

Breast Ca Survivors May See Rise in Angiosarcoma

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NAPLES, FLA. — In the last year, Michael B. Morgan, M.D., has seen four cases of angiosarcoma on the breast of women who previously underwent radiation therapy for breast cancer.

Historically, there are only about 100 cases of angiosarcoma a year in the United States, and normally they occur in "sun-battered" areas, said Dr. Morgan, a

dermatopathologist who practices in Tampa.

"I think we are at the precipice here of a real interesting and deadly epidemiologic phenomenon," said Dr. Morgan at the annual meeting of the Florida Society of Dermatology and Dermatologic Surgery.

"I don't want to be Chicken Little, but I honestly think we could be on the cusp of something big, and we need to be vigilant," he added, in an interview.

Angiosarcoma associated with irradiation of the breast was first noted back in the 1940s, and in that report it was said to be associated with chronic lymphedema. Since then, numerous other reports of angiosarcoma have appeared, but there has been controversy over whether the disease occurs frequently enough to warrant much concern.

It may be, however, that not enough women have been followed out long enough. His four cases were all women who had been treated for breast cancer 20

years previously, which corresponds roughly to the time that breast-conserving treatment with radiation became standard practice, Dr. Morgan said.

Older case series estimated an incidence of angiosarcoma in irradiated, breast-cancer patients of less than 1%; however, more recent series have suggested a prevalence of 1%, and perhaps 3%.

In a recent series of 27 cases seen at Indiana University, it was reported that only 5 of the 27 cases occurred within 3 years of irradiation treatment, and the median interval was 59 months (Am. J. Surg. Pathol. 2004;28:781-8), Dr. Morgan noted.

In that series, lymphedema was largely absent, as has been true also of Dr. Morgan's cases. However, since angiosarcoma can be associated with chronic lymphedema, Dr. Morgan said he is concerned about melanoma patients who have lymph nodes removed.

"I haven't seen this, but I worry about the rash of lymph nodes that we are taking out of people's arms and legs now



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DR. MORGAN

with melanoma, and whether this indeed is going to end up being a risk," he said.

The prognosis of angiosarcoma is very poor. In a series of 47 typical angiosarcoma patients reported by Dr. Morgan, the overall survival at 5 years was only 34%, and the local recurrence rate at 5 years was 84% (J. Am. Acad. Dermatol. 2004;50:867-74).

Clinically, a typical angiosarcoma starts out as a bruise-like macule that rapidly evolves into an erythematous patch, and then to a violaceous, ulcerated nodule or plaque. The angiosarcomas on the breast may be somewhat different, because the ones he has seen have mostly been flattened, tan-colored, indurated patches that looked a little like Kaposi's sarcoma, Dr. Morgan said. It can be multifocal at presentation.

Histologically, biopsies usually show a preserved epithelium, with extravasated red cells and lots of nuclei in the deeper dermis, as one would expect of a cancer that arises from endothelial cells of the arteriovenous or lymphatic structures, Dr. Morgan said. In later stages, one can clearly see a complex, vasiform pattern of growth. The most useful stain is CD31, which confirms the endothelial derivation of the neoplastic cells, he added.

In his case series, Dr. Morgan looked at prognostic factors. He found that mitotic rate and recurrence were bad prognostic factors. But the most important factor was the depth of invasion, with a cutoff depth of 3 mm.

"This is about the worst thing I can think of to happen in your skin," Dr. Morgan said. ■

Estring® estradiol vaginal ring

2 mg
BRIEF SUMMARY OF PRESCRIBING INFORMATION

- ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN.
Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equi-estrogenic doses.
- ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.
There is no indication for estrogen therapy during pregnancy or during immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Estrogens are not indicated for the prevention of postpartum breast engorgement.
Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. The 1985 DES Task Force concluded that the use of DES during pregnancy is associated with a subsequent increased risk of breast cancer in the mothers, although a causal relationship remains unproven and the observed level of excess risk is similar to that for a number of other breast cancer risk factors.

