Diarrhea Increased With Targeted Cancer Agents

BY CAROLINE HELWICK

CHICAGO — The incidence of the oldest side effect of anticancer treatment—diarrhea—is rising in parallel with the use of targeted agents, and clinicians need to manage this proactively in order to keep patients on treatment, said Dr. Joanna M. Brell of the Division of Cancer Prevention at the National Cancer Institute.

"Diarrhea occurs in about 80% of chemotherapy patients, and about 30% is grade 3/4 toxicity. It is common, it is associated with newer targeted therapies, it is additive with combination treatment, and patients are receiving treatment for longer periods. We'd better be good at managing it," she told attendees at the annual Chicago Supportive Oncology Conference.

Diarrhea is a class effect of many older drugs and of the small-molecule agents that are approved in treating at least 10 malignancies, with many more compounds in the pipeline. (See box.) The fact that more targeted agents will be used in maintenance therapy means that more patients will experience diarrhea for longer periods of time, Dr. Brell warned.

The physical consequences include dehydration, electrolyte imbalance, acute renal failure, renal insufficiency, weight loss, malnutrition, and risk of infection. It causes generalized malaise, diminishes activities of daily living, enhances treatment noncompliance, and reduces quality of life. Importantly, an abnormal GI tract may affect absorption of oral chemotherapy, and dose reductions of anticancer drugs or discontinuations of treatment are sometimes required.

"Treatment delays have uncertain effects on the tumor, and this is distressing to the patient, who wants full treatment," she said.

Why Diarrhea Occurs With Targeted Agents

The mechanisms by which diarrhea occurs with targeted agents were recently described (Nat. Clin. Pract. Oncol. 2008;5:268-78). They vary according to the class of agent.

With the epidermal growth factor receptor inhibitor erlotinib (Tarceva), the incidence—but not the severity—of diarrhea is dose related. Sorafenib (Nexavar), a multitargeted vascular inhibitor, causes diarrhea in 30%-43% of patients. This is thought to be related to small-vessel ischemia or ischemic colitis with mucosal changes, and to direct damage to mucosal cells. With bortezomib (Velcade), an NF kappaB inhibitor, diarrhea can have a relatively quick onset (with associated postural hypotension, syncope, or near-syncope) and can be dose limiting. Flavopiridol, which inhibits multiple cyclin-dependent kinases, enhances the efficacy of other chemotherapies. Cholestyramine can bind to flavopiridol and therefore protect against diarrhea, but how this may affect anticancer treatment is unknown, Dr. Brell said.

There is little to no evidence to guide the management of diarrhea due to targeted therapies.

DR. BRELL

Management of Diarrhea Due to Targeted Agents

There is little to no evidence to guide the management of diarrhea that is specifically associated with targeted therapies, Dr. Brell said. Unlike conventional chemotherapy, the goal with these agents is not to increase response, and they are not dosed according to body surface area. The actual effective dose of the drugs, therefore, is generally unknown.

Given these considerations, the major management strategy with these agents is dose delay, she said. Brief dose interruptions are usually adequate, and the dose can usually be maintained in spite of the toxicity, "which we don't do with [5-fluorouracil] or irinotecan," she noted. Dose reductions are done, if required, to maintain quality of life.

Cholestyramine can be tried for diarrhea that is associated with sorafenib, sunitinib (Sutent), and flavopiridol.

The usual management strategies also apply, added Dr. Brell. Clinicians should monitor stool output closely; stop supportive medications for constipation; use oral loperamide (Imodium) up to 16 mg/day, or diphenoxylate plus atropine (Lomotil) 5 mg two to four times per day; give intravenous fluids; rule out *C. difficile*; prescribe empiric antibiotics; and give octreotide (Sandostatin LAR Depot) 100 mcg three times daily, or at higher doses).

Clinicians should check for the use of medications that might increase diarrhea, such as CYP3A4 inhibitors that can affect drug metabolism such that levels of the anticancer therapy are increased and therefore toxicity is enhanced.

For prophylaxis, data are even more limited. Dr. Brell suggested trying cholestyramine prior to dosing sorafenib and sunitinib, giving octreotide LAR monthly, and giving octreotide and loperamide prior to chemoradiation to the pelvis.

