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International Collaborative Ovarian Neoplasm Trial 1 and Adjuvant ChemoTherapy In Ovarian Neoplasm Trial

ABSTRACT & COMMENTARY

THE INVESTIGATORS OF 2 MAJOR AND PARALLEL EUROPEAN RANdomized clinical trials focused on early-stage epithelial ovarian cancer (International Collaborative Ovarian Neoplasm 1 [ICON1] and Adjuvant ChemoTherapy In Ovarian Neoplasm [ACTION] performed a combined analysis. Both trials compared platinum-based adjuvant chemotherapy with observation following primary surgery. Between 1990 and 2000, 925 patients (477 in ICON1 and 448 in ACTION) who had surgery for early stage ovarian cancer were randomly assigned to receive platinum-based adjuvant chemotherapy (n = 465) or observation (n = 460) until chemotherapy was indicated. After a median follow-up of more than 4 years, 245 patients had died or had a recurrence (ICON1: 33, ACTION: 112). Overall survival at 5 years was 82% in the chemotherapy arm and 74% in the observation arm (difference = 8%; [95% confidence interval (CI) = 2-12%]; hazard ratio [HR] = 0.67; 95% CI = 0.50-0.90; *P* = .008). Recurrence-free survival at 5 years was also better in the adjuvant chemotherapy arm than it was in the observation arm (76% vs 65%; difference = 11% [95% CI = 5-16]; HR = 0.64; 95% CI = 0.50-0.82; *P* = .001). Subgroup analysis provided no evidence of a difference in the size of effect of chemotherapy on survival in any pretreatment subcategory (age, tumor stage, histologic cell type, and differentiation grade). The trial concluded that platinum-based adjuvant chemotherapy improved overall survival and recurrence-free survival at 5 years in this combined group of patients with early stage ovarian cancer defined by the inclusion criteria of the ICON1 and ACTION trials (International Collaborative Ovarian Neoplasm 1 [ICON1] and European Organisation for Research and Treatment of Cancer Collaborators-Adjuvant ChemoTherapy In Ovarian Neoplasm [EORTC-ACTION]. J Natl Cancer Inst. 2003;95:105-112).

COMMENT BY DAVID M. GERSHENSON, MD

Approximately 30% of women with epithelial ovarian cancer have stage I or II disease. Although the overall survival of patients

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INSIDE

with stage I disease is 80-90% and the overall survival of patients with stage II disease is 50-70%, there is still a wide range of survival times for various subsets of patients within this category. Over the past 2 decades or so, experts have been able to reach a consensus on the definition of "high-risk" early stage disease that is associated with a worse outcome. Most agree that high-risk early stage ovarian cancer includes stage Ia and Ib, grades 2 and 3; all clear cell carcinomas; and all stages Ic and II. There has been a difference in philosophy between the American and the European perspective regarding the conduct of early stage ovarian cancer trials. The Europeans have maintained historically that, prior to the findings of these trials, there was no evidence of benefit from adjuvant therapy; thus, their clinical trials, as demonstrated by these studies, have generally included a comparison of treatment vs observation. On the other hand, the Americans have made the assumption that the prognosis of high-risk early stage patients is not so wonderful, thereby choosing to design trials comparing 2 different treatments. Now that these trials have seemingly established the benefits of adjuvant therapy once and for all, most future trials will assume the American design. However, as always, the details are important. In the ICON1 trial, patients with well-differentiated tumors and stage III disease were included. In the ACTION trial, where eligibility criteria were more restrictive, the benefit of adjuvant chemotherapy was limited to patients with nonoptimal staging. Of course, this just underscores the fact that all clinical trials have flaws—some more major than others. In this case, the true value of adjuvant chemotherapy for patients with high-risk early stage ovarian cancer still remains somewhat uncertain. The goal of future trials will be to tease out those patients who do not require adjuvant treatment, and most of us believe that the identification of these good-prognosis patients will be based on some, as yet unknown, molecular biomarker. ■

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Magnesium Sulfate and Nimodipine for the Prevention of Eclampsia

ABSTRACT & COMMENTARY

Synopsis: *Magnesium sulfate is more effective than nimodipine for prophylaxis against seizures in women with severe preeclampsia.*

Source: Belfort MA, et al. *N Engl J Med*. 2003;348: 304-311.

