

Women Are Twice as Likely to Survive Melanoma

BY BRUCE JANCIN
Denver Bureau

AMSTERDAM — Women with melanoma are twice as likely as are men to survive 10 years after diagnosis, even after adjustment for key tumor characteristics reflecting the tendency for earlier detection in women, Dr. Esther de Vries reported at the 11th World Congress on Cancers of the Skin.

"Women are stronger, in the melanoma

sense at least," said Dr. de Vries of Erasmus University, Rotterdam, the Netherlands.

"It's true women respond better to efforts at primary prevention of melanoma. Their melanomas are more often thin, on extremities, and early stage. But we showed that doesn't explain the whole story. The strong survival difference persists after correcting for those factors," she added at the congress, which was cosponsored by the Skin Cancer Foundation and Erasmus University.

She reported on a cancer registry study of all 10,538 Dutch adults diagnosed with melanoma during 1993-2004 for whom there was more than 1 year of follow-up. Indeed, the group totalled nearly 60,000 person-years of follow-up.

Five-year crude survival was 69% for men and 89% for women. Women had superior survival for tumors of all histologic subtypes, at all body sites, and all Breslow tumor thicknesses. After corrections for differences in tumor characteristics as

well as patient age, women were 1.9-fold more likely than were men to survive 10 years with melanoma.

In European countries, the incidence of melanoma is greater in women than in men. In the United States and Australia, the opposite is true. But everywhere in the world where melanoma survival has been studied, it's better in women. What sets the new Dutch study apart from the others is that it is the first large study to control for differences in tumor characteristics, thus providing evidence that factors besides younger age, more favorable histogenetic tumor subtypes, and earlier diagnosis are probably responsible for the superior survival in women, Dr. de Vries said.

In the Netherlands, as elsewhere, there has been a substantial improvement in melanoma survival in whites since the 1980s despite the lack of any major treatment advances. For example, in the Eind-



This is the first large study to control for differences in tumor characteristics.

DR. DE VRIES

hoven Cancer Registry covering the southeastern part of the Netherlands, 5-year relative survival in women under age 60 improved from 84% in the early 1980s to 95% in 2000-2002, and from 62% to 78% in men under age 60. The only subgroup in which melanoma mortality worsened in recent decades was in men older than 60.

The explanation for the superior survival observed in women with melanoma remains unclear. It does not appear to be an estrogen-mediated phenomenon. Dr. de Vries' coinvestigator, Dr. Simone van Hattem of Amphia Hospital, Rotterdam, reported elsewhere at the congress that the survival advantage favoring women in the Dutch study was similar among melanoma patients beyond age 60 and in those in the premenopausal age group less than 45 years old.

Dr. de Vries is now looking at potential behavioral differences that might explain the marked gender-based disparity in melanoma survival. One possibility involves alcohol consumption; intake patterns differ between men and women, and there is some indication that alcohol has differential skin cancer-promoting effects in men and women as well.

But there are many other possible explanations, including differing genetics, immune status, and medication use. It's worth noting that women have better age-specific survival than do men across the board for nearly all types of cancer, with the magnitude of the survival advantage ranging from modest for some malignancies to quite pronounced for melanoma and a few others, Dr. de Vries said.

Some evidence suggests that parity and age at first birth are related to melanoma incidence and prognosis in women, but the supporting data are quite limited. ■

BenzaClin® Topical Gel (clindamycin - benzoyl peroxide gel)

Brief summary. Please see full prescribing information for complete product information.

Topical Gel: clindamycin (1%) as clindamycin phosphate, benzoyl peroxide (5%)
For Dermatological Use Only - Not for Ophthalmic Use
Reconstitute Before Dispensing

INDICATIONS AND USAGE

BenzaClin Topical Gel is indicated for the topical treatment of acne vulgaris.

CONTRAINDICATIONS

BenzaClin Topical Gel is contraindicated in those individuals who have shown hypersensitivity to any of its components or to lincomycin. It is also contraindicated in those having a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.

