

Denosumab Delays Skeletal Events in Breast Ca

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FROM THE SAN ANTONIO BREAST
CANCER SYMPOSIUM

SAN ANTONIO – Denosumab delayed time to a first skeletal-related adverse event by a median of 5 months longer than zoledronic acid in patients with advanced breast cancer and bone metastases, based on updated results from a landmark head-to-head comparative trial of the two osteoclast-inhibiting drugs.

Moreover, time to the composite secondary end point of a first skeletal-related event or hypercalcemia, a feared and life-threatening complication of metastatic bone disease, was prolonged by a median of 7.3 months in the denosumab (Xgeva) group compared with those on zoledronic acid (Zometa), Dr. Alison T. Stopeck reported.

“To put this in some perspective, the average life expectancy of these patients is 2½-3 years, so 7 additional months of freedom from these complications is a considerable period of their remaining time,” said Dr. Stopeck, director of the clinical breast cancer program at the Ari-

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zona Cancer Center at the University of Arizona, Tucson.

She presented a new extended analysis that included 4 more months of blinded treatment than previously reported in the recent publication of data from the pivotal phase III randomized, double-blind, double-dummy study (J. Clin. Oncol. 2010;28:5132-9).

The trial involved 2,046 patients with advanced breast cancer and bone metastases, 1% of them men, who were assigned to 120 mg of subcutaneous denosumab or 4 mg of intravenous zoledronic acid, with each drug given every 4 weeks.

In the extended analysis, the median time to the first on-study skeletal-related event, such as fracture, spinal cord compression, or radiotherapy or surgery to bone, was 32.4 months in the denosumab arm compared with 27.4 months in the zoledronic acid arm. This represented a highly significant 18% delay in the time to these serious events in the denosumab-treated group ($P = .0096$).

Median time to the first on-study skeletal-related event or hypercalcemia was 32.4 months in the denosumab group and 25.1 months with zoledronic acid ($P = .0076$).

At the time of the extended analysis out to 3 years, 32.9% of patients in the denosumab group had had one or more skeletal-related events compared with

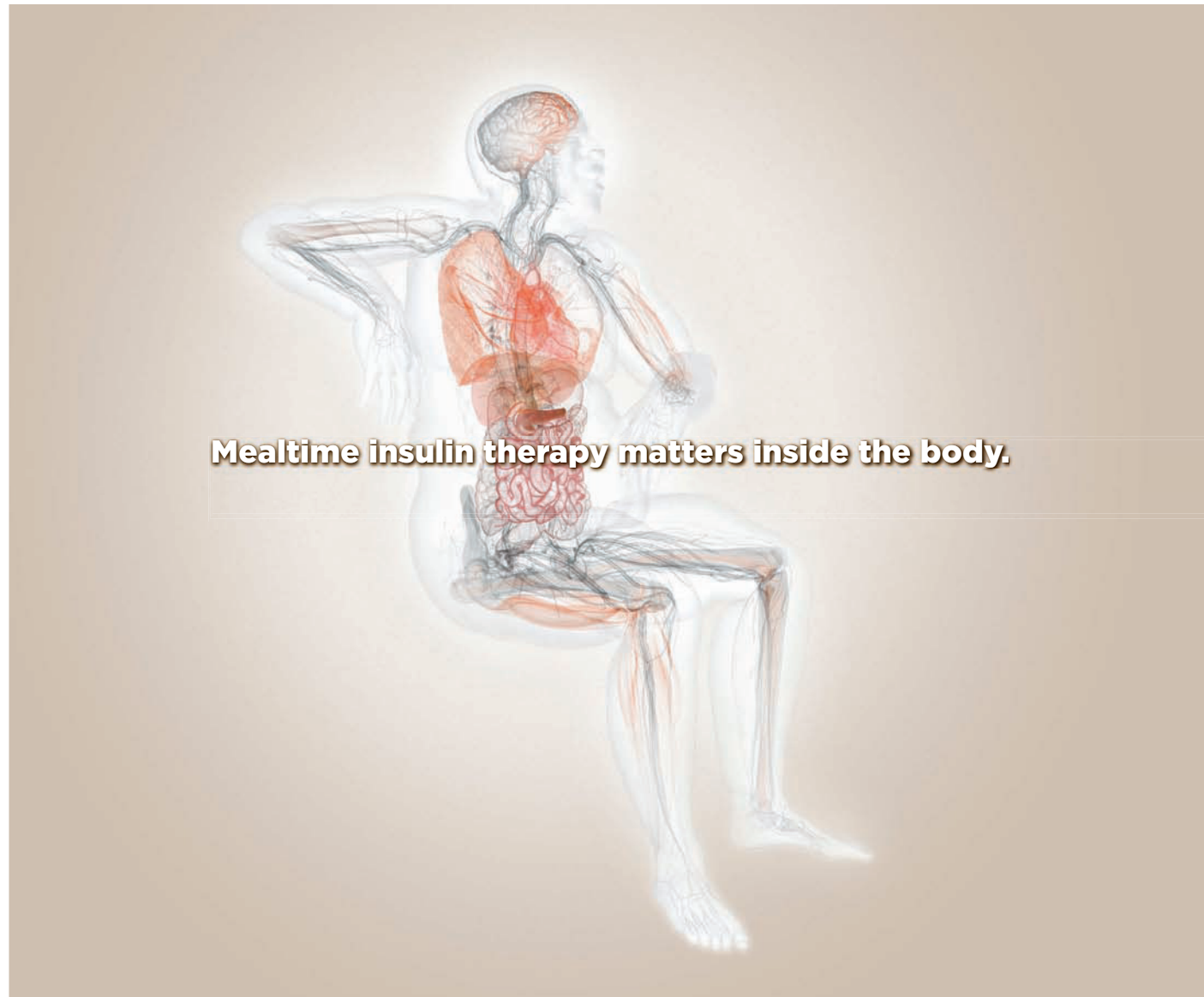
38.9% in the zoledronic acid arm, for a 15.4% relative risk reduction. One hundred additional skeletal-related events occurred during the extra 4 months of blinded treatment, bringing the total number of such events to 526 in the denosumab arm and 669 with zoledronic acid; this represents a 22% risk reduction ($P = .0008$). And the event curves are continuing to separate over time, Dr. Stopeck noted.

