Axillary Radiotherapy May Be a Safe Alternative

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Denver Bureau

SAN ANTONIO — Axillary radiotherapy appears to be a safe and vastly less morbid alternative to the standard axillary node dissection in clinically node-negative breast cancer patients who have a positive sentinel lymph node, Dr. Michele A. Gadd said at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

She presented a prospective single-center study that indicated axillary radiation plus systemic therapy provided adequate local control in such patients—and with a substantial reduction in morbidity, compared with axillary dissection.

The impetus for this study was the recognition that axillary dissection beyond the sentinel lymph node biopsy may no longer be essential in an era when the number of positive lymph nodes isn't a major consideration in decisions regarding systemic therapy, as reflected in the latest practice guidelines.

The average breast tumor size has decreased, with a simultaneous reduction in nodal involvement, noted Dr. Gadd, a surgical oncologist at the Dana-Farber Cancer Institute and Harvard Medical School, Boston.

Dissection of the axillary node basin entails significant morbidity.

Studies have routinely documented a 25%-50% reduction in standardized quality of life measures along with an average 20% incidence of lymphedema, numbness in 35% of patients, chronic pain in 10%, and limited arm range of motion in 5%-10%. Investigators believed they could safely spare patients from all of this through the use of radiotherapy to control disease in the axilla, she explained.

Dr. Gadd reported on 560 patients with clinically node-negative stage T1-2 invasive breast cancer who underwent sentinel lymph node biopsy, which proved positive in 21%. A subgroup of 77 sentinel node biopsy–positive patients underwent whole breast and nodal radiotherapy and systemic therapy and were prospectively followed. The radiotherapy regimen consisted of a total dose of 4,500 Gy delivered to the axillary and supraclavicular basins in 25 fractions, along with a 400-Gy axillary boost in most patients. The type of systemic therapy employed was left up to each patient's physician.

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During a median 34-month follow-up, there has been just one axillary recurrence, for a 1.3% rate. It occurred 23 months after initial diagnosis of breast cancer. There have been three distant recurrences.

In terms of acute morbidity, patients were able to return to work and physical activities earlier following radiotherapy, compared with axillary dissection. No drain was required, seromas needing aspiration were rare, and there was markedly less pain associated with radiotherapy than with surgical axillary clearance.

Arm circumference measurements showed no evidence of lymphedema at 2 years. Women with right-sided breast cancer experienced a mean 10% reduction in range of arm motion on the affected side, peaking at 6-9 months postoperatively and reverting to pretreatment status by 1 year. Patients with left-sided breast cancer had no decrease in range of motion.

Grip strength was significantly reduced in both hands of all patients at 2 years; the bilateral decrease suggests it was due to a global reduction in posttreatment physical fitness, Dr. Gadd said.

The vast majority of patients indicated their daily activities weren't affected at all by shoulder stiffness, arm numbness, pain, or arm swelling.

Asked if she believes axillary radiotherapy instead of axillary dissection in sentinel node biopsy–positive patients ought to be considered the new standard of care, Dr. Gadd replied that she would first like to see the Boston results replicated in other centers. "On the other hand, I have to say we are now doing it off-study. We are very confident in our ability to control disease in the axilla.

"But to really identify which patients are best for this type of therapy, we need a bigger trial," she added. ■

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CONTRAINDICATIONS
- Known hypersensitivity to BONIVA or to any of its excipients
- Uncorrected hypocalcemia (see **PRECAUTIONS: General**)
- Inability to stand or sit upright for at least 60 minutes (see **DOSAGE AND ADMINISTRATION**)

WARNINGS
BONIVA, like other bisphosphonates administered orally may cause upper gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastric ulcer (see **PRECAUTIONS**).