WARNINGS

ORALLY AND PARENTERALLY ADMINISTERED CLINDAMYCIN HAS BEEN ASSOCIATED WITH SEVERE COLITIS WHICH MAY RESULT IN PATIENT DEATH. USE OF THE TOPICAL FORMULATION OF CLINDAMYCIN RESULTS IN ABSORPTION OF THE ANTIBIOTIC FROM THE SKIN SURFACE. DIARRHEA, BLOODY DIARRHEA, AND COLITIS (INCLUDING PSEUDOMEMBRANOUS COLITIS) HAVE BEEN REPORTED WITH THE USE OF TOPICAL AND SYSTEMIC CLINDAMYCIN. STUDIES INDICATE A TOXIN(S) PRODUCED BY CLOSTRIDIUM IS ONE PRIMARY CAUSE OF ANTIBIOTIC-ASSOCIATED COLITIS. THE COLITIS IS USUALLY CHARACTERIZED BY SEVERE PERSISTENT DIARRHEA AND SEVERE ABDOMINAL CRAMPS AND MAY BE ASSOCIATED WITH THE PASSAGE OF BLOOD AND MUCUS. ENDOSCOPIC EXAMINATION MAY REVEAL PSEUDOMEMBRANOUS COLITIS. STOOL CULTURE FOR *Clostridium Difficile* AND STOOL ASSAY FOR *C. difficile* TOXIN MAY BE HELPFUL DIAGNOSTICALLY. WHEN SIGNIFICANT DIARRHEA OCCURS, THE DRUG SHOULD BE DISCONTINUED. LARGE BOWEL ENDOSCOPY SHOULD BE CONSIDERED TO ESTABLISH A DEFINITIVE DIAGNOSIS IN CASES OF SEVERE DIARRHEA. ANTIPERISTALTIC AGENTS SUCH AS OPIATES AND DIPHENOXYLATE WITH ATROPINE MAY PROLONG AND/OR WORSEN THE CONDITION. DIARRHEA, COLITIS, AND PSEUDOMEMBRANOUS COLITIS HAVE BEEN OBSERVED TO BEGIN UP TO SEVERAL WEEKS FOLLOWING CESSATION OF ORAL AND PARENTERAL THERAPY WITH CLINDAMYCIN.

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS

General: For dermatological use only; not for ophthalmic use. Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents.

The use of antibiotic agents may be associated with the overgrowth of nonsusceptible organisms including fungi. If this occurs, discontinue use of this medication and take appropriate measures.

Avoid contact with eyes and mucous membranes.

Clindamycin and erythromycin containing products should not be used in combination. *In vitro* studies have shown antagonism between these two antimicrobials. The clinical significance of this *in vitro* antagonism is not known.

Information for Patients: Patients using BenzaClin Topical Gel should receive the following information and instructions:

1. BenzaClin Topical Gel is to be used as directed by the physician. It is for external use only. Avoid contact with eyes, and inside the nose, mouth, and all mucous membranes, as this product may be irritating.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. Patients should not use any other topical acne preparation unless otherwise directed by physician.
4. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using BenzaClin Topical Gel. To minimize exposure to sunlight, a wide-brimmed hat or other protective clothing should be worn, and a sunscreen with SPF 15 rating or higher should be used.
5. Patients should report any signs of local adverse reactions to their physician.
6. BenzaClin Topical Gel may bleach hair or colored fabric.
7. BenzaClin Topical Gel can be stored at room temperature up to 25°C (77°F) for 3 months. Do not freeze. Discard any unused product after 3 months.
8. Before applying BenzaClin Topical Gel to affected areas wash the skin gently, then rinse with warm water and pat dry.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. The clinical significance of this is unknown.

Benzoyl peroxide in acetone at doses of 5 and 10 mg administered twice per week induced skin tumors in transgenic Tg.AC mice in a study using 20 weeks of topical treatment.

In a 52 week dermal photocarcinogenicity study in hairless mice, the median time to onset of skin tumor formation was decreased and the number of tumors per mouse increased following chronic concurrent topical administration of BenzaClin Topical Gel with exposure to ultraviolet radiation (40 weeks of treatment followed by 12 weeks of observation).

