La Prensa Medica Argentina

Research Article A SCITECHNOL JOURNAL

Implantable Port-a-Cath System Insertion in Patients with Metastatic Colon Cancer Receiving Bevacizumab-Based Chemotherapy

Tal Grenader[1*] and Linda Shavit[2]

[1]*Department of Oncology, Shaare Zedek Medical Center, Jerusalem, Israel*

[2]*Nephrology Unit, Shaare Zedek Medical Center, Jerusalem, Israel*

[*]**Corresponding author:** Tal Grenader, Department of Oncology, Sha'are Zedek Medical Center, P.O. Box 3235, 91031 Jerusalem, Israel, Tel.: +972 2 6567853; Fax: +972 26666731; E-mail: talgrenader65@hotmail.com

Rec date: 09 Sep, 2014 **Acc date:** 13 Feb, 2015 **Pub date:** 17 Feb, 2015

Abstract

Background: Combination of bevacizumab with continuous 5-fluoracil (5-FU)-based regimens are considered to be the backbone of colorectal cancer (CRC) systemic therapy. Administration of these continuous intravenous regimens requires insertion of an indwelling central venous catheters and implantable port systems. Certain aspects of the toxicity profile of Bevacizumab could interfere with implantable port-a-cath insertion. The aim of present study was to evaluate the safety port-a-cath insertion shortly before or during bevacizumab treatment in patients with metastatic colon cancer.

Patients and Methods: A retrospective analysis of the medical records of 75 patients with metastatic colon cancer treated with bevacizumab-based chemotherapy in period of 28 days before or during port-a-cath insertion was carried out.

Results: Median duration of bevacizumab treatment was 36.3 weeks (range 2- 156 weeks). Port-a-cath insertion had been performed less than 2 weeks before the initiation of treatment with bevacizumab in 41 patients, 2–4 weeks before the initiation of treatment with bevacizumab in 17 patients, and during the treatment with bevacizumab in 17 patients. There were no instances of delay in wound healing, wound infection, or abnormal bleeding in any of the patients. No patient showed any evidence of skin ulceration during bevacizumab treatment.

Conclusion: Implantable port-a-cath venous access may safely be inserted a short time before or during bevacizumab treatment without increasing peri procedural morbidity or device erosion through the skin in patients with metastatic colon cancer.

Keywords: Metastatic colon cancer; Port-a-cath; Implantable venous access catheter; Bevacizumab; Wound healing

Introduction

Colorectal cancer (CRC) is one of the most common types of cancer worldwide. Approximately 25% present with metastases at initial diagnosis and almost 50% of patients with CRC will develop metastases.

FOLFIRI and FOLFOX (continuous 5-fluoracil (5-FU)-based regimens) are considered to be the backbone of colorectal cancer (CRC) systemic therapy. Having a relatively short plasma half-life, 5-FUadministered by bolus injection is quickly cleared from the blood whereas infusional administration prolongs 5-FU exposure [1]. Several studies have demonstrated superior efficacy of infusional 5-FU over bolus 5-FU, with reduced toxicity. [2] VEGF inhibition with bevacizumab, a humanized anti-VEGF monoclonal antibody, has direct antivascular effects in human tumor and improves the efficacy of first-line chemotherapy including combination of continuous 5-FU with irinote can or/and oxaliplatin in patients with advanced colorectal cancer. [3-5]

Administration of continuous intravenous regimens requires insertion of an indwelling central venous catheters and implantable port systems. Furthermore, a port-a-cath is often needed for reasons other than infusional 5FU in patients with advanced colon cancer. These devices have additional value in transfusion purposes, and the acquisition of blood samples, facilitating supportive care by providing a stable conduit for hydration, pain control, and nutrition. Advanced colon cancer is a chronic disease with the need for multiple sequential chemotherapy regimens and many patients undergo placement of a port-a-cath at some point in the course of treatment simply because of inadequate peripheral venous access.