THROUGH THE YEARS CLINICIANS OUTSIDE THE COUNtry and nonobstetricians inside the country have challenged the concept of using magnesium sulfate for the prevention of eclampsia. However, each time it gets pitted against another agent in a randomized trial, magnesium sulfate wins out. [1-3]

The latest multicentered trial published in the *New England Journal of Medicine* by Belfort and colleagues assessed the antiseizure ability in preeclamptics of magnesium sulfate compared with a calcium channel blocker nimodipine. The rationale for using the latter drug is that eclamptic seizures result from cerebral vasospasm and ischemia, and that nimodipine is a specific vasodilator of the cerebral circulation.

The study involved 1650 severe preeclamptic patients randomly assigned to being treated with intravenous magnesium sulfate vs nimodipine (60 mg q.4h. p.o.). Hypertension was controlled in both

groups with hydralazine.

Twenty-one of 819 patients (2.6%) in the nimodipine group had seizures, compared with 7 of 831 (0.8%) in the magnesium sulfate group ($P = 0.01$). In effect, the chances of eclampsia were 3.2 times greater when using nimodipine. Most of the seizures occurred postpartum in the nimodipine group. Not surprisingly, the magnesium sulfate patients needed hydralazine more frequently to control blood pressure.

COMMENT BY JOHN C. HOBBINS, MD

Magnesium sulfate has become a therapeutic staple for the American obstetrician, but in some areas in Asia, where preeclampsia is very common, Valium is the drug of choice for prevention of eclampsia. In some European countries, where there is an antimagnesium mentality, various anti-epileptic medications are used for seizure prophylaxis in preeclampsia, despite a large randomized trial from Dallas showing that magnesium sulfate fared better than Dilantin in preventing eclampsia.

Magnesium sulfate has many properties that are useful in severe preeclampsia. It has a modest antihypertensive effect, is an osmotic diuretic, and decreases uterine resistance thereby causing an increase in uterine blood flow. Now we find out that magnesium sulfate decreases cerebral perfusion pressure, an action that discourages seizure activity.

Interestingly, a very recent randomized, placebo-controlled trial from the prolific group in Memphis indicates that magnesium sulfate does not affect the progression of disease in mild preeclampsia.[4]

Lest we think that magnesium sulfate can do no wrong, we must remember that intravenous magnesium needs to be carefully watched and has uncomfortable side effects. In a previous *OB/GYN Clinical Alert*, we covered a study that suggested that there was a relationship between the dose used to prevent preterm labor and adverse neonatal outcome. For these reasons, we should keep in mind that not even a tried-and-true drug such as magnesium sulfate, like the condition we are treating, should not be taken lightly. ■

References

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2. Coomarasamy A, et al. *Obstet Gynecol*. 2001;98: 861-866.
3. Belfort MA, et al. *Am J Obstet Gynecol*. 1999;181: 402-407.
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Treatment of Sexual Dysfunction After Menopause

ABSTRACT & COMMENTARY

Synopsis: *In postmenopausal patients with sexual dysfunction, it is still unclear which, if any, therapy is indicated.*

Source: Modelska K, Cummings S. *Am J Obstet Gynecol*. 2003;188:286-293.

