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

Osteonecrosis of the Jaw (ON)
• Present data limited – on both incidence & risk factors
• Primarily from retrospective chart reviews
• Frequency of ONJ in patients with metastatic bone disease (MBD) receiving IV bisphosphonate (IVBP) approx. 1-10% (Woo Annals Int Med 2006, Van Poznak Oncology 2006)
• Most common in patients with metastatic breast cancer or multiple myeloma
• Etiology of ONJ is unknown
• Management typically conservative

Definition of ONJ: An area of exposed bone in the maxillofacial region that has been identified by a health care provider and has 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)

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 related to oral health

<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>
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<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>
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 research site caring for the pt)
    - Nationally (S0702 lead study team members)

Eligibility

- Bone metastasis or involvement from multiple myeloma, solid tumors, or other malignancy for which intravenous bisphosphonate (IVBP) has clinical indication for treatment
- 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.
- 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.

Image Submission via AG Mednet

- Electronic submission of digitized images via web based program
- Dental films & other images of jaw obtained as clinically indicated
- Submitted only for ONJ pts & matched controls
- Submit within 30 days of imaging date

AG Mednet collects images for electronic central collection

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>6 m</th>
<th>12 m</th>
<th>18 m</th>
<th>24 m</th>
<th>30 m</th>
<th>36 m</th>
</tr>
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<tbody>
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<td>X</td>
<td>X</td>
<td>X</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Imaging (approx time intervals)</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>X</td>
<td>X</td>
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<td>X</td>
<td></td>
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</tbody>
</table>

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

Patient Dx with ONJ
- Study forms q 3 m
- Study labs q 3 m
- Prospective and retrospective collection of imaging performed of the jaw

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.

Patients with metastatic bone disease initiating zoledronic acid therapy

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**Image Submission & AG Mednet**
- Desktop agent provided by AG Mednet
- Link to order form on S0702 Abstract Page
- AG Mednet has study-specific link to S0702 – not interchangeable with other studies
- See Section 15.0 of protocol
- For dental hard copies, check with inst. radiology dept for digitizing capability
- Hard copies of films can be mailed with transmittal form to CRAB if site does not have digital films or digitizer

**Funding & Credit**
- Reimbursement for dental evaluation in uninsured or underinsured patients
  - Funding memorandum on SWOG website for S0702
  - Patient/subject submits dental procedure reimbursement form to SWOG-CTI
  - Payment directly to dentist or patient
- Specimen submission
  - Kits provided for specimen submission
  - Fed Ex account number provided
  - No additional funding provided for specimen handling

**Study Start-Up**
*After IRB approval:*
- 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
- Develop recruitment strategy
- Review protocol carefully

**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 & imaging – 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
- Collect completed dental forms 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 related outcome assessment per the Prestudy Form – do this prestudy.
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
- Protocol-specific zoledronic acid to start within 30 days of registration
- Yes!
- Register patient to S0702 on SWOG CRA workbench!

Common Questions

In patients who are uninsured or underinsured, can the $200 funding support be used for more than one dental evaluation?

✓ Yes, the uninsured/underinsured patient can submit bills for more than one routine (6 month) exam to SWOG CTI. However the maximum amount available to cover routine dental exams is $200 per patient

Common Questions

If the patient develops ONJ, the Medical Assessment Form submission changes from every 6 months to every 3 months. Does a history & physical need to be done every 3 months?

✓ No, the required history & physical remains at 6 month intervals. The clinical trial staff will need to gather the data to complete the Medical Assessment Form every 3 months, including the patient-related outcome assessment

Common Questions

Is a patient with metastatic disease of unknown primary eligible?

✓ Yes, as long as the patient has metastatic bone involvement. Mark as “other tumor type” on registration worksheet

More Questions?