

Lasers, PDT May Have Niche in Cancer Treatment

BY JEFF EVANS
Senior Writer

BALTIMORE — Lasers and light therapies have a limited role in the treatment of skin cancers and pigmented lesions, but their judicious use may be appropriate when standard treatments would be time consuming or provide poor cosmetic results, Dr. James Spencer said at a meeting sponsored by the Skin Disease Education Foundation.

Dr. Spencer, director of Mohs micrographic surgery at Mount Sinai Medical Center, New York, presented information to help physicians determine when it may be acceptable or unacceptable to use lasers or photodynamic therapies on skin lesions.

CO₂ Laser

Use of a CO₂ laser in continuous wave mode produces rapid and bloodless thermal destruction of tissue, but this mode has not been shown to be an effective

treatment for skin cancer, he said. In a study of 24 basal cell carcinomas (BCCs) treated this way, 50% recurred after 1 year and healing after the procedure produced hypopigmentation and atrophy (J. Dermatol. Surg. Oncol. 1979;5:803-6).

Some studies have tested the theory that treatment of superficial skin cancers with the CO₂ laser in ultrapulsed mode could destroy the tumor and avoid scarring. In a series of 51 BCCs that were treated with the CO₂ laser in ultrapulsed mode,

dermatologic surgeons were able to ablate 21 superficial BCCs reliably if the level of ablation penetrated to the midreticular dermis or deeper. Attempts to use this method with 28 nodular and 2 infiltrating BCCs were not successful (Br. J. Plast. Surg. 2000;53:286-93).

In another study, two or three passes of an ultrapulsed CO₂ laser on 17 superficial BCCs and 13 squamous cell carcinomas (SCCs) in situ with 3-mm margins onto normal skin left an unacceptably high rate of lesions positive for cancer when they were excised and examined in serial sections. For superficial BCCs, two passes left five of eight lesions positive and three passes left zero of nine lesions positive. Treatment of in situ SCC with two passes yielded two of six lesions positive while three passes resulted in three of seven lesions being positive (Arch. Dermatol. 1998;134:1247-52).

Dr. Spencer said that he did not think CO₂ lasers should realistically be a part of a dermatologist's armamentarium against skin cancer, but he suggested that the CO₂ laser may be considered to treat actinic cheilitis and basal cell nevus syndrome, "where your role is not cure, but control, and you're trying to avoid too much mutilating surgery."

Intravenous and Topical PDT

Intravenously administered photodynamic therapy (PDT) with agents such as porfimer sodium (Photofrin) is being studied for a variety of cancers, but its side effect of photosensitivity for 4-6 weeks through the skin and eyes creates a problem in using it for skin cancers. "If you're dying of a stomach cancer, you will hide in a dark room for a month, but if you've got some basal cell skin cancers, I don't think you will," Dr. Spencer said.

In a prospective study, PDT with intravenous Photofrin and red light yielded a complete response rate of 88% after an average follow-up of 29 months in 37 patients who had a total of 151 BCCs (most patients had basal cell nevus syndrome). Tumors recurred, however, in 36% of lesions on the nose and in 89% of morpheiform tumors (Arch. Dermatol. 1992;128:1597-601).

PDT researchers are studying shorter-acting light-sensitizing compounds that preferentially accumulate in malignant cells to avoid the problem of persistent photosensitivity with Photofrin. Verteporfin, an intravenously administered agent approved for ophthalmologic use that photosensitizes patients for only a few days, is undergoing clinical trials to test its efficacy in skin cancer, he said.

Topical PDT agents such as delta-aminolevulinic acid (ALA), which avoid the photosensitizing problem altogether, have had reported recurrence rates of 44% in 95 superficial BCCs and 69% in 35 superficial SCCs after 19 months of follow-up (Arch. Dermatol. 1998;134:821-6). "You should not be doing this in your practice," said Dr. Spencer, who also has a private practice in St. Petersburg, Fla.

