

Limb Infusion an Option for In-Transit Melanoma

BY DAMIAN McNAMARA

PALM BEACH, FLA. — Regional chemotherapy via isolated limb infusion is an acceptable and minimally invasive alternative to hyperthermic isolated limb perfusion to combat in-transit extremity melanoma, according to a review.

“Perfusion is appropriate with lymph node involvement. For all others, infusion should be considered,” Dr. Georgia

M. Beasley said. She, Dr. Douglas S. Tyler, and their colleagues reviewed response and toxicity for 166 isolated limb infusions in 157 patients with advanced extremity melanoma. At 3 months after the infusion of melphalan, patients’ responses were fairly evenly divided among complete response, partial response, and no response. In cases when the melphalan dose was adjusted for ideal body weight (IBW), the rate of grade 3 or

higher toxicity fell more than half, with no effect on complete response rate.

Melphalan (Alkeran) was administered at eight centers, representing the majority of institutions performing limb infusions in the United States, Dr. Beasley said at the annual meeting of the Southern Surgical Association.

Patients received melphalan at doses of 7.5 mg/L for advanced melanoma of the lower extremity and 10 mg/L for the

upper extremity. Mean ischemic time was 72 minutes. Papaverine was also administered in 60% of procedures. “We currently recommend use of papaverine in conjunction with adjustment of melphalan for ideal body weight to minimize toxicity,” Dr. Beasley said.

Among the 122 evaluable patients, 31% experienced a complete response at 3 months according to RECIST (Response Evaluation Criteria in Solid Tumors), modified for cutaneous lesions. Another 33% of patients had a partial response, and 36% did not respond at 3 months. The complete response rate for hyperthermic isolated limb perfusion is generally accepted to be 40%-80%, Dr. Beasley said. Discussant Dr. Kirby I. Bland drew attention to the 36% rate of nonresponders. “You were still unable to control local disease in [almost] 40% of that population,” said Dr. Bland, chair of the surgery department at the University of Alabama at Birmingham.

“For extensive in-transit disease in the lower extremity, I would recommend infusion, even though one-third of patients are not expected to have a response,” responded Dr. Beasley, a first-year general surgery resident at Duke University Medical Center, Durham, N.C. “This allows reservation of perfusion for those who do not respond. Also, repeat perfusions are more difficult to do.”

Dr. Beasley said that 36% of cases were associated with grade 3 or higher clinical toxicity. In 42% of the procedures, melphalan was adjusted for IBW. This modification reduced grade 3 or greater toxicities from 47% to 21%. At the same time, it did not alter the complete response rate. “By the end of the series, we were correcting everyone [at Duke] for ideal body weight,” Dr. Beasley said. She cautioned that the dose adjustment did reduce the partial response rate, however.

Limb infusion and perfusion exhibit major differences in the rates of grade 5 toxicity, Dr. Beasley said. Even though one limb infusion patient had an amputation, the rate of grade 5 toxicity “appears to be nearly 10-fold higher with perfusion,” based on all the published data for isolated limb infusion. The study did not directly compare rates of grade 3 and 4 toxicity in infusion and perfusion, but the rates appear to be somewhat similar, she said, with dose correction for IBW significantly reducing toxicity.

“How many patients had compartment syndrome, and what are your recommendations for monitoring?” asked Dr. Kelly M. McMasters, a study discussant and chair of surgery at the University of Louisville (Ky.). Nine cases of compartment syndrome were reported, Dr. Beasley replied. She recommended daily creatine phosphokinase measurements and close clinical monitoring.

Only two U.S. studies previously assessed isolated limb infusion, with both reporting single-center experience (Ann. Surg. Oncol. 2008;15:2195-205; Ann. Surg. Oncol. 2006;13:1123-9).

None of the researchers in the current study had any relevant disclosures. ■

VECTICAL™ (calcitriol) OINTMENT, 3 mcg/g

For topical use only.

