Emerging Thyroid Ca Therapies Show Promise

BY MICHELE G. SULLIVAN

Kinase inhibitors and antiangiogenic drugs may offer the first real hope of treating differentiated metastatic thyroid cancer, and seem to be especially effective in tumors exhibiting the B-type Raf kinase mutation.

Although such tumors are uncommon, there are no effective therapies for patients who develop them, Dr. Steven I. Sherman said at a thyroid cancer meeting sponsored by the American Thyroid Association.

"The standard treatment for thyroid cancer—radioactive iodine—is only effective as long as the cancer retains its ability to absorb and retain iodine," said Dr. Sherman, medical director of the Endocrine Center at the M.D. Anderson Cancer Center, Houston. "At least half the time these metastatic tumors have lost that ability, and radioactive iodine won't work."

For patients who have slow-growing, asymptomatic metastatic thyroid tumors, the adverse effects of treatment might be worse than the disease itself, Dr. Sherman said in an interview. "But for those whose cancer is progressing, affecting lung function, or causing bone problems, there is really no good option."

The low incidence of these tumors has stymied many clinical trials: From 1975 to 1999, 15 trials were initiated and only 5 ended with published results, Dr. Sherman said.

However, recent discoveries of mutations that cause aggressive thyroid tumors have inspired new hope. The B-type Raf kinase (BRAF) mutation is the most important, accounting for about 40% of papillary thyroid cancers. "In papillary thyroid cancer, the BRAF tumors are more likely to be aggressive, to recur, and to be radioiodine resistant," he said. BRAF mutations also occur in several other solid tumors, a fact that has added weight to this body of research.

The BRAF mutation interferes with tumor-suppressor genes and silences genes that metabolize iodine. It also increases the production of vascular endothelial growth factor (VEGF), making these tumors a potential target for antiangiogenics—drugs that shut off rampant tumor-feeding vascular growth.

Two small phase I trials of BRAF inhibitors have raised cautious enthusiasm, Dr. Sherman said.

Exelixis Inc. has released results of a trial of its compound, XL281, in 29 patients, 5 of whom had papillary thyroid cancer. The five patients with papillary thyroid cancer, two with a confirmed BRAF mutation, have had stable disease for up to 68 weeks, according to the company Web site.

PLX4032 is another BRAF inhibitor in phase I clinical trial, this one in joint development by Plexxikon Inc. and Roche.

"In these studies we are seeing stabilized disease, although not an overwhelmingly dramatic response, by inhibiting BRAF," Dr. Sherman said.

A second group of trials has examined the effect of directly inhibiting VEGF receptors. Last year, Dr. Sherman published the results of a phase II trial of motesanib in differentiated thyroid cancer. The open-label trial comprised 93 patients with progressive, locally advanced or metastatic, radioiodine-resistant differentiated thyroid cancer. Stable disease occurred in 67% of the patients, and was maintained for 24 weeks or longer in 35% (N. Engl. J. Med. 2008;359:31-42).

BRAF-mutation tumors were particularly sensitive to motesanib. "The ability to stop the tumor's growth was twice as high in BRAF tumors," Dr. Sherman said.

Two other 2008 trials examined the effects of sorafenib and axitinib in advanced thyroid cancers, with similar results, he said. "The thing all three trials have in common is the inhibition of the VEGF receptor. From these studies, we think there is strong evidence that antiangiogenic drugs offer a useful treatment for patients with metastatic differentiated thyroid cancer."

The American Thyroid Association now recommends that patients with these tumors who are not enrolled in clinical trials be treated with one of the approved kinase inhibitors, preferably sorafenib.

Dr. Sherman said he has received research grants, honoraria, and speaking and consulting fees from numerous companies involved in cancer drug development, including Exelixis Inc., Amgen Inc., Bayer, and Plexxikon. ■

ENDO PHARMACEUTICALS

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Brief Summary (For full Prescribing Information refer to package insert.)

INDICATIONS AND USAGE
LIDODERM is indicated for relief of pain associated with post-herpetic neuralgia. It should be applied only to **intact skin**.

CONTRAINDICATIONS
LIDODERM is contraindicated in patients with a known history of sensitivity to local anesthetics of the amide type, or to any other component of the product.

WARNINGS
Accidental Exposure in Children
Even a *used* LIDODERM patch contains a large amount of lidocaine (at least 665 mg). The potential exists for a small child or a pet to suffer serious adverse effects from chewing or ingesting a new or used LIDODERM patch, although the risk with this formulation has not been evaluated. It is important for patients to **store and dispose of LIDODERM out of the reach of children, pets, and others**. (See HANDLING AND DISPOSAL)

Excessive Dosing
Excessive dosing by applying LIDODERM to larger areas or for longer than the recommended wearing time could result in increased absorption of lidocaine and high blood concentrations, leading to serious adverse effects (see ADVERSE REACTIONS, Systemic Reactions). Lidocaine toxicity could be expected at lidocaine blood concentrations above 5 µg/mL. The blood concentration of lidocaine is determined by the rate of systemic absorption and elimination. Longer duration of application, application of more than the recommended number of patches, smaller patients, or impaired elimination may all contribute to increasing the blood concentration of lidocaine. With recommended dosing of LIDODERM, the average peak blood concentration is about 0.13 µg/mL, but concentrations higher than 0.25 µg/mL have been observed in some individuals.

PRECAUTIONS
General
Hepatic Disease: Patients with severe hepatic disease are at greater risk of developing toxic blood concentrations of lidocaine, because of their inability to metabolize lidocaine normally.

