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Timing of Administration of Bevacizumab Chemotherapy Affects Wound Healing Following Chest Wall Port Placement

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Abstract

BACKGROUND—The authors investigated how the timing of administration of bevacizumab, a targeted VEGF-inhibiting chemotherapeutic agent, affects the risk of wound healing in patients undergoing chest wall port placement.

METHODS—Retrospective search of an IRB approved, HIPAA compliant database between 2002 and 2008 identified 1108 port placements in patients who were treated with bevacizumab. 120 of these ports eventually required explant. Data analyzed included patient demographics, indication for port removal, and schedule of bevacizumab therapy.

RESULTS—Wound healing complications requiring port explant were seen in 0.9% of placements (10/1108). When bevacizumab was given within 1 day of port placement, the absolute risk (AR) of port removal for wound dehiscence was 2.4% (2/82), compared to 0.3% (3/1021) when 2 or more days had passed between port placement and bevacizumab administration, yielding a statistically significant relative risk (RR) of 8.1 ($p < 0.02$). Similarly, when bevacizumab was administered within 7 days of port insertion, there was a significant RR of dehiscence-related port explant (AR 1.4% vs 0.1%, RR 11.5, $p < 0.028$). However, no significant RR for dehiscence-related port removal was observed when bevacizumab was administered within 14 days (AR 0.9% vs 0.2%, RR 6.2, $p < 0.09$) or 30 days (AR 0.7% vs 0.2%, RR 3.7, $p < 0.23$) of port placement.

CONCLUSION—The risk of a wound dehiscence requiring chest wall port explant in patients treated with bevacizumab is inversely proportional to the interval between bevacizumab administration and port placement, with significantly higher risk seen when the interval is less than 14 days.

Condensed abstract

The risk of a wound dehiscence requiring chest wall port explant in patients treated with bevacizumab is inversely proportional to the interval between bevacizumab administration and

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port placement. There is significantly higher risk of wound dehiscence when the interval between bevacizumab administration and chest wall port placement is less than 14 days.

INTRODUCTION

Vascular endothelial growth factor (VEGF) is a potent promoter of neovascularization in both normal and malignant vasculature¹. In normal tissues, VEGF plays an integral role in vascular permeability and angiogenesis², which are vital in embryonic development³, inflammation⁴ and wound healing⁵. In malignancy, VEGF is an important regulator of tumor-induced angiogenesis⁶. Bevacizumab (Avastin, Genentech, San Francisco, CA) is a recombinant, humanized monoclonal antibody to VEGF⁷. Bevacizumab is FDA approved for use in combination with chemotherapy regimens in the treatment of solid tumors⁸: metastatic colon cancer⁹, non small cell lung cancer¹⁰, and metastatic breast cancer¹¹. Toxicities to bevacizumab therapy include gastrointestinal perforation, hemorrhage, thromboembolic events, hypertension, proteinuria and wound healing complications^{12–13}. Bevacizumab is administered intravenously every 2 weeks, due to its long half-life of 21 days¹⁴.

Chemotherapeutic agents are typically administered through an implanted chest wall port¹⁵ to minimize venous sclerosis from chemotherapy and to maximize patient comfort. Whether placed surgically or with radiologic guidance, port placement requires a 2–3 cm incisional wound to accommodate the port reservoir. Wound healing complication rates are low following image guided port placement by interventional radiologists, ranging from 0.9%¹⁶ to 1.3%¹⁷. However, inhibition of VEGF by bevacizumab in the treatment of malignancy could also reduce VEGF-mediated angiogenesis required for optimal wound healing of chest wall port incisions. Thus, the purpose of the study is to determine how the timing of administration of bevacizumab affects the risk of wound healing complications in patients undergoing chest wall port placement.

PATIENTS AND METHODS

A waiver of authorization was obtained from our Institutional Review Board for this retrospective study. The database used for this review was registered and approved by our Institutional Review Board in compliance with the Health Insurance Portability and Accountability Act.

Patient and Disease Characteristics

We retrospectively reviewed data from patients who underwent chest wall port placement by an interventional radiologist at our institution and received prior, concurrent, or subsequent administration of bevacizumab between May 2002 and April 2008. Demographics for patients undergoing port explant are shown in Table 1. We defined a “wound healing complication” as dehiscence of port reservoir or venotomy incision, erosion of skin over the port reservoir, or non-healing access needle puncture site.

