

Metastasizing Cancer Cells Face Harsh Conditions

BY DAMIAN McNAMARA
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TORONTO — “Survival of the fittest” might be the best way to explain the genetic and molecular machinery behind cancer metastasis.

Researchers believe that overexpression of some genes in melanoma and other cancers allows some cells to survive the very harsh conditions that occur as they leave a primary tumor, travel to a

distant site, and establish a new location for malignancy. “It is a similar theme to Darwin with natural selection, although it works out in a microenvironment,” Dr. Youwen Zhou said.

“Why do I think this is a big deal? We still do not have a cure for metastatic melanoma, and next year another 900 or so patients [in Canada] will die from melanoma,” Dr. Zhou said.

Melanoma was the sixth most common solid cancer for men in Canada in

2005 and 2006. There were 3,900 new cases last year. Of 840 deaths in 2006 from melanoma, 90% involved metastatic disease, said Dr. Zhou, who is on the faculty in the department of dermatology and skin science at the University of British Columbia, Vancouver.

There are some reasons for optimism, however. Understanding the molecular machinery might permit earlier intervention through better diagnostic or prognostic tools, Dr. Zhou said at the annual

conference of the Canadian Dermatology Association.

Serum protein testing, for example, might lead to more accurate estimates of prognosis. The melanoma-inhibiting activity (MIA) protein is detected in high amounts in 100% of patients with metastatic melanoma so far. “About 20% of patients with primary melanoma will have signs of this protein in their serum. If they are negative for MIA protein, not one of them developed metastasis over time,” he said.

Genetic insights also may lead to new therapeutic targets. “Selective gene silencing may work to cause metastatic cells to die,” Dr. Zhou said.

So how do invasive tumors develop? Metastasis occurs when genetically unstable cancer cells adapt to a tissue microenvironment distant from the primary tumor (Cell 2006;127:679-95).

Other investigators have identified individual genes that are amplified in

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metastatic melanoma (Cell 2006; 125:1269-81).

A high degree of heterogeneity in melanoma tumor cells may in part explain why aggressive gene clones arise.

“If you look at a melanoma clinically, it has

signs of molecular and cellular heterogeneity, for example, irregular borders. On a cellular level, pathologists use variation in cell size as a diagnostic factor,” he said.

Dominant genetic clones can cause a higher resistance to apoptosis, greater tolerance to hypoxia and nutrient deprivation, altered cell adherence, and increased genomic instability.

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Before these breakaway cells become “little tumor thrombi,” they must break through local physical barriers, he explained. They do this in part by degrading the collagen matrix. Then they have to overcome the vascular wall and survive the harsh sheering and other forces of the vasculature.

Some will survive intravasation with the right molecular defense mechanisms. Extravasation occurs when they arrive at a destination, change adhesion properties, and again pass through the vascular wall. Finally, the cells must continue to defend themselves against host defenses for distant colonization to be successful, Dr. Zhou said.

Development of novel targeting strategies against this genetic and molecular machinery is needed, he said. Once those strategies are identified, the next step would be large scale trials to assess these therapeutic targets. ■

BRIEF SUMMARY – See package insert for full prescribing information

CUTIVATE® LOTION, 0.05%

(Fluticasone propionate lotion)

FOR TOPICAL USE ONLY.

NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.

Rx Only

DESCRIPTION: CUTIVATE LOTION, 0.05% (fluticasone propionate lotion) contains fluticasone propionate [5-(fluoromethyl) 6 α ,9-difluoro-11 β ,17-dihydroxy-16 α -methyl-3-oxoandrostano-1,4-diene-17 β -carboxylate, 17-propionate], a synthetic fluorinated corticosteroid, for topical dermatologic use. The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and antipruritic agents.

Each gram of CUTIVATE LOTION contains 0.5mg fluticasone propionate in a base of cetostearyl alcohol, isopropyl myristate, propylene glycol, cetomacrogol 1000, dimethicone 360, citric acid, sodium citrate, and purified water, with imidurea, methylparaben, and propylparaben as preservatives.

Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

INDICATIONS AND USAGE: CUTIVATE LOTION (fluticasone propionate) is indicated for the relief of the inflammatory and pruritic manifestations of atopic dermatitis in patients 1 year of age or older. The safety and efficacy of drug use for longer than 4 weeks in this population have not been established. The safety and efficacy of CUTIVATE LOTION in pediatric patients below 1 year of age have not been established.

