Nerve Damage Less With Sentinel Node Biopsy

BY BRUCE JANCIN
Denver Bureau

SAN ANTONIO — Sentinel lymph node biopsy is as accurate as the traditional surgical practice of dissecting the entire axillary lymph node chain in women with breast cancer but inflicts far less nerve damage and fewer other complications, Mark Kissin, M.Chir., reported at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

The results of the first large-scale randomized trial of sentinel lymph node biopsy in breast cancer patients featuring comprehensive functional and quality of life assessment are so compelling that British health officials who have seen the data have directed that all U.K. surgeons undergo formal training in the technique, according to Dr. Kissin.

"There shouldn't really be a choice anymore. Sentinel node biopsy, for the patient, should be the standard of care," he declared.

Dr. Kissin was a coinvestigator in the Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial, a multicenter U.K. study in which 1,031 women with clinically node-negative breast cancer were randomized to sentinel lymph node biopsy (SLNB) or to the traditional surgical practice of dissecting the entire axillary lymph node chain. Participating surgeons were required to have undergone systematic training in SLNB with demonstrated technical competence in its performance.

ALMANAC featured both patient assessments of functional status and quality of life as well as objective measurements of arm and shoulder morbidity, anxiety, and resource utilization at 1, 3, 6, 12, and 18 months.

The 6-month follow-up data were the focus of presentations in San Antonio; the 18-month data are being processed and should be available soon.

Only one-quarter of patients assigned to SLNB proved to be SLN-positive. That means three-quarters of women who undergo routine axillary node clearance needlessly experience the considerable associated morbidity that was documented in ALMANAC, explained Dr. Kissin, a surgeon at Royal Surrey County Hospital in Guildford, England.

During the first 3 months of follow-up, 83% of women who received standard axillary node dissection experienced at least one arm problem—lymphedema, shoulder stiffness and loss of range of motion, and/or sensory deficits—for 79%, the problem remained at 18 months.

For example, at 1 month, 62% of women randomized to axillary node clearance experienced sensory loss secondary to damage to the intercostal-brachial nerve, as did 43% at 6 months. In contrast, this was the case at 1 month in only 18% assigned to SLNB and at 6 months in 16%.

It is worth emphasizing that ALMANAC employed an intent-to-treat analysis. Since all patients with a positive SLNB subsequently underwent full axillary clearance, and the associated morbidity was recorded on the SLNB side of the ledger, the study greatly underestimated the true benefits of having a negative SLNB.

At 6 months, 3% of women in the axillary clearance group had moderate to severe lymphedema, a rate sixfold greater than in the SLNB group.

ALMANAC principal investigator Robert E. Mansel, M.D., reported that the SLNB group had significantly lower infection rates and operating times and shorter hospital stays.

ALMANAC isn't powered to reach definitive conclusions regarding breast cancer recurrence and survival. For recurrence and survival data, oncologists will look to the results of the National Surgical Adjuvant Breast and Bowel Project B-32 trial, the largest-ever randomized prospective trial evaluating SLNB in clinically node-negative patients.

Thomas B. Julian, M.D., presented preliminary technical results from the phase III trial in which 5,210 participants were randomized to SLNB with or without immediate conventional axillary dissection. Twenty-six percent of patients in both the SLNB and conventional axillary dissection groups proved SLN-positive. In 61.5% of SLN-positive patients, it was the only positive node.

The overall accuracy of SLNB was 97.2%, with a negative predictive value of 96.1% and a false-negative rate—"the number you've all been waiting for," Dr. Julian said—a less than stellar 9.7%.

The false-negative rate was not affected by a surgeon's case experience, but it was influenced by the biopsy method employed. The highest false-negative rate—15.2%—occurred with excisional biopsy, for reasons not yet clear, according to Dr. Julian of NSABP headquarters in Pittsburgh. ■

Synthetic Marine Snail Toxin Gets FDA Approval as Intrathecal Analgesic

BY ELIZABETH MECHCATIE
Senior Writer

An intrathecal formulation of a synthetic version of a toxin used by a fish-eating marine snail to catch its prey has been approved as a treatment for severe, chronic pain.

