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

Presentations discussed in this issue:


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.

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.
### 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

<table>
<thead>
<tr>
<th>Patients with ONJ/total patients</th>
<th>AVADO*</th>
<th>RIBBON-1†</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bev</td>
<td>PL</td>
<td>Bev</td>
</tr>
<tr>
<td>Overall population</td>
<td>3/492  (0.6%)</td>
<td>0/238 (0%)</td>
<td>1/817 (0.1%)</td>
</tr>
<tr>
<td>Bisphosphonate exposure</td>
<td>1/77   (1.3%)</td>
<td>0/33 (0%)</td>
<td>1/156 (0.6%)</td>
</tr>
<tr>
<td>No bisphosphonate exposure</td>
<td>2/415  (0.5%)</td>
<td>0/205 (0%)</td>
<td>0/661 (0%)</td>
</tr>
</tbody>
</table>

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

Source: Guarneri V et al. SABCS 2009;Abstract 208.
Incidence of ONJ in the ATHENA Non-Randomized Study

<table>
<thead>
<tr>
<th></th>
<th>ONJ Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population (n=2,251)</td>
<td>0.4%</td>
</tr>
<tr>
<td>Bisphosphonate exposure (n=425)</td>
<td>2.4%*</td>
</tr>
<tr>
<td>No bisphosphonate exposure (n=1,826)</td>
<td>0%</td>
</tr>
</tbody>
</table>

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

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

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.
Surgical Complications and the Use of Neoadjuvant Bevacizumab

Golshan M et al.
SABCS 2009;Abstract 43.

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.
Trial #1: Neoadjuvant Cisplatin for TNBC

Eligibility (n=28)

ER/PR/HER2 Negative Breast Cancer
>2 cm
Stage II or III

Cisplatin 75 mg/m² q3wks X 12 weeks

Treatment

Surgery *

Standard AC or ACT

*A = doxorubicin
*C = cyclophosphamide
*T = paclitaxel

*4 weeks following last chemotherapy

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

Trial #2: Neoadjuvant Cisplatin Plus Bevacizumab for TNBC

Eligibility (n=51)

Newly diagnosed TNBC, >2 cm

Cisplatin 75 mg/m² q3wks x 4 + Bev 15 mg/kg q3wks x 3

Treatment

Surgery *

Standard AC+bev or ACT+bev no earlier than 3 weeks after surgery

*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.
## Clinical Response and Surgical Procedures

<table>
<thead>
<tr>
<th>Clinical response</th>
<th>Trial #1: Cisplatin alone (n = 28)</th>
<th>Trial #2: Cisplatin + bev (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>14%</td>
<td>27%</td>
</tr>
<tr>
<td>Partial response</td>
<td>35%</td>
<td>53%</td>
</tr>
<tr>
<td>Stable disease</td>
<td>35%</td>
<td>18%</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>14%</td>
<td>2%</td>
</tr>
</tbody>
</table>

**Surgical response**

<table>
<thead>
<tr>
<th></th>
<th>Trial #1: Cisplatin alone (n = 28)</th>
<th>Trial #2: Cisplatin + bev (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast conserving therapy</td>
<td>46%</td>
<td>57%</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>54%</td>
<td>43%</td>
</tr>
<tr>
<td>No reconstruction (n)</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Expander (n)</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>TRAM (n)</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

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

## Surgical Complications

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

* 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.
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.