MODELSKA AND CUMMINGS PERFORMED A THOROUGH search of both electronic and manual databases to identify all randomized and placebo-controlled trials (RCTs) of treatment for female sexual dysfunction (FSD) in postmenopausal women published since 1990. Only 6 RCTs evaluating the effects of various therapies on sexual functioning in postmenopausal women have been published. Of these, 3 used hormone replacement, 2 used tibolone, and 1 evaluated the use of sildenafil citrate (Viagra). A summary of the findings includes: an estrogen/progestin therapy improves sexual desire and arousal, combined estrogen/androgen increases sexual sensation, desire, and frequency of intercourse, transdermal testosterone increases the frequency of sexual activity and orgasm, sildenafil does not demonstrate improvement in sexual response in women with female sexual arousal disorder (FSAD). Results with tibolone remain inconclusive. Modelska and Cummings conclude that it remains unclear which groups of postmenopausal patients with FSD do/do not benefit from these therapies.

COMMENT BY FRANK W. LING, MD

Let's be honest: this topic is a tough one for all of us in practice. For some of us, we figure that if we don't ask, then she won't tell. For others, the approach is to ask (since we've been taught to do so), but we don't know what to do with the information when we get it. In some cases, it's a matter of a business decision—ie, there isn't enough time to address these concerns. Hopefully the case never occurs in which the clinician simply denies the reality that a postmenopausal patient can have sexual issues. This may have been the case a generation or so ago, but surely that outdated attitude has long ago exited our collective clinical mindset.

FSD is defined as a persistent/recurring decrease in sex drive or an aversion to sexual activity, difficulty becoming

aroused, inability to reach orgasm, or pain during sexual intercourse. It is estimated that up to half of women in the United States have FSD. Many therapies are used in our practices to attempt to address FSDs, but they are not supported by adequate evidence. In the absence of very much evidence-based clinical information, the physician and patient will continue to struggle to identify treatments that both might help while not causing harm.

Since patients do not always raise issues of sexual functioning as concerns, it is incumbent on the clinician to routinely include this in the well-woman evaluation. Even when patients do not specifically complain of sexual problems, it has been estimated that up to 1 in 6 have concerns in this area. The routine questions of "Are you sexually active?" and "Do you have any concerns about your sexual functioning?" take little time, but offer great insight. Even if the patient does not answer in the affirmative now, the very fact that her provider asked and continues to ask routinely, sends the message that her sexual concerns do matter and have importance. If you, as the clinician, do not feel comfortable in dealing with the problem, it should be relatively straightforward to get the patient to people or agencies who can help. Just identifying and validating the problem may prove to be a great service to the patient whose sexual concerns were heretofore left unaddressed.

This study confirms what many suspected: there are precious few RCTs addressing FSD. From the few that do exist, no conclusions can be drawn. The physician should be prudent in prescribing treatments that are not proven, but also understanding when patients express a desire to pursue untested treatments. We should be the patient's advocate in any and all cases. ■

Drug Treatments to Prevent Breast Cancer

ABSTRACT & COMMENTARY

Synopsis: *Only tamoxifen has enough evidence to recommend it for the prevention of breast cancer, and its use is limited to very high-risk women with a low risk of side effects.*

Source: Cuzick J, et al. *Lancet*. 2003;361:296-300.

Epidemiologists from England, Italy, and Australia reviewed the combined results of breast cancer prevention trials and added updated results (*see Table*). Reports are now available on 4 trials using tamoxifen, 20 mg daily for 5 years, for prophylaxis against breast cancer. In addition, data are available on the effect of raloxifene, derived from the trial investigating raloxifene prophylaxis against fractures in women with osteoporosis.

The combined data indicated a 48% reduction in estrogen receptor-positive cancers and no effect on the incidence of estrogen receptor-negative cancers. The overall relative risk of endometrial cancer with tamoxifen was increased to 2.4, and the relative risk of venous thromboembolic events was 1.9. The length of follow-up and patient numbers do not allow data regarding breast cancer mortality. Cuzick and colleagues estimated the effect of 5 years of tamoxifen treatment, given appropriate survival rates, and concluded that 1000 high-risk women would demonstrate an 18% reduction in mortality within 10 years of diagnosis.

