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(CASE REPORT)

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Successful rechallenge of bevacizumab after grade 4 bevacizumab induced hypertension in a case of carcinoma ovary, is rechallenging an option? - A Rare case report

Satish sharma, Apurva A patel *, Aruj Dhyani, Nikesh Aggarwal, Yuganshi Gupta, Goutham R Reddy, Debajyoti Maji, Harshvardhan A, Phillip G Kuttikat, Ananya Pareek, Sonia Parikh and Harsha P Panchal

GCRI, Medical Oncology, GCRI, Ahmedabad, Gujarat, India.

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Abstract

Treatment of multi-resistant ovarian cancer is palliative. Patient after receiving multiple lines of chemotherapy are neither in good PS nor have good compliance to receive further toxic treatment.

Bevacizumab is a vascular endothelial growth factor which inhibit angiogenesis. Bevacizumab is generally used in combination with chemotherapy. Due to its low toxicity profile, improvement in progression free survival (PFS), easy availability in resources limited settings, it is a good adjunct to more toxic and costly regimens. Development of hypertension is one of the most common adverse event of bevacizumab.

We present a case of patient of metastatic carcinoma ovary, who developed grade 4 hypertension post 1st cycle of bevacizumab for which treatment was withheld. After control of blood pressure, she was rechallenged with bevacizumab and patient did not had any hypertensive episode and is doing well at present.

Keywords: Carcinoma Ovary; Chemo Resistant; Biologics VEGF; Metastatic; Grade 4 Hypertension.

1. Introduction

Ovarian cancer, over period of time, become chemo resistant and there is an obvious need for biological treatment with less side effects. Bevacizumab have shown significant improvement in progression free survival (PFS) in several studies, although it is most beneficial in recurrent cases. [1,2,3] Bevacizumab has been approved either in neoadjuvant or in adjuvant setting along with paclitaxel and carboplatin along with maintenance therapy post completion of chemotherapy after results of two studies ICON 7 and GOG218. [4,5,6] became available.

Two studies (OCEANS) in platinum sensitive cases and (AURELIA) in platinum resistant cases. [7,8] reported improved progression free survival (PFS) in patients.

Bevacizumab is a recombinant humanized monoclonal antibody which inhibit angiogenesis by neutralizing VEGF and effectively cutting off tumour supply of oxygen and nutrients .It has been used in the treatment of metastatic colorectal cancer, metastatic renal cell cancer, non-squamous lung cancer, ovarian cancer, cervical cancer and multifocal hepatocellular cancer.

* Corresponding author: Satish Sharma
GCRI, Medical Oncology, GCRI, Ahmedabad, Gujarat, India.

Bevacizumab is given intravenously in range of 5-15 mg/kg every 2-3 weeks either as single agent or in combination with chemotherapy. Bevacizumab has an array of complications like gastrointestinal perforations, hemorrhage, proteinuria and hypertension.

Hypertension of all grades has been observed in up to 36% of patients treated with bevacizumab [10, 11]. Here, we present a case of bevacizumab induced grade 4 hypertension and was successfully re-challenged post blood pressure control and is performing well. After through research of database we couldn't find any case reports regarding re-challenge of bevacizumab following grade 4 hypertension. Hereby we present 1st case report.

2. Case history

45 years, non-comorbid female patient came with chief complaints of abdominal distension. CT scan (Abdomen + Pelvis) showed 11 x 8x 10 cm solid cystic lesion involving right adnexal region and both ovaries were not seen separately seen from the lesion. Biopsy (26/3/12) from the lesion on was suggestive of serous papillary adenocarcinoma. CA -125 at diagnosis was 990 U/ml. Patient was given neoadjuvant chemotherapy (NACT) with paclitaxel and carboplatin four cycles (last on 30/5/12). Post NACT, CT (Abdomen and pelvis), on 19/6/2012, showed significant decrease in size of the lesion. Interval de-bulking surgery was done on 21/6/12. Post-operative histopathology was suggestive of serous papillary cystadenocarcinoma with omental deposits with peritoneal washings positive for malignant cells corresponding stage III C. Two more cycles of adjuvant paclitaxel and carboplatin was given (last on 31/8/12) to complete adjuvant treatment. Patient was on regular follow up with ultrasound abdomen and pelvis and CA-125 levels every 3 months. Patient had disease free period (DFS) of 5 years. On 7/3/2018 there was increase in patient's CA- 125 to 78 U/ml. CT (Abdomen + Pelvis) 5/4/2018- was suggestive of omental deposits in small Intestine. Biopsy of the same showed recurrent adenocarcinoma of ovary. Since patient was platin sensitive, she was re-challenged with paclitaxel and carboplatin. She was given 3 cycles of paclitaxel and carboplatin given (last on 18/5/18). Re-evaluation with CT (Abdomen and Pelvis) on 7/6/2018 was s/o progressive disease with new appearance of liver metastasis.

