of the ovary and received bevacizumab and capecitabine were included in the present study. The primary objective of this study was to assess response rate and progression-free survival (PFS). Treatment: Patients received capecitabine at a dose of 1250 mg/m^2 twice daily from day 1 to day 14 in each cycle. Bevacizumab was given at a dose of 7.5 mg/kg on day 1 in each cycle. The cycle was repeated in every 3 weeks. Response evaluation was done using the Response Evaluation Criteria in Solid Tumor criteria and by Rustin criteria. **Statistical Analysis:** Statistical analysis was done using statistical software (SPSS 16, SPSS for Windows, SPSS Inc., Chicago, IL, USA). **Results:** We analyzed the data of 32 patients. The PFS was 10.51 (95% confidence interval [CI], 8.65–12.37) months. The overall survival (OS) was 20.53 (95% CI, 17.21–23.85) months. Four (12.5%) patients achieved complete response. Eighteen (56.25%) patients achieved partial response. The response rate was 68.75%. Four (12.5%) patients had progressive disease. **Conclusion:** Response rate, PFS, and OS of patients in this study are comparable to those of other published studies. Hence, bevacizumab + capecitabine can be used in relapsed platinum-resistant carcinoma of the ovary. The incidence and severity of bevacizumab-induced side effects are relatively lower in this study. Hence, bevacizumab can be given at a lower dose with comparable efficacy and tolerable side effects.

Keywords: *Bevacizumab, capecitabine, carcinoma, ovary, relapsed*

Introduction

Ovarian malignancy is associated with a high mortality rate. It is the sixth most common malignancy in women and the seventh most common cause of death from cancer globally.[1] In women, it is the fourth most common cause of cancer-related deaths.[2] Ovarian malignancy consists of different histopathological variant. Epithelial ovarian cancer consists of approximately 90% of ovarian malignancy.[3] Epithelial ovarian cancer is associated with poor prognosis. Symptoms of epithelial ovarian cancer are nonspecific. Symptoms include abdominal fullness, discomfort, bloating, and dyspepsia. These nonspecific symptoms ultimately result in delay in diagnosis.[4] Screening tests, such as transvaginal ultrasonography and serum cancer antigen-125 (CA-125) estimation, are also nonspecific.[5] For these reasons, patients are diagnosed at an advanced stage. Approximately 75% of patients are diagnosed at the International Federation of Gynaecology and Obstetrics Stage III and IV.[6] Early-stage disease (when the disease is confined to the ovary) is curable, with 5-year survival rate of approximately 90%. However, advanced-stage disease is associated with a high morbidity and mortality.[7] Treatment of epithelial carcinoma of the ovary in advanced stage includes surgery and neoadjuvant and adjuvant chemotherapy. Chemotherapy in first-line setting includes mainly taxane and platinum-based chemotherapy.[8,9] Objective response rate to platinum-based chemotherapy is 70%–85%.[10] Despite response to chemotherapy, overall survival (OS) in advanced epithelial ovarian carcinoma is not encouraging. The 5-year survival remains only 27%.[11]

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Recurrence is common in advanced-stage epithelial ovarian carcinoma. Most of the patients experience disease recurrence within 15 months of the completion of initial treatment.[12,13] Recurrence is classified into two types, according to the duration of response. In platinum-sensitive relapse, relapse occurs after 6 months of the completion of initial platinum-based chemotherapy. In platinum-resistant relapse, relapse occurs within 6 months of the completion of initial platinum-based chemotherapy.[14] Patients with platinum-resistant disease are treated with other chemotherapeutic agents, such as gemcitabine, pegylated liposomal doxorubicin (PLD), and topotecan. However, the response rate with these agents is only 10%–25%. Moreover, the duration of response is also short.[15]