Not for oral, ophthalmic, or intravaginal use.

Not to be applied to the eyes, lips, or facial skin.

BRIEF SUMMARY

INDICATIONS AND USAGE:

VECTICAL Ointment is a vitamin D analog indicated for the topical treatment of mild to moderate plaque psoriasis in adults 18 years and older.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Effects on Calcium Metabolism

In controlled clinical trials with VECTICAL Ointment, among subjects having laboratory monitoring, hypercalcemia was observed in 24% (18/74) of subjects exposed to active drug and in 16% (13/79) of subjects exposed to vehicle. However, the increases in calcium and albumin-adjusted calcium levels were less than 10% above the upper limit of normal.

If aberrations in parameters of calcium metabolism occur, treatment should be discontinued until these parameters have normalized. The effects of VECTICAL Ointment on calcium metabolism following treatment durations greater than 52 weeks have not been evaluated. Increased absorption may occur with occlusive use.

Ultraviolet Light Exposure

Animal data suggest that the vehicle of VECTICAL Ointment may enhance the ability of ultraviolet radiation (UVR) to induce skin tumors.

Subjects who apply VECTICAL Ointment to exposed skin should avoid excessive exposure of the treated areas to either natural or artificial sunlight, including tanning booths and sun lamps. Physicians may wish to limit or avoid use of phototherapy in patients who use VECTICAL Ointment.

Unevaluated Uses

The safety and effectiveness of VECTICAL Ointment in patients with known or suspected disorders of calcium metabolism have not been evaluated. The safety and effectiveness of VECTICAL Ointment with erythrodermic, exfoliative, or pustular psoriasis have not been evaluated.

ADVERSE REACTIONS

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Clinical Studies Experience

VECTICAL Ointment was studied in two vehicle-controlled studies (419 subjects), and in one open label study (324 subjects). The table below describes exposure to VECTICAL Ointment in 743 subjects, including 239 exposed for 6 months and 116 exposed for one year.

Four hundred and nineteen subjects were treated with VECTICAL Ointment twice daily for 8 weeks. The population included subjects ages 13 to 87, males (284) and females (135), Caucasians (372) and non-Caucasians (47); with mild (105) to moderate (313) chronic plaque psoriasis.

Selected Adverse Events Occurring in at least 1% of Subjects in the Two Pooled Vehicle-Controlled Studies

	VECTICAL Ointment (n=419)	Vehicle Ointment (n=420)
Discomfort skin	3%	2%
Pruritus	1%	1%

Among subjects having laboratory monitoring, hypercalcemia was observed in 24% (18/74) of subjects exposed to active drug and in 16% (13/79) of subjects exposed to vehicle, however the elevations were less than 10% above the upper limit of normal. The open label study enrolled 324 subjects with psoriasis who were then treated for up to 52 weeks. Adverse events reported at a rate of greater than or equal to 3% of subjects treated with VECTICAL Ointment were lab test abnormality (8%), urine abnormality (4%), psoriasis (4%), hypercalciuria (3%), and pruritus (3%). Kidney stones were reported in 3 subjects and confirmed in two.

Postmarketing Experience

The following adverse reactions have been identified during worldwide post-approval use of VECTICAL Ointment: acute blistering dermatitis, erythema, pruritus, skin burning sensation, and skin discomfort. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

DRUG INTERACTIONS

VECTICAL Ointment should be used with caution in patients receiving medications known to increase the serum calcium level, such as thiazide diuretics. Caution should also be exercised in patients receiving calcium supplements or high doses of vitamin D.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C.

VECTICAL Ointment contains calcitriol which has been shown to be fetotoxic. There are no adequate and well-controlled studies for VECTICAL Ointment in pregnant women. VECTICAL Ointment should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.