Patient was given option of bevacizumab, but due to social issues it was not added and 3 cycles of lipodox was given (last on 6/8/2018). Re-evaluation CT (Abdomen and Pelvis) 9/8/2018 -was suggestive of progressive disease with increase in the size of metastatic deposits and gross ascites. Ascites was tapped and was positive for malignant cells. Patient required repeated tapping 1-2 taps/weekly. Line of chemotherapy was changed again to gemcitabine 3 cycles. Re-evaluation CT scan (Abdomen + Pelvis) showed progressive disease. Patient was put on oral etoposide in June 2019 till Dec 2020, eventually patient had clinical, radiological and biochemical progression. Patient's performance status was progressively worsening and she required multiple admission for supportive care. Patient was started on bevacizumab. Her CBC- 13g/dl/11000 cells/500000 cells, Bilirubin/SGOT/SGPT -0.3 mg/dl,Creat – 0.7 and Urine routine microscopy – no proteinuria or cast. On (29/1/21)1st cycle of Bevacizumab (10 mg/kg) was given. Her pre and post bevacizumab (BP was 120/80 mm hg and 130/80 mm hg respectively. On 19/2/21, Patient came with complain of headache ,BP was 190/110(hypertensive crisis) , admitted routine CBC,RFT,LFT ,urine routine and microscopy including CECT brain was within normal limit. She was initially given intra venous labetalol then was later changed to oral anti-hypertensives (Telmisartan plus Hydrochlorothiazide). She was advised Blood Pressure monitoring. Patient was rechallenged with Bevacizumab 2nd cycle with Pre and post bevacizumab Blood pressure 110/70 and 120/70 respectively. Her blood pressure has been within normal limits with oral anti-hypertensives. On re-evaluation scan after 3 cycles of bevacizumab, ascites completely resolved. Now patient is due for 5th cycle bevacizumab.