Due to suboptimal results in the treatment of relapsed ovarian carcinoma, there has been every effort for the development of new chemotherapeutic agent and targeted therapy. Angiogenesis is important for the development and progression of carcinoma ovary.[16,17] It has also been observed that angiogenesis is associated with increased aggressiveness of the tumor.[18-20] Vascular endothelial growth factor (VEGF) family includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, placental growth factor, VEGF-E, and VEGF-F.[21] Angiogenesis caused by VEGF has an essential role in the normal function of the ovary. Angiogenesis also has a vital role in the cyclical growth of ovarian follicle and development of corpus luteum.[21,22] However, increased expression of VEGF is associated with uncontrolled and excessive angiogenesis. Increased angiogenesis is assessed by increased microvascular density (MVD). It has been seen that increased MVD is associated with decreased disease-free survival. A study has shown that women with ovarian carcinoma with <10 vessels/high-power field had a median survival of 7.9 years in comparison to 2.7 years where MVD was ≥10/high-power field.[18] Uncontrolled angiogenesis has a vital role in the causation and progression of ovarian carcinoma. A study has shown high serum VEGF level to be associated with higher risk of recurrence.[23] VEGF-induced increased permeability of blood vessels results in increased interstitial pressure. This increased interstitial pressure, in turn, leads to decreased access of chemotherapeutic medicine to the malignant cells.[24]

Bevacizumab is a humanized monoclonal antibody against VEGF-A. Bevacizumab inhibits VEGF, which causes the inhibition of angiogenesis. Decreased angiogenesis ultimately results in reduction in tumor growth.[25] Bevacizumab-induced inhibition of VEGF also results in decreased formation of ascites due to decreased vascular permeability.[26] Various Phase II studies have shown optimistic results when treating patients with relapsed ovarian carcinoma with bevacizumab. In Gynecologic Oncology Group (GOG)-0170D trial, 62 patients with persistent or recurrent epithelial ovarian carcinoma or primary peritoneal carcinoma received bevacizumab monotherapy. 58% of patients had platinum-resistant disease. Overall, the response rate was 21%. Median progression-free survival (PFS) and OS were 4.7 months and 17 months, respectively. Six-month PFS was 40%.[27] In another study by Cannistra *et al*., 90% of patients had platinum-resistant disease. The objective response rate was 15.9%. Median PFS was 4.4 months, and median OS was 10.7 months. Six-month PFS was 28%.[28] Bevacizumab has also shown good results when it has been combined with cyclophosphamide.[29,30] In OCEANS trial, 484 patients with platinum-sensitive relapsed ovarian carcinoma were included. The patients received either chemotherapy (gemcitabine + carboplatin) + placebo or chemotherapy (gemcitabine + carboplatin) + bevacizumab. The objective response rate was 57.4% in chemotherapy + placebo arm and 78.5% in chemotherapy + bevacizumab arm. The median PFS was 12.4 months versus 8.4 months in favor of bevacizumab arm. Differences in response rate and PFS were statistically significant. The median OS was 33.7 months versus 33.4 months in favor of bevacizumab arm.[31,32] In AURELIA trial, patients with platinum-resistant relapsed ovarian carcinoma received either chemotherapy (PLD, paclitaxel, or topotecan) or chemotherapy + bevacizumab. The objective response rate was 12.6% versus 30.9% in favor of bevacizumab arm. The PFS was 3.4 months versus 6.7 months in favor of bevacizumab arm. Differences in response rate and PFS were statistically significant. The OS was 16.6 months in chemotherapy + bevacizumab arm, in comparison to 13.3 months in chemotherapy-alone arm, which was not statistically significant.[33]

Capecitabine is a chemotherapeutic medicine. It is fluoropyrimidine carbamate prodrug form of 5-fluorouracil (FU). 5-FU is a cell cycle-specific drug. It has activity in the "S" phase. 5-FU metabolite 5-fluoro-2'-deoxyuridine monophosphate inhibits thymidylate synthase. 5-fluorouridine 5'-triphosphate is a 5-FU metabolite. It alters RNA processing. Fluorodeoxyuridine triphosphate is another metabolite of 5-FU. Incorporation of this metabolite in DNA results in the inhibition of DNA synthesis.[34] Capecitabine is converted into 5-FU in cell by the enzyme thymidine phosphorylase. This enzyme is expressed preferentially in cancerous cells. This property of preferential expression of the enzyme makes cancer cells a selective target of capecitabine.

