

Prehysterectomy Anemia Ups Transfusion Risk

BY SUSAN LONDON

FROM THE ANNUAL MEETING OF THE SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS OF CANADA

VANCOUVER, B.C. – Preoperative anemia sharply increases the odds that women undergoing elective hysterectomy for a benign condition will need a transfusion, according to a study of over 400 women.

In a retrospective cohort study of 441 women, those who were found to be anemic (defined as having a hematocrit of less than 30%) on their preoperative bloodwork were ninefold more likely to receive a transfusion intraoperatively or postoperatively after other factors were taken into account.

“Blood transfusion is a relatively safe intervention in the 21st century, but it’s not without risks, such as the risk of in-

fectious transmission or fluid overload, and blood supply is limited. So we don’t want to give blood unless we have to give blood,” lead investigator Dr. Jeffrey Mangel commented in an interview.

“Anemia is a modifiable risk factor,” he added. “In a short period of time, you can’t change a patient’s weight or their prior surgical history or other things, but you certainly can change their preoperative hematocrit.”

VITALS

Major Finding: Women who had anemia preoperatively were ninefold more likely to receive a transfusion than their nonanemic counterparts.

Data Source: A retrospective case-control study of 441 women who underwent hysterectomy for benign conditions.

Disclosures: Dr. Mangel reported that he had no relevant financial disclosures.

For example, physicians can encourage anemic women to begin or better comply with iron therapy and start them on gonadotropin-releasing hormone (GnRH) agonist therapy to halt menstruation. Still, these interventions take approximately 2 to 3 months to restore red blood cell parameters to the normal range.

“The barriers to that might be more along the lines of convenience,” he noted, in that patients and physicians alike have already scheduled and prepared for the surgery. “So there is an element of inconvenience for the patient and the doctor that may prevent people from doing this.”

“But from the quality of care point of view, it’s probably at least something that should be offered to patients before they have their surgery,” added Dr. Mangel, who is director of the division of urogynecology and pelvic surgery at MetroHealth Medical Center, and with the reproductive biology department at Case Western Reserve University, both in Cleveland. “Some patients might opt for the increased risk of getting blood if they don’t choose to delay their surgery. But if I were advising women who were going to have this type of surgery, I would like them to minimize every possible risk of getting blood if they don’t need to get it.”

For the study, he and his colleagues retrospectively queried the MetroHealth electronic medical record system to identify women who underwent an elective hysterectomy for a benign condition between 2000 and 2005. They compared characteristics between 137 women who received a perioperative transfusion and 304 women who did not.

Study results showed that the two groups were similar in terms of age (mean age was 45 years), race, body mass index (mean BMI was 31 kg/m²), and smoking status. But the transfused women had a higher Charlson comorbidity index score, signifying they were slightly less healthy. Mean preoperative hematocrit was 34.0% in the transfused group and 38.8% in the nontransfused group.

Many of the women who were transfused were anemic preoperatively (78%), compared with 25% of nonanemic women. The difference corresponded to ninefold higher odds of transfusion in adjusted analyses.

In addition, as might be expected, women were more likely to receive a

Continued on following page

Zyclara® [zi-clar-a] (imiquimod) Cream 3.75%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

External Genital Warts

ZYCLARA Cream is indicated for the treatment of external genital and perianal warts (EGW)/condyloma acuminata in patients 12 years or older.

Limitations of Use

Treatment with ZYCLARA has not been studied for prevention or transmission of HPV.

Unevaluated Populations

The safety and efficacy of ZYCLARA Cream have not been established in the treatment of:

- urethral, intra-vaginal, cervical, rectal or intra-anal human papilloma viral disease.
- actinic keratosis when treated with more than one 2-cycle treatment course in the same area.
- patients with xeroderma pigmentosum.
- superficial basal cell carcinoma.
- immunosuppressed patients.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Local Skin Reactions

Intense local skin reactions including skin weeping or erosion can occur after a few applications of ZYCLARA Cream and may require an interruption of dosing. ZYCLARA Cream has the potential to exacerbate inflammatory conditions of the skin, including chronic graft versus host disease.

Administration of ZYCLARA Cream is not recommended until the skin is healed from any previous drug or surgical treatment.

Systemic Reactions

Flu-like signs and symptoms may accompany, or even precede, local skin reactions and may include fatigue, nausea, fever, myalgias, arthralgias, malaise and chills. An interruption of dosing and assessment of the patient should be considered.

Lymphadenopathy occurred in 2% of subjects with actinic keratosis treated with ZYCLARA Cream. This reaction resolved in all subjects by 4 weeks after completion of treatment.

