Wound healing and catheter thrombosis after implantable venous access device placement in 266 breast cancers treated with bevacizumab therapy

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The aim of this study was to determine, in a population with metastatic breast cancer treated with bevacizumab therapy, the incidence of wound dehiscence after placement of an implantable venous access device (VAD) and to study the risk of catheter thrombosis. This study enrolled all VADs placed by 14 anesthetists between 1 January 2007 and 31 December 2009: 273 VADs in patients treated with bevacizumab therapy and 4196 VADs in patients not treated with bevacizumab therapy. In the bevacizumab therapy group, 13 cases of wound dehiscence occurred in 12 patients requiring removal of the VAD (4.76%). All cases of dehiscence occurred when bevacizumab therapy was initiated less than 7 days after VAD placement. Bevacizumab therapy was initiated less than 7 days after VAD placement in 150 cases (13 of 150: 8.6%). The risk of dehiscence was the same from 0 to 7 days. In parallel, the VAD wound dehiscence rate in patients not receiving bevacizumab therapy was eight of 4197 cases (0.19%) (Fisher's test significant, $P<0.001$). No risk factors of dehiscence were identified: anesthetists, learning curves, and irradiated patients. VAD thrombosis occurred in four patients (1.5%). In parallel, VAD thrombosis occurred in 51 of 4197 patients (1.2%) not receiving bevacizumab therapy (Fisher's test not significant; $P=0.43$). Bevacizumab therapy was permanently discontinued in five patients related to wound dehiscence and in one patient due to extensive skin necrosis. These data suggest the need to observe an interval of at least 7 days between VAD placement and initiation of bevacizumab therapy to avoid the risk of a wound dehiscence requiring chest wall port explant. The risk of VAD thrombosis does not require any particular primary prevention. *Anti-Cancer Drugs* **22:1020–1023** © **2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Implantable venous access devices (VADs) are widely used in oncology at all stages of disease. The complications usually reported consist of infection (0.2 infections per 1000 catheter-days), VAD thrombosis (2–4%), and catheter occlusion (1–6%). VAD extrusion with skin erosion is often a late complication reported in less than 1% of cases and is generally associated with cachexia, infection, or a technical error during placement [1].

Bevacizumab is a monoclonal antibody that binds to vascular endothelial growth factor (VEGF), a key factor in vasculogenesis and angiogenesis. Under physiological conditions, VEGF is an important factor involved in the healing process by promoting the formation of granulation tissue through increased vascular permeability. Bevacizumab delays healing and can predispose to bleeding [2]. Bevacizumab therapy is widely used, particularly for the treatment of metastatic colon cancer, metastatic non-squamous non-small cell lung cancer, and HER2-negative metastatic breast cancer. A recent review summarizes the data available on the use of VEGF-targeted therapies and their effect on perioperative wound complications [3]. Another known effect of bevacizumab therapy concerns the increased risk of venous thrombosis. Although the Summary of Product Characteristics (*www.ema.europa.eu*) provides useful information about the precautions required in the case of surgery, only limited data are available with regard to the required interval between minimally invasive procedures and initiation of bevacizumab therapy.

The objectives of this study were to determine the incidence of wound dehiscence after VAD placement in a population with metastatic breast cancer treated with bevacizumab therapy, to specify the optimal interval between VAD placement and initiation of bevacizumab therapy, to study the risk of catheter thrombosis in this population, and to highlight the possibility of other potential complications.

Patients and methods

The medical charts of 266 patients treated with bevacizumab therapy in a single cancer center between

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1 January 2007 and 31 December 2009 were reviewed up to 1 March 2010. An implantable VAD was placed in all patients, but seven patients in whom this procedure was performed in another institution were excluded. Indications for bevacizumab therapy in the 266 patients included were metastatic breast cancer. The VAD was removed and replaced in 14 patients with resumption of bevacizumab therapy after the second VAD placement. A total of 273 VADs were therefore included in this study. Over the same period, 4196 VADs were placed in patients not receiving bevacizumab therapy. All patients within this bevacizumab therapy group received an additional chemotherapy (paclitaxel; docetaxel; 5FU, epirubicin, cyclophosphamide). All these patients have received a steroid prophylaxis (40 mg methylprednisolone the day before, immediately before, and the day after chemotherapy for docetaxel; 80 mg methylprednisolone immediately before chemotherapy for paclitaxel and 5FU, epirubicin, cyclophosphamide). No patients with wound healing have received a weekly paclitaxel regimen.