INDICATIONS AND USAGE

ESTRING (estradiol vaginal ring) is indicated for the treatment of urogenital symptoms associated with post-menopausal atrophy of the vagina (such as dryness, burning, pruritus and dyspareunia) and/or the lower urinary tract (urinary urgency and dysuria).

CONTRAINDICATIONS

1. Estrogens should not be used in women with any of the following conditions:

- Known or suspected pregnancy (see **BOXED WARNING**).
- Undiagnosed abnormal genital bleeding.
- Known or suspected cancer of the breast.
- Known or suspected estrogen-dependent neoplasia.

2. ESTRING (estradiol vaginal ring) should not be used in patients hypersensitive to any of its ingredients.

WARNINGS

- Breast Cancer.**
While the majority of studies have not shown an increased risk of breast cancer in women who have ever used estrogen replacement therapy, some have reported a moderately increased risk (relative risks of 1.3 to 2.0) in those taking higher doses or those taking lower doses for prolonged periods of time, especially in excess of ten years. Other studies have not shown this relationship.
- Other.**
Congenital lesions with malignant potential, gallbladder disease, cardiovascular disease, elevated blood pressure and hypercalcemia have been associated with systemic estrogen treatment.

PRECAUTIONS

A. General

1. Use of Progestins.

It is common practice with systemic administration of estrogen to add progestin for ten or more days during a cycle to lower the incidence of endometrial proliferation or hyperplasia. From the available clinical data, it seems unlikely that ESTRING would have adverse effects on the endometrium. Furthermore, addition of progestins to a patient being treated with ESTRING is not expected to result in vaginal bleeding.

2. Physical Examination.

A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without reexamining the patient.

3. Uterine Bleeding and Mastodynia.

Although uncommon with ESTRING, certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding and mastodynia.

4. Liver Disease.

ESTRING should be used with caution in patients with impaired liver function.

5. Location of ESTRING.

Some women have experienced moving or gliding of ESTRING within the vagina. Instances of ESTRING being expelled from the vagina in connection with moving the bowels, strain, or constipation have been reported. If this occurs, ESTRING can be rinsed in lukewarm water and reinserted into the vagina by the patient.

6. Vaginal Irritation.

ESTRING may not be suitable for women with narrow, short, or stenosed vaginas. Narrow vagina, vaginal stenosis, prolapse, and vaginal infections are conditions that make the vagina more susceptible to ESTRING-caused irritation or ulceration. Women with signs or symptoms of vaginal irritation should alert their physician.

7. Vaginal Infection.

Vaginal infection is generally more common in postmenopausal women due to the lack of the normal flora of fertile women, especially lactobacillus, and the subsequent higher pH. Vaginal infections should be treated with appropriate antimicrobial therapy before initiation of ESTRING. If a vaginal infection develops during use of ESTRING, then ESTRING should be removed and reinserted only after the infection has been appropriately treated.

8. Other.

Hypercoagulability and hyperlipidemia have been reported in women on other types of estrogen replacement therapy but, these have not been seen with ESTRING patients.

Fluid retention is another known risk factor with estrogen therapy and may be harmful to patients with asthma, epilepsy, migraine and cardiac or renal dysfunction. ESTRING treatment has not been associated with any indication of increase in body weight up to 48 weeks of treatment.

B. Drug-Drug and Drug-Laboratory Interactions.

It is recommended that ESTRING be removed during treatment with other vaginally administered preparations. Drug-drug and drug-laboratory interactions have been reported with estrogen administration overall, but were not observed in clinical trials with ESTRING. However, the possibility of the following interactions should be considered when treating patients with ESTRING.

- Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III; decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
- Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.
- Carcinogenesis, Mutagenesis, and Impairment of Fertility.**
Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, and liver (see **CONTRAINDICATIONS** and **BOXED WARNING**).
- Pregnancy Category X.**
Estrogens should not be used during pregnancy (see **CONTRAINDICATIONS** and **BOXED WARNING**).

Estring®

estradiol vaginal ring

E. Nursing Mothers.

This product is not intended for nursing mothers. As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk.