COMMENT BY LEON SPEROFF, MD

Cuzick et al concluded that the evidence supports tamoxifen reduction of the risk for estrogen receptor-positive breast cancer. But at the same time, they believe that tamoxifen should not be recommended as a preventive agent, except for women at very high risk. This conclusion is based upon the degree of reduction in risk compared with the incidence of side effects. The data are too limited to support the use of raloxifene as prophylactic treatment, and a stronger position awaits the outcome of the STAR trial comparing tamoxifen with raloxifene. The Medical Research Council of the United Kingdom and the National Cancer Institute of the United States have reached similar conclusions.

The evaluation by the National Cancer Institute is very helpful.[1] This report is the result of a workshop directed to the development of a program to select the best candidates for tamoxifen treatment. Because the risks associated with tamoxifen (endometrial cancer, stroke, pulmonary embolism, and deep vein

Table

Trial Data

Trials	Breast Cancers	Endometrial Ca	VTE
Royal Marsden	62 vs 75	6 vs 2	12 vs 8
American	124 vs 244	36 vs 15	53 vs 28
Italian	34 vs 45	(all no uterus)	10 vs 9
International	69 vs 101	11 vs 5	43 vs 17
MORE (Raloxifene)	15 vs 43	1 vs 5	32 vs 12

thromboembolism) increase with age, balancing the risks and benefits indicates that tamoxifen is best for younger women with an elevated risk of breast cancer (an increased relative risk of approximately 1.7). A similar conclusion was reached by a working group of the American Society of Clinical Oncology.[2] This means that only a relatively small number of women will qualify because 85% of women who develop breast cancer do not have an identifiable risk factor.

I am still concerned that the favorable conclusion regarding tamoxifen for prevention is influenced by the American results. The other 3 trials did not achieve statistical significance, results that are usually dismissed on the basis of trial size—the American trial accounted for 47% of the treated women. The recent international trial results achieved statistical significance only when ductal carcinoma in situ cases were included.[3] Nevertheless, experts and organizations in the breast cancer world have agreed that tamoxifen reduces the incidence of estrogen receptor-positive cancers in high-risk women.

Women being treated with tamoxifen for prevention of breast cancer should receive appropriate antithrombotic measures, especially during and after major surgery, and during immobility. I disagree with the National Cancer Institute's position regarding monitoring for endometrial changes, which is to simply refer the patient to a gynecologist for evaluation when the patient bleeds. Endometrial cancer is not the only side effect of tamoxifen. Women on tamoxifen treatment should be examined every 6 months to detect the emergence of endometriosis, ovarian cysts, and uterine enlargement. I believe annual measurement of endometrial thickness by transvaginal ultrasonography is indicated, recognizing that interpretation is difficult and often requires saline instillation (sonohysterography) in order to make accurate measurements. The use of the levonorgestrel-releasing IUD is highly recommended as prophylactic treatment. Interestingly, at the San Antonio Breast Cancer Symposium in December 2002, a study was presented finding no effect of postmenopausal hormone therapy against tamoxifen-induced hot flushing, when the two treatments were administered concomitantly. Hot flushing on tamoxifen is best treated with a serotonin uptake inhibitor.

Important questions remain unanswered. Will long-term follow-up reveal an incidence of tamoxifen-resistant cancers, cancers that are actually stimulated by tamoxifen? Will the incidence of estrogen receptor-negative cancers increase over time? What is the effect of tamoxifen treatment on quality of life and cognition (including the risk of Alzheimer's disease)? ■

References

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3. IBIS Investigators. *Lancet*. 2002;360:817-824.

Increased Risk of Breast Cancer with Estrogen-Progestin Therapy

ABSTRACT & COMMENTARY

Synopsis: *Postmenopausal estrogen-progestin therapy increased the risk of breast cancer in a population-based cohort in Sweden, and estrogen-only did not.*

Source: Olsson HL, et al. San Antonio Breast Cancer Symposium, December 2002. Abstract 34. In press.