Overall survival and disease progression rates were similar in the two study arms. In terms of adverse events, renal toxicity was significantly more common in the zoledronic acid arm (9.4% vs. 5.4%), as were acute phase reactions involving bone pain and/or flulike symptoms (28.2% vs. 10.7%).

Hypocalcemia occurred in 6.1% of the denosumab group compared with 3.7% on zoledronic acid. Osteonecrosis

of the jaw occurred at similarly low rates – 2.5% or less – in both treatment arms.

On the strength of earlier data from this and two other phase III studies, in November the Food and Drug Administration approved denosumab, a fully human monoclonal antibody that acts as a RANK ligand inhibitor, for the prevention of skeletal-related events in patients with bone metastases from solid tumors.



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Indication

Humalog® (insulin lispro injection [rDNA origin]) is for use in patients with diabetes mellitus for the control of hyperglycemia. Humalog should be used with longer-acting insulin, except when used in combination with sulfonylureas in patients with type 2 diabetes.

Important Safety Information

Contraindications

Humalog is contraindicated during episodes of hypoglycemia and in patients sensitive to Humalog or one of its excipients.

Important Safety Information, continued

Warnings

Humalog differs from regular human insulin by its rapid onset of action as well as a shorter duration of action. Therefore, when used as a mealtime insulin, Humalog should be given within 15 minutes before or immediately after a meal.

Due to the short duration of action of Humalog, patients with type 1 diabetes also require a longer-acting insulin to maintain glucose control (except when using an insulin pump).

Glucose monitoring is recommended for all patients with diabetes.

The safety and effectiveness of Humalog in patients less than 3 years of age have not been established. There are no adequate and well-controlled clinical studies of the use of Humalog in pregnant or nursing women.

VITALS

Major Finding: Median time to the first on-study skeletal-related event was 32.4 months in the denosumab arm compared with 27.4 months in the zoledronic acid arm.

Data Source: Updated results on 2,046 patients with advanced breast cancer and bone metastases in a pivotal phase III trial.

Disclosures: Dr. Stopeck disclosed that she serves as a consultant to and has received research grants from both Amgen, which markets denosumab, and Novartis, which markets zoledronic acid. The trial was sponsored by Amgen in collaboration with Daiichi Sankyo.

Dr. Stopeck noted that denosumab offers significant advantages in terms of ease of use. It's given via a once-monthly subcutaneous injection rather than

the intravenous infusion required with zoledronic acid.

Furthermore, unlike for zoledronic acid, there is no need for renal moni-

toring or dose adjustments with denosumab.

The next phase of development for denosumab will be to study it in the setting of early-stage breast cancer to see if it can prevent metastases to the bone and indeed any other part of the body. The rationale is that bone acts as a reservoir for circulating tumor cells, which may spread to other parts of the body and cause metastases.

"This is a trial I think we're all enthusiastic about, to see if we can actually prevent cancer from spreading at an earlier stage by manipulating the bone mi-

croenvironment. Preventing skeletal-related events is nice, but we'd like to move earlier," Dr. Stopeck explained.

Toward this end, the D-CARE trial, a randomized, double-blind, placebo-controlled phase III study of denosumab as adjuvant treatment for women with early-stage breast cancer at high risk of recurrence, has begun enrolling a planned 4,500 patients. The Amgen-sponsored study is expected to run for 10 years, with bone metastasis-free survival as the primary end point, and overall and disease-free survival among the key secondary end points. ■



But it first needs to fit your patient's life.

Important Safety Information, continued

Warnings, continued

Starting or changing insulin therapy should be done cautiously and only under medical supervision.

Hypoglycemia

Hypoglycemia is the most common adverse effect associated with insulins, including Humalog. Hypoglycemia can happen suddenly, and symptoms may be different for each person and may change from time to time. Severe hypoglycemia can cause seizures and may be life-threatening.

Other Side Effects

Other potential side effects associated with the use of insulins include: hypokalemia, weight gain, lipodystrophy, and hypersensitivity. Systemic allergy is less common, but may be life-threatening. Because of the difference in action of Humalog, care should be taken in patients in whom hypoglycemia or hypokalemia may be clinically relevant

Important Safety Information, continued

Other Side Effects, continued

(eg, those who are fasting, have autonomic neuropathy or renal impairment, are using potassium-lowering drugs, or taking drugs sensitive to serum potassium level).

For additional safety profile and other important prescribing considerations, see the accompanying Brief Summary of full Prescribing Information.

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insulin lispro injection (rDNA origin)

