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Appendix 5: The University of Texas M.D. Anderson Cancer Center Study Protocol – Retrospective Chart Review to Collect Information on the Frequency of Osteonecrosis in Patients Treated with Intravenous Bisphosphonate

Zometa® (zoledronic acid) Injection

and

Aredia® (pamidronate disodium) Injection

Submitted: February 1, 2005

Oncologic Drugs Advisory Committee Meeting

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List of Appendices

Study Chairman: _____

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1 Objectives

Primary objectives

- To retrospectively collect information on any case of osteonecrosis of the jaw in patients that have received intravenous bisphosphonate therapy and to estimate its frequency in this patient population.
- To retrospectively collect information regarding cases of altered/delayed healing reaction in oral cavity due to oral surgery, miscellaneous trauma or denture sores in patients treated with bisphosphonates.
- Better define the diagnostic criteria, clinical presentation and natural history of osteonecrosis of the jaw.
- To identify risk factors associated with the development of osteonecrosis of the jaw in patients treated with intravenous bisphosphonates.

Secondary objective

- To retrospectively collect information on any case of osteonecrosis of other sites other than the jaw developed in patients that have received intravenous bisphosphonate therapy. This will include but not limited to estimation of frequency, clinical presentation and the risk factors for development of osteonecrosis.

2 Disease category

This study involves patients with osteonecrosis that have been treated with intravenous bisphosphonates regardless of disease state.

3 Study rationale

Bisphosphonates are widely used for the treatment of metastatic bone disease and for metabolic bone disorders associated with increased bone turnover such as osteoporosis, hypercalcemia of malignancy and Paget's disease.

Bisphosphonates are analogues of pyrophosphate, an endogenous regulator of bone mineralization (Rodan and Fleisch 1996). This class of drugs has been extensively studied in the past three decades and the newest generation of bisphosphonates has a high binding affinity to the hydroxyapatite in mineralized bone and act as potent inhibitors of osteoclastic activity (Rodan and Fleisch 1996). Both pamidronate and zoledronate have been extensively studied and their efficacy has been clearly confirmed. The use of bisphosphonates for metastatic bone disease results in reduction of skeletal complications (i.e. pathological fractures, hypercalcemic crisis, spinal cord compression) and has led to a decrease in requirement of radiation therapy (Hortobagyi 1998, Therialult 1999, Rosen 2001, Lipton 2002). In patients with metabolic bone disorders intravenous bisphosphonates are used when patients fail to tolerate oral treatment (Reid 2002, Gallacher 1991, Reid 1994).

Bisphosphonate therapy has been associated with good clinical tolerability. However, recently there have been a few cases reported of osteonecrosis of the jaw in patients that had received the intravenous bisphosphonates, pamidronate or zoledronate. In particular, Dr. Marx from the University of Miami School of Medicine identified 36 cases of avascular necrosis of the jaw in patients that had received, in addition to other therapies, bisphosphonate therapy (Marx 2003). This report included patients with multiple myeloma, metastatic breast carcinoma and osteoporosis. Many of these patients were also receiving systemic chemotherapy or systemic steroids but all patients had received bisphosphonates. In another report, five patients that were being treated with intravenous bisphosphonates presented with bone necrosis of the jaw (Migliorati 2003). These patients present with painful exposed necrotic bone in the mandible, maxilla or both; treatment is difficult and often unsuccessful.

Therefore, there is an increasing concern regarding the possible association of avascular necrosis with bisphosphonate therapy. Our goal is to perform a retrospective chart review to understand the prevalence of osteonecrosis in patients treated with the intravenous bisphosphonates pamidronate or zoledronate and to try to identify predisposing factors to its occurrence.

4 Research plan and type of information collected

A review of charts of all patients who have received intravenous bisphosphonate therapy at MDACC.

Only the medical records of patients who have developed osteonecrosis and that have been treated with intravenous bisphosphonates will be reviewed for the following information.

