# Drug Monitor

## Safe Treatment Option for Metastatic Colorectal Cancer in the Elderly

Elderly patients with advanced cancer have been conspicuously absent from clinical trials of chemotherapy, and are thus less likely to receive life-extending and life-enhancing treatment. Granted, choosing an effective regimen for an older patient vs a younger patient is "less straightforward," say researchers from the Fédération Nationale des Centres de Lutte Contre le Cancer (National Federation of Centers Fighting Cancer) in Paris. They note, for instance, that while 5-Fluorouracil (5-FU) has been a mainstay of chemotherapy for patients with metastatic colorectal cancer (mCRC), its usefulness for older people may be limited by such things as the need for an ambulatory infusion pump.

However, in their study of 60 patients, aged 70 years and older with mCRC, from 6 centers in France, the researchers found that patients responded well to treatment with capecitabine-oxaliplatin (XELOX), without impairment to functional ability or independence. Patients were eligible for the study if they had histologically proven, inoperable, locally advanced colorectal cancer or mCRC, no prior chemotherapy for metastatic disease, and adjuvant chemotherapy completed more than 6 months before the study. All patients had, on average, 3 comorbidities, and used an average of 4 concomitant medications.

The study treatment lasted for a maximum of 6 cycles. During the first 3 treatment cycles, capecitabine and oxaliplatin were administered "cautiously" at 75% of the normal young-adult dose. Capecitabine was administered orally in 2 divided doses of 750 mg/m$^2$ on days 1 to 14, followed by a 7-day rest. Oxaliplatin 90 mg/m$^2$ was administered intravenously over 2 hours on day 1. The doses of both drugs could be increased by 33% (up to 1,000 mg/m$^2$ twice daily for capecitabine and 120 mg/m$^2$ for oxaliplatin) at the start of cycle 4 in patients with no significant toxicity.

After each cycle, blood counts were performed weekly and repeated every 48 to 72 hours, in case of grade 3 or 4 toxicity. Patient independence functionality, the primary objective of the study, was assessed at baseline by a physician, and after cycles 3 and 6, using the Katz Activities of Daily Living (ADL) scale. The scale ranks adequacy of performance in 6 functions: bathing, dressing, toileting, transferring, continence, and feeding.

Most (54) patients received more than 3 cycles; 38 received all 6 cycles. The dose was increased in 14 of 45 eligible patients. Chemotherapy was terminated prematurely in 22 patients, as a result of disease progression (5), toxicity (11), patient request (2), or for other reasons.

The overall response rate to treatment was 37%: 1 patient had a complete response to treatment, and 21 had a partial response. Median progression-free survival was 7.3 months. Median overall survival was 12 months. Functional ability stabilized or improved in 36 of 40 patients after 3 cycles, and in 25 of 27 patients after 6 cycles. At baseline, 47 patients (78%) had a score of 6 on the Katz ADL; after cycle 3, that proportion had increased to 93%.

Treatment was generally well tolerated. The most common grade 3/4 adverse events were gastrointestinal, such as diarrhea, constipation, and nausea. The tolerability was due, the researchers feel, to the dose escalation. The fact that one-third of the patients were able to undergo dose escalation supports the value of this approach, they say, "while highlighting that many patients were better suited to the modified regimen." This suggests that a stepwise dosing regimen is well adapted to elderly cancer patients, they conclude. That, along with other benefits—no impairment of ADLs, an acceptable safety profile, a 37% response rate, and ease of administration (hospital attendance only once every 3 weeks)—makes XELOX an attractive option for older patients.

Source: *J Geriatr Oncol.* 2011;2(2):105-111. doi:10.1016/j.jgo.2010.11.002.

## Cyclosporin A Helps Stave Off Surgery for Ulcerative Colitis

Cyclosporin A (CyA) doesn't simply "delay the inevitable colectomy" for patients with severe ulcerative colitis, say researchers from Cambridge University Hospitals National Health Service Foundation Trust in the United Kingdom. In fact, they believe CyA is underused, but deserves a new look, because it actually may obviate surgery.

Approximately 15% of patients, with severe ulcerative colitis, are admitted to the hospital with a severe flare at some point, for which, they're often given intravenous steroids, or CyA. Studies have reported variable short- and long-term results: 74% to 91% of patients avoid colectomy in the short term, and 42% to 70% avoid colectomy in the long term (18 months to 13 years follow-up). The wide range reflects the small size of the studies, as well as the variability in dosing and route of administration, say the researchers.