Although port-a-caths have a long useful life associated with a low complication rate, central vein catheter insertion can lead to complications such as infections, bleeding, pneumothorax, and venous thrombo embolism. [6,7]

Certain toxicities of Bevacizumab, such as bleeding and impaired wound healing, could interfere with surgical procedures or techniques involved in the treatment of colon cancer. [8] On account of its extremely long half-life (17–21 days), it is commonly recommended that 6–8 weeks should elapse between the administration of bevacizumab and elective surgery. [9]

We present here a retrospective evaluation of 75 patients with metastatic colon cancer treated in the oncology department at the Shaare Zedek Medical Center, who underwent insertion of an indwelling central venous access port shortly before or during bevacizumab treatment.

Materials and Methods

A retrospective analysis of the medical records of 75 patients with a colon treated with bevacizumab in period of 28 days before or during port-a-cath insertion at Shaare Zedek Medical Center between January 2005 and December 2012 was carried out.

Patient sex, age at the time of catheter placement, and complications associated with the catheter were recorded.

In every case, an all-plastic low profile port with a 6.6F silicone tube extending to the cavo-atrial junction had been inserted under fluoroscopic guidance in the period shortly before the commencement of bevacizumab therapy, or during bevacizumab therapy itself.

Right sided veins were used in most instances in view of the direct route to the right atrium. A 0.5 cm incision at the neck was made for

an ultrasound-guided internal jugular venous puncture and a 4 cm sub clavicular incision for the port itself, with a short subcutaneous tunnel to the venotomy site. Wound closure was performed with either absorbable subcuticular sutures or interrupted dermalon skin sutures (removed after 10 days). Unwanted effects associated with the surgical procedure, and in particular, wound healing complications, were evaluated in every patient at 10 days, 2 months and 4 months after the insertion by the treating physician and by the oncology nurse on any occasion that the catheter was used.

Results

The data from 75 patients (39 male and 36 female) were analyzed. The median age was 60.61 years (range: 38–86 years).

Seven of the 75 patients had diabetes mellitus, five patient received anticoagulation and another seven received anti platelet agents.

The dose of bevacizumab per course was 5 mg/kg every 2 weeks in 70 patients and 7.5 mg/kg every 3 weeks in 5 patients. Bevacizumab was given in combination with FOLFOX (46 patients), FOLFIRI (23 patients), capecitabine (3 patients), CAPEOX (2 patients) and De gramont (one patient). Median duration of bevacizumab treatment was 36.3 weeks s (range 2- 156 weeks).

Port-a-cath insertion had been performed less than 2 weeks before the initiation of treatment with bevacizumab in 41 patients, 2–4 weeks before the initiation of treatment with bevacizumab in 17 patients, and during the treatment with bevacizumab in 17 patients.

There were no instances of delay in wound healing, wound infection, or abnormal bleeding in any of the patients. No patient showed any evidence of skin ulceration during bevacizumab treatment. There were no instances of air embolism, pneumothorax, major vessel perforation, or accidental arterial puncture.

Discussion

The value of bevacizumab as an anticancer drug has been shown in many studies, however since angiogenesis is essential for proper wound repair, bevacizumab may lead to wound-healing complications and might be expected to interfere with some of the surgical procedures involved in the treatment of cancer. [10]

Vascular endothelial growth factor plays multiple roles in wound healing process. VEGF mediates has effects for vasodilation, increased vascular permeability, and angiogenesis. [10,11]

It helps recruit macrophages, fibroblasts, and endothelial cells, stimulates monocytes to remodel clots, and increases microvascular permeability, allowing granulocytes to clear bacteria and macrophages to phagocytose wound debris. Furthermore, VEGF is involved in deposition of types I and III collagen by fibroblasts and formation of new extracellular matrix. [10,11]

There is powerful evidence, that any major surgery performed while patients are receiving bevacizumab may be associated with an increase incidence of wound healing complications. Most of the existing trials have been performed in metastatic colorectal patients.