- Indication for which the patient has received intravenous bisphosphonate.
- Site, clinical presentation and treatment used for osteonecrosis.
- Diagnostic evaluation (laboratory and imaging studies, pathologic evaluations when available).
- Identification of possible risk factors: use of steroids, chemotherapy drugs, concomitant infections, trauma or other diseases known to be associated with a higher risk for osteonecrosis (i.e. lupus, sickle cell hemoglobinopathies, inherited thrombophilia, HIV infection, gaucher's disease, etc.).
- Identification of other co-morbidities: diabetes mellitus, peripheral vascular disease, radiation exposure, infections, pancreatitis, smoking, excessive alcohol intake.
- Identify the extent of bisphosphonate therapy including duration and total dose.
- Obtain information on previous dental history and "pre-treatment" therapy (antibiotics, etc.), as well as "post-treatment" therapy/care following oral surgery.

Diagnostic criteria to be used for definition of osteonecrosis:

- Osteonecrosis of the jaw
    - Osteonecrosis is due to either miscellaneous trauma or some form of direct wounding (extraction/oral surgery) episode to the oral mucosal/dento-alveolar complex resulting in an altered tissue response leading to greater tissue breakdown than tissue repair.

This results in a non-healing bony wound and bony necrosis that does not respond to conventional corrective therapy.

- In order to identify patients with potential osteonecrosis of the jaw, we will first:

- Identify patients with any jaw bone-related disorder such as patients with osteomyelitis, alveolitis, periodontal infection and, delayed healing after dental surgery.
  - From this group of patients we will identify patients with osteonecrosis of the jaw using the criteria outlined below.
  1. Exposed non-healing bone with/without pain of at least three – six months duration, that is a result of poor/altered response of bone to trauma or infection and that does not respond to conventional corrective therapy.
  2. Pathological confirmation of osteonecrosis
  - Osteonecrosis of other sites:
  1. Osteonecrosis can occur in the anterolateral femoral head, humeral head, femoral condyles, proximal tibia, vertebrae, and small bones of the hand and foot.
  2. The diagnosis will be based on clinical manifestations (weight-bearing, motion-induced or rest pain) associated with characteristic radiological signs and pathologic findings when available.

5 Number of records reviewed

It is unknown how many charts will require review, as we don't know the frequency of osteonecrosis in this population. To identify patients with osteonecrosis of the jaw and other sites we plan to obtain:

- A list of patients that have received intravenous bisphosphonates for the past 10 years from Pharmacy.
- A list of patients with diagnosis of osteonecrosis of the jaw from Dr. Bela B. Toth, D.D.S.
- A list of patients that were seen at the M.D. Anderson Dental Clinic from Medical Informatics.
- A list of all cases of osteonecrosis (all sites) for the past 10 years from Medical Informatics.

6 Statistical analysis

Patients that have received intravenous bisphosphonates between January 1, 1994 and December 31, 2003 will be identified. From this group of patients we will identify and further evaluate patients that meet the criteria for diagnosis of osteonecrosis. The clinical characteristics including the frequency of this presentation, site of involvement, type of treatment and responses, and associated treatments and co-morbidities will be examined. Descriptive statistics will be employed for this study.

7 Confidentiality

The Principal Investigator will take steps to guard against any loss of confidentiality. Only the listed Investigators and their authorized research staff will have access to the identifiable information from this retrospective chart review study. Collected information will be kept in a locked cabinet in the Principal Investigator's office. The identifiable information will be destroyed when the retrospective review is completed and only aggregate data with no identifiers will be kept.

8 Request for waivers of informed consent and authorization

A waiver of the informed consent process and a waiver of authorization are requested (Appendix A and Appendix B).

9 References

Gallacher SJ, Boyce BF, Patel U, et al (1991) Clinical experience with Pamidronate in the treatment of Paget's disease of bone. Ann Rheum Dis; 50:930-933.

Hortobagyi GN, Theriault RL, Lipton A, et al (1998) Long-term prevention of skeletal complications of metastatic breast carcinoma with pamidronate. J Clin Oncol; 16:2038-2044.

Lipton A, Small E, Saad F, et al (2002) The new bisphosphonate Zometa (Zoledronic acid), decreases skeletal complications in both osteolytic and osteoblastic lesions: a comparison to pamidronate. Cancer Invest; 20(Suppl):45-47.