CONTRAINDICATIONS: CUTIVATE LOTION is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

Absorption: The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusive dressing enhances penetration. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption.

Special Population (Pediatric): Plasma fluticasone levels were measured in patients 2 years - 6 years of age in an HPA axis suppression study. A total of 13 (62%) of 21 patients tested had measurable fluticasone at the end of 3 - 4 weeks of treatment. The mean \pm SD fluticasone plasma values for patients aged under 3 years was 47.7 \pm 31.7 pg/mL and 175.5 \pm 243.6 pg/mL. Three patients had fluticasone levels over 300 pg/mL, with one of these having a level of 819.81 pg/mL. No data was obtained for patients < 2 years of age.

CLINICAL STUDIES: CUTIVATE LOTION applied once daily was superior to vehicle in the treatment of atopic dermatitis in two studies. The two studies enrolled 438 patients with atopic dermatitis aged 3 months and older, of which 169 patients were selected as having clinically significant signs of erythema, infiltration/population and erosion/oozing/crusting at baseline. Table 1 presents the percentage of patients who completely cleared of erythema, infiltration/population and erosion/oozing/crusting at Week 4 out of those patients with clinically significant baseline signs.

Table 1: Complete Clearance Rate

	CUTIVATE LOTION	Vehicle
Study 1	9/45 (20%)	0/37 (0%)
Study 2	7/44 (16%)	1/43 (2%)

*Clinically significant was defined as having moderate or severe involvement for at least two of the three signs (erythema, infiltration/population, or erosion/oozing/crusting) in at least 2 body regions. Patients who had moderate to severe disease in a single body region were excluded from the analysis.

PRECAUTIONS:

General: Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal from treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Patients applying a potent topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using cosyntropin (ACTH 1-24) stimulation testing.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios (see PRECAUTIONS: Pediatric Use).

Fluticasone propionate Lotion, 0.05% may cause local cutaneous adverse reactions (see ADVERSE REACTIONS).

If irritation develops, CUTIVATE LOTION should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of CUTIVATE LOTION should be discontinued until the infection has been adequately controlled.

CUTIVATE LOTION should not be used in the presence of preexisting skin atrophy and should not be used where infection is present at the treatment site. CUTIVATE LOTION should not be used in the treatment of rosacea and perioral dermatitis.

Laboratory Tests: The cosyntropin (ACTH 1-24) stimulation test may be helpful in evaluating patients for HPA axis suppression.

Information for Patients: Patients using CUTIVATE LOTION should receive the following information and instructions:

- CUTIVATE LOTION is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
- CUTIVATE LOTION should not be used for any disorder other than that for which it was prescribed.
- The treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician.
- Patients should report to their physician any signs of local adverse reactions.
- Parents of pediatric patients should be advised not to use this medication in the treatment of diaper dermatitis unless directed by the physician. CUTIVATE LOTION should not be applied in the diaper areas as diapers or plastic pants may constitute occlusive dressing (see DOSAGE AND ADMINISTRATION).
- CUTIVATE LOTION should not be used on the face, underarms, or groin areas unless directed by a physician.
- CUTIVATE LOTION therapy should be discontinued if control is achieved before 4 weeks. If no improvement is seen within 2 weeks, contact a physician. The safety of the use of CUTIVATE LOTION for longer than 4 weeks has not been established.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: No studies were conducted to determine the photo-carcinogenic potential of CUTIVATE LOTION.

In an oral (gavage) mouse carcinogenicity study, doses of 0.1, 0.3 and 1 mg/kg/day fluticasone propionate were administered to mice for 18 months. Fluticasone propionate demonstrated no tumorigenic potential at oral doses up to 1 mg/kg/day (less than the MRHD in adults based on body surface area comparisons) in this study.

In a dermal mouse carcinogenicity study, 0.05% fluticasone propionate ointment (40 mg/l) was topically administered for 1, 3 or 7 days/week for 80 weeks. Fluticasone propionate demonstrated no tumorigenic potential at dermal doses up to 6.7 mg/kg/day (less than the MRHD in adults based on body surface area comparisons) in this study.

