

Denser Breasts: Risk for Local Cancer Recurrence

BY MARY ANN MOON

Breast density on mammography is a significant risk factor for local cancer recurrence, based on a study of more than 300 women.

In a study of 335 women with breast cancer, the actuarial risk of local disease recurrence at 10 years was 5% for women with the lowest breast density, 13% for those with intermediate breast

density, and 21% for women with the highest breast density, said Dr. Tulin Cil of the University Health Network, Toronto, and associates.

None of the 34 women who had low breast density and who did not receive adjuvant radiotherapy developed a recurrence, suggesting that they were not harmed by foregoing radiotherapy. If larger studies confirm that women with less dense breasts can safely avoid radio-

therapy, that could result in “considerable savings, reduced morbidity, and improved quality of life,” the researchers said. If women with dense breasts are found in larger studies to be at higher risk for local recurrence, radiotherapy would indeed be beneficial for these patients, they added.

Several recent studies have suggested that high breast density corresponds with a higher risk of local recurrence,

but the biologic basis for this association is unknown. Dr. Cil and colleagues assessed breast density on pretreatment mammograms taken in 335 women who underwent breast-conserving surgery for invasive cancer at Women’s College Hospital in Toronto between 1987 and 1998.

The patients were categorized as having low (less than 25%) density, intermediate (25%-50%) density, or high (greater than 50%) density according to a variation of the Wolfe classification system. The study population was fairly equally distributed among these three classifications. Patients in these three groups had similar tumor characteristics, received similar adjuvant therapies, and had similar estrogen receptor status.

Sixteen percent of the women with high breast density developed a local recurrence, compared with 10% of the women with intermediate breast density and 3% of those with low breast density. After age, menopausal status, and radiotherapy status were controlled for, women with high breast density were found to have a hazard ratio of 5.7 for developing local cancer recurrence, compared with the low-density group (Cancer 2009;115:5780-7). Women with intermediate breast density had a hazard ratio of 3.6, compared with the low-density group (see box). There were no differences in rates of distant cancer recurrence among the three groups.

Among women who received adjuvant radiotherapy, “the prognostic effect of mammographic density was found to be minimal and nonsignificant.” However, among women who did not receive radiotherapy—who constituted 29% of this study population—the difference in prognostic effect was marked.

It is not yet known whether attempting to reduce breast density through dietary or lifestyle alterations might influence recurrence risk, they said. ■

ALDARA® (imiquimod) Cream, 5%

Brief Summary of External Genital Wart Prescribing Information See Package Insert for Full Prescribing Information

INDICATIONS AND USAGE: External Genital Warts: Aldara Cream is indicated for the treatment of external genital and perianal warts/condyloma acuminata in patients 12 years or older. **Unvaluated Populations:** The safety and efficacy of Aldara Cream in immunosuppressed patients have not been established. Aldara Cream should be used with caution in patients with pre-existing autoimmune conditions. Efficacy and safety of Aldara Cream have not been established for patients with Basal Cell Nevus Syndrome or Xeroderma Pigmentosum.

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS: Local Inflammatory Reactions: Intense local inflammatory reactions including skin weeping or erosion can occur after few applications of Aldara Cream and may require an interruption of dosing. Aldara Cream has the potential to exacerbate inflammatory conditions of the skin, including chronic graft versus host disease. Administration of Aldara Cream is not recommended until the skin is completely healed from any previous drug or surgical treatment. **Systemic Reactions:** Flu-like signs and symptoms may accompany, or even precede, local inflammatory reactions and may include malaise, fever, nausea, myalgias and rigors. An interruption of dosing should be considered. **Ultraviolet Light Exposure:** Exposure to sunlight (including sunlamps) should be avoided or minimized during use of Aldara Cream because of concern for heightened sunburn susceptibility. Patients should be warned to use protective clothing (e.g., a hat) when using Aldara Cream. Patients with sunburn should be advised not to use Aldara Cream until fully recovered. Patients who may have considerable sun exposure, e.g., due to their occupation, and those patients with inherent sensitivity to sunlight should exercise caution when using Aldara Cream. Aldara Cream shortened the time to skin tumor formation in an animal photocarcinogenicity study. The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Therefore, patients should minimize or avoid natural or artificial sunlight exposure. **Unvaluated Uses: External Genital Warts** Aldara Cream has not been evaluated for the treatment of urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma viral disease.

