DRUGMonitor

Brief summaries of recent drug approvals, interactions, and adverse events

OnabotulinumtoxinA for Bladder Problems

OnabotulinumtoxinA is thought of mostly as a treatment for facial wrinkles, but it's also approved for other medical conditions, including cervical dystonia; chronic migraine; and now, overactive bladder (OAB), a condition in which the bladder squeezes too often or without warning. OnabotulinumtoxinA, injected into the bladder, blocks the transmission of nerve impulses to the bladder muscle, calming contractions, which helps increase the bladder's storage capacity. It also reduces episodes of urinary incontinence.

The FDA recently approved onabotulinumtoxinA for patients with OAB who don't respond to, or who experience intolerable adverse events (AEs) of, anticholinergic drugs. In clinical trials, 1,105 patients were randomly assigned to receive injections of 100 U (20 injections of 5 U) of onabotulinumtoxinA or placebo. After 12 weeks, the onabotulinumtoxinA treatment reduced episodes of incontinence by 50% or more (2.5 to 3 episodes, from a baseline of 5.5), compared with placebo (0.9 to 1.1 episode, from a baseline of 5.1 to 5.7). The patients prescribed onabotulinumtoxinA urinated 1 to 2 times fewer per day; when they did, they urinated about 30 mL more than patients on placebo. Moreover, 3 times as many patients prescribed onabotulinumtoxinA eliminated leakage episodes entirely (23% and 31%, vs 7% and 10% of placebo patients).

In clinical trials, 36 of 552 patients (7%) initiated clean intermittent catheterization for urinary retention after onabotulinumtoxinA treatment, compared with 2 of 542 placebo patients (0.4%).

The median duration for efficacy with onabotulinumtoxinA for reducing urinary leakage and other symptoms of OAB in the 2 studies was 135 to 168 days, compared with 88 to 92 days for placebo.

Adverse events included urinary tract infections, painful urination, and urinary retention. Patients with type 2 diabetes treated with onabotulinumtoxinA were more likely to develop urinary retention than people without diabetes. The FDA advises antibiotics before, during, and for a few days after treatment, to lower the risk of infection. The manufacturer and FDA advise allowing at least 12 weeks between treatments.

Source: U.S. Food and Drug Administration. FDA approves Botox to treat overactive bladder [news release]. U.S. Food and Drug Administration Website. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm336101.htm. Updated January 22, 2013. Accessed February 22, 2013.
BOTOX [package insert]. Irvine, CA: Allergan, Inc; 2013.

Older Cancer Patients Not Getting Full Treatment

Older adults with stage II or III colorectal cancer have 25% lower odds of getting all the treatment they need, according to a study of 267 patients at Boston Medical Center and VA Boston Healthcare System, both in Boston, Massachusetts.

Standard therapy for colorectal cancer is defined as surgical resection of a tumor and at least 1 dose of both chemotherapy and radiation. In the study, patients aged ≥ 71 years were significantly less likely to have surgery than were patients aged ≤ 70 years (84% vs 94%), and only 45 (49%) of the older patients were started on all 3 modes of therapy vs 115 (66%) of the younger patients. Of the patients on full treatment, only 56% completed all 3 modes without a dose reduction, dose held, or dose delayed. More patients with stage III completed therapy, compared with stage II patients (54% vs 38%). Half of each age group was receiving neoadjuvant chemoradiation; those patients were more likely to complete therapy than were patients receiving postoperative adjuvant therapy.

One confounding factor could be tumor location. In current practice, the researchers say, neoadjuvant chemoradiation is recommended for those with cancers from up to 12 cm from the anal verge; whereas patients with more proximal cancers are not considered candidates for preoperative radiation. More of the older patients had more proximal rectal cancers.

Another factor for older patients is comorbidity, an important predictor of survival and treatment-related outcomes. However, the researchers say, there's currently no consensus on a standard, comprehensive assessment for comorbidity in older patients with cancer. Moreover, a substantial number of patients in their study did not have complete data on comorbidities.

If only 49% of patients aged ≥ 71 years start all 3 modes of therapy, and nearly half don't complete the therapy, then only about 25% complete all standard therapy at full doses and without delays, the researchers estimate. This finding is of significant concern, they say, especially given that their study was carried out at 2 prestigious academic centers with a "high awareness of appropriate therapy."