Marx RE (2003) Pamidronate (Aredia) and zoledronate Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg; 61:1115-1118.

Migliorati CA (2003) Bisphosphonates and oral cavity avascular bone necrosis. J Clin Oncol; 21:4253-4254.

Reid IR, Brown JP, Burckhardt P, et al (2002) Intravenous zoledronic acid in postmenopausal women with low bone mineral density. N Engl J Med; 346:653-661.

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Rodan GA and Fleisch HA (1996). Bisphosphonates: mechanisms of action. J Clin Invest; 97:2692-2696.

Rosen LS, Gordon D, Kaminski M, et al (2001) Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a Phase III, double-blind, comparative trial. Cancer J; 7:377-387.

Therialult RL, Lipton A, Hortobagyi GN, et al (1999) Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. J Clin Oncol; 17:846-895.

Appendix A

Request for Waiver of Informed Consent

Protocol # (entered by PI)

Principal Investigator : **Ana O. Hoff**, **M.D.**
Protocol Name: **Retrospective Chart Review to Collect Information on the Frequency of Osteonecrosis in Patients Treated with Intravenous Bisphosphonate Therapy**
Please provide information substantiating the following. Use additional pages if needed.
The research involves no more than minimal risk to the subjects. **This study does not include any intervention, which might entail risk. The only theoretical risk to the patients is the potential for inadvertent breach of confidentiality. The Principal Investigator will take steps to guard against this occurring. Only the Investigators and their authorized research staff will have access to the identifiable information from this retrospective chart review study. Collected information will be kept in a locked cabinet in the principal investigator's office.**
The waiver or alteration will not adversely affect the rights and welfare of the subjects. **Due to the nature of this study, granting of this waiver will not adversely affect the rights and welfare of the subjects.**
The research could not practicably be carried out without the waiver or alteration; and **This research could not practicably be conducted without this waiver as some of these patients are no longer seen at this institution and cannot be contacted.**
Whenever appropriate, the subjects will be provided with additional pertinent information after participation. **Due to the nature of this request, we cannot perceive of a situation where this would be applicable. However, if such a situation were to occur, subjects will be provided with additional pertinent information.**
For IRB use only: ☐ ☐ **Waiver Approved Yes No Reviewer:**

Appendix B

Waiver of Authorization to Use and Disclose

Protected Health Information (PHI)

Protocol # (entered by PI)

Principal Investigator: Ana O. Hoff, M.D.
Protocol Name: **Retrospective Chart Review to Collect Information on the Frequency of Osteonecrosis in Patients Treated with Intravenous Bisphosphonate Therapy**
Please provide information substantiating the following. Use additional pages if needed.
1. The use or disclosure of the PHI involves no more than minimal risk to the individual's privacy. This is based on the following 3 criteria:
The research protocol includes adequate plans to protect identifiers from improper use. **Only the Principal Investigator and his authorized research staff will have access to the identifiable information from this retrospective chart review study. Collected information will be kept in a locked cabinet in the principal investigators office.**
The research protocol includes an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research. **The identifiable information will be destroyed when the retrospective review is completed and only aggregate data with no identifiers will be kept.**
The research protocol includes adequate written assurances that the PHI will not be reused or disclosed to any other person or entity, or for other research. **The Principal Investigator guarantees that the protected health information will not be reused or disclosed to any other person or entity or for other research.**
2. The research could not practicably be conducted without this waiver or alteration. **This research could not practicably be conducted without this waiver as some of the patients are no longer seen at this institution and cannot be contacted.**
3. The research could not practicably be conducted without access to and use of the PHI **Due to the nature of this study as previously described, the research may only be conducted with access to and use of the PHI.**
Date of IRB Approval of Waiver:
Print Name of IRB Authorized Individual Signature
This Waiver was reviewed and approved ☐ ☐ By the following method: Full Committee Expedited Review
The IRB responsible for review and approval of this waiver was The University of Texas M D Anderson IRB #1 IRB00000121