In pooled assessment of postoperative wound healing complications of bevacizumab in two randomized trials in colorectal cancer treatment, Scappaticci et al [8] found wound healing complications, including perforation, fistula, and abscess in 10 of the 75 patients (13%) who had undergone a major surgery on bevacizumab compared the 3 of 230 (1.3%) wound healing complications rate in patients treated with bevacizumab 28 to 60 days after surgery. [8]

The BRITE observational cohort study of 622 patients who had undergone surgery after bevacizumab treatment, the incidence of serious wound complications in the patients was inversely proportional to the time elapsing between the last dose of bevacizumab and surgery. In the patients who had received their last dose 0–2 weeks , 2-4 weeks, 4-6 weeks , 6-8 weeks and more than 8 weeks before surgery, the wound healing complications rates were 9.7%, 3.2%, 3.0%, 5.9% and 1.8%, respectively. [12]

As well, the absolute number of wound healing complications was higher following major surgery (e.g., abdominal: nine of 157 cases, 5.7%; hepatic metastectomy, five of 88 cases, 5.7%) versus minor surgery (i.e., placement of indwelling central venous access device: two of 67 cases, 3.0%).

The feasibility and safety of hepatic metastasectomy in association with perioperative bevacizumab has been addressed in numerous retrospective series, none of which suggest an increase in the incidence of bleeding or wound healing problems in patients who received bevacizumab in the period surrounding resection. [9,13,14]

In adjuvant setting, the NSABP C-08 randomized-controlled trial found a 1.7% wound healing complications rate in 1326 patients received combination of FOLFOX6 with bevacizumab started 28-56 days after surgery that was significantly higher than the 0.3% WHC rate in 1321 patients received chemotherapy alone. [15]

Skin erosion has been reported to occur in 1–3% of the patients who have had a port inserted [16,17]. This seems to be a risk, albeit a small one, of the technique itself. Port cath skin erosion has been associated port-a-cath placement by inexperienced interventionist, wound infections or poor wound healing, repeated placing of the port at the same location, patient's weight loss.

Almhanna et al. [18] reported two cases of standard titanium ports eroding through the skin in patients treated with bevacizumab. [18] One patient with advanced breast cancer was started on 10 mg/kg bevacizumab every other week. One week later, a port was inserted. This port eroded through the skin 5 months after insertion, and a new port eroded through after 3 months. In another patient with colon cancer, a port was inserted 2 weeks before the initiation of bevacizumab and the port eroded after 2 weeks of treatment with the drug. Although the investigators suggest that this complication was bevacizumab-related, this may simply be a reflection of the normal occurrence of this complication in patients receiving a port.

Our previous study had not revealed wound healing and bleeding complications in patients with a variety of cancers, who were receiving bevacizumab shortly before or during the insertion of an indwelling central venous access. [19]

With the recent development of oral fluoropyrimidine, capecitabine, implantation of a port-a-cath venous access can be avoided. Capecitabine is a more convenient, alternative to infusional 5-FU. Administration of bevacizumab based chemotherapy via peripheral vein is safe and efficient. A systematic review of trials comparing first-line capecitabine and oxaliplatin (CAPEOX, XELOX) versus oxaliplatin plus infusional FU/LV concluded that XELOX was associated with consistently more prominent thrombocytopenia and hand and foot syndrome consistently more prominent and a significantly lower response rate, but this did not translate into lower progression free or overall survival. [20] Because a significant number

of patients report local pain, requiring switching of drip infusion route during XELOX when oxaliplatin is infused via peripheral vein, many centers routinely infuse the oxaliplatin via port-a-cath. Addition of dexamethasone to oxaliplatin drip infusion controlsthe vascular pain caused by administration of oxaliplatinvia the peripheral vein, enabling the continuation ofXELOX therapy. [21] Consequently, port-free chemotherapy via the median cubital vein may beefficacious option for patients with colorectal cancer, permitting to avoid serious complications associated with port –a-caths [22].

In conclusion, although the study is a retrospective analysis of the experience of a single institution in a relatively small number of patients, and it is not possible to draw definitive conclusions at this stage, our data suggest that an implantable port-a-cath venous access may safely be inserted a short time before or during bevacizumab treatment without increasing periprocedural morbidity or device erosion through the skin in patients with metastatic colon cancer.

