Analysis of the Incidence of Osteonecrosis of the Jaw and Surgical Complications with Neoadjuvant Therapy in Patients Receiving Bevacizumab

Presentations discussed in this issue:

Guarneri V et al. **Analysis of bevacizumab therapy, bisphosphonate use, and osteonecrosis of the jaw in >3500 patients treated in three large clinical trials.** San Antonio Breast Cancer Symposium 2009;**Abstract 208**.

Golshan M et al. **Surgical complications and the use of neoadjuvant bevacizumab.** San Antonio Breast Cancer Symposium 2009;**Abstract 43**.

Slides from presentations at SABCS 2009

Introduction

- Osteonecrosis of the jaw (ONJ) is a serious complication typically associated with intravenous bisphosphonate therapy.
- Cases of ONJ have been reported among patients receiving bevacizumab (bev).
  - A small retrospective analysis of patients receiving bev or sunitinib reported 16% incidence of ONJ (*Oncology* 2009;76:209).
- **Current study objectives**
  - Determine the incidence of ONJ in a large population of patients receiving bev-containing regimens as first-line therapy for locally recurrent (LR) or metastatic breast cancer (MBC) in prospective clinical trials
  - Assess whether bev administration increases risk of ONJ

Source: Guarneri V et al. SABCS 2009;Abstract 208.

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Methods

- Case reviews were performed of ONJ from clinical trials of bev-containing first-line treatment regimens for LR/MBC.
  - AVADO:
    - Randomized, placebo-controlled trial of docetaxel with bev, 7.5 or 15 mg/kg, every three weeks
  - RIBBON-1:
    - Randomized, placebo-controlled trial of chemotherapy with 15 mg/kg bev every three weeks
  - ATHENA:
    - Single-arm safety study of bev with standard, first-line non-anthracycline-containing chemotherapy conducted in the context of general oncology practice
- Comparison of ONJ incidence carried out between:
  - Bev versus placebo (PL) arms
  - Patients with and without exposure to bisphosphonates in AVADO and RIBBON-1 trials

Source: Guarneri V et al. SABCS 2009;Abstract 208.

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Study Population

- A total of 3,650 patients treated with bev were included in the analysis.
  - Randomized trials: n=1,309
  - Open-label ATHENA: n=2,251
- Median follow-up in the data sets used in this analysis:
  - Randomized trials:
    - AVADO: 10.2 mos
    - RIBBON-1 taxane/anthracycline cohort: 19.2 mos
    - RIBBON-1 capecitabine cohort: 15.6 mos
  - Open-label, non-randomized trial:
    - ATHENA: 12.7 mos

Source: Guarneri V et al. SABCS 2009;Abstract 208.

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Incidence of ONJ in Placebo-Controlled Randomized Bev Trials

	AVADO*		RIBBON-1†		Total	
Patients with ONJ/total patients	**Bev**	**PL**	**Bev**	**PL**	**Bev**	**PL**
Overall population	3/492 (0.6%)	0/238 (0%)	1/817 (0.1%)	0/412 (0%)	4/1309 (0.3%)	0/650 (0%)
Bisphosphonate exposure	1/77 (1.3%)	0/33 (0%)	1/156 (0.6%)	0/66 (0%)	2/233 (0.9%)	0/99 (0%)
No bisphosphonate exposure	2/415 (0.5%)	0/205 (0%)	0/661 (0%)	0/346 (0%)	2/1076 (0.2%)	0/551 (0%)

*Bev 7.5 and 15 mg/kg arms pooled.
†Taxane/anthracycline and capecitabine cohorts pooled

Source: Guarneri V et al. SABCS 2009;Abstract 208.

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Incidence of ONJ in the ATHENA Non-Randomized Study

	ONJ Incidence
Overall population (n=2,251)	0.4%
Bisphosphonate exposure (n=425)	2.4%*
No bisphosphonate exposure (n=1,826)	0%

*Additional risk factors for ONJ: previous dental extractions (n=2); maxillary surgery (n=1)

Source: Guarneri V et al. SABCS 2009;Abstract 208.

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Conclusions

- This analysis of the largest population of patients treated with bev for LR/MBC suggests an incidence of <1% of ONJ with bev.
  - ONJ incidence was higher among patients exposed to bisphosphonates.
    - ONJ incidence of 0.9-2.4% in bisphosphonate-exposed patients receiving bev is within the range reported with bisphosphonates alone (1-6%).
    - ONJ incidence of 0-0.2% among patients without bisphosphonate exposure is consistent with previous analysis (investigator's experience, not reported).
- Good oral hygiene, dental examination and avoidance of invasive dental procedures remain important in patients receiving bisphosphonates, irrespective of treatment with bev.

Source: Guarneri V et al. SABCS 2009;Abstract 208.

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Surgical Complications and the Use of Neoadjuvant Bevacizumab

Golshan M et al.

SABCS 2009;Abstract 43.

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Introduction

- BRCA1-deficient cells and BRCA-deficient tumors have shown susceptibility to cisplatin-based therapy in preclinical studies.
- Sporadic triple-negative breast cancer (TNBC) and BRCA1-associated breast cancers share many histopathologic features, therefore TNBC may also be susceptible to cisplatin-based therapy.
- Neoadjuvant chemotherapy is increasingly being used in operable breast cancer, but data on the safety of bevacizumab in combination with chemotherapy in this setting is limited.
- **Current study objectives:**
  - Assess the incidence of surgical complications in two sequential phase II trials for patients with TNBC evaluating neoadjuvant cisplatin and neoadjuvant cisplatin plus bevacizumab.