F. Geriatric Use.

Of the total number of subjects in clinical studies of ESTRING (including subjects treated with ESTRING, placebo, and comparator drug; n=951), 25% were 65 and over, while 4% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

The biological safety of the silicone elastomer has been studied in various *in vitro* and *in vivo* test models. The results show that the silicone elastomer is non-toxic, non-pyrogenic, non-irritating, and non-sensitizing. Long-term implantation induced encapsulation equal to or less than the negative control (polyethylene) used in the USP test. No toxic reaction or tumor formation was observed with the silicone elastomer.

In general, ESTRING (estradiol vaginal ring) was well tolerated. In the two pivotal controlled studies, discontinuation of treatment due to an adverse event was required by 5.4% of patients receiving ESTRING and 3.9% of patients receiving conjugated estrogens vaginal cream. The most common reasons for withdrawal from ESTRING treatment due to an adverse event were vaginal discomfort and gastrointestinal symptoms.

The adverse events reported with a frequency of 3% or greater in the two pivotal controlled studies by patients receiving ESTRING or conjugated estrogens vaginal cream are listed in Table 2.

TABLE 2: ADVERSE EVENTS REPORTED BY 3% OR MORE OF PATIENTS RECEIVING EITHER ESTRING OR CONJUGATED ESTROGENS VAGINAL CREAM IN TWO PIVOTAL CONTROLLED STUDIES

ADVERSE EVENT	ESTRING (n=257) %	Conjugated Estrogens Vaginal Cream (n=129) %
Musculoskeletal		
Back Pain	6	8
Arthritis	4	2
Arthralgia	3	5
Skeletal Pain	2	4
CNS/Peripheral Nervous System		
Headache	13	16
Psychiatric		
Insomnia	4	0
Gastrointestinal		
Abdominal Pain	4	2
Nausea	3	2
Respiratory		
Upper Respiratory Tract Infection	5	6

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ADVERSE EVENT	ESTRING (n=257) %	Conjugated Estrogens Vaginal Cream (n=129) %
Sinusitis	4	3
Pharyngitis	1	3
Urinary		
Urinary Tract Infection	2	7
Female Reproductive		
Leukorrhea	7	3
Vaginitis	5	5
Vaginal Discomfort/Pain	4	5
Vaginal Hemorrhage	4	6
Asymptomatic Genital Bacterial Growth	1	7
Breast Pain		
Resistance Mechanisms		
Genital Moniliasis	6	7
Body as a Whole		
Flu-Like Symptoms	3	2
Hot Flashes	2	3
Allergy	1	4
Miscellaneous		
Family Stress	2	3

Other adverse events (listed alphabetically) occurring at a frequency of 1 to 3% in the two pivotal controlled studies by patients receiving ESTRING include: anxiety, bronchitis, chest pain, cystitis, dermatitis, diarrhea, dyspepsia, dysuria, flatulence, gastritis, genital eruption, genital pruritus, hemorrhoids, leg edema, migraine, otitis media, skin hypertrophy, syncope, toothache, tooth disorder, urinary incontinence.

The following additional adverse events were reported at least once by patients receiving ESTRING in the worldwide clinical program, which includes controlled and uncontrolled studies. A causal relationship with ESTRING has not been established.

Body as a Whole: allergic reaction

CNS/Peripheral Nervous System: dizziness

Gastrointestinal: enlarged abdomen, vomiting

Metabolic/Nutritional Disorders: weight decrease or increase

Psychiatric: depression, decreased libido, nervousness

Reproductive: breast engorgement, breast enlargement, intermenstrual bleeding, genital edema, vulval disorder

Skin/Appendages: pruritus, pruritus ani

Urinary: micturition frequency, urethral disorder

Vascular: thrombophlebitis

Vision: abnormal vision

OVERDOSAGE

Given the nature and design of ESTRING (estradiol vaginal ring), it is unlikely that overdosage will occur. However, should overdosage occur, it may manifest itself as nausea, vomiting, and/or vaginal bleeding. Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing oral contraceptives by young children.

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