Teratogenicity studies with calcitriol were performed in which rats were treated orally at dosages up to 0.9 mcg/kg/day (5.4 mcg/m²/day) and in which rabbits received topical application of calcitriol ointment (3 ppm) to 6.4% of the body surface area. No effects on reproductive or fetal parameters were observed in rats. In rabbits, topically applied calcitriol induced a significantly elevated mean post-implantation loss and an increased incidence of minor skeletal abnormalities due to retarded ossification of the pubic bones. A slightly increased incidence of skeletal variation (extra 13th rib, reduced ossification of epiphyses) was also observed. These effects may have been secondary to maternal toxicity. Based on the recommended human dose and instructions for use, it is not possible to calculate human dose equivalents for animal exposures in these studies.

Nursing Mothers

It is not known whether calcitriol is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VECTICAL Ointment is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of VECTICAL Ointment did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported experience has not identified differences in responses between the elderly and younger patients.

OVERDOSAGE

Topically applied calcitriol can be absorbed in sufficient amounts to produce systemic effects.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

When calcitriol was applied topically to mice for up to 24 months, no significant changes in tumor incidence were observed. Concentrations of calcitriol in ointment base of 0 (vehicle control), 0.3, 0.6 and 1.0 ppm were evaluated.

A two-year carcinogenicity study was conducted in which calcitriol was orally administered to rats at dosages of approximately 0.005, 0.03, and 0.1 mcg/kg/day (0.03, 0.18, and 0.6 mcg/m²/day, respectively). The incidence of benign pheochromocytomas was significantly increased in female rats. No other significant differences in tumor incidence data were observed.

In a study in which albino hairless mice were exposed to both ultra-violet radiation (UVR) and topically applied calcitriol ointment, a reduction in the time required for UVR to induce the formation of skin tumors was observed in all groups that received the ointment base, including the vehicle-treated control group, relative to animals that received no ointment but which were exposed to UVR. The time required for UVR to induce the formation of skin tumors did not differ between animals that received plain vehicle and those that received vehicle that contained calcitriol. Concentrations of calcitriol in ointment base of 0 (vehicle control), 0.3, 0.6 and 1.0 ppm were evaluated. These data suggest that the vehicle of VECTICAL Ointment may enhance the ability of UVR to induce skin tumors.

Calcitriol did not elicit genotoxic effects in the mouse lymphoma TK locus assay. Studies in which male and female rats received oral doses of calcitriol of up to 0.6 mcg/kg/day (3.6 mcg/m²/day) indicated no impairment of fertility or general reproductive performance.

Based upon the recommended human dose and instructions for use, it is not possible to calculate human dose equivalents for animal exposure in these studies.

PATIENT COUNSELING INFORMATION

This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. Patients using VECTICAL Ointment should receive the following information:

Instructions for Use

This medication is to be used as directed by the physician. It is for external use only. This medication is to be applied only to areas of the skin affected by psoriasis, as directed. It should be gently rubbed into the skin so that no medication remains visible.

Adverse Reactions

Patients should report any signs of adverse reactions to their physician.

Marketed by:

GALDERMA LABORATORIES, L.P.
Fort Worth, Texas 76177 USA

Manufactured by:

Galderma Production Canada Inc.
Baie d'Urfé, QC, H9X 3S4 Canada
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References: 1. Data on file. Galderma Laboratories. 2. Lebwohl M, Menter A, Weiss J, et al. Calcitriol 3 µg/g ointment in the management of mild to moderate plaque type psoriasis: results from 2 placebo-controlled, multicenter, randomized double-blind, clinical studies. *J Drugs Dermatol.* 2007;6:428-435. 3. Ortonne JP, Humbert P, Nicolas JF, et al. Intra-individual comparison of the cutaneous safety and efficacy of calcitriol 3 µg g-1 ointment and calcipotriol 50 µg g-1 ointment on chronic plaque psoriasis localized in facial, hairline, retroauricular or flexural areas. *Br J Dermatol.* 2003;148:326-333. 4. Vectical™ Prescribing Information. Fort Worth, TX: Galderma Laboratories, L.P.; 2009.