

Does Neoadjuvant Bevacizumab Increase Surgical Complications in Breast Surgery?

M. Golshan, MD¹, J. E. Garber, MD², R. Gelman, PhD², Nadine Tung, MD³, B. L. Smith, MD, PhD⁴, S. Troyan, MD¹, C. C. Greenberg, MD¹, E. P. Winer, MD², and P. Ryan, MD, PhD⁵

¹Department of Surgery, Brigham and Women's Hospital, Boston, MA; ²Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA; ³Department of Medical Oncology, Beth Israel Deaconess Medical Center, Boston, MA; ⁴Department of Surgery, Massachusetts General Hospital, Boston, MA; ⁵Department of Medical Oncology, Massachusetts General Hospital, Boston, MA

ABSTRACT

Background. Neoadjuvant chemotherapy is being increasingly used in operable breast cancer. There are limited data on the safety of bevacizumab (bev) in the neoadjuvant setting. We sought to explore the safety of neoadjuvant cisplatin/bev in a protocol for triple negative breast cancer (TNBC).

Materials and Methods. A total of 51 patients with confirmed TNBC were enrolled in a single-arm trial of neoadjuvant cisplatin plus bev. Of the 51 patients, 28 with confirmed TNBC were enrolled in our trial of single-agent neoadjuvant cisplatin. Two-sided Fisher exact test were used for comparing the 2 trials.

Results. The 51 patients received neoadjuvant protocol therapy with cisplatin/bev and underwent definitive local therapy. Breast conserving therapy (BCT) was performed in 29 (57%) and mastectomy with or without reconstruction in 22 (43%). Postoperative complications were reported in 22 patients (43%); 4 (8%) required explanation of expanders. Also, 28 patients completed neoadjuvant cisplatin therapy. BCT was performed in 13 (46%) and mastectomy with or without reconstruction in 15 (54%). Postoperative complications were reported in 11 patients (39%). None of the 5 reconstructions were lost. We compared all toxicities between the two trials ($P = .81$ NS), and wound healing related complications between the two trials ($P = .10$ NS).

Conclusions. Cisplatin/bevacizumab and cisplatin alone neoadjuvant therapy resulted in a significant number of postoperative complications. Specifically, use of expanders/implants may be problematic for patients treated with bev. However, this was a single-arm trial; randomized controlled studies will be needed to determine the optimal use of bevacizumab in the timing of breast cancer surgery.

Preoperative or neoadjuvant systemic therapies (NAC) are being used increasingly in the treatment of breast cancer. NAC has been shown to convert inoperable breast cancer to operable breast cancer and to increase breast conserving therapy rates without a detrimental effect on overall survival.^{1,2} The use of chemotherapy, endocrine and/or targeted therapy in the preoperative setting allows for the in vivo monitoring of breast tumor response and allows for the possibility of switching to a different therapy or proceeding to surgery if the tumor progresses on NAC. Women are offered similar local therapy options including breast conserving therapy or mastectomy with or without reconstruction after NAC; one benefit to date has been an increase in breast conserving therapy with equivalent local recurrence rates. For women who elect or are recommended to undergo mastectomy, the use of immediate reconstruction increases the complexity of the surgical procedure and operative time, but it allows a woman to have a reconstructed breast at the earliest possible time. Breast cancer surgery with or without reconstruction is a clean operation with a low rate of infectious complications.³

Angiogenesis has been shown to play an important role in tumor growth and is mediated in part by the vascular endothelial growth factor (VEGF).^{4,5} Many tumors

overexpress VEGF, and studies have correlated VEGF expression with poor clinical outcome. Recently bevacizumab, an inhibitor of (VEGF), in combination with paclitaxel has been approved in the treatment of patients who have not received chemotherapy for HER2 negative metastatic breast cancer. It is now being explored in prospective clinical trials in the adjuvant and neoadjuvant settings.^{6,7} Limited data are available on bevacizumab in combination with neoadjuvant chemotherapy with respect to safety outcomes following breast cancer surgery. Increased rates of surgical complications, including arterial thrombosis and wound healing problems, have been associated with bevacizumab in the treatment of other tumor types.⁸⁻¹⁰ A single small study of preoperative therapy and breast surgery with bevacizumab in patients with locally advanced disease revealed a 39% complication rate.¹¹ We conducted two NAC trials in patients diagnosed with estrogen receptor, progesterone receptor, and HER2/neu negative breast cancer (triple negative or TNBC). In the first trial single-agent cisplatin was administered for a total of 4 cycles, and in the second trial bevacizumab was added to cisplatin for the first 3 of 4 cycles of therapy. We describe the incidence of surgical complications in these 2 breast cancer trials.