The meeting was sponsored by Elsevier Oncology, a sister company to this news organization. ■

Selected Drugs Associated With Treatment-Induced Diarrhea

Older Agents	Targeted Biologics	New Compounds*
5-FU-based regimens	Lapatinib (plus capecitabine)	Histone deacetylase inhibitors (chidamide)
Capecitabine	Erlotinib	Heat shock protein 90 inhibitor (AUY922)
Irinotecan	Cetuximab, panitumumab	Raf kinase inhibitor (XL281)
Taxanes	Sorafenib, sunitinib	Proteasome inhibitor (carfilzomib)
Cisplatin	Bortezomib	
Methotrexate	Imatinib	
Raltitrexed		

*Reported at ASCO 2009 to have dose-limiting toxicity.
Source: Dr. Brell

ELSEVIER GLOBAL MEDICAL NEWS

Young Adults With Cancer Fare Better at Pediatric Centers

BY BRUCE JANCIN

COLORADO SPRINGS — Older adolescents and young adults with certain cancers have markedly better outcomes when treated in pediatric centers than in adult oncology centers, based on multiple studies conducted in the United States and Western European countries.

"The cancers that are more pediatric in nature—acute lymphoblastic leukemia, acute myeloid leukemia, bone and soft tissue sarcomas—all have evidence that treatment in pediatric settings yields better results," said Dr. Stephen P. Hunger, professor of pediatrics, director of the center for cancer and blood disorders, and chief of pediatric hematology/oncology/bone marrow transplantation at the University of Colorado at Denver.

Even when adult oncologists employ treatment protocols similar to those used in children's hospitals, the outcomes seem to be better in the pediatric setting. The explanation for the difference in the results remains unclear.

Some adult oncologists argue that they're treating a different population of young people than is encountered in children's hospitals: that is, emancipated youths who are less likely to be treatment compliant than are young patients who are still living with their parents.

Pediatric oncologists counter that their superior outcomes result from their treatment teams' far greater experience with these types of cancers—and a correspondingly greater willingness to treat aggressively, Dr. Hunger explained at the annual conference of the Colorado Academy of Family Physicians.

'Treatment in pediatric settings yields better results' in young adults with certain cancers.

DR. HUNGER

There are key biologic differences between pediatric and adult cancers. Pediatric cancers such as acute lymphoblastic leukemia (ALL) are typically mesodermal in origin, whereas adult malignancies are generally epithelial. Mendelian genetics and lifestyle risk factors play only a limited role in most childhood tumors, so routine screening and risk reduction efforts aren't emphasized. Pediatric cancers are often microscopically disseminated—rather than localized—at the time of diagnosis, so systemic therapy is almost always required.

Pediatric cancers are more treatment responsive than most adult cancers, and children tolerate intensive systemic therapy far better than adults. Also, cancer patients at a children's hospital are routinely enrolled in a clinical trial under the auspices of the National Cancer Institute–sponsored Children's Oncology Group, with all that implies in terms of state-of-the-art treatment, whereas older adolescents and young adults treated in adult oncology centers are not typically part of a clinical trial, Dr. Hunger continued.

ALL accounts for 80% of all cases of childhood leukemia, and acute leukemia is the most common cause of cancer death before age 35. Outcomes in young adults with ALL have historically been worse than in younger patients with the malignancy. However, a recent Spanish study showed that outcomes in ALL patients (aged 19-30 years) who received the standard pediatric ALL regimen were equal to those in patients aged 15-18 years (J. Clin. Oncol. 2008;26:1843-9).

A retrospective study of 321 ALL patients (aged 16-20 years) who participated in clinical trials conducted by the Children's Cancer Group vs. the adult oncology Cancer and Leukemia Group B showed a 63% event-free survival rate at 7 years for those treated in pediatric centers, compared with just 34% in those treated in adult settings (Blood 2008; 112:1646-54).

Similarly, a series of retrospective European studies has shown ALL cure rates to be an absolute 20%-30% higher in older adolescents and young adults treated in pediatric versus adult clinical trials (Hematology January 2006;128-32). ■