OLSSON AND COLLEAGUES FROM LUND SWEDEN reported about 2 years ago[1] the incidence of breast cancer in a population-based cohort of 29,508 women. The women were recruited between 1990-1992, and followed for a median time of 7.6 years. There were 434 cases of breast cancer compared with 388 cases expected according to national statistics, which amounted to an increased risk of 1.92 with 4-10 years of postmenopausal estrogen-progestin use. There was no interaction with family history of breast cancer among first-degree relatives or previous use of oral contraceptives. That report was recently updated at the San Antonio Breast Cancer Symposium in December 2002. The number of breast cancers now totals 556 vs 508 expected. This produced a calculated overall increased risk of 1.09 that almost but not quite reached statistical significance. The risk for users of combined estrogen-progestin daily therapy for 4 years or more was calculated to be 3.68 (CI = 2.14-6.34). Sequential estrogen-progestin therapy had a risk of 2.81 (CI = 1.57-5.08). The use of estradiol without progestins was reported to have no increased risk.

■ COMMENT BY LEON SPEROFF, MD

These results, highlighted in the media, are no different than those recently reported by the Women's Health Initiative. One could argue that this Swedish study is more impressive because the size of the risks associated

with estrogen-progestin therapy is much larger, but there are problems with the study that make such a conclusion a little shaky.

The strength of the study is in the size of the cohort and the prospective design. Added to that is the ability to accurately track individuals in Sweden through a comprehensive registry system. Nevertheless, there are several problems. The risk ratios are calculated by comparing the observed number of cases with an expected number based upon the reference data in the government registries. Therefore, hormone users were not compared to nonusers; both users and nonusers were compared to expected outcomes. This is not a bad technique, but it provides approximations not absolutely accurate determinations.

The study carefully adjusted for many factors that affect the risk of breast cancer, including age of menarche, age at menopause, age at first full-term pregnancy, parity, and age at diagnosis. However, there are at least 4 more critical influences that were unaccounted for: use of mammography, presence of benign breast disease (specifically with atypical hyperplasia), body size, and alcohol intake.

The specific estrogen and progestin drugs were not identified, but in Sweden we know that the most popular regimen is composed of estradiol and norethindrone. This at least is evidence that American reports based mainly on the use of conjugated equine estrogens and medroxyprogesterone acetate do not indicate results limited to one formulation.

As in the Women's Health Initiative, the appearance of an increased risk by 4 years of use is relatively rapid. This is consistent with an effect on pre-existing tumors. Therefore, the recent data have not answered our most fundamental question: is there a slightly increased risk of breast cancer with combined estrogen-progestin postmenopausal therapy or are we seeing the results of earlier detection of tumors because of effects on pre-existing tumors? The now well-recognized better survival rates in postmenopausal women who develop breast cancer while on hormone therapy argues in favor of an effect on pre-existing tumors.

The good news is that the Swedish study reported no increase in risk associated with the use of estrogen alone. This is the reason that the estrogen-only arm of the Women's Health Initiative has not been discontinued. Only time will tell if estrogen-only is a different story. ■

Reference

1. Olsson H, et al. *Br J Cancer*. 2001;85:674-677.

Radical Trachelectomy and Pelvic Lymphadenectomy with Uterine Preservation in Treatment of Cervical Cancer

ABSTRACT & COMMENTARY

Synopsis: *Radical trachelectomy combined with pelvic lymphadenectomy can be a feasible method of treatment for early-stage cervical cancer in women who want to preserve their fertility.*

Source: Schlaerth JB, et al. *Am J Obstet Gynecol*. 2003;188:29-34.