Chest Wall Port Placement

Chest wall port placement was performed by an experienced, fellowship-trained interventional radiologist. Briefly, ultrasound guidance was used to access a central vessel (typically an internal jugular vein), and a guidewire was placed into the inferior vena cava. A 2–3 cm incision was made over the chest wall to accommodate the port reservoir (Bard, Murray Hill, NJ; single or double lumen). The port catheter was tunneled from the chest wall site to the venotomy, and the catheter was placed into the right atrium through a peel away sheath. In patients whose port would be used the same day, the incision closed with 4-0 Dexon (Ethicon, Somerville, NJ), followed by a running subcuticular closure, and Steri-Strips (3M, St. Paul, MN). In the remaining patients who would receive treatment on a subsequent day, the incision was closed in layers with 4-0 Dexon, followed by Dermabond (Ethicon, Somerville, NJ), and Steri-Strips. Prophylactic antibiotics (1 gm Cefazolin intravenously) were only given to patients whose absolute neutrophil count was less than 1000 before the procedure.

Data Analysis

In order to determine the effect of timing of bevacizumab administration on wound healing complications, we calculated the total length of time of port placement and total length of time of bevacizumab therapy, as well as the time interval between port placement and administration of bevacizumab for all patients, those who experienced wound healing complication, and those who did not experience wound healing complications (Table 1). Comparison between the group of patients that experienced wound healing complication and the group that did not were performed using two-sided t-tests and chi-square tests. To minimize underlying biochemical differences between these groups of patients, we calculated the mean serum levels of biochemical markers which could affect or be related to wound healing capacity: albumin (nutritional status), INR liver synthetic function), blood glucose (diabetes), and absolute neutrophil count (infection fighting capacity). We also calculated the relative risk of wound dehiscence requiring port explant for patients who underwent port placement within 1, 7, 14, and 30 days of bevacizumab administration (Table 3). Confidence intervals and p-values were calculated according to the method described by Morris and Gardner¹⁸.

RESULTS

During the 72 month period, 1059 patients on or to be treated with bevacizumab underwent 1108 port placements: 1014 patients with 1 port placed, 41 patients with 2 ports placed, 4 patients with 3 ports placed. 120 of the 1108 ports were subsequently removed. 0.9% (10/1108) ports were removed because of a wound healing complication. Other indications for port removal include completion of therapy (n=76, 7%), infection without wound healing complication (n=26, 3%), pain (n=3, 0.3%), fever (n=2, 0.2%), and port malfunction (n=2, 0.2%). There was no significant difference in the distribution of age, gender, race, or primary malignancy of patients who experience wound healing complications when compared with those who did not experience wound healing complications (Table 1).

There was no significant difference in the proportions of patients who received bevacizumab before, during, or after port placement when comparing the group of patients who experienced wound complications to the group that did not ($p < 0.75$). For example, 80% (8/10) of patients with wound healing complications began bevacizumab therapy after port placement compared to 84% (92/110) in patients without wound healing complications. There were no significant differences in serum levels of albumin, international normalized ratio (INR), glucose, or absolute neutrophil count (ANC) between patients who experienced wound healing complications and those that did not.

Patients who experienced wound healing complications had a shorter duration of port implantation than patients who did not (216 $\pm$ 223 days vs 431 $\pm$ 342 days, $p < 0.02$). In addition, there was a significantly shorter time interval between port placement and bevacizumab administration in patients who experienced wound healing complications compared to those that did not (55 $\pm$ 96 days vs 262 $\pm$ 369 days, $p < 0.001$). However, there was no significant difference in the total length of bevacizumab therapy between patients who experienced wound healing complications compared to those that did not (214 $\pm$ 171 days vs 300 $\pm$ 328 days, $p < 0.19$). We observed 5 cases of incisional wound dehiscence, 2 cases of a non-healing puncture site, and 3 cases of erosion over the port reservoir (Table 2). There was a trend toward shorter interval between port insertion and bevacizumab therapy for patients who experienced wound dehiscence (10 $\pm$ 16 days) vs those that experienced non-healing puncture sites (91 $\pm$ 127 days) or erosions over the reservoir (104 $\pm$ 151 days), although this difference did not reach significance ($p < 0.19$).

