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Does Bevacizumab Cause Headache to the Onco-Surgeon? An Evidence-Based Review with Experience from A Tertiary Care Referral Oncology Center, India

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ABSTRACT

Introduction: Bevacizumab is an antibody against VEGF-A which has recently been used in the pre-operative setting in malignancies, specially colo-rectal and ovarian cancers. We aim to review the surgical complications associated with such use of this molecule. **Methods:** Cases of ovarian and colorectal cancers that received preoperative Bevacizumab and underwent surgery at our center were included and their postoperative complications were evaluated. A review of literature was done for evaluating the complications associated with Bevacizumab. **Cases and review:** Four such cases were evaluated, all of whom developed postoperative complications. Patients developed perforations, urinary fistulae and incisional hernia postoperatively. Bevacizumab is known to cause GI perforations, genitourinary fistulae and delayed wound healing and such complications have been known to have a poor impact on quality of life and survival. **Conclusion:** Patients who have received Bevacizumab as Neo-adjuvant Therapy, should be considered as a special entity. A minimum of 8 weeks' time interval before major surgery is recommended after stopping Bevacizumab.

Keywords: Bevacizumab, Surgical Complications, Perforation.

INTRODUCTION

Bevacizumab is a humanized monoclonal antibody against VEGF-A. It inhibits microvascular growth and angiogenesis and is used in cancer treatment to inhibit malignant cell growth and blood vessel formation [1]. Recent studies have shown that use of pre-operative Bevacizumab has beneficial effects with acceptable toxicity [2,3]. This has led to an increase in use of Bevacizumab in the preoperative setting. Does Bevacizumab cause headache to the Onco-surgeon? In this paper we review it effects on major Onco-surgeries with experience from a tertiary oncological referral centre.

CASE 1

A 52 years old female, known case of HTN, presented with complaints of vaginal spotting and pain lower abdomen. On evaluation she was

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diagnosed with Carcinosarcoma of the uterus, Stage IV. The patient received 4 cycles of neoadjuvant Paclitaxel-carboplatin following which she underwent Interval CRS + HIPEC (with Adriamycin) in March of 2023 followed by Radical RT. The patient developed abdominal recurrence in September 2023. She was started on Paclitaxel-carboplatin along with Bevacizumab. After 3 cycles of Bevacizumab, the patient presented with an enterocutaneous fistula in the midline scar. The patient was explored after stabilization and was found to have 3 perforations in the small bowel at 180cm, 210 cm, and 230 cm from DJ. Resection and anastomosis were done.

CASE 2

A 66 years old male known case of DM and HTN, presented complaints of altered bowel habits and was diagnosed with CA rectosigmoid with liver metastasis to segment 3, 4 and 7 on evaluation. The patient had received 9#FOLFOX and 6# Bevacizumab (last on 2/5/23) at another center. The patient was discussed in a tumour board and planned for Anterior resection with RFA of liver lesions. The patient underwent Laparoscopic AR with diversion ileostomy on 30/6/23. On POD 6, the patient developed bile leak from drains. On re-exploration the patient was found to have 2 ileal perforations, 140 and 160 cm from ICJ. The perforations were friable, they were repaired and a proximal diversion ileostomy was made. On F/U the patient underwent stoma closure in December 23 and i/v/o disease progression, is being treated with palliative intent at present.

CASE 3

A 32 years old female, known case of Diabetes Insipidus, presented with an abdominopelvic mass and was diagnosed with Pseudomyxoma peritonei with colonic primary in view of IHC positive for CDX 2 and CK 20. The patient was started on CAPOX + Bevacizumab, and received 5 cycles, last on 17/6/19. The patient underwent CRS + HIPEC (with cisplatin) on 26/9/19. The patient developed pain lower abdomen on POD 12, and on evaluation was found to have a pelvic collection. On aspiration, the fluid showed increased urea and creatinine and the patient was diagnosed with a urinary leak. Site of leak could not be identified on contrast study. This was managed conservatively with pigtail insertion. The patient was later started on FOLFIRI + Bevacizumab in January 2020.

CASE 4

A 54 years old female, presented with complaints of pain lower abdomen and was diagnosed with CA ovary Stage IIIC on evaluation. She received 6# neoadjuvant Paclitaxel-carboplatin following which she underwent Interval CRS + EPIC (Paclitaxel) in July 2020. The patient presented again in 2022 with recurrence and a VVF. She underwent CRS + VVF repair + diversion ileostomy on 25/6/22 after which she received 6# Paclitaxel-carboplatin and 1# Bevacizumab. Patient underwent stoma closure in February 23. On F/U the patient developed an incisional hernia in the midline of 10x10cm and is now being planned for hernia repair.

DISCUSSION

Bevacizumab was approved by the US FDA as first line treatment along with standard chemotherapy for metastatic colorectal cancer in 2004 and for epithelial ovarian, fallopian tube and primary peritoneal cancer Stage III and IV in 2018 [2,4]. As the surgical indications have expanded for metastatic cancers, along with a few studies showing beneficial effects of preoperative therapy with Bevacizumab, there is now a subset of patients who receive this drug preoperatively. In India, more and more such patients have started showing up for surgeries and oncologists need to be aware of the challenges faced during the use of this drug.