VADs were placed in the operating room according to a standardized protocol by a team of 14 anesthetists including seven juniors anesthetists: 90% of VADs were placed under local anesthesia and 10% were placed under general anesthesia.

In patients with breast cancer, the VAD was placed on the opposite side to the lesion. Thirteen VADs were placed on the side of a previously irradiated breast (contralateral breast cancer).

All VADs used in this series were Hélioscopie 6.5 F preconnected access ports (EV6P 1020) with a silicone catheter and a silicone-coated low-profile port (Vienne, France).

The choice of vein for VAD placement was left to the operator's discretion (internal jugular vein with ultrasound guidance or subclavian vein): 172 VADs were placed in the internal jugular vein (53%), 154 (47%) VADs were placed in the subclavian vein, and four VADs were placed in the femoral vein.

The port compartment was as narrow as possible to avoid any risk of inversion and the port was not sutured to deep planes. The 1.5-cm wound in the line of the axillary fold was closed by a running Vicryl 3–0 suture (Ethicon. inc (Johnson and Johnson Company, USA)). Two operators also closed the deep plane of all their VADs with interrupted sutures.

Results

One patient was lost to follow-up.

(1) In the bevacizumab therapy group, 13 cases of wound dehiscence were observed in 12 patients requiring removal of the device (4.76%). All cases of wound dehiscence occurred when administration of bevacizumab was started during the 7 days after VAD placement. Bevacizumab therapy was initiated less than 7 days after VAD placement in 150 cases, requiring removal of the device in 8.6% of patients. The risk of dehiscence was the same from 0 to 7 days The VAD wound dehiscence rate in the 123 cases in whom bevacizumab therapy was started after 7 days was zero. The VAD wound dehiscence rate in patients not receiving bevacizumab therapy over the same period (between 1 January 2007 and 31 December 2009) was eight of 4197 cases (0.19%) (Fisher's test significant, $P < 0.001$). Wound dehiscence was rare in this setting, clearly related to a technical error during closure and did not raise any subsequent closure problems. Conversely, the peculiarity with bevacizumab therapy is linked to the persistent closure problems. One patient received a first VAD with treatment initiated on day 6, followed by wound dehiscence requiring removal of the device; a second VAD with treatment initiated on day 7, also followed by wound dehiscence requiring removal of the device; and a third VAD with treatment initiated on day 25 that remained functional and was kept in place. One patient developed wound dehiscence at the site of an old VAD removed for obstruction, requiring surgical revision and prolonged interruption of chemotherapy. Another patient required surgical revision with excision-suture some time after removal of the VAD and after stopping bevacizumab therapy. However, the VAD was replaced in four patients with treatment initiated the same day for one case and after 48 h for the other three cases without dehiscence. Five of the 13 cases of wound dehiscence were accompanied by local superinfection, associated with systemic superinfection in one case (four Meth-S *Staphylococcus aureus* infections and one *Staphylococcus lugdunensis* infection). Finally, six patients had to stop bevacizumab therapy and chemotherapy after wound dehiscence and seven patients continued the treatment. No case of wound dehiscence was observed in the 13 previously irradiated patients. This notion was sought to ensure that the radiation screening was not the cause of wound healing. There was not a learning curve for port placement in these results and the knowledge of the risk with bevacizumab therapy has not reduced the incidence of wound healing. There were no differences among anesthetists. Juniors placed 70 ports with six dehiscences, whereas seniors placed 80 ports with seven dehiscences.

