Urinary Cytology Not Useful as Screen for Bladder Invasion

Snowmass, Colo. — A gonadotropin-releasing hormone agonist can prevent ovarian failure and invasion of cyclophosphamide, according to a small, case-control study conducted at the University of Michigan.

Evidence suggests that by the time a patient with lupus has taken a total 30 g of cyclophosphamide (equivalent to about a year of treatment at 100 mg a day) the rate of ovarian failure is about 70%, W. Joseph McCune, M.D., said at a symposium sponsored by the American College of Rheumatology.

The regimen can also result in cervical dysplasia, which is why patients started on cyclophosphamide should have a Pap smear early in the course of their treatment, advised McCune, a lupus expert and the codirector of the nephrology/rheumatology vasculitis clinic at the University of Michigan, Ann Arbor.

In their prospective study, Dr. McCune and his colleagues enrolled 40 patients with lupus nephritis or severe systemic lupus erythematosus (SLE), whose average age was 23 years. Their regimen was sequential, with monthly intravenous cyclophosphamide for 6 months followed by a switch to azathioprine and then to prednisone. The disease did not respond after 6 months of cyclophosphamide, patients were treated with 4 more months of cyclophosphamide.

Among the 20 patients treated with leuprolide acetate in depot suspension (Lupron, 3.75 mg a month), only 1 developed ovarian failure at the end of 3 years, compared with 6 of 20 matched women who did not receive GnRH.

Treatment group patients received their first monthly injection of depot leuprolide acetate after receiving their first dose of cyclophosphamide, and the hormone agonist therapy was readministered after each course of cyclophosphamide—including when the patients had a flare after initial treatment and had to go back on the alkylating agent.

Patients who developed menopausal symptoms from the GnRH agonist were given an estrogen patch, together with depot medroxyprogesterone acetate (Depo Provera) to prevent a pregnancy.

The average cumulative dose of cyclophosphamide received by the patients and controls during the study was 12.9 g.

“These patients were relatively young, their cumulative dose was relatively low, and yet they died or appeared to benefit from a leuprolide treatment,” Dr. McCune said. “A randomized controlled trial obviously would be more convincing, and we are going to try to do that. But, this study suggests that this approach benefits patients, particularly if they are going to have relapses and if they are young.”

Dr. McCune noted that his study did not address those patients who are on oral cyclophosphamide, but he predicted that leuprolide treatment would be of greater merit in those patients because they generally are exposed to higher cumulative doses.

The incidence of high accuracy for detecting increased risk of cervical dysplasia associated with cyclophosphamide use has been documented at his own institution. In that report, 61 patients with SLE were given cyclophosphamide at baseline and then followed annually or as practice indicated for 7 years (J. Rheumatol. 2004;31:1763-7).

At enrollment, patients were excluded from the study if they had an abnormal smear or a history of cervical dysplasia. The study also did not enroll any patients on daily oral cyclophosphamide. However, use of monthly intravenous cyclophosphamide was permitted. Patients with a biopsy-proven cervical intraepithelial neoplasia in those who had taken only prednisone (23 patients) or prednisone and azathioprine (four patients). But there were two cases among eight patients treated with intravenous cyclophosphamide alone, and four cases among the 26 patients treated with intravenous cyclophosphamide together with azathioprine and/or prednisone.

In 3-7 years of follow-up, fewer cases of dysplasia occurred. Three of the 45 patients who remained in the study developed cervical intraepithelial neoplasia, and none of these cases occurred among patients who had received prednisone alone.

Overall, most patients with abnormal smears had resolution of their cervical dysplasia, but three patients required surgery and one continued to have persistently abnormal smears throughout the 7-year follow-up period.

In a retrospective study using databases at two medical centers, the researchers reviewed the findings on urine samples collected from 93 women with pelvic cancer (mean age 48 years) who were treated between 1999 and 2004. The samples were collected when the women underwent cystoscopy for staging of their pelvic cancer.

Most of the women had primary cervical cancer; three had locally extensive endometrial cancer; three each had vulvar, vaginal, or recurrent cervical cancer; one had ovarian cancer; and one had a primary rectal cancer that also involved the vagina, said Dr. Michael M. Suman, the McClure L. Smith Professor of Gynecologic Oncology at the University of Nebraska, Omaha.

Two-thirds of the samples were classified as normal on urinary cytology. The other one-third showed some abnormality, but these turned out to reflect benign changes such as inflammation or subclinical cystitis in most cases.

Urinary cytology detected malignant cells in only four women (4.3%), all of whom had extensive, locally advanced tumors. It failed to detect bladder invasion in three. In contrast, biopsy confirmed cancerous invasion of the bladder in all seven subjects (7.5%).

Thus, urinary cytology showed only a 57% sensitivity as a screen for detecting bladder invasion. It yielded “no additional information on the extent of disease in any patient with known stage I or II pelvic cancer,” so it was judged to be “of limited diagnostic value,” Dr. Molpus said.

However, given its 100% specificity and 100% positive predictive value in this study, urinary cytology may be useful in specific situations, such as when bladder biopsy results are inconclusive or biopsy samples are inadequate or unavailable, he said.