Bevacizumab has been known to be associated with a variety of adverse events. We can classify them into non-surgical and surgical adverse events. Non-surgical adverse events would include hypertension (along with hypertensive emergencies and encephalopathy), arterial thromboembolic events (MI/CVA), reversible posterior leukoencephalopathy syndrome, nephrotic syndrome, arterial thrombosis, headache, epistaxis, proteinuria, rhinitis, dry skin, exfoliative dermatitis and taste alteration. Surgical adverse events would include gastrointestinal perforation, non-gastrointestinal fistula formation, wound healing related complications and hemorrhage [5]. GI perforations and fistula formations are specially seen with ovarian and colorectal cancer patients.

In the AVANT phase 3 trial, evaluating bevacizumab plus oxaliplatin based chemotherapy as adjuvant treatment for colorectal cancer, surgical complications were seen in 44 patients out of 2280 receiving bevacizumab-based therapy (1.9%). GI perforations and fistulas were seen in 36 out of these 44 patients with the rest of the patients developing wound healing complications [6]. Hurwitz et al reported a 1.5% incidence of GI perforations in metastatic colorectal cancers with Bevacizumab [7]. Saltz et al reported a 1.5% incidence of surgical complications in mCRC [8]. Kabbinavar et al reported a 1.9% occurrence of GI perforations in mCRC with Bevacizumab [9].

Cannistra et al, in a phase II trial evaluating use of Bevacizumab in ovarian cancer patients, reported an 11% incidence of GI perforations [10]. The ICON-7 trial reported a 1.4% incidence of GI perforation/fistula, the AURELIA trial reported a 4.4% incidence of GI perforations/fistulas (2.2% incidence of GI perforations, 2.2 % of GI fistulas)

and the GOG-218 trial reported a 2.8% incidence of GI perforations [11-13]. Vatsa et al reported a 10% incidence of GI perforations with Bevacizumab in ovarian cancer [14]. Two other published articles report an incidence of 9% and 5.6% of perforations with Bevacizumab [15,16].

In our limited experience, there appears to be an increased incidence of perioperative complications with the use of Bevacizumab. Herein we report a patient of recurrent carcinosarcoma of uterus with multiple bowel perforations and a subsequent EC fistula formation, a patient with metastatic colorectal cancer with bowel perforation in the immediate postoperative period, a patient with PMP with colonic primary with a urinary fistula formation and a patient with ovarian carcinoma with development of incisional hernia post Bevacizumab related therapy.

While most studies report GI perforations and fistulae, Bevacizumab has also been known to be associated with fistulae of the genitourinary system. Sturdza et al reported 30% incidence of VVF and 10% of RVF in patients receiving Bevacizumab for recurrent cervical cancer [17]. Hwang et al reported an incidence of 16.4% for perforations/fistulae in patients of previously irradiated recurrent CA cervix. On multivariate analysis they found Bevacizumab to be the only independent risk factor associated with perforations/fistulae of any grade [18]. Takahashi et al have also recently reported a case of rectovesical fistula post Bevacizumab related therapy in a case of metastatic rectal cancer [19].

The largest case series of Bevacizumab induced GI perforations was published by Storandt et al. They included 89 patients out of which the most common malignancy associated with Bevacizumab related perforations were colorectal (42/89) followed by ovarian (22/89). Only 21 patients had perforations at the primary tumour site while others had perforations at other sites [20]. Multiple factors have been associated with increased risk of perforations and fistulae formation with Bevacizumab administration but the exact mechanism remains unknown. Since Bevacizumab inhibits VEGF which helps in wound healing, it seems rational to assume difficulties in wound healing with its administration. VEGF inhibition also leads to thrombosis of small mesenteric vessels, alteration of bowel microcirculation and exacerbation of pre-existing bowel ulcers [21].

Factors which increase the risk of perforation/fistulae with Bevacizumab include old age with comorbidities such as atherosclerosis, hypertension and diabetes which predispose to ischemia; surgery within 2 months of drug administration, peptic ulcer disease, acute diverticulitis, intestinal obstruction, cancer at the site of perforation, peritoneal carcinomatosis and prior abdominopelvic radiation therapy [22].

Studies have analyzed the survival of patients who develop perforations and fistulas after Bevacizumab administration and have found worse outcomes for these patients. Storandt et al reported a median overall survival of 2.73 months and 36% patients died within 30 days of the perforation [20]. Badgwell et al reported a 30 day mortality rate of 12.5%. (23) Reports of 30 day mortalities of up to 50% and 66% have also been published [15,16].

CONCLUSION

As the indications for Bevacizumab increasing in oncological practice, surgeons are likely to come across more and more patients who have received this drug. While multiple studies have reported the beneficial effects of Bevacizumab, the adverse outcomes must not be overlooked before selecting patients for major Onco-surgical procedures. This is a small case series, but made us understood the need of evaluation of perioperative morbidity and mortality associated with Bevacizumab, specially in the Indian population as most of the published literature is from the Western world. Being an onco-surgeon, one must evaluate this patient thrice, plan twice and get the surgery done once after stopping Bevacizumab for at least 8 weeks otherwise it may be the cause of surgeon's headache utterly.

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