Allergic Reactions: Patients allergic to para aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine. However, LIDODERM should be used with caution in patients with a history of drug sensitivities, especially if the etiologic agent is uncertain.

Non-intact Skin: Application to broken or inflamed skin, although not tested, may result in higher blood concentrations of lidocaine from increased absorption. LIDODERM is only recommended for use on intact skin.

Eye Exposure: The contact of LIDODERM with eyes, although not studied, should be avoided based on the findings of severe eye irritation with the use of similar products in animals. If eye contact occurs, immediately wash out the eye with water or saline and protect the eye until sensation returns.

Drug Interactions
Antiarrhythmic Drugs: LIDODERM should be used with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the toxic effects are additive and potentially synergistic.

Local Anesthetics: When LIDODERM is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: A minor metabolite, 2, 6-xylidine, has been found to be carcinogenic in rats. The blood concentration of this metabolite is negligible following application of LIDODERM.

Mutagenesis: Lidocaine HCl is not mutagenic in Salmonella/mammalian microsome test nor clastogenic in chromosome aberration assay with human lymphocytes and mouse micronucleus test.

Impairment of Fertility: The effect of LIDODERM on fertility has not been studied.

Pregnancy
Teratogenic Effects: **Pregnancy Category B**. LIDODERM (lidocaine patch 5%) has not been studied in pregnancy. Reproduction studies with lidocaine have been performed in rats at doses up to 30 mg/kg subcutaneously and have revealed no evidence of harm to the fetus due to lidocaine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, LIDODERM should be used during pregnancy only if clearly needed.

Labor and Delivery
LIDODERM has not been studied in labor and delivery. Lidocaine is not contraindicated in labor and delivery. Should LIDODERM be used concomitantly with other products containing lidocaine, total doses contributed by all formulations must be considered.

Nursing Mothers
LIDODERM has not been studied in nursing mothers. Lidocaine is excreted in human milk, and the milk: plasma ratio of lidocaine is 0.4. Caution should be exercised when LIDODERM is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS
Application Site Reactions
During or immediately after treatment with LIDODERM (lidocaine patch 5%), the skin at the site of application may develop blisters, bruising, burning sensation, depigmentation, dermatitis, discoloration, edema, erythema, exfoliation, irritation, papules, petechia, pruritus, vesicles, or may be the locus of abnormal sensation. These reactions are generally mild and transient, resolving spontaneously within a few minutes to hours.

Allergic Reactions
Allergic and anaphylactoid reactions associated with lidocaine, although rare, can occur. They are characterized by angioedema, bronchospasm, dermatitis, dyspnea, hypersensitivity, laryngospasm, pruritus, shock, and urticaria. If they occur, they should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

Other Adverse Events
Due to the nature and limitation of spontaneous reports in postmarketing surveillance, causality has not been established for additional reported adverse events including:

Asthenia, confusion, disorientation, dizziness, headache, hyperesthesia, hypoesthesia, lightheadedness, metallic taste, nausea, nervousness, pain exacerbated, paresthesia, somnolence, taste alteration, vomiting, visual disturbances such as blurred vision, flushing, tinnitus, and tremor.

Systemic (Dose-Related) Reactions
Systemic adverse reactions following appropriate use of LIDODERM are unlikely, due to the small dose absorbed (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Systemic adverse effects of lidocaine are similar in nature to those observed with other amide local anesthetic agents, including CNS excitation and/or depression (light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold, or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression, and arrest). Excitatory CNS reactions may be brief or not occur at all, in which case the first manifestation may be drowsiness merging into unconsciousness. Cardiovascular manifestations may include bradycardia, hypotension, and cardiovascular collapse leading to arrest.

OVERDOSAGE
Lidocaine overdose from cutaneous absorption is rare, but could occur. If there is any suspicion of lidocaine overdose (see ADVERSE REACTIONS, Systemic Reactions), drug blood concentration should be checked. The management of overdose includes close monitoring, supportive care, and symptomatic treatment. Dialysis is of negligible value in the treatment of acute overdose with lidocaine.

In the absence of massive topical overdose or oral ingestion, evaluation of symptoms of toxicity should include consideration of other etiologies for the clinical effects, or overdosage from other sources of lidocaine or other local anesthetics.

The oral LD_{50} of lidocaine HCl is 459 (346-773) mg/kg (as the salt) in non-fasted female rats and 214 (159-324) mg/kg (as the salt) in fasted female rats, which are equivalent to roughly 4000 mg and 2000 mg, respectively, in a 60 to 70 kg man based on the equivalent surface area dosage conversion factors between species.

DOSAGE AND ADMINISTRATION
Apply LIDODERM to intact skin to cover the most painful area. Apply up to three patches, only once for up to 12 hours within a 24-hour period. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. (See HANDLING AND DISPOSAL) Clothing may be worn over the area of application. Smaller areas of treatment are recommended in a debilitated patient, or a patient with impaired elimination.

If irritation or a burning sensation occurs during application, remove the patch (es) and do not reapply until the irritation subsides.

When LIDODERM is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.

HANDLING AND DISPOSAL
Hands should be washed after the handling of LIDODERM, and eye contact with LIDODERM should be avoided. Do not store patch outside the sealed envelope. Apply immediately after removal from the protective envelope. Fold used patches so that the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get to them. LIDODERM should be kept out of the reach of children.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, Pennsylvania 19317

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