References

1. Vogelzang NJ (1984) Continuous infusion chemotherapy: a critical review. J ClinOncol 2: 1289–1304.
2. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administrationin advanced colorectal cancer: Meta-analysis Group in Cancer. J Clin Oncol 16: 301–308.
3. Sobrero A, Ackland S, Clarke S, et al (2009) AVIRI Trial investigators. Phase IV study of bevacizumab in combination with infusional fluorouracil, leucovorin and irinotecan (FOLFIRI) in first-line metastatic colorectal cancer. Oncology 77: 113-119.
4. Giantonio BJ, Catalano PJ, Meropol NJ, et al. (2007) Eastern Cooperative Oncology Group Study E3200: Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J ClinOncol 25: 1539–1544.
5. Hochster HS, Hart LL, Ramanathan RK, et al. (2008) Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. J ClinOncol 26: 3523-3529.
6. Torramadé JR, Cienfuegos JA, Hernández JL, et al. (1993) The complications of central venous access systems: a study of 218 patients. Eur J Surg 159: 323-327.
7. Poorter RL, Lauw FN, Bemelman WA, et al. (1996) Complications of an implantable venous access device (Port-a-Cath) during intermittent continuous infusion of chemotherapy. Eur J Cancer 32A: 2262-2266.
8. Scappaticci FA, Fehrenbacher L, Cartwright T, et al. (2005) Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. J SurgOncol 91: 173Y180.
9. D'Angelica M, Kornprat P, Gonen M, et al. (2007) Lack of evidence for increased operative morbidity after hepatectomy with perioperative use of bevacizumab: a matched case-control study. Ann SurgOncol 14: 759–765.
10. Sharma K, Marcus JR (2012) Bevacizumab and Wound-Healing Complications: Mechanismsof Action, Clinical Evidence, and Management Recommendations for the Plastic Surgeon. Ann Plast Surg 124: 1497–1511
11. Bates DO, Jones RO (2003) The role of vascular endothelial growth factor in wound healing. Int J Low Extrem Wounds 2: 107-120.
12. Kozloff M, Yood MU, Berlin J, et al. (2009) Investigators of the BRiTE study. Clinical outcomes associated with bevacizumab-containing treatment of metastatic colorectal cancer: the BRiTE observational cohort study. Oncologist 14: 862-870.
13. Reddy SK, Morse MA, Hurwitz HI, et al. (2008) Addition of bevacizumab to irinotecan- and oxaliplatin-based preoperative chemotherapy regimens does not increase morbidity after resection of colorectal liver metastases. J Am CollSurg 206: 96–106.
14. Kesmodel SB, Ellis LM, Lin E, et al. (2008) Preoperative bevacizumab does not significantly increase postoperative complication rates in patients undergoing hepatic surgery for colorectal cancer liver metastases. J ClinOncol 26: 5254-5260.
15. Allegra CJ, Yothers G, O'Connell MJ, et al. (2009) Initial safety report of NSABP C-08: A randomized phase III study of modified FOLFOX6 with or without bevacizumab for the adjuvant treatment of patients with stage II or III colon cancer. J ClinOncol 27: 3385-3390.
16. Yip D, Funaki B (2002) Subcutaneous chest ports via the internal jugular vein. A retrospective study of 117 oncology patients. ActaRadiol 43: 371–375.
17. Starkhammar H, Bengtsson M (1985) Totally implanted device for venous access. Experience in tumour patients. ActaRadiolOncol 4: 173–176.
18. Almhanna K, Pelley RJ, Thomas Budd G, et al. (2008) Subcutaneous implantable venous access device erosion through the skin in patients treated with anti-vascular endothelial growth factor therapy: a case series. Anticancer Drugs 19: 217–219.
19. Grenader T, Goldberg A, Verstandig A, Shavit L (2010) Indwelling central venous access port insertion during bevacizumab-based therapy. Anticancer Drugs 21: 704-707.
20. Arkenau HT, Arnold D, Cassidy J, et al. (2008) Efficacy ofoxaliplatin plus capecitabine or infusional fluorouracil/ leucovorin in patientswith metastatic colorectal cancer: a pooled analysis of randomized trials. J ClinOncol 26: 5910-5917.
21. Yoshida Y, Hoshino S, Aisu N et al. (2012) Dexamethasone as ameans not only for controlling vascular pain caused by theadministration of oxaliplatin via the peripheral vein but also for controlling oxaliplatin-induced hypersensitivity reactions. Br JMed Med Res 2: 132–141.
22. Yoshida Y, Hoshino S, Aisu N, et al. (2014) Administration of chemotherapy via the median cubital veinwithout implantable central venous access ports: port-free chemotherapy formetastatic colorectal cancer patients. Int J ClinOncol.