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clinical symptoms),” saying that such questions “are best answered by a health care provider who is trained and licensed specifically to make differential diagnoses and to treat disease entities.”

The new labeling will be phased in over six years. The simplified standard language includes “uses,” not “indications,” and the terms “precautions” and “contraindications” are no longer used. The rule specifies graphic features, including a minimum 6-point type size, and describes adjustments that can be made to accommodate various package sizes and shapes. FDA recommends that manufacturers include a telephone number so that consumers can call with questions.

FDA estimates that implementing the requirements will cost the nonprescription drug industry about $58 million—and that the new labeling will save consumers about $100 million annually in health care costs.

—NTL

Combined chemotherapy-radiation therapy recommended for invasive cervical cancer

The National Cancer Institute (NCI) has recommended that clinicians strongly consider giving cisplatin-based chemotherapy along with radiation therapy to women who require radiation therapy for invasive cervical cancer. Up to now, surgery or radiation therapy alone has been considered standard care for cervical cancer that has spread locally (within the cervix) or regionally (within the pelvis), said the NCI. According to the NCI, five recent trials have yielded “remarkably consistent” results: Combining cisplatin-based chemotherapy with radiation therapy reduces the risk of death by 30–50%. NCI director Richard D. Klausner, M.D., said that he expects the results of these five trials will change the standard of care.

Reports on three of the trials are scheduled for publication in the April 15 issue of the New England Journal of Medicine. Because of their importance, the reports were posted on the journal’s Web site (www.nejm.org) prior to the issue publication date. The other two trials will be published in medical journals later this year. The five trials were conducted by the NCI’s Clinical Trials Cooperative Groups.

The trials differed somewhat in the stage of disease studied, the dose of radiation administered, and the chemotherapy and radiation schedules. In three trials, patients were randomly assigned to treatment with radiation therapy alone or with radiation therapy plus chemotherapy (cisplatin in one trial and cisplatin plus fluorouracil in two trials). In each of these three trials, survival rates were higher when chemotherapy was given. In the other two trials, all patients received radiation therapy plus some form of chemotherapy—either hydroxyurea or cisplatin (alone or in combination with other agents). Patients who received a cisplatin-based regimen had higher survival rates than those who received hydroxyurea.

Brief study descriptions and survival rates, as reported by the NCI, follow:

- Some 386 patients with stage IIB, III, or IVA disease were enrolled in Gynecologic Oncology Group (GOG) trial 85. Three-year survival rates were 67% with radiation therapy plus cisplatin plus fluorouracil versus 57% with radiation therapy plus hydroxyurea. Survivors have been followed for a median of 8.4 years.
- A total of 389 patients with stage IIB, III, or IVA disease or with stage IB or IA disease with positive pelvic lymph nodes or tumor size of ≥5 cm were enrolled in Radiation Therapy Oncology Group (RTOG) trial 9001. Three-year survival rates were 75% with radiation therapy plus fluorouracil and cisplatin versus 63% with radiation therapy. Survivors have been followed for a median of 43 months.
- GOG 120 included 526 patients with stage IIB, III, or IVA disease. Three-year survival rates were 65% with radiation therapy plus cisplatin or radiation therapy plus cisplatin, fluorouracil, and hydroxyurea versus 47% with radiation therapy plus hydroxyurea. Survivors have been followed for a median of 34.7 months.
- Southwest Oncology Group trial 8797 included 243 patients with stage IA2, "combined chemotherapy-radiation therapy recommended for invasive cervical cancer"
A total of 368 patients with bulky stage IB, or IIA disease with positive pelvic lymph nodes, parametrial involvement, or positive surgical margins at the time of primary radical hysterectomy. Three-year survival rates were 87% with radiation therapy plus cisplatin and fluorouracil versus 77% with radiation therapy. Survivors have been followed for a median of 43 months.

- A total of 368 patients with bulky stage IB disease were enrolled in GOG trial 123. Survival rates were 83% with radiation therapy plus cisplatin versus 74% with radiation therapy. Survivors have been followed for a median of 37.5 months.

The chemotherapy and radiation schedules are described in greater detail on the NCI's Web site (http://rex.nci.nih.gov/INTRFCE_GIFS/WHTNEW_INTR_DOC.htm).

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New cases of vancomycin-intermediate MRSA infection reported

Resistant mutants probably selected during prolonged vancomycin use

In May 1996, a patient in Japan was diagnosed as having an infection caused by an isolate of Staphylococcus aureus with intermediate resistance to vancomycin. Three additional cases—these occurring in Michigan, New Jersey, and New York—were documented in reports published in February.1,2

The three new cases involved similar setups for the emergence of resistance: The patients had renal failure requiring dialysis, as well as multiple other medical problems; peritoneal catheters or other indwelling devices; and infections caused by methicillin-resistant strains of S. aureus (MRSA) for which they received repeated or prolonged courses of vancomycin therapy (a total of 18 weeks in two cases and 6 weeks in one). In all three patients, intermediate resistance to vancomycin (a minimum inhibitory concentration of 8–16 µg/mL) emerged over the course of treatment. In each case, the S. aureus isolate was susceptible to other antimicrobials.

In all four cases reported thus far, intermediate resistance was documented in association with failed vancomycin treatment of MRSA. Resistance appears to have emerged “through the selection of naturally occurring resistant mutants during prolonged exposure to vancomycin,” said Smith et al.1

The three S. aureus isolates recovered from one of the patients (in New York) over a span of nearly three months produced identical DNA-fingerprint patterns, suggesting that the intermediate-resistant isolate was the result of in vivo selection during vancomycin therapy.2 Furthermore, three of these isolates were very closely related to MRSA isolates obtained from eight different hospitals in the New York metropolitan area. Several of those MRSA isolates contained subpopulations of bacteria with reduced susceptibility to vancomycin. Those isolates could be “prompted” in vitro to acquire intermediate resistance to glycoproteins.

A mechanism involving alterations of the bacterial cell wall is suspected. It will be important to determine the mechanism, because current drug development strategies are focused on enterococcal mechanisms of resistance. The transfer of resistance genes from vancomycin-resistant enterococci to S. aureus has not yet been observed in clinical isolates.

Altogether, these reports suggest that, with prolonged exposure to vancomycin and possibly under other environmental influences, MRSA can develop intermediate resistance to vancomycin. Thus, with continued extensive use of vancomycin, surveillance of vancomycin susceptibility in MRSA isolates is of “primary importance,” said Sieradzki et al.2

Smith et al. reported no evidence of carriage of the intermediate-resistant organism among household or medical contacts of the patients in either case that they investigated. They reported that the institutions involved in the care of the two patients had implemented recommended infection control procedures.

To prevent further emergence of S. aureus strains with intermediate resistance to vancomycin, the researchers called for optimization of the use of vancomycin, enhancement of laboratory procedures for detection of resistant organisms, strict infection control practices, and active surveillance for S. aureus isolates with intermediate resistance to vancomycin, particularly in high-risk populations. Patients who are treated often with vancomycin (for example, dialysis patients) may need to be monitored for colonization or infection with S. aureus with intermediate resistance to vancomycin.

Even partial resistance of S. aureus to vancomycin seems to be clinically im-