The effectiveness and safety of capecitabine was assessed in a Phase II trial done by Vasey *et al*. In this study, 29 patients with relapsed ovarian carcinoma were included and received single-agent capecitabine. The response rate was 29% (95% confidence interval [CI], 13%–49%). The median PFS and OS were 3.7 (95% CI, 2.8–4.6) months and 8 (95% CI, 4.1–11.8) months, respectively. Six-month PFS was 28% (95% CI, 13%–48%).[35] In another study by Boehmer *et al*., 14 patients with platinum-resistant recurrent ovarian carcinoma were included. One patient (8.3%)

showed complete response (CR). Two patients (16.7%) were partial responders. Stable disease (SD) was seen in 25% of the patients.[36]

Hence, both bevacizumab and capecitabine have shown their efficacy in controlling disease in relapsed ovarian carcinoma. To our knowledge, till now, there has been no published study assessing the efficacy of capecitabine + bevacizumab in platinum-resistant relapsed epithelial ovarian carcinoma. Hence, we have done a retrospective single-institutional study to assess the efficacy and safety of capecitabine + bevacizumab in platinum-resistant relapsed epithelial ovarian carcinoma.

Materials and Methods

Patients

In this retrospective single-institutional study, we have analyzed data of patients suffering from platinum-resistant relapsed epithelial ovarian carcinoma, who had received chemotherapy with capecitabine + bevacizumab. The primary objective of this study was to assess response rate and PFS. The secondary objective was to assess OS and toxicity.

Treatment

Patients received capecitabine at a dose of 1250 mg/m^2 twice daily from day 1 to day 14 in each cycle. Bevacizumab was given at a dose of 7.5 mg/kg on day 1 in each cycle. The cycle was repeated in every 3 weeks. Treatment was continued until progression of the disease or excessive toxicity. Contrast-enhanced computed tomography (CT) scan of the whole abdomen and thorax was done before the initiation of treatment and after every three cycles of chemotherapy. Serum CA-125 was done before the initiation of treatment and before each cycle of chemotherapy. Response evaluation was done using the Response Evaluation Criteria in Solid Tumors criteria (by CT scan in case of measurable disease) and by Rustin criteria (using serum CA-125 level).[37-39] CR was declared when there was no detectable disease in CT scan and serum CA-125 was less than the upper limit of the normal value. Partial response (PR) was declared when in CT scan, there was at least 30% reduction in the size of measurable disease or 50% reduction in serum CA-125 level in serial four measurements. Progressive disease (PD) was declared when there was at least 20% increase in the size of measurable disease or when serum CA-125 was increasing in consecutive three measurement and the final value was more than double of the upper limit of the normal value. Patients, whose disease was not among these three categories, were included in SD category.

Statistical analysis

Statistical analysis was done using statistical software (SPSS 16, SPSS for Windows, SPSS Inc., Chicago, IL, USA). The means of numerical data were described as mean ± standard error.

Results

From June 2015 to September 2017, 34 patients, suffering from platinum-resistant relapsed epithelial ovarian carcinoma, had received capecitabine + bevacizumab. Among them, 32 patients received capecitabine + bevacizumab for at least two cycles. These 32 patients were included in our study. The dose of capecitabine had to be reduced in six patients due to Grade 3 toxicities. No dose reduction or escalation of bevacizumab had been done. In ten patients, who experienced Grade 3 toxicities, few cycles of chemotherapy were delayed.

