The addition of mitoxantrone (Novantrone) to interferon beta-1b (IFN beta-1b, Betaseron) therapy for the treatment of patients with aggressive multiple sclerosis (MS) unresponsive to standard therapy may reduce the number of new enhancing lesions as well as life-threatening risks associated with mitoxantrone therapy.

"When we added mitoxantrone to the therapeutic regimen of patients who were breaking through with IFN beta-1b, the disease activity measured by MRI in clinical parameters was remarkably diminished," said Douglas Jeffery, MD, PhD, associate professor in neurology at Wake Forest University School of Medicine in Winston-Salem, North Carolina. "One of the drawbacks of mitoxantrone—and it has several—is that once a cumulative dose of 140 mg/m$^2$ has been reached, risk of leukemia and cardiotoxicity in the form of congestive heart failure emerges." The combination of IFN beta-1b and mitoxantrone reduces these adverse effects, which are associated with mitoxantrone therapy, while effectively suppressing MS-associated inflammation, explained Jeffery. Mitoxantrone is an immunosuppressive drug for worsening forms of MS, and it has been shown to extend the time between relapses.\(^1\)\(^2\) The drug was approved by the FDA in 2000 for the treatment of secondary progressive, progressive relapsing, and worsening relapsing-remitting MS. IFN beta-1b, a naturally occurring interferon, was approved for the treatment of relapsing-remitting and early secondary progressive MS in 1993 and has been found to effectively reduce the number of flare-ups.\(^3\)

When Jeffery and colleagues combined mitoxantrone and IFN beta-1b therapies, symptoms and disease activity substantially declined in patients participating in a pilot trial.\(^4\) The group studied 10 patients with worsening relapsing-remitting or secondary progressive MS using monthly MRI with triple-dose gadolinium contrast, which measured the frequency of new enhancing lesions as well as relapse rate and T1 hypointense and T2 lesion burden. The patients had received treatment with IFN beta-1b for at least 6 months, had 1 or more enhancing lesions, had 1 or more relapses while taking IFN beta-1b at some point within the 6 months before entry into the study, and were neutralizing antibody-negative.

Baseline was established at months 1 and 2. Patients received 12 mg/m$^2$ mitoxantrone at month 3 and 5 mg/m$^2$ at months 4 and 5. After this initial treatment, patients were given 5 mg/m$^2$ every 3 months. After mitoxantrone was added to the initial IFN beta-1b therapy, enhancing lesion frequency was reduced by an average of 90%, enhancing lesion volume decreased by 96%, and relapse rates decreased by 70% at month 7. T2 lesion burden and T1 hypointense lesion burden increased slightly during the baseline phase and decreased after initiation of mitoxantrone therapy.

**PLACE FOR MITOXANTRONE**

According to statistics from 2002, about 10% of patients with MS are treated with some form of immunosuppressant therapy; of these patients, about 30% are treated with mitoxantrone.\(^5\) Because of possible cardiotoxicity, the drug should be used only in those patients with normal cardiac function. Recommended dosage is 12 mg/m$^2$ once every 3 months. The lifetime cumulative dose is limited to 140 mg/m$^2$ (approximately 8 to 12 doses over 2 to 3 years).

"We use mitoxantrone in patients who have had an inadequate response to optimal immunomodulating therapy, whose MS is worsening, or in those who have extremely aggressive disease right from the onset," said Jeffery. "In these patient populations, mitoxantrone has been extremely useful. But because of its toxicity profile, the drug is pretty much reserved for those
patient populations who are worsening on standard immunologic therapy."
The results of Jeffery's study suggest that a longer duration of treatment with mitoxantrone may result in a greater reduction in disease activity. The results also suggest that mitoxantrone therapy alone may be associated with decreases in relapse rates and lesion frequency; however, authors of the Mitoxantrone in Multiple Sclerosis trial6 reported that mitoxantrone 5 mg/m² was associated with a 34% decrease in relapse rates.

Bianca Weinstock-Guttman, MD, associate professor of neurology at University at Buffalo, State University of New York, and director of the William C. Baird Multiple Sclerosis Center at Buffalo General Hospital, also takes advantage of mitoxantrone/IFN beta-1b combination therapy. In patients who do not respond to initial treatment with IFN beta-1b therapy, Weinstock-Guttman administers lower doses (8 mg/m²) of mitoxantrone for 4 to 6 months. Then she restarts IFN beta-1b therapy.