(2) In this series of 273 VADs with bevacizumab therapy, on 1 March 2010, 243 VADs were in place and 56 patients had died. Three VADs had been removed after completion of treatment. The other indications for VAD removal were:

(i) One case of Meth-S *S. aureus* local infection without wound dehiscence (0.31%) requiring removal of the device 10 days after placement;

(ii) Six VADs were removed due to mechanical problems other than thrombosis (1.8%);
(iii) Six VADs were removed due to device thrombosis (1.8%).

Thrombosis occurred 2.5 months, 3 months, 5 months, 7 months, and 22 months after VAD placement, which was concomitant with initiation of bevacizumab therapy for the five patients. The VAD thrombosis rate in patients not receiving bevacizumab therapy was 51 of 4197 cases (1.2%) (Fisher's test not significant, $P = 0.43$). All cases of thrombosis in patients treated with bevacizumab therapy were treated by anticoagulants and by removal of the catheter. In the group not receiving bevacizumab therapy, 28 of 51 (50%) patients were treated conservatively by anticoagulants without removal of the catheter.

Twenty-five (7.6%) VADs in this series were therefore removed because of a complication.

Discussion

VAD placement is the standard of care in our institution for all patients who receive chemotherapy or bevacizumab therapy, more so when they are metastatic. The VAD wound dehiscence rate is low in the same period of port placement (0.19%) but the VAD wound dehiscence rate is 4.76% after bevacizumab therapy and 8.6% when bevacizumab therapy is started during the 7 days after VAD placement.

It is now generally accepted that VADs can be used immediately after placement, and Ozdemir *et al.* [4] reported only one case of wound dehiscence in a series of 180 patients who received chemotherapy on the day of placement, but 11 (6.1%) cases of thrombosis were also reported in this series. However, Laurenzi *et al.* [5] showed that the risk of catheter colonization all caused by *Staphylococcus*, occurring both through extraluminal and endoluminal routes, was higher when the device was used earlier.

The minimum interval between minimally invasive procedures and initiation of bevacizumab therapy has been poorly documented, and published data tend to be contradictory. The data reported in this study are very similar to those published by Zawacki *et al.* [6], who reported a wound dehiscence rate of 10.2% in patients receiving bevacizumab therapy during the week after VAD placement. In this study, six of 195 ports (3.1%) were associated with wound dehiscence requiring port removal. The mean interval between bevacizumab dosing and port placement in patients without dehiscence was 16.9 days. The mean interval in patients with dehiscence was 10.8 days. A two-tailed Wilcoxon test was performed, which yielded a P value of 0.0150. Zawacki *et al.* [6] concluded that wound dehiscence within 10 days of port placement had a higher incidence of wound dehiscence. Fong *et al.* [7] showed that the absolute risk of wound dehiscence was 2.1 versus 0.5% when the VAD was placed during the previous week (relative ratio: 4.3, $P < 0.022$). In a poster presented at the 2006 Gastrointestinal Cancer Symposium, Berry *et al.* [8] reported a low wound dehiscence rate of 1.1% (six of 534 patients) and one (0.6%) wound healing complication in 182 patients who started bevacizumab therapy within 7 days after port placement. Finally, Almahanna *et al.* [9] reported a series of three patients with extrusion of the port several months after placement.

The five superinfections are important to consider. Poor healing is a major complication of VAD, associated with a risk of infection and interfering with continuation of chemotherapy and the patient's subsequent management, resulting in a real risk of loss of chance.

The classical increased risk of thrombosis with bevacizumab therapy was not observed in this series. The thrombosis rate in our hospital is low, probably reflecting very careful device placement (limited number of vein punctures, use of ultrasound, active search for a history of thrombosis in the case of repeat placement).

Conclusion

These data suggest the need to observe an interval of at least 7 days between VAD placement and initiation of bevacizumab therapy. The risk of VAD thrombosis does not require any particular primary prevention. Poor healing is a major complication of VAD, interfering with continuation of chemotherapy and the patient's subsequent management, resulting in a real risk of loss of chance.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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