PRECAUTIONS: General
Mineral Metabolism: Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting BONIVA therapy. Adequate intake of calcium and vitamin D is important in all patients.
Upper Gastrointestinal Effects: Bisphosphonates administered orally have been associated with dysphagia, esophagitis, and esophageal or gastric ulcers. This association has been reported for bisphosphonates in postmarketing experience but has not been found in most preapproval clinical trials, including those conducted with BONIVA. Therefore, patients should be advised to pay particular attention to and be able to comply with the dosing instructions to minimize the risk of these effects (see **DOSAGE AND ADMINISTRATION**).
Severe Renal Impairment: BONIVA is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min).
Jaw Osteonecrosis: Osteonecrosis, primarily in the jaw, has been reported in patients treated with bisphosphonates. Most cases have been in cancer patients undergoing dental procedures, but some have occurred in patients with postmenopausal osteoporosis or other diagnoses. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (eg, chemotherapy, radiotherapy, corticosteroids), and co-morbid disorders (eg, anemia, coagulopathy, infection, pre-existing dental disease). Most reported cases have been in patients treated with bisphosphonates intravenously but some have been in patients treated orally. For patients who develop osteonecrosis of the jaw (ONJ) while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.
Musculoskeletal Pain: In postmarketing experience, severe and occasionally incapacitating bone, joint, and/ or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see **ADVERSE REACTIONS**). However, such reports have been infrequent. This category of drugs include BONIVA (ibandronate sodium) Tablets. Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate. In placebo-controlled studies with BONIVA, the percentages of patients with these symptoms were similar in the BONIVA and placebo groups.
Information for Patients: Patients should be instructed to read the Patient Information Leaflet carefully before taking BONIVA, to re-read it each time the prescription is renewed and to pay particular attention to the dosing instructions in order to maximize absorption and clinical benefit.
-BONIVA should be taken at least 60 minutes before the first food or drink (other than water) of the day and before taking any oral medications containing multivalent cations (including antacids, supplements or vitamins).
-To facilitate delivery to the stomach, and thus reduce the potential for esophageal irritation, BONIVA tablets should be swallowed whole with a full glass of plain water (6 to 8 oz) while the patient is standing or sitting in an upright position. Patients should not lie down for 60 minutes after taking BONIVA.
-Plain water is the only drink that should be taken with BONIVA. Please note that some mineral waters may have a higher concentration of calcium and therefore should not be used.
-Patients should not chew or suck the tablet because of a potential for oropharyngeal ulceration.
-The BONIVA 150-mg tablet should be taken on the same date each month (ie, the patient's BONIVA day).
-If the once-monthly dose is missed, and the patient's next scheduled BONIVA day is more than 7 days away, the patient should be instructed to take one BONIVA 150-mg tablet in the morning following the date that it is remembered (see **DOSAGE AND ADMINISTRATION**). The patient should then return to taking one BONIVA 150-mg tablet every month in the morning of their chosen day, according to their original schedule.
-The patient must not take two 150-mg tablets within the same week. If the patient's next scheduled BONIVA day is only 1 to 7 days away, the patient must wait until their next scheduled BONIVA day to take their tablet. The patient should then return to taking one BONIVA 150-mg tablet every month in the morning of their chosen day, according to their original schedule.
Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate. Intake of supplemental calcium and vitamin D should be delayed for at least 60 minutes following oral administration of BONIVA in order to maximize absorption of BONIVA.
Physicians should be alert to signs or symptoms signaling a possible esophageal reaction during therapy, and patients should be instructed to discontinue BONIVA and seek medical attention if they develop symptoms of esophageal irritation such as new or worsening dysphagia, pain on swallowing, retrosternal pain, or heartburn.