The median age of patients was 53.5 years. Among these patients, five patients had Stage II disease at the time of initial diagnosis. Eighteen patients and nine patients had Stage III and Stage IV diseases, respectively. Twenty-three patients had performance status of Eastern Cooperative Oncology Group (ECOG 1), and nine patients had performance status of ECOG 2. Eighteen patients received previously one chemotherapy regimen. Twelve patients and two patients received two and three chemotherapy regimen previously, respectively. Mean serum CA-125 was 350.44 units/ml (95% CI: 292.02–408.86). PFS was 10.51 (95% CI, 8.65–12.37) months [Figure 1]. OS was 20.53 (95% CI: 17.21–23.85) months [Figure 2]. Four (12.5%) patients achieved CR. Eighteen (56.25%) patients achieved PR. The response rate was 68.75%. Six (18.75%) patients had SD. Four (12.5%) patients had PD.

Two patients experienced Grade 3 diarrhea. Four patients experienced Grade 3 palmoplantar erythrodysesthesia (hand-foot syndrome). Four patients experienced Grade 3 hypertension. Hypertension in these patients reduced satisfactorily after treatment with antihypertensive medication. Grade 2 proteinuria was seen in five patients [Table 1]. One patient suffered from a bowel perforation. Bevacizumab was stopped in this patient. After treatment of this acute condition, she was treated with chemotherapy other than bevacizumab and capecitabine. Other toxicities were nausea, anorexia, vomiting, fatigue, neutropenia, and thrombocytopenia. These toxicities were of Grade 1 or Grade 2 severity.

Discussion

The lifetime risk of developing ovarian carcinoma in women is 1 in 75.[40] Epithelial ovarian carcinoma is well known due to its nonspecific symptoms in early stage, late presentation, chemosensitivity, early relapse, and nonoptimistic PFS and OS. Due to poor survival of patients suffering from advanced-stage epithelial ovarian carcinoma, there has been every effort for the development of newer chemotherapeutic medicine, targeted therapy including monoclonal antibody. Bevacizumab is a humanized monoclonal antibody, which binds and inhibits VEGF-A. Bevacizumab is being used successfully in advanced

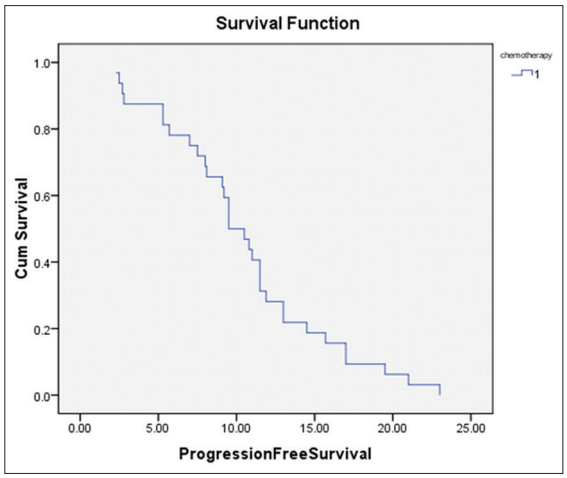

Figure 1: Survival curve for progression-free survival

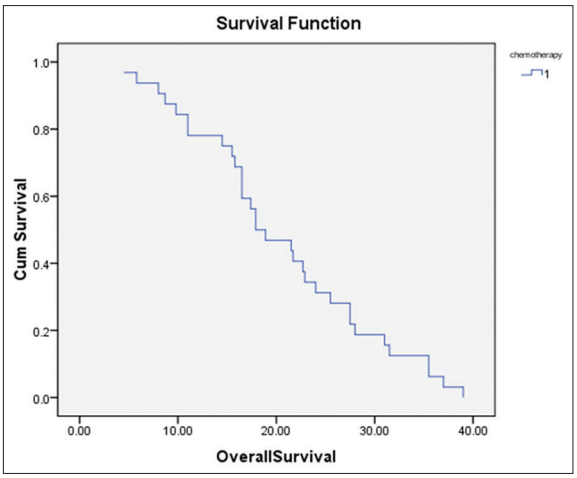

Figure 2: Survival curve for overall survival

Table 1: Toxicity analysis

Toxicity	Grade 1 or 2 (%)	Grade 3 (%)
Hypertension	5 (15.63)	4 (12.5)
Proteinuria	5 (15.63)	0
Diarrhea	5 (15.63)	2 (6.25)
Palmoplantar erythrodysesthesia	7 (21.88)	4 (12.5)
Vomiting	11 (34.38)	0
Anemia	7 (21.88)	5 (15.63)
Neutropenia	11 (34.38)	0
Thrombocytopenia	4 (12.5)	0

