Indwelling central venous access port insertion during bevacizumab-based therapy

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Indwelling central venous catheters and implantable port systems are widely used in the care of patients with cancer. Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor, significantly prolongs survival when added to intravenous 5-fluorouracil-based chemotherapy as first-line treatment for metastatic colorectal cancer. It has also been shown to be of value in a range of other malignant diseases. Some elements of the toxicity profile of bevacizumab, however, such as bleeding and impaired wound healing, could interfere with surgical procedures involved in the treatment of the diseases. The aim of this study was to evaluate the possible effect of bevacizumab in increasing the morbidity associated with an indwelling central venous access port in patients currently receiving the drug, or those who had received it in the preoperative run-up to surgery. An analysis of the medical records of 57 patients with a variety of cancers, who had received an indwelling central venous access port, either during the course of treatment with bevacizumab or in the 4-week period before the commencement of therapy was carried out, with particular emphasis on periprocedural complications. Eight of the patients also had diabetes mellitus. There were no instances of delay in wound healing, abnormal bleeding, or wound infection in any of the patients and no episodes of skin ulceration during bevacizumab treatment. Although this is a relatively small study, and no definitive conclusions can be drawn at this stage, our data suggest that an indwelling central venous access port insertion may be carried out shortly before or during bevacizumab treatment without increasing periprocedural morbidity. ***Anti-Cancer Drugs*** **21:704–707 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Indwelling central venous catheters and implantable port systems are widely used in the care of patients with cancer for the administration of chemotherapy, transfusion purposes, and the acquisition of blood samples. They have additional value in facilitating supportive care by providing a stable conduit for hydration, pain control, and nutrition. These devices have a long useful life associated with a low complication rate, and are of great value to patients who require long-term or cyclical intravenous treatment [1].

Bevacizumab [Avastin; rhuMab vascular endothelial growth factor (VEGF)], a humanized monoclonal antibody against VEGF, was the first angiogenesis inhibitor to be approved for the treatment of cancer in the United States. When added to intravenous 5-fluorouracil-based chemotherapy for the first-line treatment of metastatic colorectal cancer (CRC), it has been shown to prolong survival significantly [2,3]. Encouraging results have also emerged from clinical trials in non-small cell lung cancer, breast and renal cell carcinoma, and glioblastoma [4–7].

Certain aspects of the toxicity profile of Bevacizumab, however, such as bleeding and impaired wound healing, could, in theory, interfere with surgical procedures or techniques involved in the treatment of these diseases [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 57 patients with metastatic cancer treated in our department at the Shaare Zedek Medical Center, who underwent an indwelling central venous access port insertion shortly before or during bevacizumab treatment.

Materials and methods

A retrospective analysis of the medical records of 57 patients with a variety of cancers treated with bevacizumab at Shaare Zedek Medical Center between January 2005 and November 2009 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

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therapy, or during bevacizumab therapy itself. Right-sided veins were used in most instances in view of the direct route to the right atrium. The left internal jugular vein was only used when the right-sided veins could not be accessed and in three patients with a history of radiotherapy to the right breast. A 0.5 cm incision at the neck was made for an ultrasound-guided internal jugular venous puncture and a 4 cm subclavicular 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 57 patients (25 male and 32 female) were analyzed. The median age was 60.2 years (range: 38–86 years). There were 51 cases of colon cancer, four of breast cancer, and two lung cancers. Eight of the 57 patients had diabetes mellitus in addition to their malignant disease. The dose of bevacizumab per course was 5 mg/kg every 2 weeks in the patients with colon cancer, 15 mg/kg every 3 weeks in the patients with breast cancer, and 10 mg/kg every 3 weeks in the patients with lung cancer. Bevacizumab was given in combination with Folfox (36 patients), Folfiri (13 patients), De gramont (two patients), paclitaxel (three patients) and gemcitabine/cisplatinum (three patients).

Port-a-cath insertion had been performed 2–4 weeks before the initiation of treatment with bevacizumab in 13 patients, less than 2 weeks before the initiation of treatment with bevacizumab in 24 patients, and during the treatment with bevacizumab in 20 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.