Drug Interactions
Calcium Supplements/Antacids: Products containing calcium and other multivalent cations (such as aluminum, magnesium, iron) are likely to interfere with absorption of BONIVA. BONIVA should be taken at least 60 minutes before any oral medications containing multivalent cations (including antacids, supplements or vitamins) (see **PRECAUTIONS: Information for Patients**).
H2 Blockers and Proton Pump Inhibitors (PPIs): Of over 3500 patients enrolled in the BONIVA osteoporosis Treatment and Prevention Studies, 15% used anti-peptic agents (primarily H2 blockers and PPIs). Among these patients, the incidence of upper gastrointestinal adverse experiences in the patients treated with BONIVA was similar to that in placebo-treated patients. Similarly, of over 1600 patients enrolled in a study comparing once-monthly with daily dosing regimens of ibandronate, 14% of patients used anti-peptic agents. Among these patients, the incidence of upper gastrointestinal adverse experiences in the patients treated with BONIVA 150 mg once monthly was similar to that in patients treated with BONIVA 2.5 mg once daily.
Aspirin/Nonsteroidal Antiinflammatory Drugs (NSAIDs): In the large, placebo-controlled osteoporosis Treatment Study, aspirin and nonsteroidal antiinflammatory drugs were taken by 62% of the 2946 patients. Among aspirin or NSAID users, the incidence of upper gastrointestinal adverse events in patients treated with ibandronate 2.5 mg daily (28.9%) was similar to that in placebo-treated patients (30.7%). Similarly, in the 1-year monthly comparison study, aspirin and nonsteroidal antiinflammatory drugs were taken by 39% of the 1602 patients. The incidence of upper gastrointestinal events in patients concomitantly taking aspirin or NSAIDs was similar in patients taking ibandronate 2.5 mg daily (21.7%) and 150 mg once monthly (22.0%). However, since aspirin, NSAIDs, and bisphosphonates are all associated with gastrointestinal irritation, caution should be exercised in the concomitant use of aspirin or NSAIDs with BONIVA.
Drug/Laboratory Test Interactions: Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with ibandronate have not been performed.
Carcinogenesis, Mutagenesis, Impairment of Fertility: *Carcinogenesis:* In a 104-week carcinogenicity study, doses of 3, 7, or 15 mg/kg/day were administered by oral gavage to male and female Wistar rats (systemic exposures up to 12 and 7 times, respectively, human exposure at the recommended daily oral dose of 2.5 mg, and cumulative exposures up to 3.5 and 2 times, respectively, human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). There were no significant drug-related tumor findings in male or female rats. In a 78-week carcinogenicity study, doses of 5, 20, or 40 mg/kg/day were administered by oral gavage to male and female NMRI mice (exposures up to 475 and 70 times, respectively, human exposure at the recommended daily oral dose of 2.5 mg and cumulative exposures up to 135 and 20 times, respectively, human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). There were no significant drug-related tumor findings in male or female mice. In a 90-week carcinogenicity study, doses of 5, 20, or 80 mg/kg/day were administered in the drinking water to NMRI mice (cumulative monthly exposures in males and females up to 70 and 115 times, respectively, human exposure at the recommended dose of 150 mg, based on AUC comparison). A dose-related increased incidence of adrenal subcapsular adenoma/carcinoma was observed in female mice, which was statistically significant at 80 mg/kg/day (220 to 400 times human exposure at the recommended daily oral dose of 2.5 mg and 115 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). The relevance of these findings to humans is unknown.
Mutagenesis: There was no evidence for a mutagenic or clastogenic potential of ibandronate in the following assays: in vitro bacterial mutagenesis assay in *Salmonella typhimurium* and *Escherichia coli* (Ames test), mammalian cell mutagenesis assay in Chinese hamster V79 cells, and chromosomal aberration test in human peripheral lymphocytes, each with and without metabolic activation. Ibandronate was not genotoxic in the in vivo mouse micronucleus tests for chromosomal damage.
Impairment of Fertility: In female rats treated from 14 days prior to mating through gestation, decreases in fertility, corpora lutea, and implantation sites were observed at an oral dose of 16 mg/kg/day (45 times human exposure at the recommended daily oral dose of 2.5 mg and 13 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison).
Pregnancy: *Pregnancy Category C:* In female rats given oral doses of 1, 4, or 16 mg/kg/day beginning 14 days before mating and continuing through lactation, maternal deaths were observed at the time of delivery in all dose groups (≥3 times human exposure at the recommended daily oral dose of 2.5 mg or ≥1 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). Perinatal pup loss in dams given 16 mg/kg/day (45 times human exposure at the recommended daily oral dose of 2.5 mg and 13 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison) was likely related to maternal dystocia. In pregnant rats given oral doses of 6, 20, or 60 mg/kg/day during gestation, calcium supplementation (32 mg/kg/day by subcutaneous injection from gestation day 18 to parturition) did not completely prevent dystocia and periparturient mortality in any of the treated groups (≥16 times human exposure at the recommended daily oral dose of 2.5 mg and ≥4.6 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). A low incidence of postimplantation loss was observed in rats treated from 14 days before mating throughout lactation or during gestation, only at doses causing maternal dystocia and periparturient mortality. In pregnant rats dosed orally with 1, 5, or 20 mg/kg/day from gestation day 17 through lactation day 21 (following closure of the hard palate through weaning), maternal toxicity, including dystocia and mortality, fetal perinatal and postnatal mortality, were observed at doses ≥5 mg/kg/day (equivalent to human exposure at the recommended daily oral dose of 2.5 mg and ≥4 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). Periparturient mortality has also been observed with other bisphosphonates and appears to be a class effect related to inhibition of skeletal calcium mobilization resulting in hypocalcemia and dystocia. Exposure of pregnant rats during the period of organogenesis resulted in an increased fetal incidence of RPU (renal pelvis ureter) syndrome at oral doses ≥10 mg/kg/day (≥30 times human exposure at the recommended daily oral dose of 2.5 mg and ≥9 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). Impaired pup neuromuscular development (cliff avoidance test) was observed at 16 mg/kg/day when dams were dosed from 14 days before mating through lactation (45 times human exposure at the recommended daily oral dose of 2.5 mg and 13 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). In pregnant rabbits given oral doses of 1, 4, or 20 mg/kg/day during gestation, dose-related maternal mortality was observed in all treatment groups (≥8 times the recommended human daily oral dose of 2.5 mg and ≥4 times the recommended human once-monthly oral dose of 150 mg, based on body surface area comparison, mg/m²). The deaths occurred prior to parturition and were associated with lung edema and hemorrhage. No significant fetal anomalies were observed. Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake of bisphosphonates into fetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of fetal harm (eg, skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been established. There are no adequate and well-controlled studies in pregnant women. BONIVA should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.
Nursing Mothers: In lactating rats treated with intravenous doses of 0.08 mg/kg, ibandronate was present in breast milk at concentrations of 8.1 to 0.4 ng/mL from 2 to 24 hours after dose administration. Concentrations in milk averaged 1.5 times plasma concentrations. It is not known whether BONIVA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BONIVA is administered to a nursing woman.
Pediatric Use: Safety and effectiveness in pediatric patients have not been established.
Geriatric Use: Of the patients receiving BONIVA 2.5 mg daily in postmenopausal osteoporosis studies, 52% were over 65 years of age, and 10% were over 75 years of age. Of the patients receiving BONIVA 150 mg once monthly in the postmenopausal osteoporosis 1-year study, 52% were over 65 years of age, and 9% were over 75 years of age. No overall differences in effectiveness or safety were observed between these patients and younger patients but greater sensitivity in some older individuals cannot be ruled out.