Eyelid tumors may represent the best opportunity to try topical ALA because it is usually desirable to avoid surgery in that

Continued on following page



BRIEF SUMMARY

For Dermatologic Use Only—Not for Ophthalmic, Oral, or Intravaginal Use
Rx only

CONTRAINDICATIONS

FINACEA® Gel, 15%, is contraindicated in individuals with a history of hypersensitivity to propylene glycol or any other component of the formulation.

WARNINGS

FINACEA® Gel, 15%, is for dermatologic use only, and not for ophthalmic, oral, or intravaginal use.

There have been isolated reports of hypopigmentation after use of azelaic acid. Since azelaic acid has not been well studied in patients with dark complexion, these patients should be monitored for early signs of hypopigmentation.

PRECAUTIONS

General: Contact with the eyes should be avoided. If sensitivity or severe irritation develops with the use of FINACEA® Gel, 15%, treatment should be discontinued and appropriate therapy instituted. The safety and efficacy of FINACEA® Gel, 15%, has not been studied beyond 12 weeks.

Information for Patients: Patients using FINACEA® Gel, 15%, should receive the following information and instructions:

- FINACEA® Gel, 15%, is to be used only as directed by the physician.
- FINACEA® Gel, 15%, is for external use only. It is not to be used orally, intravaginally, or for the eyes.
- Cleanse affected area(s) with a very mild soap or a soapless cleansing lotion and pat dry with a soft towel before applying FINACEA® Gel, 15%. Avoid alcoholic cleansers, tinctures, and astringents, abrasives, and peeling agents.
- Avoid contact of FINACEA® Gel, 15%, with the mouth, eyes and other mucous membranes. If it does come in contact with the eyes, wash the eyes with large amounts of water and consult a physician if eye irritation persists.
- The hands should be washed following application of FINACEA® Gel, 15%.
- Cosmetics may be applied after FINACEA® Gel, 15%, has dried.
- Skin irritation (e.g., pruritus, burning, or stinging) may occur during use of FINACEA® Gel, 15%, usually during the first few weeks of treatment. If irritation is excessive or persists, use of FINACEA® Gel, 15%, should be discontinued, and patients should consult their physician (See ADVERSE REACTIONS).
- Avoid any foods and beverages that might provoke erythema, flushing, and blushing (including spicy food, alcoholic beverages, and thermally hot drinks, including hot coffee and tea).
- Patients should report abnormal changes in skin color to their physician.
- Avoid the use of occlusive dressings or wrappings.

Drug Interactions: There have been no formal studies of the interaction of FINACEA® Gel, 15%, with other drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential of FINACEA® Gel, 15%. Azelaic acid was not mutagenic or clastogenic in a battery of *in vitro* (Ames assay, HGPRT in V79 cells [Chinese hamster lung cells], and chromosomal aberration assay in human lymphocytes) and *in vivo* (dominant lethal assay in mice and mouse micronucleus assay) genotoxicity tests.

Oral administration of azelaic acid at dose levels up to 2500 mg/kg/day (162 times the maximum recommended human dose based on body surface area) did not affect fertility or reproductive performance in male or female rats.

Pregnancy: Teratogenic Effects: Pregnancy Category B

There are no adequate and well-controlled studies of topically administered azelaic acid in pregnant women. The experience with FINACEA® Gel, 15%, when used by pregnant women is too limited to permit assessment of the safety of its use during pregnancy.

Dermal embryofetal developmental toxicology studies have not been performed with azelaic acid, 15%, gel. Oral embryofetal developmental studies were conducted with azelaic acid in rats, rabbits, and cynomolgus monkeys. Azelaic acid was administered during the period of organogenesis in all three animal species. Embryotoxicity was observed in rats, rabbits, and monkeys at oral doses of azelaic acid that generated some maternal toxicity. Embryotoxicity was observed in rats given 2500 mg/kg/day (162 times the maximum recommended human dose based on body surface area), rabbits given 150 or 500 mg/kg/day (19 or 65 times the maximum recommended human dose based on body surface area) and cynomolgus monkeys given 500 mg/kg/day (65 times the maximum recommended human dose based on body surface area) azelaic acid. No teratogenic effects were observed in the oral embryofetal developmental studies conducted in rats, rabbits, and cynomolgus monkeys.