Longstanding reluctance to treat older patients may be behind the poor numbers, the researchers say. Remedies include better education about the benefits of therapy, the long life expectancy of most healthy older adults, and the relatively good tolerance of the types of chemotherapy used for colorectal cancer. Geriatric assessment tools, they suggest, may provide a more scientific basis for predicting toxicity. One practical outcome of their own study was the initiation of a Navigator program at BMC intended to guide patients with rectal cancer through the full therapeutic protocol, who may otherwise feel daunted by its complexity. In addition, nearly all patients at both centers are now evaluated in a multidisciplinary manner with dedicated oncologic surgery input.

Finally, the researchers suggest reducing the toxicity of the therapies (eg, by using more neoadjuvant chemoradiation and conformal or intensity modulated radiation) and performing less extensive surgery where possible.

Source: Bohac GC, Guaqueta D, Cheng DM, Aschengrau A, Hartshorn KL. *J Geriatr Oncology.* 2013;4(1):90-97. doi: 10.1016/j.jgo.2012.10.173.

Vitamin B Reduces Diabetic Neuropathy

Bumping up vitamin B dosage has an "encouraging and statistically significant impact" on neuropathy and quality of life (QOL) for patients with diabetes, according to researchers from Tulane University and Southeast Louisiana Veterans Health Care System, both in New Orleans, Louisiana; Scott & White Memorial Hospital in Temple, Texas; Baylor Health Care System and Dallas Diabetes and Endocrine Center at Medical City, both in Dallas, Texas; VA Nebraska-Western Iowa Health Care System in Omaha, Nebraska; and the University of Alabama at Birmingham School of Medicine in Birmingham, Alabama.

The researchers point out that vitamin B deficiency is common in diabetes, and may contribute to neurologic deficits. But current treatments for diabetic neuropathy have a high risk of AEs and don't address the underlying pathology. They theorized that a combination of L-methylfolate, methylcobalamin, and pyridoxal-5´-phosphate, the biologically active and immediately bioavailable forms of folate (which improves vascular function), vitamin B_{12}, and vitamin B_6, could improve sensory neuropathy more safely.

They randomly assigned 214 patients to receive the combination treatment or placebo. The primary endpoint was the measured vibration perception threshold on the big toe of each foot; secondary endpoints included scores on neuropathy, pain-perception, disability, and QOL scales.

Vibration perception threshold did not differ significantly between the 2 groups. (The researchers say the measure may not be sensitive enough to detect changes in nerve function attributable to the combination treatment.) However, neuropathy symptoms improved both significantly and clinically in the treatment group, which also experienced significantly less neuropathy-related disability and a "modest but significant improvement" in QOL measures. Moreover, scores on the mental scales improved by almost 2 points, as opposed to a decrease in the placebo group. Adverse events were rare and mostly mild to moderate.

The researchers point out that, from the patient's perspective, the improved symptoms could be the most important goal of neuropathy management. The clinical change would, of course, depend on the patient's baseline level of symptoms. For example, even a small decline from a lower baseline of 5.7 on the Neuropathy Total Symptom Score (NTSS-6), which measures sensation as well as pain over 1 year, leads to "meaningful changes in other parameters of neuropathy." In this study, the patients had only mild symptoms on NTSS-6, with a mean baseline of 3.6. That is, they had 3 to 4 mild symptoms, or 1 to 2 moderate symptoms, at baseline. The observed 1-point decrease over the 6-month study suggests that at least 1 mild symptom was completely eliminated, or 1 moderate symptom could be classified as mild, the researchers conclude.

Metformin use was associated with less improvement in NTSS-6 scores. Metformin interferes with the absorption of cobalamin, which leads to progressive deterioration of nerve tissue, frequently misdiagnosed as diabetic peripheral neuropathy, according to the researchers. They add that the negative association between NTSS-6 scores and metformin use suggests that methylcobalamin may have corrected a B_{12} deficiency.

Source: Fonseca VA, Lavery L, Thethi TK, et al. *Am J Med.* 2013;126(2):141-149. doi: 10.1016/j.amjmed.2012.06.022.

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