Paroxetine/Tamoxifen: More Breast Ca Deaths

BY BETSY BATES

SAN ANTONIO — Breast cancer patients who took the antidepressant paroxetine during their course of tamoxifen therapy were up to 91% more likely to die of their disease than were those who did not take the two drugs together, according to a retrospective, population-based cohort study conducted in the Canadian province of Ontario.

Investigators used health card identification numbers to track women aged 66 years and older who were treated with tamoxifen for breast cancer between 1993 and 2005. Almost a third of patients were taking an antidepressant during their tamoxifen therapy, including 2,430 who were also taking a selective serotonin reuptake inhibitor. As a class, SSRIs are known to inhibit cytochrome P450 2D6 (CYP 2D6), an enzyme critical for the conversion of tamoxifen to endoxifen, its active metabolite, in the body. The ability of SSRIs to interfere with the efficacy of tamoxifen—at least in some women—has been theorized, but studies attempting to clarify the issue have reported conflicting results.

In the Canadian study reported at the annual meeting of the San Antonio Breast Cancer Symposium, 1,074 (42.2%) of the women taking an SSRI during tamoxifen therapy were up to 91% more likely to die of their disease than were those who did not take the two drugs together, according to a retrospective, population-based cohort study conducted in the Canadian province of Ontario.

CERVARIX®

[Hum Papillomavirus Bivalent (Types 16 and 16) Vaccine, Recombinant]

Suspension for Intramuscular Injection

The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE

1.1 Indications: CERVARIX® is indicated for the prevention of the following diseases caused by oncogenic human papillomavirus (HPV) types 16 and 18 (see Clinical Trials (14) of full prescribing information) cervical cancer, cervical intraepithelial neoplasia (CIN) grade 2 or worse, and cervical intraepithelial neoplasia (CIN) grade 1. CERVARIX® is approved for use in females 10 through 25 years of age.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration: Shake vial or syringe well before withdrawal and use. Parenteral drug products should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit. CERVARIX® also should be inspected visually for color or discoloration of the vial or syringe prior to administration. If any of these conditions exist, the vaccine should not be administered. With thorough agitation, CERVARIX® is a homogenous, turbid, white suspension. Discard it if it appears otherwise.

2.2 Dose and Schedule: Immunization with CERVARIX® consists of 3 doses of 0.5 mL each, by intramuscular injection according to the following schedule: 0, 2, and 6 months. The preferred site of administration is the deltoit region of the upper arm. Do not administer this product intravenously, intradermally, or subcutaneously.

4 CONTRAINDICATIONS

Severe allergic reactions (e.g., anaphylaxis) to any component of CERVARIX® (see [Description] (11) of full prescribing information)

5 WARNINGS AND PRECAUTIONS

5.1 Syncope: Because vaccines may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following vaccination with CERVARIX®. When syncope is associated with tonic-clonic movement, the episode is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position. 5.2 Later: The tip cap and the rubber plunger of the needless prefilled syringes contain dry natural latex rubber that may cause allergic reactions in latex sensitive individuals. The vial stopper contains latex. 5.3 Preventing and Managing Allergic Vaccine Reactions: Prior to administration, the healthcare provider should carefully examine the vaccination history for possible vaccine hypersensitivity and previous vaccine-related adverse reactions to allow an assessment of benefits and risks. Appropriate treatment and supervision should be readily available in case of anaphylactic reactions following administration of CERVARIX®.

6 ADVERSE REACTIONS

The most common local adverse reactions (≥20% of subjects) were pain, redness, and swelling at the injection site. The most common general adverse events (≥20% of subjects) were fatigue, headache, myalgia, gastrointestinal symptoms, and arthralgia.

6.1 Clinical Studies Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine, and may not reflect the rates observed in practice. There is the possibility that broad use of CERVARIX® could reveal adverse reactions not observed in clinical trials.

Studies in females 15 Through 25 Years of Age: The safety of CERVARIX® was evaluated by pooling data from controlled and uncontrolled clinical trials (involving 23,713 females 10 through 25 years of age) in 17 countries in the post-license clinical development program. In these studies, 12,285 females (10 through 25 years of age) received at least one dose of CERVARIX® and 10,928 females received at least one dose of control. Data on solicited local and general adverse events were collected from subjects or parents using standardized diary cards for 7 consecutive days following each vaccine dose (i.e., day of vaccination and the next 6 days). Unsolicited adverse events were reported with a diary card for 30 days following each vaccination (day of vaccination and 29 subsequent days). Parents and/or subjects were also asked at each visit about the occurrence of any adverse events and instructed to immediately report serious adverse events throughout the study period. These studies were conducted in North America, Latin America, Europe, Asia, and Australia. Overall, the majority of subjects were white (55%), followed by Asian (25%), Hispanic (9%), black (2%), and other racial/ethnic groups (3%). The reported frequencies of solicited local injection site reactions and general adverse events are presented in Table 1. An analysis of solicited local injection site reactions by dose is presented in Table 2. Local reactions were reported more frequently with CERVARIX® compared with the control groups. In ≥84% of recipients of CERVARIX®, these local reactions were mild to moderate in intensity. Compared with dose 1, pain was reported less frequently after doses 2 and 3 of CERVARIX®, in contrast to redness and swelling where there was a small increased incidence. There was no increase in the frequency of general adverse events with successive doses.