ADVERSE REACTIONS: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. **Clinical Trials Experience: External Genital Warts** In controlled clinical trials for genital warts, the most frequently reported adverse reactions were local skin and application site reactions. Some subjects also reported systemic reactions. Overall, 1.2% (4/327) of the subjects discontinued due to local skin/application site reactions. The incidence and severity of local skin reactions during controlled clinical trials are shown in the following table.

Table 1: Local Skin Reactions in the Treatment Area as Assessed by the Investigator (External Genital Warts)

	Aldara Cream		Vehicle	
	Females n=114	Males n=156	Females n=99	Males n=157
	All Grades* Severe	All Grades* Severe	All Grades* Severe	All Grades* Severe
Erythema	74 (65%) 4 (4%)	90 (58%) 6 (4%)	21 (21%) 0 (0%)	34 (22%) 0 (0%)
Erosion	35 (31%) 1 (1%)	47 (30%) 2 (1%)	8 (8%) 0 (0%)	10 (6%) 0 (0%)
Excoriation/ Flaking	21 (18%) 0 (0%)	40 (26%) 1 (1%)	8 (8%) 0 (0%)	12 (8%) 0 (0%)
Edema	20 (18%) 1 (1%)	19 (12%) 0 (0%)	5 (5%) 0 (0%)	1 (1%) 0 (0%)
Scabbing	4 (4%) 0 (0%)	20 (13%) 0 (0%)	0 (0%) 0 (0%)	4 (3%) 0 (0%)
Induration	6 (5%) 0 (0%)	11 (7%) 0 (0%)	2 (2%) 0 (0%)	3 (2%) 0 (0%)
Ulceration	9 (8%) 3 (3%)	7 (4%) 0 (0%)	1 (1%) 0 (0%)	1 (1%) 0 (0%)
Vesicles	3 (3%) 0 (0%)	3 (2%) 0 (0%)	0 (0%) 0 (0%)	0 (0%) 0 (0%)

*Mild, Moderate, or Severe

Remote site skin reactions were also reported. The severe remote site skin reactions reported for females were erythema (3%), ulceration (2%), and edema (1%); and for males, erosion (2%), and erythema, edema, induration, and excoriation/flaking (each 1%). Selected adverse reactions judged to be probably or possibly related to Aldara Cream are listed below.

Table 2: Selected Treatment Related Reactions (External Genital Warts)

	Females		Males	
	Aldara Cream n=117	Vehicle n=103	Aldara Cream n=156	Vehicle n=158
Application Site Disorders:				
Application Site Reactions				
Wart Site:				
Itching	38 (32%)	21 (20%)	34 (22%)	16 (10%)
Burning	30 (26%)	12 (12%)	14 (9%)	8 (5%)
Pain	9 (8%)	2 (2%)	3 (2%)	1 (1%)
Soreness	3 (3%)	0 (0%)	0 (0%)	1 (1%)
Fungal Infection*	13 (11%)	3 (3%)	3 (2%)	1 (1%)
Systemic Reactions:				
Headache	5 (4%)	3 (3%)	8 (5%)	3 (2%)
Influenza-like symptoms	4 (3%)	2 (2%)	2 (1%)	0 (0%)
Myalgia	1 (1%)	0 (0%)	2 (1%)	1 (1%)

*Incidence reported without regard to causality with Aldara Cream.