Fluticasone propionate revealed no evidence of mutagenic or clastogenic potential based on the results of five in vitro genotoxicity tests (Ames assay, E. coli fluctuation test, S. cerevisiae gene conversion test, Chinese hamster ovary cell chromosome aberration assay and human lymphocyte chromosome aberration assay) and one in vivo genotoxicity test (mouse micronucleus assay).

No evidence of impairment of fertility or effect on mating performance was observed in a fertility and general reproductive performance study conducted in male and female rats at subcutaneous doses up to 50 mg/kg/day (less than the MRHD in adults based on body surface area comparisons).

Pregnancy: Teratogenic Effects: Pregnancy Category C. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

Systemic embryofetal development studies were conducted in mice, rats and rabbits. Subcutaneous doses of 15, 45 and 150 mg/kg/day of fluticasone propionate were administered to pregnant female mice from gestation days 6 - 15. A teratogenic effect characteristic of corticosteroids (cleft palate) was noted after administration of 45 and 150 mg/kg/day (less than the MRHD in adults based on body surface area comparisons) in this study. No treatment-related effects on embryofetal toxicity or teratogenicity were noted at 15 mg/kg/day (less than the MRHD in adults based on body surface area comparisons).

Subcutaneous doses of 10, 30 and 100 mg/kg/day of fluticasone propionate were administered to pregnant female rats in two embryofetal development studies (one study administered fluticasone propionate from gestation days 6 - 15 and the other study from gestation days 7 - 17). In the presence of maternal toxicity, fetal effects noted at 100 mg/kg/day (less than the MRHD in adults based on body surface area comparisons) included decreased fetal weights, omphalocele, cleft palate, and retarded skeletal ossification. No treatment-related effects on embryofetal toxicity or teratogenicity were noted at 10 mg/kg/day (less than the MRHD in adults based on body surface area comparisons).

Subcutaneous doses of 0.08, 0.57 and 4 mg/kg/day of fluticasone propionate were administered to pregnant female rabbits from gestation days 6 - 18. Fetal effects noted at 4 mg/kg/day (less than the MRHD in adults based on body surface area comparisons) included decreased fetal weights, cleft palate and retarded skeletal ossification. No treatment-related effects on embryofetal toxicity or teratogenicity were noted at 0.57 mg/kg/day (less than the MRHD in adults based on body surface area comparisons).

Oral doses of 3, 30 and 300 mg/kg/day fluticasone propionate were administered to pregnant female rabbits from gestation days 8 - 20. No fetal or teratogenic effects were noted at oral doses up to 300 mg/kg/day (less than the MRHD in adults based on body surface area comparisons) in this study. However, no fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration.

Fluticasone propionate crossed the placenta following administration of a subcutaneous or an oral dose of 100 mg/kg tritiated fluticasone propionate to pregnant rats.

There are no adequate and well-controlled studies in pregnant women. During clinical trials of CUTIVATE LOTION, women of childbearing potential were required to use contraception to avoid pregnancy. Therefore, CUTIVATE LOTION should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when CUTIVATE LOTION is administered to a nursing woman.

Pediatric Use: CUTIVATE LOTION may be used in pediatric patients as young as 1 year of age. The safety and efficacy of CUTIVATE LOTION in pediatric patients below 1 year of age have not been established.

Forty-two pediatric patients (4 months to < 6 years of age) with moderate to severe atopic eczema who were treated with CUTIVATE LOTION for at least 3 - 4 weeks were assessed for HPA axis suppression and 40 of these subjects applied at least 90% of applications. None of the 40 evaluable patients suppressed, where the sole criterion for HPA axis suppression is a plasma cortisol level of less than or equal to 18 micrograms per deciliter after cosyntropin stimulation. Although HPA axis suppression was observed in 0 of 40 pediatric patients (upper 95% confidence bound is 7.2%), the occurrence of HPA axis suppression in any patient and especially with longer use cannot be ruled out.

In other studies with fluticasone propionate topical formulations, adrenal suppression has been observed. CUTIVATE (fluticasone propionate) Cream, 0.05% caused HPA axis suppression in 2 of 43 pediatric patients, ages 2 and 5 years old, who were treated for 4 weeks covering at least 35% of the body surface area. Follow-up testing 12 days after treatment discontinuation, available for 1 of the 2 patients, demonstrated a normally responsive HPA axis.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients include low plasma cortisol levels to an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilloedema. In addition, local adverse events including cutaneous atrophy, striae, telangiectasia, and pigmentation change have been reported with topical use of corticosteroids in pediatric patients.