ADVERSE REACTIONS
Daily Dosing: Daily treatment with oral BONIVA was studied in over 3900 patients in postmenopausal osteoporosis trials of up to 3 years duration. The overall adverse event profile of BONIVA 2.5 mg once daily in these studies was similar to that of placebo.
Treatment and Prevention of Postmenopausal Osteoporosis: Most adverse events were mild or moderate and did not lead to discontinuation. The incidence of serious adverse events was 20% in the placebo group and 23% in the BONIVA 2.5 mg daily group. The percentage of patients who withdrew from treatment due to adverse events was approximately 17% in both the BONIVA 2.5 mg daily group and the placebo group. Overall, and according to body system, there was no difference between BONIVA and placebo, with adverse events of the digestive system being the most common reason for withdrawal.
Table 1 lists adverse events from the Treatment and Prevention Studies reported in ≥2% of patients and in more patients treated daily with BONIVA than patients treated with placebo. Adverse events are shown without attribution of causality.

Table 1: Adverse Events Occurring at a Frequency ≥2% and in More Patients Treated with BONIVA than in Patients Treated with Placebo Daily in the Osteoporosis Treatment and Prevention Studies

Body System	Placebo % (n=1134)	BONIVA 2.5 mg % (n=1140)
Body as a Whole		
Back Pain	12.2	13.5
Pain in Extremity	6.4	7.8
Infection	3.4	4.3
Asthenia	2.3	3.5
Allergic Reaction	1.9	2.5
Digestive System		
Dyspepsia	9.8	11.9
Diarrhea	5.0	6.8
Tooth Disorder	2.3	3.5
Vomiting	2.1	2.7
Gastritis	1.9	2.2
Metabolic and Nutritional Disorders		
Hypercholesterolemia	4.2	4.8
Musculoskeletal System		
Myalgia	5.1	5.7
Joint Disorder	3.3	3.6
Arthritis	2.7	3.2
Nervous System		
Headache	5.8	6.5
Dizziness	2.6	3.7
Vertigo	2.5	3.0
Nerve Root Lesion	1.9	2.2
Respiratory System		
Upper Respiratory Infection	33.2	33.7
Bronchitis	6.8	10.0
Pneumonia	4.3	5.9
Pharyngitis	1.5	2.5
Urogenital System		
Urinary Tract Infection	4.2	5.5