Adverse reactions judged to be possibly or probably related to Aldara Cream and reported by more than 1% of subjects included: **Application Site Disorders:** burning, hypopigmentation, irritation, itching, pain, rash, sensitivity, soreness, stinging, tenderness. **Remote Site Reactions:** bleeding, burning, itching, pain, tenderness, tinea cruris. **Body as a Whole:** fatigue, fever, influenza-like symptoms. **Central and Peripheral Nervous System Disorders:** headache. **Gastro-Intestinal System Disorders:** diarrhea. **Musculo-Skeletal System Disorders:** myalgia. **Clinical Trials Experience: Dermal Safety Studies** Provocative repeat insult patch test studies involving induction and challenge phases produced no evidence that Aldara Cream causes photoallergenicity or contact sensitization in healthy skin; however, cumulative irritancy testing revealed the potential for Aldara Cream to cause irritation, and application site reactions were reported in the clinical studies. **Postmarketing Experience:** The following adverse reactions have been identified during post-approval use of Aldara Cream. 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. **Application Site Disorders:** tingling at the application site. **Body as a Whole:** angioedema. **Cardiovascular:** capillary leak syndrome, cardiac failure, cardiomyopathy, pulmonary edema, arrhythmias (tachycardia, atrial fibrillation, palpitations), chest pain, ischemia, myocardial infarction, syncope. **Endocrine:** thyroiditis. **Gastro-Intestinal System Disorders:** abdominal pain. **Hematological:** decreases in red cell, white cell and platelet counts (including idiopathic thrombocytopenic purpura), lymphoma. **Hepatic:** abnormal liver function. **Infections and Infestations:** herpes simplex. **Musculo-Skeletal System Disorders:** arthralgia. **Neuropsychiatric:** agitation, cerebrovascular accident, convulsions (including febrile convulsions), depression, insomnia, multiple sclerosis aggravation, paresis, suicide. **Respiratory:** dyspnea. **Urinary System Disorders:** proteinuria. **Skin and Appendages:** exfoliative dermatitis, erythema multiforme, hyperpigmentation. **Vascular:** Henoch-Schönlein purpura syndrome.

USE IN SPECIFIC POPULATIONS: Pregnancy: Pregnancy Category C: Oral doses of 1, 5 and 20 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6–15) to pregnant female rats. In the presence of maternal toxicity, fetal effects noted at 20 mg/kg/day (577X MRHD based on AUC comparisons) included increased resorptions, decreased fetal body weights, delays in skeletal ossification, bent limb bones, and two fetuses in one litter (2 of 1567 fetuses) demonstrated exencephaly, protruding tongue and low-set ears. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 5 mg/kg/day (98X MRHD based on AUC comparisons). Intravenous doses of 0.5, 1 and 2 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6–18) to pregnant female rabbits. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 2 mg/kg/day (1.5X MRHD based on BSA comparisons), the highest dose evaluated in this study, or 1 mg/kg/day (407X MRHD based on AUC comparisons). A combined fertility and peri- and post-natal development study was conducted in rats. Oral doses of 1, 1.5, 3 and 6 mg/kg/day imiquimod were administered to male rats from 70 days prior to mating through the mating period and to female rats from 14 days prior to mating through parturition and lactation. No effects on growth, fertility, reproduction or post-natal development were noted at doses up to 6 mg/kg/day (87X MRHD based on AUC comparisons), the highest dose evaluated in this study. In the absence of maternal toxicity, bent limb bones were noted in the F1 fetuses at a dose of 6 mg/kg/day (87X MRHD based on AUC comparisons). This fetal effect was also noted in the oral rat embryofetal development study conducted with imiquimod. No treatment related effects on teratogenicity were noted at 3 mg/kg/day (41X MRHD based on AUC comparisons). There are no adequate and well-controlled studies in pregnant women. Aldara Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** It is not known whether imiquimod is excreted in human milk following use of Aldara Cream. Because many drugs are excreted in human milk, caution should be exercised when Aldara Cream is administered to nursing women. **Pediatric Use:** Safety and efficacy in patients with external genital/perianal warts below the age of 12 years have not been established. Aldara Cream was evaluated in two randomized, vehicle-controlled, double-blind trials involving 702 pediatric subjects with molluscum contagiosum (MC) (470 exposed to Aldara; median age 5 years, range 2–12 years). Subjects applied Aldara Cream or vehicle 3 times weekly for up to 16 weeks. These studies failed to demonstrate efficacy. Similar to the studies conducted in adults, the most frequently reported adverse reaction from 2 studies in children with MC was application site reaction. Adverse events which occurred more frequently in Aldara-treated subjects compared with vehicle-treated subjects generally resembled those seen in studies in indications approved for adults and also included otitis media (5% Aldara vs. 3% vehicle) and conjunctivitis (3% Aldara vs. 2% vehicle). Erythema was the most frequently reported local skin reaction. Severe local skin reactions reported by Aldara-treated subjects in the pediatric studies included erythema (28%), edema (8%), scabbing/crusting (5%), flaking/scaling (5%), erosion (2%) and weeping/exudate (2%). Systemic absorption of imiquimod across the affected skin of 22 subjects aged 2 to 12 years with extensive MC involving at least 10% of the total body surface area was observed after single and multiple doses at a dosing frequency of 3 applications per week for 4 weeks. The investigator determined the dose applied, either 1, 2 or 3 packets per dose, based on the size of the treatment area and the subject’s weight. Among the 20 subjects with evaluable laboratory assessments, the median WBC count decreased by 1.4*10⁹/L and the median absolute neutrophil count decreased by 1.42*10⁹/L. **Geriatric Use:** Of the 215 subjects treated with Aldara Cream in the actinic keratosis clinical studies, 127 subjects (59%) were 65 years and older, while 60 subjects (28%) were 75 years and older. Of the 185 subjects treated with Aldara Cream in the superficial basal cell carcinoma clinical studies, 65 subjects (35%) were 65 years and older, while 25 subjects (14%) were 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. No other clinical experience has identified differences in responses between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