The Food and Drug Administration approved the nonopiod ziconotide for intrathecal (IT) infusion for managing severe chronic pain "in patients for whom intrathecal therapy is warranted and who are intolerant of or refractory to other treatment, such as systemic analgesics, adjunctive therapies, or IT morphine." It is being marketed under the trade name Prialt by Elan Pharmaceuticals Inc.

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***Conus magus*'s toxin inspired Prialt.**

Ziconotide is a synthetic version of a conopeptide used by the *Conus magus* sea snail to sting fish. In nature the toxin "is so powerful it stops the fish dead in its track, and the snail eats it," said Mark Wallace, M.D., director, center for pain and palliative medicine at the University of California, San Diego.

The synthetic version of this "conotoxin" is an N-type calcium channel antagonist. N-type calcium channels are located mainly in the dorsal horn cells of the spinal cord, predominantly on the superficial layers, in the area of substantia gelatinosa where pain fibers synapse, Dr. Wallace explained.

Ziconotide "blocks those calcium channels at the level where these pain fibers meet up," essentially shutting them down, he said, noting that opioids also have the same effect.

The three trials that led to the approval included patients with "really refractory" pain due to various causes, including low back pain, cancer pain, neuropathic pain, pain from nervous system injuries, and HIV-related pain, said Dr. Wallace, an investigator in the studies and a consultant to the manufacturer.

The most recent trial was a multicenter study in 220 patients with severe chronic pain, described by most as refractory to treatments including IT morphine.

Patients were first taken off IT medications and stabilized on analgesics that included opiates and then treated with placebo or ziconotide.

At 3 weeks, pain scores had improved by a mean of 12% from baseline vs. a mean of 5% for patients given placebo therapy, which was a highly significant difference.

During treatment, the use of non-IT opioids dropped by 24% among patients on ziconotide, compared with 17% among those on placebo. ■

New Agent Approved for Two Neuropathic Pain Conditions

BY ELIZABETH MECHCATIE
Senior Writer

Pregabalin, a drug that binds to calcium channels in the central nervous system, has received Food and Drug Administration approval for the management of pain associated with postherpetic neuralgia and diabetic peripheral neuropathy, making it the first drug indicated for both neuropathic pain conditions.

Pregabalin is the second drug approved specifically for treating pain associated with diabetic peripheral neuropathy (DPN); duloxetine (Cymbalta), was approved in September for this use. Other drugs approved for postherpetic neuralgia (PHN) pain are gabapentin (Neurontin) and the 5% lidocaine patch.

Pregabalin will not be available until the Drug Enforcement Administration decides on its controlled substance category. A company spokesperson would not speculate about when pregabalin would become available in pharmacies and declined to provide details on why it is under review as a controlled substance.

The two approvals were based on six placebo-controlled, double-blind studies involving more than 1,000 patients—three studies in patients with PHN and three in patients with DPN. Findings showed the drug provided quick and clinically meaningful pain reduction in a significant proportion of patients, according to Pfizer, which will market pregabalin under the trade name Lyrica.

In DPN trials, about half the patients had at least a 50% response rate and in PHN trials, the response rates were a little lower, but "still considered impressive," said Brett R. Stacey, M.D., one of the trial investigators.

Pregabalin will act more quickly to lessen pain than tricyclic antidepressants, which need to be started at a low dose, said Dr. Stacey, medical director of the comprehensive pain center at Oregon Health and Science University, Portland.

The time to onset of pain relief can begin the day after the start of treatment, he added. Pregabalin also has a narrow dose range, which will make it easier to prescribe than gabapentin, which has a "huge" dose range because of variable absorption across the GI tract, he said.

Dr. Stacey has done paid research for Pfizer and has been a consultant to the company for gabapentin and pregabalin.

The recommended dosage for pain after shingles is 150-300 mg per day, given in two or three doses; the dosage can be increased up to 600 mg per day, based on tolerability, if patients do not experience sufficient reductions in pain, according to the Pfizer spokesperson. The diabetic nerve pain recommended dosage is 300 mg per day, given in three doses.

Where this fits in with other available treatments depends on various factors, including price, he said. If it is reasonably priced, he said he would be more likely to start patients on the drug. It will be helpful in patients with contraindications to tricyclics and is worth trying in patients who have been treated with gabapentin and continue to have pain, he added. (Price was not available at press time.) ■