nonsquamous non-small cell carcinoma of the lung and relapsed or metastatic carcinoma of the colorectum. Bevacizumab has also shown its activity in carcinoma of the ovary. Capecitabine is also active in the treatment of ovarian carcinoma. In this retrospective single-institutional, single-arm study, our aim was to assess the efficacy and safety of bevacizumab + capecitabine in platinum-resistant relapsed epithelial ovarian carcinoma.

In GOG-0170D trial, the median age was 57 years. The median age was 59.5 years in the study by Cannistra *et al*. The median age in our study was 53.5 years.[28] Hence, the median age of patients was lower in our study. In the study by Cannistra *et al*., patients had performance status of either ECOG 0 or 1. In the study by Garcia *et al*., only 5.71% of the patients had a performance status of ECOG 2.[30] However, in our study, 28.13% of the patients had a performance status of ECOG 2. In the study by Cannistra *et al*., 52.3% and 47.7% of the patients received prior two and three chemotherapy regimens, respectively. In GOG-0170D trial, 66.1% of the patients received two prior chemotherapy regimens. In our study, 37.5% and 6.25% of the patients had received prior two and three chemotherapy regimens, respectively. Rest of the patients received only one prior chemotherapy regimen for this disease. No patient in our study had received bevacizumab or capecitabine previously. In the study by Cannistra *et al*., median serum CA-125 was 825 units/ml. In the study by Wright *et al*., median serum CA-125 was 376 units/ml.[41] Median serum CA-125 in our study was 303 units/ml.

In the study by Wright *et al*., 35% of the patients achieved PR. SD was seen in 44% of the patients. In 21% of the patients, disease progressed. The median time to progression was 5.6 months in patients who achieved PR. In this study, bevacizumab combination therapy was used. One probable explanation of low PFS is that patients in this study were heavily pretreated. A median of seven prior chemotherapy regimen was used. In AURELIA trial, the objective response rate was 30.9%. The median PFS was 6.7 months (95% CI, 5.7–7.9 months) in bevacizumab + chemotherapy arm. The OS was 16.6 months (95% CI, 13.7–19 months). Low PFS and low OS in this trial may be due to platinum-resistant nature of the disease. In our study, CR was seen in 12.5% of the patients. PR was seen in 56.25% of the patients. 18.75% of the patients had SD, and 12.5% of the patients experienced PD. Hence, the response rate was 68.75%. The PFS was 10.51 (95% CI, 8.65–12.37) months in our study. The OS was 20.53 (95% CI: 17.21–23.85) months. Most of the patients in our study received only one chemotherapy regimen previously; this may be one possible cause of relatively higher response rate, PFS, and OS in our study. The objective response rate in OCEANS trial was 78.5% in bevacizumab + chemotherapy group. The median PFS was 12.4 months in bevacizumab + chemotherapy group. The median OS in combination arm was 33.3 months. In the OCEANS trial, patients were suffering from platinum-sensitive recurrent epithelial ovarian, primary peritoneal or fallopian tube carcinoma. Due to platinum-sensitive nature of the disease, there might be improved PFS and OS in comparison to our study. Patients who received chemotherapy previously due to disease relapse in carcinoma ovary were not included in the OCEANS study; this might be another cause of improved PFS and OS in that study. In the study by Garcia *et al*., bevacizumab and low-dose oral cyclophosphamide were used in recurrent ovarian carcinoma. The median PFS was

7.2 months (95% CI, 5.3–8.7 months). The median OS was 16.9 months (95% CI, 11.4–25.2 months).