METHODS

Institutional review board approval was obtained for the 2 sequential preoperative therapy trials. The first trial of single-agent cisplatin (active between November 2004 and May 2006) administered cisplatin at 75 mg/m² every 21 days for 4 cycles. Surgery was performed a minimum of 4 weeks after the last cycle of neoadjuvant therapy. Newly diagnosed patients with T1, N1-3, M0 or T2-4, N0-3, M0 breast cancers (with tumors > 1.5 cm), negative for estrogen, and progesterone receptors defined as <1% nuclear staining by immunohistochemistry, HER2/neu 0 or 1+ by immunohistochemistry, or HER2 nonamplified by fluorescent in situ hybridization were eligible for this trial. Upfront imaging was performed with mammogram, ultrasound, and magnetic resonance imaging (MRI). A core biopsy was performed to obtain tumor tissue for study, and a clip was placed in the tumor bed. Clinically node positive women underwent ultrasound-guided fine needle aspiration of lymph nodes and if positive also underwent a completion node dissection at the completion of chemotherapy. Clinically node negative women underwent sentinel node biopsy prior to or after NAC at the discretion of the treating surgeon. Cisplatin was initiated, and 2 weeks later the patient underwent repeat imaging and core biopsy for research purposes. A minimum of 4 weeks after the completion of NAC surgery was performed after review of the

imaging, clinical imaging, and a joint decision of the surgeon and patient. An axillary lymph node dissection was performed in all patients with a positive sentinel lymph node biopsy or a fine-needle biopsy positive lymph node prior to the induction of NAC. Patients undergoing mastectomy met with a reconstruction surgeon prior to definitive surgery. Surgical technique was at the discretion of the surgeon and included the use of electrocautery, knife, scissors, and/or harmonic scalpel. No patients received tumescence for their mastectomy. Patients received chemotherapy with doxorubicin and cytoxan with or without paclitaxel (at the discretion of the treating oncologist), beginning a minimum of 3 weeks after definitive local therapy.

The second trial was conducted between November 2006 and November 2008. The patient selection criteria, imaging, and initial core biopsy mirrored our first trial. The imaging and core biopsy at 2 weeks were not done in this trial. In addition to cisplatin at 75 mg/m², bevacizumab at 15 mg/kg was given for the first 3 of 4 cycles of therapy. Surgery was performed a minimum of 6 weeks after the last cycle of bevacizumab. Decisions on the type of surgery offered were the same across both trials. After a minimum of 3 weeks following definitive surgery, bevacizumab with established chemotherapy (dose dense doxorubicin and cyclophosphamide followed by dose dense paclitaxel) was administered. Patients with wound complications immediately postoperatively did not restart postoperative therapy until the complication resolved. We compared the 2 trials for all surgical complications and specific categories of complications, both in all patients and the subset that underwent reconstruction. We collected all surgical complications by a detailed surgical follow-up and chart review for all operative cases at 2 weeks, 6 weeks, 3 months, 6 months, and yearly. These were performed in addition to any subspecialty appointment that the patient attended. Specifically, we collected data on hematomas, abscesses, seromas requiring aspiration and the volume aspirated, native flap necrosis, reconstruction flap necrosis, and cellulitis that required antibiotics. Fisher exact test was used for these comparisons, and power calculations are based on the exact binomial distribution. All *P* values are two-sided, and there was no adjustment for multiple comparisons.

RESULTS

The cisplatin trial enrolled 28 patients; 51 patients enrolled in the cisplatin plus bevacizumab trial. Patient demographics were similar across the 2 trials, see Table 1. The addition of bevacizumab appeared to be associated with an increase in the percentage of patients having breast conserving therapy, from 46% to 57% despite a larger

TABLE 1 Patient demographics

	Trial 1 Platinum alone	Trial 2 Plat/bev
Number of patients	28	51
Median age, years (range)	50 (29–69)	50 (30–65)
ECOG PS 0	28 (100%)	51 (100%)
Clinical stage		
Stage IIA	15 (54%)	30 (59%)
Stage IIB	6 (21%)	18 (35%)
Stage IIIA	7 (25%)	3 (6%)
Mean tumor size by MRI, cm (range)	2.8 (1.3–10)	3.5 (1.0–11.6)
Clinical N0	17 (61%)	33 (65%)
Upfront sentinel node biopsy	15 (54%)	22 (43%)
Negative for tumor	10 (35%)	16 (31%)
Positive for tumor	5 (18%)	6 (12%)
Clinical N1	11 (39%)	18 (35%)
Upfront positive FNA	11 (39%)	18 (35%)
Breast conserving therapy	13 (46%)	29 (57%)
Mastectomy	15 (54%)	22 (43%)