To determine the degree to which the interval between port insertion and bevacizumab therapy affects the risk of wound dehiscence requiring port explants, we calculated the absolute risk (AR) and relative risk (RR) of wound dehiscence when the interval between port placement and bevacizumab therapy was less than 1, 7, 14 and 30 days (Table 3). When bevacizumab was given within 1 day of port placement, the absolute risk of port removal for a wound dehiscence was 2.4% (2/82). This was higher than the 0.7% (3/1021) absolute risk when 2 or more days had passed between port placement and bevacizumab administration, yielding a statistically significant relative risk of 8.1 ($p < 0.02$). Similarly, when bevacizumab was administered within 7 days of port insertion, there was a significant relative risk of port explant for wound dehiscence (AR 1.4% vs 0.5%, RR 11.5, $p < 0.028$). However, no significant relative risk was observed for dehiscence-related port removal when bevacizumab was administered within 14 days (AR 0.9% vs 0.2%, RR 6.2, $p < 0.09$) or 30 days (AR 0.7% vs 0.2%, RR 3.7, $p < 0.23$) of port placement.

DISCUSSION

Wound healing complications with bevacizumab therapy were first recognized during the pivotal phase III trial of bevacizumab, which was conducted on 813 previously untreated patients with metastatic colorectal cancer⁹. The control arm consisted of patients who received irinotecan, 5-fluorouracil (5-FU), and leukovorin (LV) while the treatment arm added bevacizumab as targeted therapy. In patients who underwent surgery after beginning study treatment, 15% (6/39) of patients in the treatment arm experienced wound healing/bleeding complications compared with 4% (1/25) in the control arm¹⁹. To investigate how

the interval between bevacizumab therapy and surgery affects the risk of wound healing complication, Scappaticci et al performed a metaanalysis²⁰ which included patients from the pivotal phase III trial, as well as patients from a trial comparing 5-FU/LV with or without bevacizumab²¹. In patients who underwent surgery after beginning study treatment, 3.4% (1/29) experienced wound healing complications in the chemotherapy alone arm compared to 13% (10/75) of patients in the bevacizumab+chemotherapy arm, however this difference did not reach significance ($p<0.28$). Of these 10 patients who experienced wound healing complication after surgery with bevacizumab+chemotherapy, the time interval between bevacizumab and surgery were: 5 patients within 0–29 days, 5 patients within 30–59 days, and 0 patients greater than 60 days. D’Angelica et al²² also found no significant difference in postoperative complications with patients who were treated with bevacizumab an average of 6.9 weeks prior or 7.4 weeks after surgery when compared to a group of matched historical controls. Currently, the precise timing to hold bevacizumab prior to and/or following surgery to avoid postoperative wound healing complications is not clear²³, but an interval of at least 5 weeks²⁴ and up to 8 weeks^{25–26} has been suggested.

The half life of bevacizumab is 21 days, and with a typical clinical dose of bevacizumab of 5 mg/kg, VEGF concentrations can be reduced to undetectable levels in serum at doses as low as 0.3 mg/kg¹⁴. This suggests that VEGF inhibition following bevacizumab therapy may be present for more than 4 half lives (84 days, 12 weeks)²⁷. However, wound healing angiogenesis mediated by VEGF produced by stimulated macrophages takes place between 4 and 14 days post incision²⁸. Therefore, despite the potentially long acting effect of bevacizumab, the most important period for VEGF inhibition by bevacizumab that could result in poor wound healing and dehiscence should be within the first two weeks after the incision. Postoperative status, systemic chemotherapy, low serum albumin, or other factors relating to the patient’s overall status might increase the time required for the completion of wound healing angiogenesis to greater than 14 days. Typically, patients undergoing chest wall port placement have a near normal physical status, which is better than the clinical status of patients in a postoperative state. Thus, it is not surprising that in our study we identified an increased risk of wound healing complications in patients when bevacizumab was administered within 14 days of port placement, while studies of surgical patients (see previous paragraph) showed wound healing complications up to 60 days following surgery. Our results correlate well with the work of Zawacki et al, who found that patients receiving bevacizumab within 10 days of port placement had a higher incidence of wound dehiscence²⁹.

In addition to wound dehiscence, we also observed a high number of puncture site wounds and erosions which may be related to bevacizumab therapy. Although puncture site wounds and erosions have a different mechanism of injury than surgical incisions, angiogenesis likely plays a role in wound repair in both of these classes of repetitive traumas. Thus, we anticipate that both non-healing puncture site wounds and skin erosions over the port site would be seen at higher rates in patients treated with bevacizumab than in patients treated with other chemotherapies.

Our study has several limitations. First, because wound healing complications following chest port placement occurs infrequently, the small sample size of the study makes it

difficult to determine the exact cutoff for the interval at which bevacizumab administration increases the risk of wound healing complication following mediport placement. There is a potential selection bias, because we only evaluated wound healing complications in patients who eventually required port explant. It is possible there is a small subset of patients for which a wound healing complication occurred but port explant was not necessary. Our study is also limited by its retrospective nature, which surveyed port placements and removals over a 6 year period.