Discussion

The proliferation of new blood vessels is essential for tumor growth and facilitates the spread of blood-borne metastases [10]. VEGF induces angiogenesis, functions as a survival factor for endothelial cells, and promotes the abnormal phenotype of blood vessels in tumors [11]. Thus, although VEGF seems to prevent apoptosis in the induced endothelial cells of these tumor blood vessels, normal adult vasculature is for the most part independent of VEGF for stability, survival, and normal function [12,13]. This difference has formed the basis of the rationale for the use of VEGF inhibitors such as bevacizumab as anti-tumor agents, as their activity will be focused primarily on the tumor vessels and not on the normal vasculature. The value of bevacizumab as an anti-cancer drug has since been shown in many studies, but elements of its toxicity profile, such as bleeding and wound healing complications, might be expected to interfere with some of the surgical procedures involved in the treatment of these diseases.

Currently, there are limited data on the surgical outcomes in patients who have received bevacizumab in the period before or during surgical procedures. There is some evidence, however, that any major surgery performed while patients are receiving bevacizumab may be associated with an increase in wound healing complications. This is derived from a pooled analysis of two randomized first-line mCRC studies [8]. This analysis identified wound healing complications, including perforation, fistula, and abscess in 10 of the 75 patients (13%) who had undergone a major surgery while on bevacizumab. Although this represents a three-fold increase in the wound healing complications as compared with the patients who were not on bevacizumab, statistical significance was not achieved because of the relatively small number of patients involved.

There are a number of studies in the literature that have assessed the incidence of unwanted events in patients who have undergone major surgery at varying time points after the completion of treatment with bevacizumab. Okines *et al.* analyzed prospectively collected data from 225 patients who had undergone curative-intent surgery 42–100 days (median 64 days) after the last dose of bevacizumab, including an exploratory comparison of the resection rate in patients treated with different regimens. There were no surgery-related deaths and serious post-operative complications were uncommon, with grade 3/4 bleeding and wound-healing complications reported in 0.4% and 1.8% of the patients, respectively [14].

In a preliminary report from the community-based BRiTE observational cohort of 622 patients who had undergone surgery after bevacizumab treatment, the incidence of serious wound complications in the patients was more or less inversely proportional to the time elapsing between surgery and the last dose of bevacizumab. Thus, in the patients who had received their last dose 0–13, 14–27, 28–59, and ≥ 60 days before surgery, the complication rates were 6.5, 3.4, 5.4, and 1.8%, respectively. Among the 23 patients with serious wound complications, other possible contributory factors included infection (12 patients), tumor involvement at the operative site (four patients), a history of diabetes under medication (two patients), and obesity (four patients) [15].

Metastasectomy, and in particular, resection of hepatic metastases represents a major form of surgery in cancer patients 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. In the data reported by D'Angelica *et al.* [9], no significant difference in the overall morbidity was observed between patients who received perioperative CTX and bevacizumab as compared with those who received CTX alone (40.6 vs. 37.5%; $P = 1.00$). Reddy *et al.* [16] also showed no significant difference in overall complications in patients treated with or without preoperative bevacizumab (43.6 vs. 38.6%; $P = 0.78$). The investigators, however, did find that in the patients treated with bevacizumab, overall complications were more common in the patients who had received bevacizumab within 8 weeks of surgery as compared with those in whom the time elapsing was greater (62.5 vs. 30.4%; $P = 0.06$). As can be seen, this did not quite reach statistical significance, and the small number of patients in this study makes it difficult to draw conclusions about the timing of bevacizumab discontinuation before surgery.

Kesmodel *et al.* [17] showed that the addition of bevacizumab to the neoadjuvant cytotoxic CTX in patients with liver metastases from CRC did not result in an increase in the postoperative complications compared with that in patients receiving neoadjuvant cytotoxic alone (49 vs. 43%). In addition, there was no association between the incidence of postoperative complications and the time interval between the discontinuation of bevacizumab and surgery, but in the event, all patients underwent surgery at least 30 days after the last dose of bevacizumab.

Our own study has examined wound healing and bleeding complications in patients who were receiving bevacizumab shortly before or during the insertion of an indwelling central venous access port. Although this is a technique of relatively low invasivity, it may, nonetheless, be associated with a degree of morbidity in its own right, and this must be taken into account in the evaluation of our own results.

Skin erosion has been reported to occur in 1–3% of the patients who have had a port inserted [18–21]. This seems to be a risk, albeit a small one, of the technique itself. A recent report by Almhanna *et al.* has described two cases of standard titanium ports eroding through the skin in patients treated with bevacizumab. One patient with locally advanced breast cancer was started on bevacizumab (10 mg/kg) 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 [22]. 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.

In summary, 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 indwelling central venous access port may safely be inserted a short time before or during bevacizumab treatment without increasing periprocedural morbidity.

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