In the study done by Vasey *et al*., single-agent capecitabine was used in relapsed ovarian carcinoma. The response rate was 29%. PFS and OS were 3.7 and 8 months, respectively.[35] The probable cause of low PFS in this study is the use of single-agent capecitabine.

In the AURELIA trial, Grade ≥2 hypertension was seen in 20% of patients in bevacizumab + chemotherapy arm. Gastrointestinal perforation was seen in 2% of patients. In this trial, bevacizumab was used at a dose of 15 mg/kg in every three weeks or 10 mg/kg in every two weeks. Grade 3 hypertension was seen in 17.4% of patients in bevacizumab + chemotherapy arm in the OCEANS study. Bevacizumab was used at a dose of 15 mg/kg in this study. Proteinuria was seen in 8.5% of patients. In the study by Cannistra *et al*., only bevacizumab was used for the treatment of relapsed platinum-resistant epithelial ovarian carcinoma. 15.9% of patients experienced proteinuria up to Grade 2 severity. Grade ≥3 hypertension was seen in 9.1% of patients. In the ICON 7 trial, patients with epithelial ovarian carcinoma, primary peritoneal carcinoma, or fallopian tube carcinoma received adjuvant chemotherapy or chemotherapy + bevacizumab after surgery. In this study, hypertension was seen in 6% of the patients in Grade ≥3 severity. 17% of patients experienced Grade ≥3 neutropenia. Grade ≥3 thrombocytopenia was seen in 3% of patients. In this study, bevacizumab was used at a dose of 7.5 mg/kg.[42] In our study, 12.5% of patients experienced Grade 3 hypertension. Hypertension in these patients reduced satisfactorily after treatment with antihypertensive medication. No dose reduction of bevacizumab was done in these patients. However, the next cycle of treatment was delayed in these patients. The incidence of Grade 3 hypertension was higher in patients in our study in comparison to the ICON 7 trial. However, it was lower in comparison to the OCEANS study. Probably, the lower incidence and severity of hypertension in our study was due to the lower dose of bevacizumab. Severity of neutropenia and thrombocytopenia was lower in our patients in comparison to the ICON 7 trial. In the ICON 7 trial, paclitaxel and carboplatin were given along with bevacizumab. However, in our study, only capecitabine was given along with bevacizumab, which may be the cause of decreased severity of neutropenia and thrombocytopenia in our study. Twelve patients in our study experienced anemia. At the time of initiation of chemotherapy with capecitabine + bevacizumab, these patients had hemoglobin percentage in the range of 9–10 g/dl. Probably, this was one of the causes of anemia in these patients.

In the study by Vasey *et al*., 14% of patients experienced Grade 3 palmoplantar erythrodysesthesia, and 10% of patients suffered from Grade 3 vomiting. 6.25% of patients in our study experienced Grade 3 diarrhea and 12.5% of patients suffered from Grade 3 palmoplantar erythrodysesthesia. These toxicities were controlled by medication and delaying of the next cycle of chemotherapy. From the next cycle of chemotherapy, the dose of capecitabine was reduced by 25%. This 25% dose reduction ultimately results in good tolerance of capecitabine. After that, no further dose reduction or delaying of chemotherapy was required.

Conclusion

Response rate, PFS, and OS of patients in this study are comparable to other published studies regarding the treatment of relapsed epithelial carcinoma of the ovary. Hence, bevacizumab + capecitabine can be used in relapsed platinum-resistant carcinoma of the ovary. Bevacizumab had been used at relatively lower dose in our patients. The incidence and severity of bevacizumab-induced side effects were relatively lower in comparison to studies using bevacizumab at a higher dose. Hence, bevacizumab can be given at a lower dose with comparable efficacy and tolerable side effects. Limitations of our study are it is a retrospective study and the number of patients is small. To have a better result, prospective study with more number of patients can be considered.