initial tumor size. The time to surgery was 27 days for the cisplatin trial and 44 days for the cisplatin plus bevacizumab trial. Immediate reconstruction was performed in 5 of 15 patients undergoing mastectomy in the cisplatin alone trial, 3 with TRAM and 2 with expanders. In the cisplatin/bevacizumab trial, immediate reconstruction was performed in 8 of 22 patients who underwent mastectomy with immediate reconstruction, 2 with TRAM and 6 with expanders. Surgical complications were common across both studies (Table 2), but none of the differences were significant. It should be noted that the sample sizes were small enough that only very large true differences would have adequate (80%) power. Surgical complications included: seromas requiring multiple aspirations, wound break downs, hematomas, abscesses, and loss of reconstruction. All 8 wound breakdowns in the cisplatin/plus bevacizumab trial required operative debridement and/or

TABLE 2 Operative complications occurring within 4 weeks of surgery prior to adjuvant therapy

	Trial 1, cisplatin (n = 28)	Trial 2, cisplatin/ bev (n = 51)	P value
All complications	11 (39%)	22 (43%)	.82
Seromas requiring multiple aspirations	5 (18%)	5 (10%)	.31
Wound breakdown	2 (7%)	8 (16%)	.48
Hematoma	2 (7%)	5 (10%)	1.00
Abscess	2 (7%)	0 (0%)	.12
Loss of reconstruction	0 of 5 (0%)	4 of 8 (50%)	.10

TABLE 3 Operative complications by procedure: cisplatin trial N = 28

	Lumpectomy	Mastectomy	Mastectomy and reconstruction
Seroma	3	2	0
Wound breakdown	0	2	0
Hematoma	1	0	1
Abscess	1	1	0
Loss of reconstruction	N/A	N/A	0 of 5

TABLE 4 Operative complications by procedure: cisplatin/bev trial N = 51

	Lumpectomy	Mastectomy	Mastectomy and reconstruction
Seroma	4	1	0
Wound breakdown	2	4	2
Hematoma	4	0	1
Abscess	0	0	0
Loss of reconstruction	N/A	N/A	4 of 8

wound vacuum placement, while neither of the 2 patients in the cisplatin alone trial required the above interventions. Tables 3 and 4 describe the surgical complications for both trials in relation to the type of surgical therapy performed.

None of the 5 patients in the cisplatin trial lost their reconstructions, while 4 of 8 (50%) in the cisplatin plus bevacizumab lost their reconstruction, $P = .10$.

All 4 reconstruction losses were implant and/or expander reconstructions with partial fill or a permanent implant placement with the use of Alloderm. Patient 1 had an immediate silicone implant placement (300 cc); she underwent multiple seroma aspirations, failure of incision to heal followed by a rapidly progressive soft tissue infection, and loss of both implants. Patient 2 had a saline expander (120 cc); she underwent multiple seroma aspirations, failure of wound to heal, and subsequent removal of 1 expander after rapidly progressive soft tissue infection. Patient 3 had a saline expander (120 cc) with failure of wound to heal; expander became exposed and removed. Patient 4 had a saline expander (300 cc) with failure of wound to heal; expander became exposed and removed expander.

DISCUSSION

Increasingly NAC is being offered to patients with locally advanced and early-stage breast cancer. Surgical decision making not only involves determining whether a patient is a candidate for breast conserving therapy or

mastectomy, but also complex decision making on the use of reconstruction and the timing of surgery in relationship to the last cycle of NAC. Specific issues with reconstruction and breast surgery include the fact that many of these women have large tumors that may be node positive, necessitating the need for post-mastectomy radiation (PMRT). The complexities of radiation and reconstruction include the difficulty in adequately radiating specific fields of the chest wall.¹² From the reconstruction surgery standpoint, flap and implant complications increase significantly with the use of radiation.¹³

Studies of NAC and complications associated with surgery are few in the literature. Breast surgery is a clean surgical procedure and by definition should have a low complication rate.¹⁴ Our group has extensive experience in the use of NAC and surgery. Our group reviewed data on mastectomy performed on 180 patients in the neoadjuvant setting (not including any patients who were in the 2 trials in this present report) and found an overall complication rate of 36% for patients undergoing mastectomy after NAC. The subset of patients with mastectomy without immediate reconstruction had a 33% surgical complication rate, while the subset of patients having mastectomy and immediate reconstruction had a 45% surgical complication rate. Importantly, none of the 180 patients received bevacizumab and no implant based reconstructions were lost in this cohort (manuscript in preparation). The complication rates for breast surgery in patients undergoing local therapy first at our institution during the same time period was 12%; however, this included all patients undergoing breast surgery, many of whom did not require adjuvant chemotherapy and/or radiation therapy.