Once-Monthly Dosing: In a 1-year, double-blind, multicenter study comparing BONIVA 2.5 mg once daily and BONIVA 150 mg once monthly in women with postmenopausal osteoporosis, the overall safety and tolerability profiles of the two oral dosing regimens were similar. The incidence of serious adverse events was 4.8% in the BONIVA 2.5 mg daily group and 7.1% in the BONIVA 150 mg once-monthly group. The percentage of patients who withdrew from treatment due to adverse events was approximately 8.9% in the BONIVA 2.5 mg daily group and 7.8% in the BONIVA 150 mg once-monthly group. **Table 2** lists the adverse events reported in ≥2% of patients without attribution of causality.

Table 2: Adverse Events with an Incidence of at Least 2% in Patients Treated with BONIVA 150 mg Once Monthly or 2.5 mg Daily

Body System/Adverse Event	BONIVA 2.5 mg daily % (n=395)	BONIVA 150 mg monthly % (n=396)
Vascular Disorders		
Hypertension	7.3	6.3
Gastrointestinal Disorders		
Dyspepsia	7.1	5.6
Nausea	4.8	5.1
Diarrhea	4.1	5.1
Constipation	2.5	4.0
Abdominal Pain[a]	5.3	7.8
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	3.5	5.6
Back Pain	4.3	4.5
Pain in Extremity	1.3	4.0
Localized Osteoarthritis	1.3	3.0
Myalgia	0.8	2.0
Muscle Cramp	2.0	1.8
Infections and Infestations		
Influenza	3.8	4.0
Nasopharyngitis	4.3	3.5
Bronchitis	3.5	2.5
Urinary Tract Infection	1.8	2.3
Upper Respiratory Tract Infection	2.0	2.0
Nervous System Disorders		
Headache	4.1	3.3
Dizziness	1.0	2.3
General Disorders and Administration Site Conditions		
Influenza-like Illness[b]	0.8	3.3
Skin and Subcutaneous Tissue Disorders		
Rash[c]	1.3	2.3
Psychiatric Disorders		
Insomnia	0.8	2.0

[a]Combination of abdominal pain and abdominal pain upper
[b]Combination of influenza-like illness and acute phase reaction
[c]Combination of rash pruritic, rash macular, rash papular, rash generalized, rash erythematous, dermatitis, dermatitis allergic, dermatitis medicamentosa, erythema and exanthem

Patients with a previous history of gastrointestinal disease, including patients with peptic ulcer without recent bleeding or hospitalization and patients with dyspepsia or reflux controlled by medication, were included in the once-monthly treatment study. For these patients, there was no difference in upper gastrointestinal adverse events with the 150 mg once-monthly regimen compared to the 2.5 mg once-daily regimen.
Ocular Adverse Events: Reports in the medical literature indicate that bisphosphonates may be associated with ocular inflammation such as uveitis and scleritis. In some cases, these events did not resolve until the bisphosphonate was discontinued. There were no reports of ocular inflammation in studies with BONIVA 2.5 mg daily. Two patients who received BONIVA once monthly experienced ocular inflammation, one was a case of uveitis and the other scleritis.
Laboratory Test Findings: In the 3-year treatment study with BONIVA 2.5 mg daily, there were no clinically significant changes from baseline values or shifts in any laboratory variable for each of the treatment groups. As expected with bisphosphonate treatment, a decrease in total alkaline phosphatase levels was seen in the active treatment groups compared to placebo. There was no difference compared with placebo for laboratory abnormalities indicative of hepatic or renal dysfunction, hypocalcemia, or hypophosphatemia. Similarly, no changes were noted for the 150 mg once-monthly administration in the 1-year study.
OVERDOSAGE: No specific information is available on the treatment of overdosage with BONIVA. However, based on knowledge of this class of compounds, oral overdosage may result in hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, dyspepsia, esophagitis, gastritis, or ulcer. Milk or antacids should be given to bind BONIVA. Due to the risk of esophageal irritation, vomiting should not be induced, and the patient should remain fully upright. Dialysis would not be beneficial.

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