S0702: A Prospective Observational Multicenter Cohort Study to Assess the Incidence of Osteonecrosis of the Jaw (ONJ) in Cancer Patients with Bone Metastasis Starting Zoledronic Acid Treatment

Study Team: Van Poznak, Gralow, Unger, Hansen, Schubert, Bagramian

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Incidence of Bone Mets</th>
<th>Median Survival (m)</th>
<th>% patients with 5 Yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloma</td>
<td>95-100%</td>
<td>20</td>
<td>10%</td>
</tr>
<tr>
<td>Breast</td>
<td>65-75%</td>
<td>24</td>
<td>20%</td>
</tr>
<tr>
<td>Prostate</td>
<td>65-75%</td>
<td>40</td>
<td>25%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>60%</td>
<td>48</td>
<td>45%</td>
</tr>
<tr>
<td>Renal</td>
<td>20-25%</td>
<td>6</td>
<td>5%</td>
</tr>
<tr>
<td>Lung</td>
<td>30-40%</td>
<td>3</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

Osteonecrosis of the Jaw (ON)

- Present data has come primarily from retrospective chart reviews which has only provided coarse estimates incidence & risk factors
- ONJ in patients with Metastatic Bone Disease (MBD) receiving IV bisphosphonate (IVBP) appears to occur with a frequency that ranges from 1-10% (Woo Annals Int Med 2006, Van Poznak Oncology 2006) and appears to occur most commonly in patients with metastatic breast cancer or multiple myeloma
- The etiology of ONJ is unknown
- Management of ONJ is typically conservative
- ONJ is defined as an area of exposed bone in the maxillofacial Region that had been identified by a health care provider and had been present for 8 weeks or more in a patient who was receiving or had been exposed to a bisphosphonate, and had not had radiation therapy to the craniofacial region. (Journal American Dental Association 2006, Journal of Bone and Mineral Research 2007)
A case of ONJ

Non-healing extraction socket with exposed bone following extraction of a maxillary right molar tooth three months prior. Spontaneous exfoliation of four teeth on the opposite side of the ONJ. The remaining dentition has severe mobility @ 6m

Another case of ONJ

Extraction 1 y ago
Non-Healing

6m follow up
ONJ has progressed

12m follow up
Continued progression of ONJ

1 year later
with healing

Primary Objective:
Incidence ONJ in patients with bone metastasis for up to 3 years after starting zoledronic acid treatment

Secondary Objectives
(a) clinical presentation and natural history
(b) risk factors for the development
(c) incidence rate in different tumors
(d) correlative science & Case-Control
  • specimen bank: serum & DNA
  • imaging bank
(e) patient related outcomes
Registration & Entry (n = 7000)
Baseline Medical & Dental Evaluation & Surveys
Baseline Blood for WBC & Serum Bank
H & P and Dental evaluation q 6 months for 3 years
Cancer & Dental care as clinically indicated

Protocol Follow-Up (No ONJ)
• Study follow-up forms x 6 months
• Serum collection x 6 months
• Retrospective collection of imaging performed for clinical indications that include images of the jaw (head/neck/dental) in a subset of patients deemed as controls for cases of ONJ

Incorporating Our Dental Colleagues into S0702
• This Registry requires interdisciplinary care and data collection
• Study Appendix includes a letter to the dental health professional
  • Explaining the clinical study
  • Explaining that the study does not dictate care
  • Explaining what is being requested of them with completion of the form
  • Explaining who to contact with questions or problems
    • Locally (SWOG participating site caring for the pt)
    • Nationally (S0702 lead study team members)

The “Skeleton” of the Study Calendar as Presented in the Letter to the Dental Health Profession

<table>
<thead>
<tr>
<th>Dental exam &amp; study form</th>
<th>Base</th>
<th>6 m</th>
<th>12 m</th>
<th>18 m</th>
<th>24 m</th>
<th>30 m</th>
<th>36 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental exam</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Imaging (approx time intervals)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Eligibility

- Bone metastasis from multiple myeloma, solid tumors, or other malignancy for which intravenous bisphosphonate (IVBP) has clinical indications in the treatment of metastatic bone disease.
- Participants who have been treated with IVBP (ibandronate, pamidronate or zoledronic acid)
  - IVBP to treat low bone mass, < 3 doses of IVBP is permitted
  - IVBP to treat MBD, < 3 months of IVBP is permitted.
  - All participants must be planning to receive zoledronic acid therapy within 30 days of registration.
  - Prior exposure to oral bisphosphonate therapy permitted.

Eligibility – Cont.

- Participants must not have a pre-existing diagnosis of ONJ.
- No prior radiation to the maxillofacial area administered for therapeutic intent in the treatment of cancer.
- Participants can concurrently participate in other therapeutic and non-therapeutic clinical trials.

Latest Update

- Protocol slated for activation 11/1/08
  - Imaging submission
    - AG Mednet
    - Dental films & other images of jaw obtained as clinically indicated

AG Mednet collects images for electronic central collection
Latest Update

• Protocol slated for activation 11/1/08
  – Reimbursement for dental evaluation in pts. without dental insurance
  • Funding memorandum on SWOG website for S0702
  – Details on per-case institutional reimbursements and CCOP credit will be available soon

Study Start-Up

After local IRB approval:
• Contact AG Mednet to order hardware/software agent (see protocol and special website instructions for S0702)
• Complete AG Mednet linkage
• Order blood collection kits from SWOG Repository at U of CO
• Identify dentists who will work with your institution on the study (esp. for uninsured)
• Inform medical oncologists of study

Patient Enrollment Hints

• Identify patient beginning IVBP for metastatic bone disease
• Verify eligibility, prior BP therapy, if any
• Informed consent – incl. HIPAA, specimen banking and image submission
• Date of last dental exam
  – (if > 6 mo from planned registration, have pt. schedule dental evaluation per S0702- see protocol)
• Date of last dental imaging
  – (if > 12 mo from planned registration, have pt. schedule dental evaluation & imaging – see protocol)
Patient Enrollment Hints

• Send “letter to dental health professional” with copies of S0702 dental forms for completion
• Collect completed dental forms and dental imaging before S0702 registration
• H & P with performance status required
  – Blood work per GMP: CBC, calcium, albumin, creatinine, creatinine clearance, pregnancy test
• Interview patient to complete smoking and alcohol history plus patient reported outcome assessment on Prestudy form

Patient Enrollment Hints

• Obtain prestudy blood samples for DNA analysis & banking (optional but encouraged)
• Verify all eligibility criteria are met, dental imaging and forms obtained
• Zoledronic acid to start within 30 days of registration
• Yes!
• Register patient to S0702 on SWOG CRA workbench!

More information to come!

Look for more detailed training session at the Spring Group Meeting – your questions, challenges and success stories welcome!