OVERDOSAGE: Topical overdosing of Aldara Cream could result in an increased incidence of severe local skin reactions and may increase the risk for systemic reactions. The most clinically serious adverse event reported following multiple oral imiquimod doses of >200 mg (equivalent to imiquimod content of >16 packets) was hypotension, which resolved following oral or intravenous fluid administration.

CLINICAL STUDIES: In a double-blind, placebo-controlled clinical study, 209 otherwise healthy subjects 18 years of age and older with genital/perianal warts were treated with Aldara Cream or vehicle control 3 times per week for a maximum of 16 weeks. The median baseline wart area was 69 mm² (range 8 to 5525 mm²). Data on complete clearance are listed in the table below. The median time to complete wart clearance was 10 weeks.

Table 14: Complete Clearance Rates (External Genital Warts)- Study EGW1

Treatment	Subjects with Complete Clearance of Warts		Subjects with Warts Remaining at Week 16	
	Subjects with Complete Clearance of Warts	Subjects Without Follow-up	Subjects with Warts Remaining at Week 16	Subjects with Warts Remaining at Week 16
Overall				
Aldara Cream (n=109)	54 (50%)	19 (17%)	36 (33%)	62 (62%)
Vehicle (n=100)	11 (11%)	27 (27%)		
Females				
Aldara Cream (n=46)	33 (72%)	5 (11%)	8 (17%)	19 (48%)
Vehicle (n=40)	8 (20%)	13 (33%)		
Males				
Aldara Cream (n=63)	21 (33%)	14 (22%)	28 (44%)	43 (72%)
Vehicle (n=60)	3 (5%)	14 (23%)		

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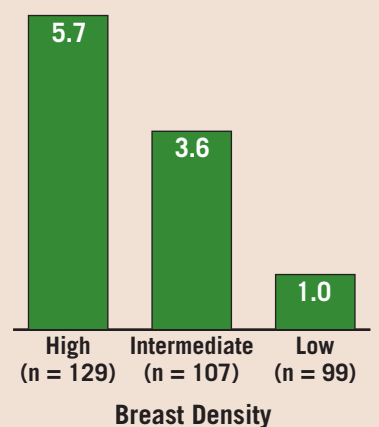
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Hazard Ratios for Local Cancer Recurrence Risk



Source: Cancer