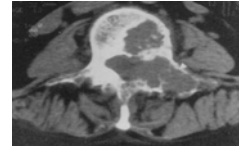


S0702: A Prospective Observational Multicenter Cohort Study to Assess the Incidence of Osteonecrosis of the Jaw (ONJ) in Cancer Patients with Bone Metastasis Starting Zoledronic Acid Treatment

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

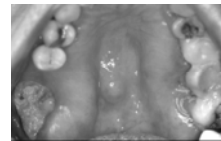
Cancer	Incidence of Bone Mets	Median Survival (m)	% patients with 5 Yr Survival
Myeloma	95-100%	20	10%
Breast	65-75%	24	20%
Prostate	65-75%	40	25%
Thyroid	60%	48	45%
Renal	20-25%	6	5%
Lung	30-40%	3	<5%



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*)

A case of ONJ



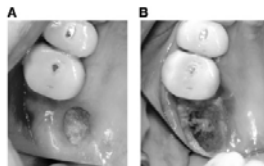
Non-healing extraction socket with exposed bone following extraction of a maxillary right molar tooth three months prior.



Spontaneous exfoliation of four teeth on the opposite side of the ONJ. The remaining dentition has severe mobility @ 6m

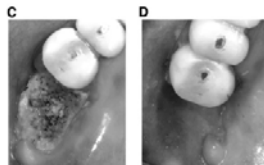
Another case of ONJ

Extraction 1 y ago non-healing



6 m follow up ONJ has progressed

12 m follow-up with continued progression of ONJ



1 year later with healing

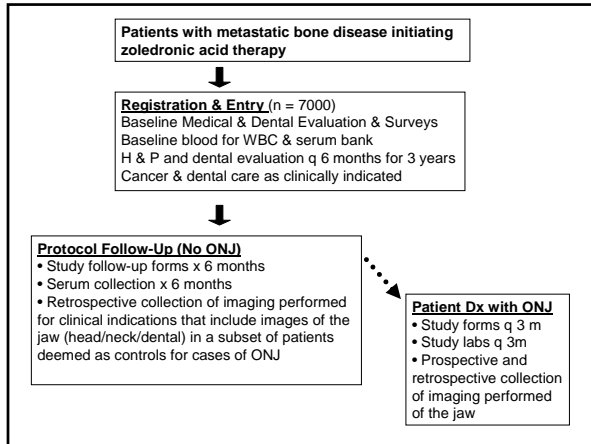
Estilio Oncologist 2008

Primary Objective:

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

Secondary Objectives

- clinical presentation and natural history
- risk factors for the development
- incidence rate in different tumors
- correlative science & case-control
 - specimen bank: serum & DNA
 - imaging bank
- patient related outcomes related to oral health



- ### 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)

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

Dental	Base	6 m	12 m	18 m	24 m	30 m	36 m
Dental exam & study form	X	X	X	X	X	X	X
Imaging (approx time intervals)	X		X		X		X

- ### 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.

- ### 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.

Image Submission via AG Mednet

<http://www.agmednet.com/doc/TrialUserGuide.pdf>

- 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

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

Funding & Credit

- CCOP Credit:
 - 0.5 per patient for enrollment
 - No ONJ: 0.3 at completion – all forms submitted
 - ONJ: 0.5 for confirmation of ONJ
 - 0.1 for each of 2 ONJ follow-up forms submitted
- Non-CCOP Institutions:
 - \$1,250 per patient for enrollment
 - No ONJ: \$125 for each follow-up form and the off-study form
 - \$1,250 for confirmation of ONJ
 - \$250 for each of 2 ONJ follow-up forms submitted

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 - 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?