An oral peri- and postnatal developmental study was conducted in rats. Azelaic acid was administered from gestational day 15 through day 21 postpartum up to a dose level of 2500 mg/kg/day. Embryotoxicity was observed in rats at an oral dose that generated some maternal toxicity (2500 mg/kg/day; 162 times the maximum recommended human dose based on body surface area). In addition, slight disturbances in the postnatal development of fetuses was noted in rats at oral doses that generated some maternal toxicity (500 and 2500 mg/kg/day; 32 and 162 times the maximum recommended human dose based on body surface area). No effects on sexual maturation of the fetuses were noted in this study. Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly needed during pregnancy.

Nursing Mothers:

Equilibrium dialysis was used to assess human milk partitioning *in vitro*. At an azelaic acid concentration of 25 µg/mL, the milk/plasma distribution coefficient was 0.7 and the milk/buffer distribution was 1.0, indicating that passage of drug into maternal milk may occur. Since less than 4% of a topically applied dose of azelaic acid cream, 20%, is systemically absorbed, the uptake of azelaic acid into maternal milk is not expected to cause a significant change from baseline azelaic acid levels in the milk. However, caution should be exercised when FINACEA® Gel, 15%, is administered to a nursing mother.

Pediatric Use: Safety and effectiveness of FINACEA® Gel, 15%, in pediatric patients have not been established.

Geriatric: Clinical studies of FINACEA® Gel, 15%, did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

Overall, treatment related adverse events, including burning, stinging/tingling, dryness/tightness/scaling, itching, and erythema/irritation/redness, were 19.4% (24/124) for FINACEA® Gel, 15%, and 7.1% (9/127) for the active comparator gel at 15 weeks.

In two vehicle controlled, and one active controlled U.S. clinical studies, treatment safety was monitored in 788 patients who used twice daily FINACEA® Gel, 15%, for 12 weeks (N=333) or for 15 weeks (N=124), or the gel vehicle (N=331) for 12 weeks.

Table 3. Cutaneous Adverse Events Occurring in ≥1% of Subjects in the Rosacea Trials by Treatment Group and Maximum Intensity*

	FINACEA® Gel, 15% N=457 (100%)			Vehicle N=331 (100%)		
	Mild n=99 (22%)	Moderate n=61 (13%)	Severe n=27 (6%)	Mild n=46 (14%)	Moderate n=30 (9%)	Severe n=5 (2%)
Burning/ stinging/ tingling	71 (16%)	42 (9%)	17 (4%)	8 (2%)	6 (2%)	2 (1%)
Pruritus	29 (6%)	18 (4%)	5 (1%)	9 (3%)	6 (2%)	0 (0%)
Scaling/dry skin/xerosis	21 (5%)	10 (2%)	5 (1%)	31 (9%)	14 (4%)	1 (<1%)
Erythema/ irritation	6 (1%)	7 (2%)	2 (<1%)	8 (2%)	4 (1%)	2 (1%)
Contact dermatitis	2 (<1%)	3 (1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Edema	3 (1%)	2 (<1%)	0 (0%)	3 (1%)	0 (0%)	0 (0%)
Acne	3 (1%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)

*Subjects may have >1 cutaneous adverse event; thus, the sum of the frequencies of preferred terms may exceed the number of subjects with at least 1 cutaneous adverse event.

FINACEA® Gel, 15%, and its vehicle caused irritant reactions at the application site in human dermal safety studies. FINACEA® Gel, 15%, caused significantly more irritation than its vehicle in a cumulative irritation study. Some improvement in irritation was demonstrated over the course of the clinical studies, but this improvement might be attributed to subject dropouts. No phototoxicity or photoallergenicity were reported in human dermal safety studies.

In patients using azelaic acid formulations, the following additional adverse experiences have been reported rarely: worsening of asthma, vitiligo depigmentation, small depigmented spots, hypertrichosis, reddening (signs of keratosis pilaris), and exacerbation of recurrent herpes labialis.