Researchers analyzed data on 38

patients (24 men, 12 women, ranging from 17 to 72 years of age), who received CyA for an acute, steroid-refractory flare of colitis in their center, over a period of 9 years. (Records were unavailable for 2 patients and 2 patients received therapy twice, making for 38 cases analyzed.) On admission, 20 patients were taking oral steroids; 8 were taking a thiopurine; 7 were on no treatment. Patients were started on CyA, with a median of 8 days after admission (1 to 28 days). Most (32) patients were given an oral dose of 4.5 mg/kg to 8.3 mg/kg daily. The other 6 patients were administered intravenous CyA at 2 mg/kg to 5 mg/kg, which changed to oral CyA 2 to 8 days after starting.

Of the 36 patients who received CyA, 15 had a colectomy during the follow-up period of 11 to 118 months. After a mean of 6.1 days, 11 surgeries were carried out, for lack of response in the acute phase.

However, of the 25 patients who were discharged without surgery, still on CyA therapy, 21 (84%) still have not required colectomy, after a median follow-up of 3.8 years.

The 4 patients, who had surgery, did so 3 to 8 months after discharge. One patient had stopped all medication to seek alternative therapies, and then required emergency colectomy; 1 did not respond to immunomodulators, flared again, and opted for surgery; and 1 developed drug-related adverse effects, including central serous retinopathy and neutropenia, and then made the decision for elective surgery.

The authors say, in their center, CyA is used as a bridging therapy to azathioprine, which is started at a median of 5 weeks after hospital discharge, ranging from 0 to 34 weeks. The CyA treatment in their center was associated with tolerability and safety, the researchers say, which they attribute to careful management of the transition from CyA to azathioprine, as well as close monitoring by the inflammatory bowel disease nurses, and careful adjustment of drug doses, according to drug levels, colitis symptoms, and signs of toxicity.

Source: *J Crohns Colitis.* 2011;5(2):91-94. doi:10.1016/j.chrons.2010.10.004.

## Naproxcinod: "Blood Pressure Neutral"?

Patients, who take nonsteroidal anti-inflammatory drugs (NSAIDs) for osteoarthritis, may be at risk for increased blood pressure (BP). Findings from an integrated safety analysis of 3 trials, involving 2,734 patients should be encouraging: Naproxcinod, an NSAID in development for osteoarthritis, had the same effect on BP as placebo—which is to say, very little—but similar pain control to naproxen.

Patients in this study were over the age of 40 years, with a confirmed diagnosis of osteoarthritis of the knee or hip. They also were concurrent chronic users of NSAIDs or acetaminophen for osteoarthritis pain, with a flair of pain after experiencing a break in treatment.

The patients were given 13 weeks of therapy with naproxcinod (375 mg and 750 mg), naproxen 500 mg (equipotent to naproxcinod 750 mg), or placebo twice daily. Changes in systolic BP were measured in all patients, and in the subgroup taking renin-angiotensin system inhibitors, using a mercury column or aneroid manometry, at baseline, 2, 6, and 13 weeks of the treatment period. Clinic BP was measured in the morning hours, 2 to 4 hours after a dose of the study drug.

Changes from baseline in systolic BP were significantly less with naproxcinod 750 mg, compared with naproxen 500 mg. In fact, naproxen tended to raise systolic BP. In the patients with hypertension, who were taking renin-angiotensin system (RAS) drugs, the mean change in systolic BP was 4 mm Hg to 5 mm Hg greater with naproxen than with naproxcinod, at week 13. Moreover, the proportion of patients whose systolic BP had increased by 10 mm, or more, Hg after 13 weeks of therapy, was larger with naproxen (21%) than with naproxcinod (15%).

The researchers note that relatively small differences in systolic BP can have major physical implications. For instance, they cite research that found increases of 3 mm Hg to 4 mm Hg systolic BP in older patients with hypertension and vascular diseases significantly increased cardiac events, within 4 to 6 months. They also point out that RAS inhibitors are commonly used in clinical practice; thus their finding that naproxcinod was less likely to raise the systolic BP in patients treated with RAS inhibitors was important.

Source: *Am J Cardiol.* 2011;107(9):1338-1345. doi:10.1016/j.amjcard.2010.12.046.