

Selected Summary

Phase II Trial of Bevacizumab in Persistent or Recurrent Epithelial Ovarian Cancer

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SUMMARY

Management of advanced epithelial ovarian cancer (EOC) is a therapeutic challenge. Initial debulking surgery followed by paclitaxel and platinum based chemotherapy is currently treatment of choice. Despite objective response in 60-80% of patients, five-year survival rates vary between 10% to 30% for advanced disease¹. Failures are due to development of primary or secondary resistance. Treatment-free interval (TFI) from last cycle of chemotherapy is important guiding factor for choosing salvage treatment for treatment of relapse. Patients with more than 6 months of TFI are called platinum sensitive and are candidates for repeat platinum based therapy. Patients with TFI of < 6 months are considered platinum refractory.² For later patients – options are use of non platinum drugs e.g. gemcitabine, liposomal doxorubicin, topotecan, oral etoposide (VP-16) etc. Response rate to salvage therapy in platinum refractory disease varies from 15 to 28% with progression-free survival (PFS) of 3-4 months. Recently, newer approaches such as targeted therapy are being evaluated. Bevacizumab – an antiangiogenesis agent is one such drug. Though the drug was initially described for metastatic colon cancer,³ various trials are currently evaluating its role in treatment of EOC both in upfront (primary) and recurrent setting.

Present study is a phase II trial, conducted to assess the efficacy and tolerability of Bevacizumab in patients of recurrent or persistent epithelial ovarian cancer (EOC) or primary peritoneal cancer (PPC).⁴ Both platinum sensitive and platinum resistant EOC patients who had received one or two prior chemotherapy regimens were included. Bevacizumab was given at a dose of 15 mg/kg intravenously every 21 days until disease progression or prohibitive toxicity. Primary end points were - progression-free survival (PFS) at 6 months and clinical response.

Of the 62 patients assessed - 41(66.1%) had received at least two prior therapy and 26 (41.9%) were platinum resistant. Clinical response was seen in 13 (21%) patients: complete- 2, and partial responses in 11 patients. Stable disease was seen in 32(51.6%). Median time to response was 2.6 months. Median response duration was 10 months, median progression free survival (PFS) and overall survival were 4.7 and 17 months, respectively. 40.3% patients had a PFS of at least 6 months. There was no significant association of prior platinum sensitivity, age, number of prior chemotherapeutic regimens, or performance status with the hazard of progression or death. Grade 3 adverse events included -hematologic in 1, gastro-intestinal-3, hypertension -6, thromboembolism 1, allergy-2,

hepatic-1, pain-3, coagulation-1, constitutional -1, and dyspnoea -1. Grade 4 adverse events seen were pulmonary embolus (1), vomiting and constipation (1), and proteinuria (1). The authors concluded that Bevacizumab seems to be well tolerated and active as a second and third line treatment for patients with EOC/PPC and merits phase III investigation.

COMMENTS

Angiogenesis is a key component of the normal physiologic function of the ovaries during the reproductive years. A key characteristic of physiologic angiogenesis is its transient nature and tight regulation. Normal and abnormal angiogenesis is regulated by a variety of pro- and anti-angiogenic factors. The homeostatic balance of these factors is dysregulated in malignancy, leading to continued growth of tumours enabled by sustained angiogenesis. Many malignancies, including epithelial ovarian carcinoma, are characterized by increased levels of pro-angiogenic factors including VEGF⁵. VEGF signaling is also required during normal ovulation. Over expression of VEGF is associated with formation of ascites, carcinomatosis and therefore poor prognosis.⁶ Hence the rationale for using vascular endothelial growth factor (VEGF) inhibitors in ovarian cancer. Bevacizumab is a recombinant humanized monoclonal antibody (IgG1) with affinity for all isoforms of VEGF-A with an estimated half life of approximately 20 days. In contrast to its use in colon cancer where it has shown improvement in overall survival and PFS only in combination with other chemotherapy prospective trials in ovarian cancer have clearly established the single agent activity of Bevacizumab in patients with recurrent disease⁷. Several other phase II trials have used Bevacizumab in combination with other chemotherapeutic drugs⁸⁻¹⁰ (Table 1).

In the present study hypertension was observed more frequently. Bowel perforation is another potential complication seen in 3 to

15% of patients. Bowel perforation has also been observed in earlier studies and in another similar recent study by Cannistra et al.¹¹ In the later study, patients were more heavily pre-treated (48% having received three prior regimens) and all had platinum resistant disease. A careful analysis revealed - prior therapy with three regimens was associated with increased risk of bowel perforation. Although an increased risk was associated with radiologic factors like bowel wall thickening and bowel obstruction it was not statistically significant.¹¹

Thus, present study and other similar studies have demonstrated definitive activity of Bevacizumab as a second or third line drug in relapsed or refractory EOC as later use may be associated with an increased risk of bowel perforations. It needs to be established if Bevacizumab as second line is better than other presently used second line agents like liposomal doxorubicin or gemcitabine, docetaxel, vinorelbine. Also degree of benefit, if any in those relapsing after two or three years needs to be determined. It is also important to select patients most likely to benefit by identifying appropriate biomarkers. What is the optimum dose schedule, whether to use as a single agent or in combination and whether this drug can be given upfront with chemotherapy agents (so as to achieve higher response rates) are some of other questions which need to be answered in future studies. Two such phase III randomized studies are currently in progress, one by Gynecologic Oncology Group of USA (GOG-218) and another by International Co-operative Network (ICON-7) on Ovarian cancer.¹² Both these studies are evaluating the benefit of adding Bevacizumab to paclitaxel plus carboplatin in front line management of primary ovarian cancer. ICON 7 is also prospectively evaluating a panel of fourteen biomarkers in both treatment arms. Results from these trials are awaited with great interest.

Table-1 Bevacizumab in combination with chemotherapy in the treatment of ovarian cancer (adapted from reference 7)

	Bevacizumab, carboplatin, Paclitaxel⁸ (n=43)	Bevacizumab, cyclophosphamide⁹ (n=70)	Bevacizumab, Erlotinib¹⁰ (n=13)
Doses	Bevacizumab 15mg/Kg every 3 weeks (+ maintenance) Carboplatin AUC 5 Paclitaxel 175 mg/m ² every 21days	Bevacizumab 10 mg/Kg every 2 weeks Cyclophosphamide 50mg/day	Bevacizumab 15 mg/m ² every 3 weeks Erlotinib 150 mg/day
Number of previous regimens	0	≤ 3	≤ 3
Platinum sensitivity	—	Refractory	4 refractory , 2 resistant, 7 sensitive
Toxicity	Grade 4 neutropenia, hematuria, epistaxis nasal perforation, delayed wound healing, autonomic neurotoxicity, pulmonary embolism	Pain, hypertension, hyponatremia, fatigue, lymphopenia, GI obstruction, increased transaminases, thrombosis, CNS ischemia	Diarrhoea, bowel perforation
Incidence of GI perforations	0%	1 / 29 (3%)	2/13 (15%)
Response	CT : CR-56% ,PR 22% CA-125 :CR-89%,PR- 7%	CR-0%, PR -21%, SD-59%, PD-21%	CR-1 (8%), SD- 8 (67%)
Median PFS (months)	-	5.8	4.1
PFS at 6 months (%)	-	47	9

Abbreviations: n, number of patients; CR, complete response; CT, computed tomography; PR, partial response; SD, stable disease; PFS, progression free survival

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