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Conflicts of interest

There are no conflicts of interest.

References

1. Basu P, De P, Mandal S, Ray K, Biswas J. Study of 'patterns of care' of ovarian cancer patients in a specialized cancer institute in Kolkata, Eastern India. Indian J Cancer 2009;46:28-33.
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893-917.
3. Colombo N, Peiretti M, Parma G, Lapresa M, Mancari R, Carinelli S, *et al*. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21:23-30.
4. Gaitskell K, Martinek I, Bryant A, Kehoe S, Nicum S, Morrison J. Angiogenesis inhibitors for the treatment of ovarian cancer. Cochrane Database Syst Rev 2011;(9):CD007930.
5. Saini SK, Shrivastava S, Singh Y, Dixit AK, Prasad SN. Epidemiology of epithelial ovarian cancer, a single institution-based study in India. Clin Cancer Investig J 2016;5:20-4.
6. Shepherd JH. Revised FIGO staging for gynaecological cancer. Br J Obstet Gynaecol 1989;96:889-92.
7. Heintz AP, Odicino F, Maisonneuve P, Quinn MA, Benedet JL, Creasman WT, *et al*. Carcinoma of the ovary. FIGO 26th annual report on the results of treatment in gynecological cancer. Int J Gynaecol Obstet 2006;95 Suppl 1:S161-92.
8. McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE,

