Comparing the Incidence of Acute Phase Reactions in Patients with Advanced Cancer and Bone Metastases or Multiple Myeloma Following Treatment with Denosumab or Zoledronic Acid: Results from a Combined Analysis of Three Phase 3 Randomized Trials

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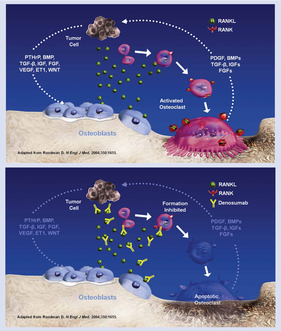
BACKGROUND

- Patients with advanced cancers and bone metastases are at long-term risk for skeletal complications including the skeletal-related events (SREs) of radiation or surgery to bone, pathologic fracture, and spinal cord compression.[1-3]
- Oncology nurses have the ability to provide proactive patient care by educating patients on SREs and the treatments available.
- Subcutaneous (SC) denosumab or intravenous bisphosphonate (IV, BP) therapy is often used to manage these patients and has been shown to delay the onset of SREs.[2-4]
- In some patients, reported toxicities associated with IV BPs may interfere with quality of life and limit or prevent optimal dosing, potentially influencing the overall benefits of this therapy.[5]
- When IV BP treatment is initiated, patients occasionally experience mild to moderate flu-like adverse events (AEs) characterized by symptoms such as pyrexia, chills, flushing, bone pain, arthralgias, and myalgias.[6-9]
- This acute-phase reaction (APR) appears to be a transient immune-driven response following the first or second dose of IV BP and lasting from one to three days.[6,10]
- The reaction occurs in about 15% to 30% of patients within the first three days and up to four weeks after starting therapy.[11]
- The flu-like symptoms associated with APRs create an additional burden for patients, potentially requiring extended monitoring, treatment, or both.
- Denosumab (XGEVA™) is a fully human monoclonal antibody that binds to human RANK ligand (RANKL) produced by osteoblasts and other cells, thereby inhibiting osteoclast activity and the resulting bone destruction and SREs (Figure 1).

Figure 1. The Role of RANKL in Bone Destruction in Metastatic Cancer and the Proposed Mechanism of Action of Denosumab



- In a combined analysis of 3 identically designed, active controlled, phase 3 trials comparing SC denosumab with IV zoledronic acid in patients with advanced cancer and bone metastases, denosumab was superior to zoledronic acid in preventing SREs ($P < 0.0001$).[12]
- Unlike zoledronic acid, denosumab can be used in patients regardless of renal status or concomitant use of nephrotoxic drugs; renal monitoring or dose adjustments are not required with denosumab.[13-15]

OBJECTIVE

- This safety analysis compares denosumab and zoledronic acid for the incidence of APRs (flu-like syndrome including pyrexia, chills, flushing, bone pain, arthralgias, and myalgias) during the first 3 days after initial treatment.

METHODS / STUDY DESIGN

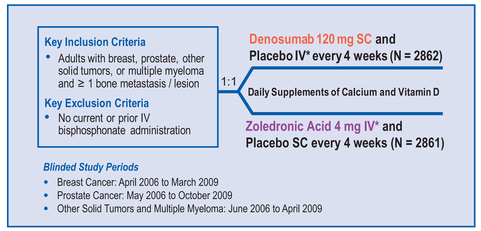
Study Design

- Patient level data was combined in the preplanned, analysis from 3 pivotal studies with identical design (Figure 2)
  - Patients with breast cancer (NCT00321464)
  - Patients with prostate cancer (NCT00321620)
  - Patients with other solid tumors or multiple myeloma (NCT00330759)

Enrollment Criteria

- Radiographic evidence of ≥ 1 bone metastasis or bone disease
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
- Adequate organ function
- Life expectancy ≥ 6 months

Figure 2. Study Design: International, Randomized, Double-Blind, Double-Dummy, Active-Controlled Study



*Per protocol and Zometa® label, IV product was dose adjusted for baseline creatinine clearance and subsequent dose intervals were determined by serum creatinine levels. No SC dose adjustments were required.

- The safety analysis in this study included data from all randomized patients who received ≥ 1 dose of denosumab or zoledronic acid. Patients were analyzed according to the actual treatment received.
- Patient records were searched for AEs and serious AEs (SAEs) that occurred during the first 3 days after the first administration of denosumab or zoledronic acid, using 37 prespecified MedDRA 12.1 preferred terms potentially indicating APRs (Table 1).
- Per the study protocol, AEs were considered serious if they were fatal, life-threatening, required or prolonged in-patient hospitalization, resulted in a persistent or significant disability, or were considered to present a significant medical hazard.
- Acute phase AEs for the denosumab and zoledronic acid groups were compared using a Cochran-Armitage test stratified by study.