Table 1. Rates of Solicited Local Adverse Reactions and General Adverse Events in Females 10 Through 25 Years of Age Within 7 Days of Vaccination (Total Vaccinated Cohort)
therapy had died as of Dec. 31, 2007, when primary data analysis began. After statistical adjustment for age, socioeconomic status, comorbidity, use of other CYP 2D6 drugs, and timing and duration of tamoxifen therapy, investigators found that the breast cancer mortality risk was increased 24% among women who were coprescribed paroxetine during 25% of their tamoxifen treatment.

If patients took paroxetine longer (that is, more than half of their tamoxifen course) their breast cancer mortality risk rose to 54%. Patients who took both drugs for 75% of the time they received tamoxifen had a 91% risk of breast cancer mortality (P=0.028).

Mortality from any cause was also sharply elevated among women who took paroxetine for 75% or more of their tamoxifen course (P=0.027).

The striking results were significant only for paroxetine, and not for other SSRI—includes fluoxetine, sertraline, fluvoxamine, or citalopram—that were taken concurrently with tamoxifen, reported Dr. Catherine M. Kelly at the annual meeting of the American Society of Clinical Oncology.

Dr. Kelly hypothesized that the explanation lies in the degree to which various SSRIs CYP 2D6. “Paroxetine is the only SSRI that is an irreversible— or ‘suicide’—inhibitor of CYP 2D6,” she said in an interview.

The dose-response curve of the study, with escalating mortality risk paralleling tamoxifen, is consistent with a significant degree of weight to the findings with regard to paroxetine, marketed as Paxil by GlaxoSmithKline. (The company did not respond to a request for a comment.)

Fluoxetine is also a potent inhibitor of CYP 2D6. But that was not shown to increase breast cancer mortality in the study. “I would like to see further data on that and would use caution in using any of the drugs that inhibit CYP 2D6 in women who are taking tamoxifen,” said Dr. Kelly, who was with the University of Toronto Sunnybrook Health Sciences Centre while conducting the study and is currently a breast medical oncology fellow at the University of Texas M.D. Anderson Cancer Center in Houston.

“There are other options,” she added, including non-SSRIs antidepressants that do not inhibit CYP 2D6.

Several patients discussed their choices with a medical oncologist, psychiatrist, or family physician before undergoing tamoxifen therapy, she suggested.

Survival: Breast Conservation vs. Mastectomy

SAN ANTONIO — Breast conservation therapy resulted in significantly better 5-year overall survival, compared with mastectomy, investigators found in a study of 202 patients with triple receptor–negative breast cancers. Triple receptor–negative breast tumors lack estrogen-, progesterone-, and Her-2/neu-receptor expression.

These aggressive cancers account for 15%-20% of the more than 1 million breast cancers diagnosed each year worldwide.

“Despite the aggressive nature of these tumors, our hypothesis was that breast conservation therapy [might be] a viable option for some patients,” Dr. Catherine C. Parker said at the annual Academic Surgical Congress.

She and her colleagues at Louisiana State University Shreveport, studied outcomes of 63 patients (31%) who had breast conservation therapy and 139 who received mastectomy. Cancer recurrence rates and survival were the primary outcomes.

Mean tumor size at baseline was significantly smaller in patients who received breast conservation treatment (2.5 cm) versus 3.1 cm in the mastectomy group. The difference was not statistically significant.

All patients were offered standard care treatment and surveillance. The mean follow-up was 33 months.

Disease-free survival at 5 years was 56% for the mastectomy group and 69% for the breast conservation therapy group. The difference was statistically significant, Dr. Parker said.

“Five-year overall survival was significantly better for conservation therapy (89% vs. 69%),” said Dr. Parker of the department of surgery at LSU. For women with hormone receptor–negative breast cancers, breast conservation and mastectomy come of the more than 1 million breast cancers diagnosed each year. A study of 202 patients with triple receptor–negative breast cancers accounted for 15%-20% of these cases.

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