Look KY, *et al.* Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med 1996;334:1-6.
9. Piccart MJ, Bertelsen K, James K, Cassidy J, Mangioni C, Simonsen E, *et al.* Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: Three-year results. J Natl Cancer Inst 2000;92:699-708.
10. Hennessy BT, Coleman RL, Markman M. Ovarian cancer. Lancet 2009;374:1371-82.
11. Siegel R, Naishadham D, Jemal A. Cancer statistics for hispanics/ Latinos, 2012. CA Cancer J Clin 2012;62:283-98.
12. Hurt JD, Richardson DL, Seamon LG, Fowler JF, Copeland LJ, Cohn DE, *et al.* Sustained progression-free survival with weekly paclitaxel and bevacizumab in recurrent ovarian cancer. Gynecol Oncol 2009;115:396-400.
13. Markman M. Pharmaceutical management of ovarian cancer: Current status. Drugs 2008;68:771-89.
14. Markman M, Rothman R, Hakes T, Reichman B, Hoskins W, Rubin S, *et al.* Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. J Clin Oncol 1991;9:389-93.
15. Agarwal R, Kaye SB. Ovarian cancer: Strategies for overcoming resistance to chemotherapy. Nat Rev Cancer 2003;3:502-16.
16. Santin AD, Hermonat PL, Ravaggi A, Cannon MJ, Pecorelli S, Parham GP. Secretion of vascular endothelial growth factor in ovarian cancer. Eur J Gynaecol Oncol 1999;20:177-81.
17. Penson RT, Dizon DS, Cannistra SA, Roche MR, Krasner CN, Berlin ST, *et al.* Phase II study of carboplatin, paclitaxel, and bevacizumab with maintenance bevacizumab as first-line chemotherapy for advanced mullerian tumors. J Clin Oncol 2010;28:154-9.
18. Alvarez AA, Krigman HR, Whitaker RS, Dodge RK, Rodriguez GC. The prognostic significance of angiogenesis in epithelial ovarian carcinoma. Clin Cancer Res 1999;5:587-91.
19. Gasparini G, Weidner N, Bevilacqua P, Maluta S, Dalla Palma P, Caffo O, *et al.* Tumor microvessel density, p53 expression, tumor size, and peritumoral lymphatic vessel invasion are relevant prognostic markers in node-negative breast carcinoma. J Clin Oncol 1994;12:454-66.
20. Hollingsworth HC, Kohn EC, Steinberg SM, Rothenberg ML, Merino MJ. Tumor angiogenesis in advanced stage ovarian carcinoma. Am J Pathol 1995;147:33-41.
21. Masoumi Moghaddam S, Amini A, Morris DL, Pourgholami MH. Significance of vascular endothelial growth factor in growth and peritoneal dissemination of ovarian cancer. Cancer Metastasis Rev 2012;31:143-62.
22. Geva E, Jaffe RB. Role of vascular endothelial growth factor in ovarian physiology and pathology. Fertil Steril 2000;74:429-38.
23. Bandiera E, Franceschini R, Specchia C, Bignotti E, Trevisiol C, Gion M, *et al.* Prognostic significance of vascular endothelial growth factor serum determination in women with ovarian cancer. ISRN Obstet Gynecol 2012;2012:245756.
24. Kerbel RS. Antiangiogenic therapy: A universal chemosensitization strategy for cancer? Science 2006;312:1171-5.
25. Presta LG, Chen H, O'Connor SJ, Chisholm V, Meng YG, Krummen L, *et al.* Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res 1997;57:4593-9.
26. Mesiano S, Ferrara N, Jaffe RB. Role of vascular endothelial growth factor in ovarian cancer: Inhibition of ascites formation by immunoneutralization. Am J Pathol 1998;153:1249-56.
27. Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JI. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: A Gynecologic oncology group study. J Clin Oncol 2007;25:5165-71.
28. Cannistra SA, Matulonis UA, Penson RT, Hambleton J, Dupont J, Mackey H, *et al.* Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. J Clin Oncol 2007;25:5180-6.
29. Chura JC, Van Iseghem K, Downs LS Jr. Carson LF, Judson PL. Bevacizumab plus cyclophosphamide in heavily pretreated patients with recurrent ovarian cancer. Gynecol Oncol 2007;107:326-30.
30. Garcia AA, Hirte H, Fleming G, Yang D, Tsao-Wei DD, Roman L, *et al.* Phase II clinical trial of bevacizumab and low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer: A trial of the California, Chicago, and princess Margaret hospital phase II consortia. J Clin Oncol 2008;26:76-82.
31. Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A, *et al.* 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 2012;30:2039-45.
32. Aghajanian C, Goff B, Nycum LR, Wang YV, Husain A, Blank SV, *et al.* Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. Gynecol Oncol 2015;139:10-6.
33. Lauraine EP, Hilpert F, Beatrice W, Reuss A, Poveda A, Kristensen G, *et al*. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol 2014;13:1302-8.
34. Chu E, DeVita VT. Physicians' Cancer Chemotherapy Drug Manual. New Delhi: Jones & Barlett India Private Ltd; 2009. p. 64-5.
35. Vasey PA, McMahon L, Paul J, Reed N, Kaye SB. A phase II trial of capecitabine (Xeloda) in recurrent ovarian cancer. Br J Cancer 2003;89:1843-8.
36. Boehmer Ch, Jaeger W. Capecitabine in treatment of platinum-resistant recurrent ovarian cancer. Anticancer Res 2002;22:439-43.
37. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, *et al.* New guidelines to evaluate the response to treatment in solid tumors. European organization for research and treatment of cancer, national cancer institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205-16.
38. Rustin GJ, Nelstrop AE, McClean P, Brady MF, McGuire WP, Hoskins WJ, *et al.* Defining response of ovarian carcinoma to initial chemotherapy according to serum CA 125. J Clin Oncol 1996;14:1545-51.
39. Guppy AE, Rustin GJ. CA125 response: Can it replace the traditional response criteria in ovarian cancer? Oncologist 2002;7:437-43.
40. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, AlteKruse SF, *et al*. SEER Cancer Statistics Review. National Cancer Institute; 1975-2013.
41. Wright JD, Hagemann A, Rader JS, Viviano D, Gibb RK, Norris L, *et al.* Bevacizumab combination therapy in recurrent, platinum-refractory, epithelial ovarian carcinoma: A retrospective analysis. Cancer 2006;107:83-9.
42. Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, *et al.* A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 2011;365:2484-96.