With the ever-increasing use of newer agents and targeted therapies in early-phase trials, it will be important to monitor for possible unforeseen operative morbidity against which to balance the benefit of a novel therapy. Bevacizumab has been increasingly used in solid tumors with promising results. Specific to breast cancer, several trials in the metastatic and advanced setting have all shown improvement in progression-free survival.^{7,15} With this data and preliminary work published in 2006 by Wedam et al., we looked at 2 successive trials of NAC, one with single-agent cisplatin and the follow-up trial of cisplatin and bevacizumab.¹¹ The half-life of bevacizumab in the literature is suggested to be 20 days with a wide range (11–50 days). The only previous study of the use of bevacizumab and NAC (in patients with inflammatory or locally advanced breast cancer) allowed surgery 4 weeks after the last dose of bevacizumab, and this study had an overall complication rate of 39% for patients who underwent local therapy.¹¹ In our cisplatin/bevacizumab trial, we mandated 6 weeks free of bevacizumab before surgery and held bevacizumab from the last dose of chemotherapy.

Despite these efforts, complication rates were high in both trials. Wound-related complications and loss of reconstruction were numerically higher in the cisplatin and bevacizumab trial, although this did not achieve statistical significance. Importantly, from a local therapy standpoint the loss of reconstruction is a severe complication, and despite not achieving statistical significance in this study it is a finding that requires close monitoring in future clinical trials and studies. Theories on the increased rate of wound-related complications with the use of bevacizumab point toward poor wound healing. In the case of mastectomy a possibility is that this surgery by definition creates an ischemic flap, the addition of a foreign body under tension exacerbates an already tenuous situation leading to wound healing failures. In our study, after surgery all patients received adjuvant chemotherapy with the addition of bevacizumab. However, the timing of the start of wound complications preceded the resumption of chemotherapy and often led to cessation of adjuvant chemotherapy. The loss of implant and/or expander occurred prior to any form of radiotherapy.

The literature on bevacizumab with bleeding and surgical complications is still nascent in many tumor types including breast cancer. Preclinical studies have shown that the binding and neutralization of VEGF can impair wound healing.¹⁶ In the clinical literature, a phase II study on bevacizumab in metastatic colorectal carcinoma revealed increased rates of gastrointestinal hemorrhage from 0% to 16%.¹⁷ Two studies showed numerically increased risk of wound healing complications in the colorectal surgery literature with the use of bevacizumab: 15% versus 4% and 13% versus 3%, although they did not achieve statistical significance.^{18,19} A pooled analysis looking at wound healing issues in primary colorectal surgery in patients who underwent surgery a minimum of 30 days prior to the start of bevacizumab wound complications were 1.3% versus 0.5% in the control arm. When surgery occurred during treatment on bevacizumab, the complication rate was 13% versus 1% not statistically significant.²⁰ Clearly, the immediate perioperative complications that may be associated with bevacizumab remain to be elucidated. Possibly more importantly little long-term data exist on delayed complications associated with anti-VEGF therapy. Reports in the literature on delayed complications are few; however, recent reports of delayed anastomotic events in colorectal surgery have been reported, and further careful long-term monitoring of patients will be necessary.²¹

In conclusion, in our 2 small neoadjuvant therapy trials, we found a high rate of overall complications in both studies. Reconstruction-based complications tended to be more common in the patients who received neoadjuvant bevacizumab, but this did not achieve statistical significance. These sample sizes were so small that there would

be adequate (80%) power to detect a significant difference only if the true probabilities of loss of reconstruction were as different as 1% and 81%. The 95% confidence intervals for the percent of patients with loss of reconstruction were 0%–45% for reconstruction patients on the cisplatin trial and 16%–84% for reconstruction patients on the cisplatin plus bevacizumab trial. With the numeric increase in complications seen in the implant/expander group at this time, we think that expander and implant based immediate reconstructions must be looked upon with hesitation in the setting of NAC and bevacizumab. The outcomes of two large national trials (NSABP B40 and CALGB 40603), both using neoadjuvant bevacizumab, will shed further light on the surgical complication rates and optimal sequencing of surgery when bevacizumab is given in the setting of NAC for breast cancer.

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