METHODS / STUDY DESIGN (continued)

Table 1. MedDRA Version 12.1 Preferred Terms Used to Define AEs Potentially Associated With APRs

MeDRA Version 12.1 Preferred Terms							
Acute-phase reaction	Chest pain	Fatigue	Flushing	Influenza-like illness	Musculoskeltal discomfort	Myofascial pain syndrome	Sluggishness
Arthralgia	Chills	Feeling cold	Headache	Lethargy	Musculoskeltal pain	Non-cardiac chest pain	Tenderness
Asthenia	Decreased activity	Feeling hot	Hyperpyrexia	Listless	Musculoskeltal stiffness	Pain	
Back pain	Decreased appetite	Feeling of body temperature change	Hyperthermia	Malaise	Myalgia	Pain in extremity	
Bone pain	Discomfort	Flank pain	Inflammatory pain	Muscle tightness	Myalgia intercostal	Pyrexia	

RESULTS

Table 2. Baseline Demographics and Disease Characteristics

Baseline Characteristics* Characteristics, n (%) or median (Q1, Q3)	Zoledronic Acid (N = 2861)	Denosumab (N = 2862)
Women	1349 (47)	1316 (46)
ECOG performance status of 0 or 1	2546 (89)	2585 (90)
Previous SRE†	1157 (40)	1112 (39)
Time from first bone metastasis to randomization, months	2.3 (1.0, 7.6)	2.2 (1.0, 7.1)
Tumor type††		
Breast	1020 (36)	1026 (36)
Prostate	951 (33)	950 (33)
Non-small cell lung	352 (12)	350 (12)
Multiple myeloma	93 (3)	87 (3)
Other	445 (16)	449 (16)

*Full Analysis set; †Based on randomization; ††Numbers may not total 100% due to rounding.

- AEs associated with APRs in the first 3 days after treatment occurred in fewer patients treated with denosumab than in the patients treated with zoledronic acid (8.7% vs 20.2%; $P < 0.0001$; Figure 3).
- The most common APRs included pyrexia, fatigue, bone pain, arthralgia, chills, and asthenia (Table 3 and Figure 4).
- 2 patients (< 0.1%) treated with denosumab and 17 patients (0.6%) treated with zoledronic acid experienced SAEs associated with APRs during the first 3 days. Pyrexia was the most common SAE.

RESULTS (continued)

Figure 3. Patients Experiencing AEs Indicative of APRs Occurring Within the First 3 Days After Initial Treatment

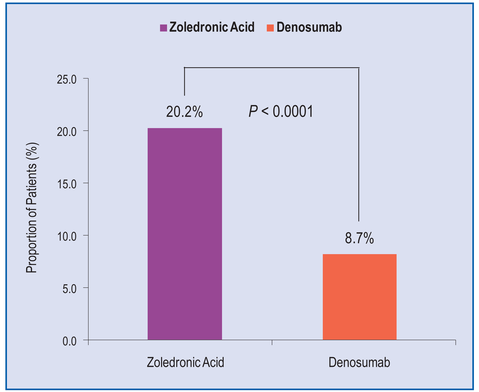
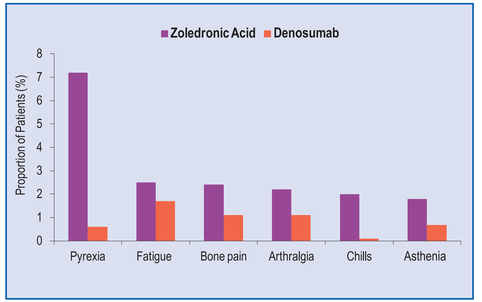


Table 3. Number of Patients Experiencing AEs Indicative of APRs Occurring Within the First 3 Days After Initial Treatment

Events reported in ≥ 1% of patients in either group	Zoledronic Acid N = 2836* N (%)	Denosumab N = 2841* N (%)
Pyrexia	(7.2)	(0.6)
Fatigue	(2.5)	(1.7)
Bone pain	(2.4)	(1.1)
Arthralgia	(2.2)	(1.1)
Chills	(2.0)	(0.1)
Asthenia	(1.8)	(0.7)
Influenza-like illness	(1.8)	(0.2)
Headache	(1.7)	(0.6)
Back pain	(1.6)	(0.9)
Myalgia	(1.4)	(0.4)
Pain in extremity	(1.3)	(0.5)
Pain	(1.0)	(0.4)

*Randomized patients who received ≥ 1 dose of active drug.

Figure 4. Most Common Symptoms of AEs Indicative of APRs Occurring Within the First 3 Days After Initial Treatment



CONCLUSIONS

- In this combined analysis of 3 phase 3 studies of denosumab versus zoledronic acid for the treatment of patients with advanced cancers and bone metastases, APRs occurred significantly more frequently with zoledronic acid than with denosumab ($P < 0.0001$).
- The most common AEs associated with APRs were pyrexia, fatigue, bone pain, arthralgia, chills, and asthenia.
- AEs indicative of APRs experienced in the denosumab group were lower than in the zoledronic acid group.
- Fewer denosumab-treated patients than zoledronic acid-treated patients experienced SAEs indicative of APRs (< 0.1% vs 0.6%, respectively).
- By identifying APRs, nurses can help implement treatment strategies and options that may further enhance patient compliance.

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