In a 2-year dermal carcinogenicity study in rats, treatment with BenzaClin Topical Gel at doses of 100, 500 and 2000 mg/kg/day caused a dose-dependent increase in the incidence of keratoacanthoma at the treated skin site of male rats. The incidence of keratoacanthoma at the treated site of males treated with 2000 mg/kg/day (8 times the highest recommended adult human dose of 2.5 g BenzaClin Topical Gel, based on mg/m²) was statistically significantly higher than that in the sham- and vehicle-controls.

Genotoxicity studies were not conducted with BenzaClin Topical Gel. Clindamycin phosphate was not genotoxic in *Salmonella typhimurium* or in a rat micronucleus test. Clindamycin phosphate sulfonate, an oxidative degradation product of clindamycin phosphate and benzoyl peroxide, was not clastogenic in a mouse micronucleus test. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *S. typhimurium* tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells. Studies have not been performed with BenzaClin Topical Gel or benzoyl peroxide to evaluate the effect on fertility. Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g BenzaClin Topical Gel, based on mg/m²) revealed no effects on fertility or mating ability.

Pregnancy: Teratogenic Effects: Pregnancy Category C:

Animal reproductive/developmental toxicity studies have not been conducted with BenzaClin Topical Gel or benzoyl peroxide. Developmental toxicity studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (240 and 120 times amount of clindamycin in the highest recommended adult human dose based on mg/m², respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (100 and 50 times the amount of clindamycin in the highest recommended adult human dose based on mg/m², respectively) revealed no evidence of teratogenicity.

There are no well-controlled trials in pregnant women treated with BenzaClin Topical Gel. It also is not known whether BenzaClin Topical Gel can cause fetal harm when administered to a pregnant woman.

Nursing Women: It is not known whether BenzaClin Topical Gel is excreted in human milk after topical application. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of this product in pediatric patients below the age of 12 have not been established.

ADVERSE REACTIONS

During clinical trials, the most frequently reported adverse event in the BenzaClin treatment group was dry skin (12%). The table below lists local adverse events reported by at least 1% of patients in the BenzaClin and vehicle groups.

	Local Adverse Events - all causalities in >= 1% of patients	
	BenzaClin n = 420	Vehicle n = 168
Application site reaction	13 (3%)	1 (<1%)
Dry skin	50 (12%)	10 (6%)
Pruritus	8 (2%)	1 (<1%)
Peeling	9 (2%)	-
Erythema	6 (1%)	1 (<1%)
Sunburn	5 (1%)	-

The actual incidence of dry skin might have been greater were it not for the use of a moisturizer in these studies.

DOSAGE AND ADMINISTRATION

BenzaClin Topical Gel should be applied twice daily, morning and evening, or as directed by a physician, to affected areas after the skin is gently washed, rinsed with warm water and patted dry.

HOW SUPPLIED AND COMPOUNDING INSTRUCTIONS

Size (Net Weight)	NDC 0066-	Benzoyl Peroxide Gel	Active Clindamycin Powder (in plastic vial)	Purified Water To Be Added to each vial
25 grams	0494-25	19.7g	0.3g	5 mL
50 grams	0494-50	41.4g	0.6 g	10 mL
50 grams (pump)	0494-55	41.4g	0.6 g	10 mL

Prior to dispensing, tap the vial until powder flows freely. Add indicated amount of purified water to the vial (to the mark) and immediately shake to completely dissolve clindamycin. If needed, add additional purified water to bring level up to the mark. Add the solution in the vial to the gel and stir until homogenous in appearance (1 to 1 1/2 minutes). For the 50 gram pump only, reassemble jar with pump dispenser. BenzaClin Topical Gel (as reconstituted) can be stored at room temperature up to 25°C (77°F) for 3 months. Place a 3 month expiration date on the label immediately following mixing.

Store at room temperature up to 25°C (77°F) (See USP).

Do not freeze. Keep tightly closed. Keep out of the reach of children.

US Patents 5,446,028; 5,767,098; 6,013,637

Brief Summary of Prescribing Information as of May 2007.

Rx Only

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