This approach is catching on; however, it is far from a standard practice. "Although it is true that many of us are combining IFN beta-1b and mitoxantrone, combined use is not approved by the FDA," said Bruce Cohen, MD, professor in the Ken and Ruth Davee Department of Neurology in the Feinberg School of Medicine at Northwestern University, Chicago.

TROUBLESHOOTING RISKS

In 2005, the FDA issued a black box warning on the risks of cardiotoxicity and secondary acute myelogenous leukemia associated with the use of mitoxantrone. The agency also sent a letter to physicians stating that left ventricular ejection fraction should be reevaluated by echocardiogram or multigated radionuclide angiography before each dose was administered to patients with MS. Jeffrey thinks this recommendation may be "overkill." "Once you get over 70 mg/m², that's when you want to keep your eye on it," he said. The reported risks of cardiotoxicity and leukemia may have deterred some healthcare providers from using mitoxantrone in patients who could have benefited from it, said Jeffrey.

Cardiotoxicity and leukemia risk become an issue with high doses of mitoxantrone, according to Jeffrey. "My impression has been that when mitoxantrone is used at a dose of 12 mg/m² every 3 months, incidence of cardiotoxicity is greater than when it is used at lower doses in combination with IFN beta-1b."

Robert Fox, MD, medical director of the Mellen Center for Multiple Sclerosis Treatment and Research at the Cleveland Clinic, supports this observation. "The best evidence we currently have suggests that mitoxantrone cardiotoxicity is related to total cumulative dose. This clinical observation is supported by autopsy evidence indicating that drug levels within the tissues are related to the total cumulative dose received." He added that "cardiac toxicity is sometimes reversible, but sometimes not-and there is no way to predict when it will reverse and when it will not."

"Neurologists are informed of the dangers, but they are not aware of how effective the drug really is," argued Jeffrey. "It's important to use it earlier instead of at a time when it's too late and won't do any good. Because of the risk of toxicity, we only use it in patients who are really worsening," he stressed.

Nevertheless, the risk of cardiotoxicity is a sore point and at what time it becomes a serious risk is in debate. A team from McGill University Health Centre in Montreal found that 25% off 55 patients treated with 12 mg/m² of mitoxantrone once per month for 3 months and then once every 3 months thereafter to a maximum cumulative dose of 110 mg/m² experienced depressed left ventricular ejection fraction.7 One case of leukemia also was recorded.

"We don't know why 25% of the study participants had a fall in left ventricular ejection fraction because our neurologists generally used low doses," said study coauthor James Brophy, MD, PhD, associate professor of medicine in the Division of Cardiology and Clinical Epidemiology at McGill. "Perhaps we found more because we looked harder. However, the number of patients with permanent ventricular dysfunction was, as in other studies, very small." Although mitoxantrone is widely used in America and Europe, it has not been approved for the treatment of MS in Canada.

ALTERNATIVE AGENT FOR MS

The number of alternatives to mitoxantrone are increasing. Natalizumab (Tysabri) was reintroduced to the market in June 2006. Although controversy has surrounded use of natalizumab and protocols are currently being designed to guide how it is used because of possible risk of progressive multifocal leukoencephalopathy (PML) (see Reintroduction of MS Drug Offers More Flexible Treatment Options, Applied Neurology, August 2006, page 48). "I have used mitoxantrone sparingly and will likely use it even less now that natalizumab is available," Fox remarked.

Nevertheless, as much as certain clinicians shy away from mitoxantrone use because of its association with cardiotoxicity, some clinicians—such as Jeffrey—believe that many neurologists will
be reluctant to use natalizumab because of its association with PML. The risk of promyelocytic leukemia in association with mitoxantrone, however, may also cause physicians to view natalizumab in a more favorable light. The issue has been receiving increasing recognition, according to Fox. He cited 3 abstracts that appeared in the proceedings of this year's annual meeting of the American Academy of Neurology (held April 1-8 in San Diego) that described the risk of leukemia in patients treated with mitoxantrone; incidence rates were as high as 3%. "The true incidence is unknown, but it seems that the rate of leukemia is higher than the 1 in 1000 estimated risk of PML associated with natalizumab use," said Fox. "So leukemia, along with the risk of cardiac toxicity, may lead many neurologists to favor natalizumab over mitoxantrone."

Jeffery expects to see further studies of combination therapies that include mitoxantrone. The most promising, in his view, is the mitoxantrone/IFN beta-1b combination. Jeffery also hopes to see future studies in which mitoxantrone is used in combination with another agent for induction therapy. "If you can get control of the disease very early on and suppress it with mitoxantrone, it will be easier to control after you switch to a standard immunomodulating agent," he said.

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