Ultraviolet Light Exposure Risks

Exposure to sunlight (including sunlamps) should be avoided or minimized during use of ZYCLARA Cream. Patients should be warned to use protective clothing (e.g., a hat) when using ZYCLARA Cream. Patients with sunburn should be advised not to use ZYCLARA 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 ZYCLARA Cream.

In an animal photo-carcinogenicity study, imiquimod cream shortened the time to skin tumor formation. The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Therefore, patients should minimize or avoid natural or artificial sunlight exposure.

Increased Risk of Adverse Reactions with Concomitant Imiquimod Use

Concomitant use of ZYCLARA and any other imiquimod products, in the same treatment area, should be avoided since they contain the same active ingredient (imiquimod) and may increase the risk for and severity of local skin reactions.

The safety of concomitant use of ZYCLARA Cream and any other imiquimod products has not been established and should be avoided since they contain the same active ingredient (imiquimod) and may increase the risk for and severity of systemic reactions.

Immune Cell Activation in Autoimmune Disease

ZYCLARA Cream should be used with caution in patients with pre-existing autoimmune conditions because imiquimod activates immune cells.

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 two double-blind, placebo-controlled studies 602 subjects applied up to one packet of ZYCLARA Cream or vehicle daily for up to 8 weeks.

The most frequently reported adverse reactions were application site reactions and local skin reactions. Selected adverse reactions are listed in Table 1.

Table 1: Selected Adverse Reactions Occurring in ≥2% of ZYCLARA Treated Subjects and at a Greater Frequency than with Vehicle in the Combined Trials (EGW)

Preferred Term	ZYCLARA Cream 3.75% (N=400)	Vehicle Cream (N=202)
Application site pain	28 (7%)	1 (<1%)
Application site irritation	24 (6%)	2 (1%)
Application site pruritus	11 (3%)	2 (1%)
Vaginitis bacterial*	6 (3%)	2 (2%)
Headache	6 (2%)	1 (<1%)

*Percentage based on female population of 6/216 for ZYCLARA Cream 3.75% and 2/106 for vehicle cream. Local skin reactions were recorded as adverse reactions only if they extended beyond the treatment area, if they required any medical intervention, or they resulted in patient discontinuation from the study. The incidence and severity of selected local skin reactions are shown in Table 2.

Table 2: Selected Local Skin Reactions in the Treatment Area Assessed by the Investigator (EGW)

All grades*, (%)	ZYCLARA Cream 3.75% (N=400)		Vehicle Cream (N=202)	
	Severe, (%)			
Erythema*		70%		27%
	Severe erythema	9%		<1%
Edema*		41%		8%
	Severe edema	2%		0%
Erosion/ulceration*		36%		4%
	Severe erosion/ulceration	11%		<1%
Exudate*		34%		2%
	Severe exudate	2%		0%

*Mild, Moderate, or Severe

The frequency and severity of local skin reactions were similar in both genders, with the following exceptions: a) flaking/scaling occurred in 40% of men and in 26% of women and b) scabbing/crusting occurred in 34% of men and in 18% of women.

In the clinical trials, 32% (126/400) of subjects who used ZYCLARA Cream and 2% (4/202) of subjects who used vehicle cream discontinued treatment temporarily (required rest periods) due to adverse local skin reactions, and 1% (3/400) of subjects who used ZYCLARA Cream discontinued treatment permanently due to local skin/application site reactions.

Other adverse reactions reported in subjects treated with ZYCLARA Cream include: rash, back pain, application site rash, application site cellulitis, application site excoriation, application site bleeding, scrotal pain, scrotal erythema, scrotal ulcer, scrotal edema, sinusitis, nausea, pyrexia, and influenza-like symptoms.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of imiquimod. 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, supraventricular 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, urinary retention, dysuria.

Skin and Appendages: exfoliative dermatitis, erythema multiforme, hyperpigmentation, hypertrophic scar, hypopigmentation.

Vascular: Henoch-Schönlein purpura syndrome.

USE IN SPECIFIC POPULATIONS

Pregnancy Pregnancy Category C:

There are no adequate and well-controlled studies in pregnant women. ZYCLARA Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The animal multiples of human exposure calculations were based on daily dose comparisons for the reproductive toxicology studies described in this label. The animal multiples of human exposure were based on weekly dose comparisons for the carcinogenicity studies described in this label. For the animal multiple of human exposure ratios presented in this label, the Maximum Recommended Human Dose (MRHD) was set at 2 packets (500 mg cream) per treatment of actinic keratosis with ZYCLARA Cream (imiquimod 3.75%, 18.75 mg imiquimod) for BSA comparison. The maximum human AUC value obtained in the treatment of external genital and perianal warts was higher than that obtained in the treatment of actinic keratosis and was used in the calculation of animal multiples of MRHD that were based on AUC comparison.