In conclusion, the risk of a wound dehiscence requiring chest wall port explant in patients treated with bevacizumab is inversely proportional to the interval between bevacizumab administration and port placement, with significantly higher risk seen when the interval is less than 14 days. This data suggests that those patients on or beginning typical biweekly bevacizumab therapy who require chest wall port placement may benefit from skipping a cycle, or delaying the onset of therapy at least 14 days after port placement, to reduce the risk of subsequent wound dehiscence.

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Table 1

Patient Demographics

Parameter	All N=120	Wound Healing Complication		P-value
		Yes N=10	No N=110	
Age	56(14)	55(17)	56(13)	0.98
Gender				
Males	64 [53]	6 [60]	58 [53]	0.66
Females	56 [47]	4 [40]	52 [47]	
Race				
White, Non-Hispanic	86 [72]	6 [60]	80 [73]	0.78
Black, Non-Hispanic	12 [10]	2 [20]	10 [9]	
Asian	11 [9]	1 [10]	10 [9]	
White, Hispanic	8 [7]	1 [10]	7 [6]	
Other/Unknown	3 [3]	0 [0]	3 [3]	
Primary Malignancy				
Colorectal	98 [82]	7 [70]	91 [83]	0.16
Breast	11 [9]	1 [10]	10 [9]	
Appendiceal	5 [4]	0 [0]	5 [5]	
Lung	2 [2]	1 [10]	1 [1]	
Other	4 [3]	1 [10]	2 [3]	
Biochemical Markers				
Albumin	3.6 [0.7]	3.6 [0.7]	3.3 [0.7]	0.22
INR	1.1 [0.2]	1.1 [0.2]	1.1 [0.2]	0.5
Glucose	113 [46]	113 [46]	114 [38]	0.95
ANC	5.4 [4.6]	5.3 [4.6]	6.7 [5.1]	0.4
Timing of Bevacizumab Chemotherapy				
Completed therapy <i>before</i> port placement	6 [5]	1 [10]	5 [5]	0.75
Began therapy <i>after</i> port placement	100 [83]	8 [80]	92 [84]	
Therapy <i>before and after</i> port placement	14 [12]	1 [10]	13 [12]	
Duration of Bevacizumab Therapy	293 (318)	213 (171)	300 (328)	0.19
Duration of Port Implantation	413 (338)	216 (223)	431 (342)	0.02
Interval between Port Insertion and Bevacizumab	245 (359)	55 (96)	262 (369)	0.0001

Note.- Duration and Interval data is expressed in days. Values in parentheses are standard deviation. Values in brackets are percentages.

Table 2

Wound Healing Complication in Patients Treated with Bevacizumab

Individual Patients	Timing of Bevacizumab Therapy	Duration of Bevacizumab Therapy	Duration of Chest Port Implantation	Interval Between Port Insertion & Bevacizumab
Patient 1	After port	321	109	1
Patient 2	After port	168	240	1
Patient 3	After port	110	19	5
Patient 4	After port	42	23	6
Patient 5	Before port	56	48	39
Patient 6	After port	492	465	1
Patient 7	After port	155	369	181
Patient 8	Before and after port	243	91	6
Patient 9	After port	55	114	29
Patient 10	After port	490	685	279
Summary				
Incisional Wound Dehiscence		216 (191)	177 (182)	10 (16)
Non-healing Puncture Site		324 (238)	417 (68)	91 (127)
Erosion over Reservoir		263 (217)	297 (336)	104 (151)

Note.- Duration and interval data is expressed in days. Summary data is expressed as averages. Values in parentheses are standard deviations.

Table 3
Effect of Timing of Bevacizumab Administration on Wound Dehiscence Following Chest Wall Port Placement

Interval Between Port Placement and Bevacizumab	Wound Healing Complication		Absolute Risk	Relative Risk	Confidence Interval	P-value
	Yes	No				
0-1 day	2	82	0.024	8.1	1.4-47.9	0.02
2+ days	3	1021	0.0029			
<7 days	4	281	0.014	11.5	1.3-102.9	0.028
7+ days	1	822	0.0012			
<14 days	4	427	0.0092	6.2	0.7-56.0	0.09
14+ days	1	676	0.0015			
<30 days	4	570	0.0069	3.7	0.4-33.1	0.23
30+ days	1	533	0.0018			