Schlaerth and colleagues reported their series of 12 women with stage I cervical cancer who were scheduled to undergo radical trachelectomy and pelvic lymphadenectomy. The purpose of this pilot study was to determine whether this procedure could be a feasible method for the treatment of early-stage cervical cancer in women who want to preserve their fertility. The procedure was abandoned in 2 women because endometrial extension of the cancer was discovered at the time of surgery. Surgical margins were clear in all other women. No lymph node metastases were encountered. The proximal cervical remnant was reinforced in 10 women. Hospitalization ranged from 2 to 8 days (mean, 3.2 days). Estimated blood loss averaged 203 mL (range, 50-600 mL). Complications included 2 intraoperative cystotomies and 1 pelvic hematoma. Four pregnancies have occurred, with 2 third-trimester deliveries and 2 preterm losses at 24 and 26 weeks of gestation, respectively. The follow-up period ranged from 28 to 84 months (mean, 47.6 months). Schlaerth et al concluded that radical trachelectomy combined with pelvic lymphadenectomy could be a feasible method of treatment for early stage cervical cancer in women who want to preserve their fertility.

COMMENT BY DAVID M. GERSHENSON, MD

In 1994, Dargent first described radical vaginal trachelectomy. Subsequently, a few other groups in North America and Europe have reported their experience with this procedure. Of course, the traditional approach for treatment of early stage cervical cancer—stages IA2, IB, or IIA—involves either radical hysterectomy, radiation alone, or chemoradiation. Radical trachelectomy allows preservation of fertility.

Criteria proposed by Dargent and others have included the following: 1) desire for fertility preservation; 2) stage IA2 or IB; 3) lesion size < 2 cm; 4) absence of adenocarcinoma; 5) absence of vascular/lymphatic space involvement; 6) limited endocervical involvement on colposcopic examination; and 7) no evidence of lymph node metastasis. In the present series, Schlaerth et al did not consider adenocarcinoma as a contraindication; 5 patients had an adenocarcinoma, and 1 had an adenosquamous lesion. Laparoscopic lymphadenectomy was initially performed; if lymph node metastasis is noted on frozen section examination (which was not the case in any patient in this series), then radical trachelectomy is not performed. Schlaerth et al also expanded the surgical techniques used in this series; while 6 women underwent a radical vaginal trachelectomy, 4 underwent a laparoscopically assisted vaginal trachelectomy. These were all small lesions, with the largest lesion being 2 cm in diameter. One of the unresolved issues is the importance of preoperative imaging to select patients for radical trachelectomy. As groups continue to report and update their experience with this procedure, selection criteria and intraoperative techniques will be refined. In the meantime, radical trachelectomy and pelvic lymphadenectomy is an option for young women with early cervical cancer for whom fertility preservation is an issue. ■

CME Questions

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9. Which of the following is an absolute contraindication to radical trachelectomy to preserve fertility in women with invasive cervical cancer?

a. Adenocarcinoma
b. Lymph node metastasis
c. Stage IB
d. Age 45
e. 3 mm invasion

10. The following statements regarding drug prevention of breast cancer are true *except*:

a. Tamoxifen and raloxifene are associated with an increased risk of endometrial cancer.
b. Drugs that have anti-estrogenic activity in the breast reduce the risk of breast cancer in high risk women.
c. A risk-benefit analysis indicates that only tamoxifen treatment is warranted, and only in a select group of women.
d. The long-term impact of drugs used to prevent breast cancer is not known.

11. The following statements are true regarding postmenopausal hormone therapy and the risk of breast cancer *except*:

a. An increased risk of postmenopausal breast cancer has been reported with the use of more than one type of progestin.
b. The appearance of breast cancer in postmenopausal hormone users is relatively slow.
c. Thus far, most studies have not found an increased risk of breast cancer associated with the use of unopposed estrogen.
d. Postmenopausal estrogen-progestin therapy may cause earlier detection of breast cancer by affecting pre-existing tumors.

Answers: 9 (b); 10 (a); 11 (b)

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Attention CME Subscribers

An error appeared in the February edition of OB/GYN Clinical Alert. Question #5 should have read: "Which of the following is NOT a reasonable strategy for menopausal women to reduce their risk of hip fracture?" So, given that change, the answer to the question is still "b." Thank you to subscribers who alerted us to the mistake. ■

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