High-Dose Aspergillosis Treatment Not Superior

BY NANCY WALSH
New York Bureau

LAS VEGAS — The use of high-dose liposomal amphotericin B was no more effective than standard doses for the treatment of invasive aspergillosis in a large randomized study, and was associated with significantly more adverse effects.

Invasive fungal infections remain a significant cause of morbidity and mortality in seriously immunocompromised patients, such as those with hematologic malignancies. Conventional amphotericin B deoxycholate has long been used, but is limited in efficacy and has significant toxicity. Three lipid formulations of the drug now are available and they are more easily tolerated, Dr. Mark Bresnik said at a meeting on fungal infections sponsored by Imedex.

For one of these, liposomal amphotericin B, the standard dose in invasive fungal infections is 3 mg/kg per day. However, preclinical studies have suggested that efficacy may increase with higher doses, and preliminary human studies found no significant increase in adverse effects with doses of 10 mg/kg per day, he reported.

To test the hypothesis that higher doses of liposomal amphotericin B might improve outcomes, a prospective, double-blind study was done to compare dosages of 10 mg/kg and 3 mg/kg daily in 201 highly immunocompromised patients. After the first 2 weeks of therapy, all patients could remain on the standard 3-mg/kg dosage for as long as the investigators deemed appropriate. The trial was conducted at 46 sites in Europe and Australia.

In both groups, 93% of patients had hematologic malignancies, and in two-thirds, the disease was uncontrolled. More than 70% were neutropenic at baseline. All patients had proven or probable invasive aspergillosis, or infection with another filamentous fungus; 95% had invasive pulmonary aspergillosis.

A favorable overall response rate (complete plus partial responses) was seen in 50% and 46% of the standard- and high-dose groups, respectively. Survival at 12 weeks in the two groups was 72% and 59%, said Dr. Bresnik, director of medical affairs for Gilead Sciences, manufacturer of liposomal amphotericin B (Ambisome).

The two groups did not differ significantly in overall response rate or survival. These rates were comparable with those previously reported for voriconazole, a broad-spectrum triazole agent, vs. conventional amphotericin B (N. Engl. J. Med. 2002;347:408-15).

A favorable overall response rate (complete plus partial responses) was seen in 50% and 46% of the standard- and high-dose groups, respectively.

Median duration of treatment was 15 days in the standard-dose arm and 14 days in the high-dose arm; treatment duration for some patients in both arms extended upward of 5 weeks, he said.

No unusual or previously unrecognized safety issues were seen. Discontinuations due to toxicity were more frequent in the high-dose group, at 32%, vs. 20% in the standard-dose group. Nephrotoxicity and hypokalemia occurred more often in the high-dose group, at 31% and 30%, compared with 14% and 16%, respectively, in the low-dose group, Dr. Bresnik reported.

"So what the trial has told us is that the appropriate dose is 3 mg/kg per day, but 95% of patients in this trial had invasive pulmonary aspergillosis. What that means is that the data are not yet available to determine whether benefits could be obtained with higher doses in nonpulmonary sites of infection or with non-*Aspergillus* molds such as zygomycetes," he said. ■

Web Site Offers Flu Information

The Department of Health and Human Services has launched a Web site to provide one-stop access to U.S. government information about avian and pandemic influenza.

Visitors can access up-to-date response plans; learn about current tests, vaccines, and medications; and see alerts and advisories for travelers. For more information, visit www.pandemicflu.gov.