Geriatric Use: A limited number of patients above 65 years of age have been treated with CUTIVATE LOTION in US and non-US clinical trials. Specifically only 8 patients above 65 years of age were treated with CUTIVATE LOTION in controlled clinical trials. The number of patients is too small to permit separate analyses of efficacy and safety.

ADVERSE REACTIONS: In 2 multicenter vehicle-controlled clinical trials of once-daily application of CUTIVATE LOTION by 196 adult and 242 pediatric patients, the total incidence of adverse reactions considered drug related by investigators was approximately 4%. Events were local cutaneous events, usually mild and self-limiting, and consisted primarily of burning/stinging (2%). All other drug-related events occurred with an incidence of less than 1%, and inclusively were contact dermatitis, exacerbation of atopic dermatitis, folliculitis of legs, pruritus, pustules on arm, rash, and skin infection. [Actual number of drug-related events for CUTIVATE LOTION (N=221) were burning/stinging skin, 4 (2%); contact dermatitis, 0; exacerbation of atopic dermatitis, 0; folliculitis of legs, 2 (<1%); irritant contact dermatitis, 0; pruritus, 1 (<1%); pustules on arms, 1 (<1%); rash, 1 (<1%); and skin infection, 0. Actual number of drug-related events for Vehicle (N=217) were burning/stinging skin, 3 (1%); contact dermatitis, 1 (<1%); exacerbation of atopic dermatitis, 1 (<1%); folliculitis of legs, 0; irritant contact dermatitis, 1 (<1%); pruritus, 1 (<1%); pustules on arms, 0; rash, 2 (<1%); and skin infection, 3 (1%).]

The incidence of drug-related events on drug compared to vehicle (4% and 5%, respectively) was similar. The incidence of drug-related events between study populations of 242 pediatric patients (age 3 months to < 17 years) and 196 adult patients (17 years or older) (4% and 5%, respectively) was also similar.

In an open-label study of 44 pediatric patients applying CUTIVATE LOTION to at least 35% of body surface area twice daily for 3 or 4 weeks, the overall incidence of drug-related adverse events was 14%. Events were local, cutaneous, and inclusively were dry skin, 3 events (7%); stinging at application site, 2 events (5%); and excretion, 1 event (2%).

During the clinical trials, eczema herpeticum occurred in a 33-year-old male patient treated with CUTIVATE LOTION. Additionally, a 4-month-old patient treated with CUTIVATE LOTION in the open-label trial had marked elevations of the hepatic enzymes AST and ALT. Reported systemic post-marketing adverse events with CUTIVATE Cream and CUTIVATE Ointment have included: immunosuppression/Pneumocystis carinii pneumonia/leukopenia/thrombocytopenia; hyperglycemia/glycosuria; Cushing syndrome; generalized body edema/blurred vision; and allergic urticarial reaction (edema, urticaria, pruritus, and throat swelling). A causal role of CUTIVATE in most cases could not be determined because of the concomitant use of topical corticosteroids, confounding medical conditions, and insufficient clinical information.

The following local adverse reactions have been reported infrequently with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions are listed in an approximately decreasing order of occurrence: irritation, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, and milium. Also, there are reports of the development of pustular psoriasis from chronic plaque psoriasis following reduction or discontinuation of potent topical corticosteroid products.

OVERDOSAGE: Topically applied CUTIVATE LOTION can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION: CUTIVATE LOTION may be used in adult and pediatric patients 1 year of age or older. The safety and efficacy of CUTIVATE LOTION in pediatric patients below 1 year of age have not been established (see PRECAUTIONS: Pediatric Use).

Atopic Dermatitis: Apply a thin film of CUTIVATE LOTION to the affected skin areas once daily. Rub in gently.

As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary. The safety and efficacy of drug use for longer than 4 weeks have not been established.

CUTIVATE LOTION should not be used with occlusive dressings or applied in the diaper area unless directed by a physician.

HOW SUPPLIED: CUTIVATE LOTION is supplied in 60mL bottle (NDC 0462-0434-60).

Store between 15° and 30°C (59° and 86°F). Do not refrigerate. Keep container tightly sealed.

PharmaDerm®

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