Systemic embryofetal development studies were conducted in rats and rabbits. 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 (163X 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 tongues and low-set ears. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 5 mg/kg/day (28X 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 (2.1X MRHD based on BSA comparisons), the highest dose evaluated in this study, or 1 mg/kg/day (115X 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 (25X 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 (25X 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 (12X MRHD based on AUC comparisons).

Nursing Mothers

It is not known whether imiquimod is excreted in human milk following use of ZYCLARA Cream. Because many drugs are excreted in human milk, caution should be exercised when ZYCLARA 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.

Geriatric Use

Clinical studies of ZYCLARA Cream for EGW did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Of the 400 subjects treated with ZYCLARA Cream in the EGW clinical studies, 5 subjects (1%) were 65 years or older.

OVERDOSAGE

Topical overdosing of ZYCLARA Cream could result in an increased incidence of severe local skin reactions and may increase the risk for systemic reactions.

Hypotension was reported in a clinical trial following multiple oral imiquimod doses of >200 mg (equivalent to ingestion of the imiquimod content of more than 21 packets of ZYCLARA). The hypotension resolved following oral or intravenous fluid administration.

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FDA Approves Test for HER2 Gene in Breast Ca

BY ELIZABETH MEHCATIE

A test that measures the number of copies of the HER2 gene in breast tumor tissue has been approved by the Food and Drug Administration.

If the Inform Dual ISH test is positive, then the patient is a candidate for treatment with trastuzumab, the recombinant monoclonal antibody directed against HER2 that is marketed as Herceptin by Genentech for the treatment of HER2 overexpressing breast cancer. The test is manufactured by Tucson, Ariz.-based Ventana Medical Systems, a member of the Roche group, as is Genentech.

Continued from previous page

transfusion if they had a greater estimated blood loss during the surgery. Age, body mass index, and prior history of surgeries did not influence this outcome, he said at the meeting.

Further analyses showed that the odds of transfusion were also higher for women whose indication for surgery was fibroids and/or menorrhagia versus prolapse, and for women having an abdominal hysterectomy versus women who had a transvaginal or laparoscopic procedure.

In the case of menorrhagia, women usually have a known history of anemia, according to Dr. Mangel. But the anemia can be much more severe preoperatively than anticipated, possibly related to a longer time between deciding to have the surgery and actually having it.

There are no formal guidelines when it comes specifically to managing anemia in patients undergoing hysterectomy, he said, but a general surgical principle is that the healthier a patient is going into surgery, the better the likelihood of a good outcome.

"I'm not advocating to have a hard and fast guideline published because I do think you need to leave room for patient counseling, discussion of what matters to the patient, and for there to be some physician judgment involved regarding the risks of postponing this person's surgery versus not," he said. For instance, a patient who is unlikely to return for a rescheduled hysterectomy in 2 to 3 months may get into an emergent situation where, ironically, she needs a transfusion.

"But if given the opportunity, surgeons should consider intervening," he recommended. "I think we are all a little bit guilty of this, that we have become a little bit lax with our concern about transfusing patients in general. ... To the extent we don't have to give people blood, we are better off not giving them blood. And while this may pose inconvenience to patients and surgeons, if they are willing to consider doing this type of an intervention, blood transfusion rates will go down for hysterectomy. So sometimes, the right thing to do is not always the most convenient thing to do." ■

"When used with other clinical information and laboratory tests, this test can provide health care professionals with additional insight on treatment decisions for patients with breast cancer," Alberto Gutierrez, Ph.D., director of the Office of In Vitro Diagnostic Device Evaluation and Safety in the FDA's Center for Devices and Radiological Health, said in the statement announcing the approval. The test makes it possible "to see and