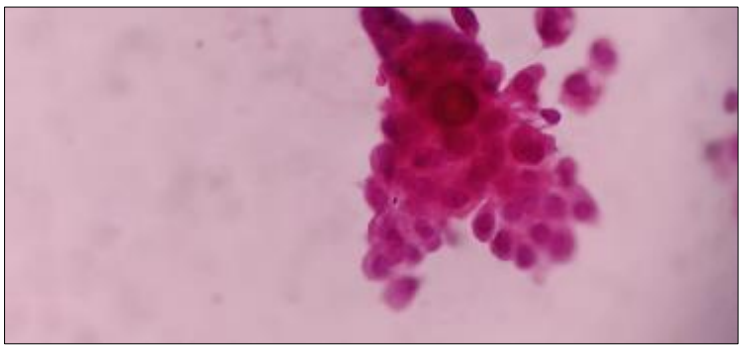

Figure 1 Adeno carcinoma cells in Ascitic fluid

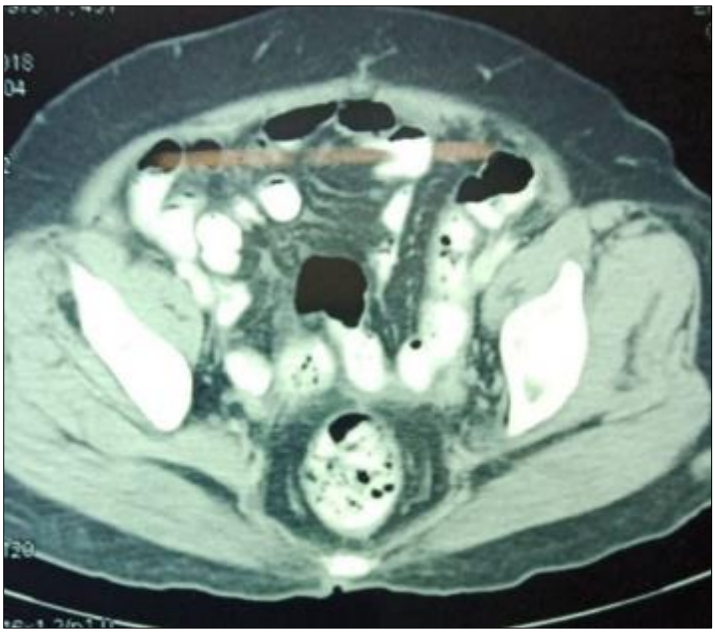

Figure 2 CT (Abdomen +Pelvis) - scan before bevacizumab

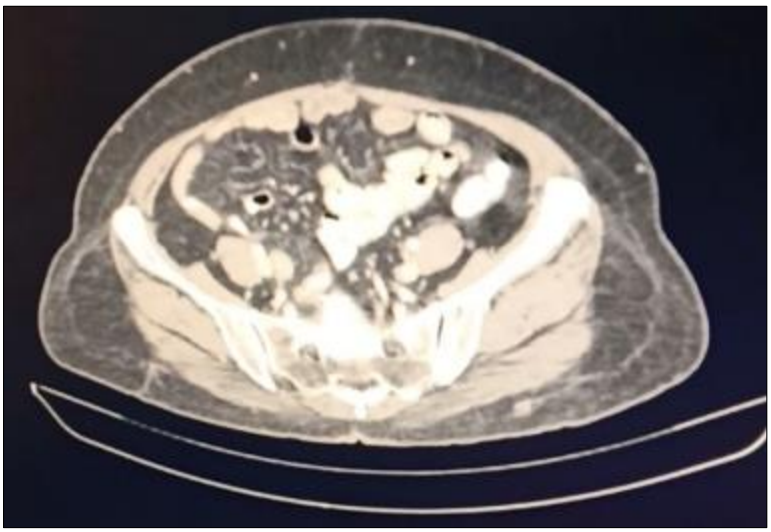

Figure 3 CT (Abdomen +Pelvis) scan - showing partial response after starting Bevacizumab

3. Discussion

Bevacizumab is a VEGF inhibitor which has been used in multi- resistant carcinoma ovary either in combination with chemotherapy or as a single agent in different dosages. It has proven to have both overall survival (OS), and Progression Free survival (PS) benefit in both platinum sensitive and resistant cases.

Patient of Carcinoma ovary progresses over period of time become chemo resistant, so there is obvious need for biological treatment with minimal side effects. Bevacizumab is an affordable biological alternative in resource limited population. [4,5,6]

One of the dose limiting side effect which we experienced at our tertiary high-volume center was development hypertension after 1 and 2 dose of bevacizumab. Patient in report is case of Ca ovary relapsed on multiple lines of chemotherapy, she developed hypertensive crisis after 1st dose of bevacizumab. After aggressive BP control patient, she was rechallenged after explaining risks, Patient tolerated further dose of Bevacizumab and is doing well.

Bivatuzumab induced HTN assessed on a scale of 1-5, with grade 3-4 considered high grade HTN. [12,13] .In meta-analysis , bevacizumab was reported to increase high grade HTN by 5 times. The time of BP elevation after receiving bevacizumab varies but is frequently observed after first cycle as it was observed in our patient.

Hypertension is also side effect of other VEGF pathway inhibitor such as sunitinib, sorafenib, and pazopanib. incidence of hypertension increases with more potent inhibitor axitinib, regorafenib, and cediranib. There is various mechanism of development of HTN – decreased vasodilation, renal dysfunction, endothelial dysfunction. [14,15]

All patients with Bevacizumab treatment, is recommended to have Blood Pressure checked every 2-3 weeks, as it was done our patient. Bevacizumab is discontinued in event of hypertensive crisis or hypertensive encephalopathy. Our patient developed hypertensive crisis after first dose of bevacizumab. Patient BP was aggressively controlled by ACE inhibitors, diuretics, bevacizumab was discontinued. [16,17] As patient had affordability issue, with high risk consent we rechallenged with bevacizumab, patient is doing good with no ascetic tap for last 3 months, well controlled BP same as Pretreatment level with dual Anti-hypertensive agent.

Abbreviations

- ACE: angiotensin-converting enzyme
- BP; blood pressure
- HTN: hypertension
- VEGF: vascular endothelial growth factor
- OS: overall survival
- PFS: progression-free survival

4. Conclusion

Bevacizumab is easily available biological drug in chemo resistant carcinoma ovary. Bevacizumab has dose limiting side effect of hypertension, which led to discontinuation of bevacizumab. Here, our patient was successfully rechallenged with bevacizumab even after developing grade 4 hypertension. Bevacizumab can be seen as continuum of therapy even after developing Hypertension if is controlled.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that there are no conflicts of interest.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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