Post-marketing safety—Skin: facial burning and irritation; Eyes: iridocyclitis on accidental exposure with FINACEA® Gel, 15%, to the eye (see PRECAUTIONS).

OVERDOSAGE

FINACEA® Gel, 15%, is intended for cutaneous use only. If pronounced local irritation occurs, patients should be directed to discontinue use and appropriate therapy should be instituted (See PRECAUTIONS).

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New Leg Vein Tx Combines Laser and RF Energy

BY SHARON WORCESTER
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ATLANTA — A novel technology that combines diode laser and radiofrequency energy may be safe and effective for treating leg veins, Dr. Neil Sadick reported at the joint annual meeting of the American Society for Dermatologic Surgery and the American College of Mohs Micrographic Surgery and Cutaneous Oncology.

In a two-center study involving 50

women with lower extremity red or blue leg veins up to 4 mm in diameter, the Polaris LV system (Syneron Inc., Richmond Hill, Ont.) provided at least 50% vessel clearance in 76% of patients. The clearing persisted at 6 months of follow-up, said Dr. Sadick of Cornell University, New York.

The system uses a 915-nm laser. Patients were treated with one to three passes at each of three treatment sessions scheduled at 2-week intervals.

Pre- and posttreatment photographs

were graded by patients and an independent physician at a 2-month follow-up visit to determine the level of vessel clearance, and a score was generated by a novel computer-based assessment system. Independent observer analysis was corroborated by the computer imaging analysis.

Biopsy specimens also were provided for histologic assessment, which showed signs of coagulation and prominent endothelial degeneration in all treated vessels, said Dr.

Sadick, who is a research consultant for Syneron.

A subsequent study showed that the Polaris LV system's effects were comparable histopathologically with those of the 1064-nm wavelength laser.

Complications with the Polaris LV system were minimal. A slight increase in the amount of hyperpigmentation and bruising was noted, compared with the 1064-nm laser, but pain was considerably less with the 915-nm laser. ■

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area and ALA may be able to more fully penetrate the thin skin of the eyelid, he suggested. In one study, topical PDT ALA treatment clinically resolved 8 of 19 nodular BCCs on the eyelids and periocular skin, while the other lesions had partial or no response (*Acta Ophthalmol. Scand.* 1999;77:182-8).

In a study of topical PDT with methyl-5 ALA, 79% of 350 nodular BCCs that were curetted before treatment with PDT were clinically clear. After 2-4 years' follow-up, 11% of the clinically clear lesions recurred (*Br. J. Dermatol.* 2001;145:467-71).

Lasers That Target Melanin

Lasers should not be used as a substitute for surgical removal of lentigo maligna, Dr. Spencer said.

In 11 patients with lentigo maligna who were treated with the Q-switched ruby laser on four occasions in a 6-month period, 6 of 13 biopsies taken after treatment were still positive for the lesion. Studies of lentigo maligna treatments with 532-nm and 1,064-nm Q-switched Nd:YAG lasers have shown similar results.

Some people may want to undergo laser removal of common acquired nevi for cosmetic reasons. There is a variable response to such treatment, in which nevi partially or completely lighten in color. This "debulks" and superficially removes the nevus from the epidermis but leaves residual nevus cells in the dermis, he said.

It is unclear if laser treatment of dysplastic or congenital, especially giant, nevi reduces the risk of melanoma. Treatment of atypical-appearing melanocytic lesions with lasers can provide an excellent cosmetic result, but it may run the risk of promoting malignant transformation. Lasers strip a lesion of its outer layer of UV-protecting melanin and create a scar in the papillary dermis that may clinically mask a deeper component, Dr. Spencer said.

"These concerns are very real," he said, but "people have been cautiously trying lasers on nevi for 20 years, and we haven't seen any malignant transformation."

Dr. Spencer said that laser removal of nevi "should be studied in a more formal way, but people have been very afraid to do this."

Clinicians have widely accepted the removal of nevi of Ota with lasers for only cosmetic improvement, so laser removal of large congenital and common acquired nevi should be considered, he said.

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