Source: Golshan M et al. SABCS 2009;Abstract 43.

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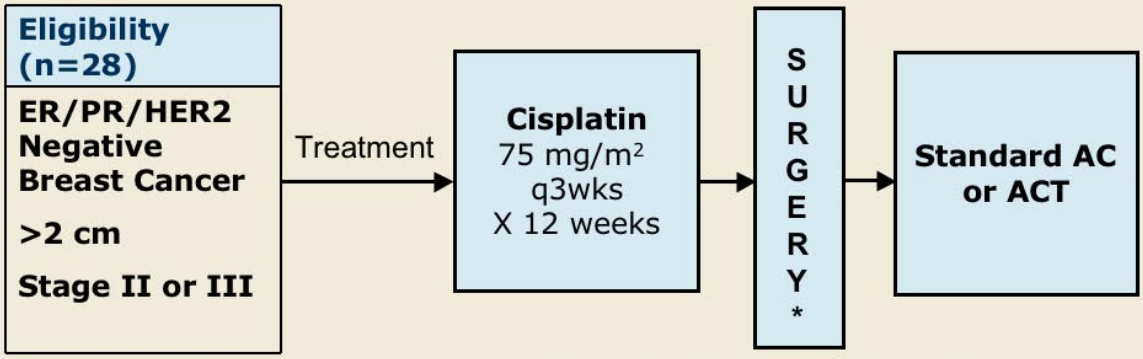
Trial #1: Neoadjuvant Cisplatin for TNBC



A= doxorubicin
C= cyclophosphamide
T= paclitaxel

*4 weeks following last chemotherapy

Source: Golshan M et al. SABCS 2009;Abstract 43.

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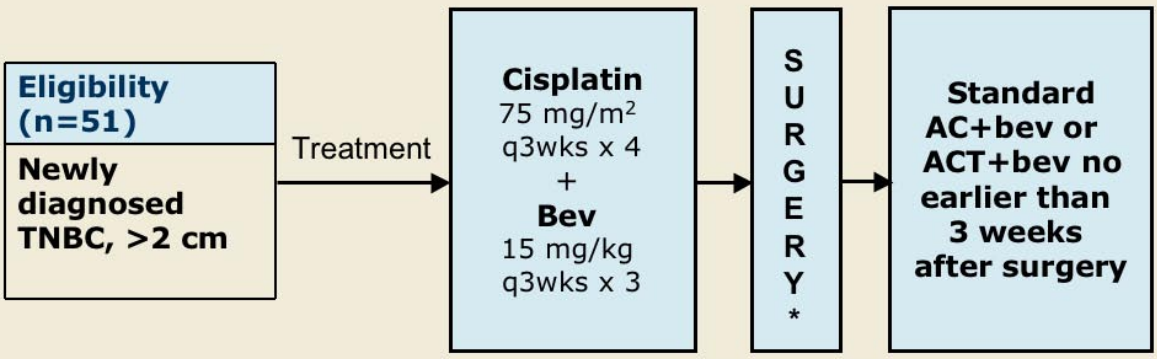
Trial #2: Neoadjuvant Cisplatin Plus Bevacizumab for TNBC



*No earlier than 6 weeks from last cycle of neoadjuvant bevacizumab

Research biopsies were obtained before treatment and at surgery.

Source: Golshan M et al. SABCS 2009;Abstract 43.

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Clinical Response and Surgical Procedures

Clinical response	Trial #1: Cisplatin alone (n = 28)	Trial #2: Cisplatin + bev (n = 51)
Complete response	14%	27%
Partial response	35%	53%
Stable disease	35%	18%
Progressive disease	14%	2%
Surgical response		
Breast conserving therapy	46%	57%
Mastectomy	54%	43%
No reconstruction (n)	10	14
Expander (n)	3	6
TRAM (n)	2	2

Source: Golshan M et al. SABCS 2009;Abstract 43.

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Surgical Complications

	Trial #1: Cisplatin alone (n = 28)	Trial #2: Cisplatin + bev (n = 51)	*p*-value
All complications	39%	43%	0.82
Seromas requiring multiple aspirations	18%	10%	NS
Wound breakdown*	7%	16%	NS
Progressive disease	14%	2%	NS
Hematoma	7%	10%	NS
Abscess	7%	0%	NS
Loss of reconstruction (n)	0% (0/5)	50% (4/8^{+})	0.10

* All of the patients with wound breakdown on Trial #2 required surgical debridement and/or wound vac placement, though the same was not required in any of the patients on Trial #1 with wound breakdown; $^{+}$ three patients with saline expanders and one with silicone implant; NS = not significant.

Source: Golshan M et al. SABCS 2009;Abstract 43.

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Summary and Conclusions

- Surgical complications were common in both preoperative cisplatin therapy single arm trials.
- Addition of bevacizumab did not increase the overall risk of surgical complications.
- Reconstruction-related complications trended higher on Trial #2 (cisplatin + bev) but did not reach statistical significance.
  - Four patients required removal of expanders or implants due to infection and/or wound healing failure.
    - Data suggests the use of tissue expanders could be problematic in patients treated with neoadjuvant bev.
- Evaluation in a randomized trial is necessary to determine the safest approach(es) to bev usage in the timing of BC surgery.

Source: Golshan M et al. SABCS 2009;Abstract 43.

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