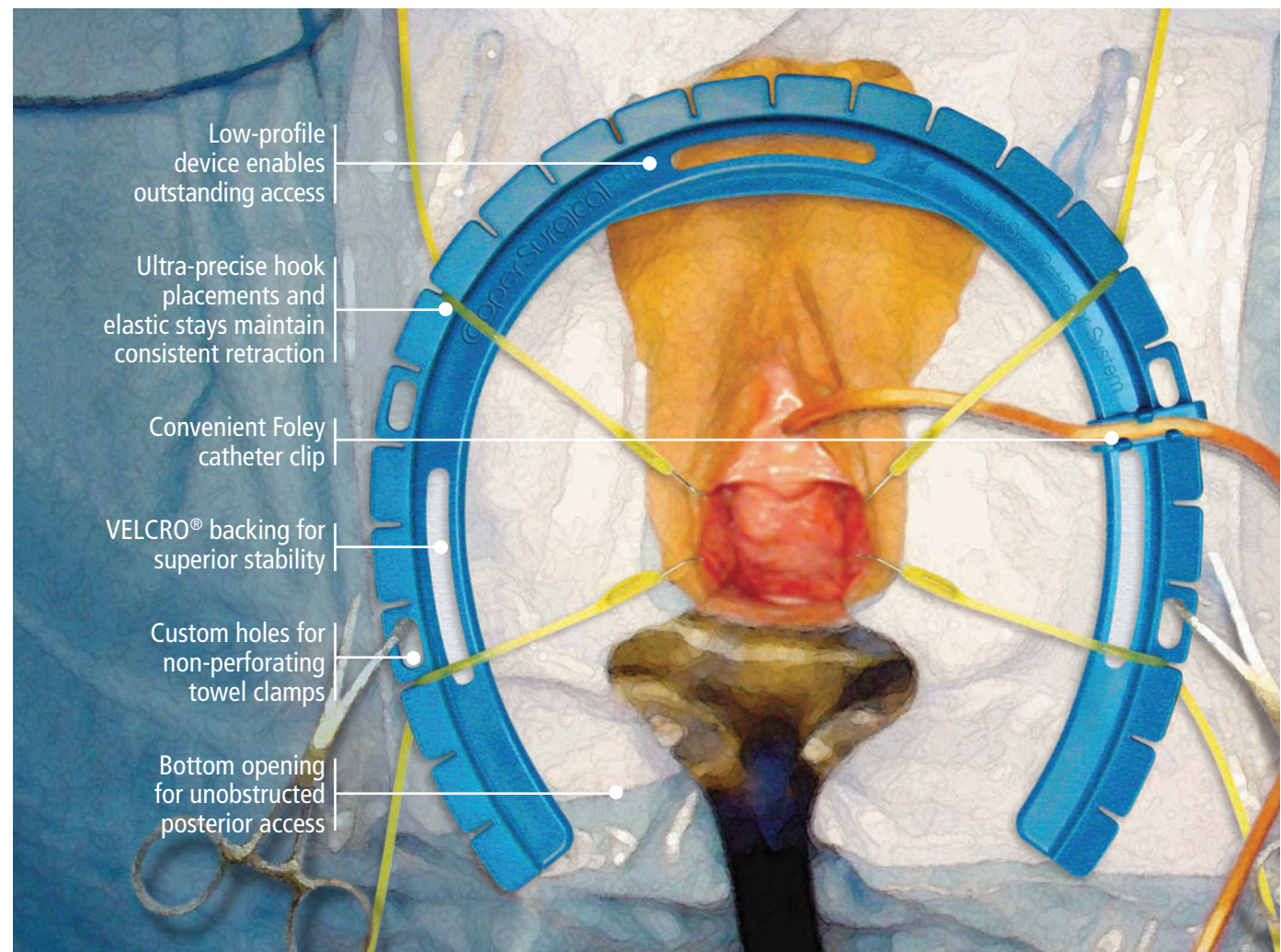
count copies of chromosome 17 and HER2 genes on the same slide, similar to HER2 amplification measurements that have traditionally only been available using fluorescence microscopes," the statement said.

But the new test, "allows lab staff to see the HER2 and chromosome 17 signals directly under a microscope, for longer periods of time."

Approval is based on a study

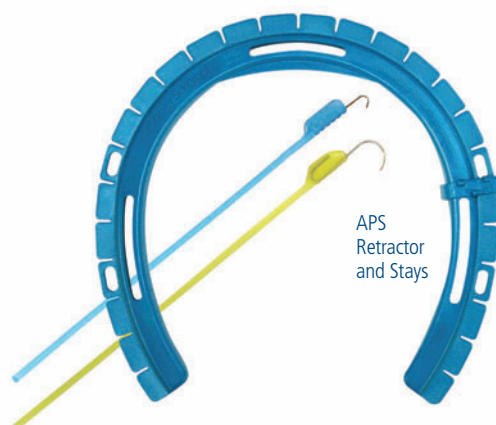
conducted in the United States that evaluated the test in 510 women with breast cancer. The test confirmed that the tumor sample contained more than the normal number of copies of the HER2 gene, located on chromosome 17, in 96% of the HER2 positive samples, according to the statement.

About 20% of women diagnosed with breast cancer are HER2-positive, according to the FDA. ■



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