The decision to modify a patient’s chemotherapy regimen is one that is frequently made in the clinic, often because of toxicity experienced by the patient. But a study published late last year unveiled the extent to which courses of cancer drugs are altered: More than half of patients studied who were receiving adjuvant chemotherapy for breast cancer received less than 85% of the recommended dose of chemotherapy. One-quarter of these patients had delays between cycles; the rest received a reduced dose of the drugs.

“We [in the community] assumed everything appropriate was being done for our patients, but this data clearly showed alarming numbers,” said Gary Lyman, M.D., lead author of the study, which appeared in the Journal of Clinical Oncology. “Randomized clinical trials show that a [significant] reduction in chemotherapy dose affects survival and compromises the chance for a cure.” He added that suboptimal dosing is a prevalent problem that will not prove to be unique to breast cancer.

Dose intensity protocols are developed as a result of clinical trials in which regimens are rigorously adhered to by researchers. “But 95% of patients don’t get treated by protocols,” said Lyman, associate center director for health services and outcomes research at the James P. Wilmot Cancer Center in Rochester, N.Y. The reality is that community oncologists are often not as faithful to the protocol in clinical practice as researchers likely were during the clinical trials.

“There really isn’t a lot of hard data on under-dosing, although there needs to be,” said Howard Ozer, M.D., chief of hematology/oncology and director of the Oklahoma University Cancer Center in Oklahoma City.

Neutropenia

The major factor in under-dosing and chemotherapy delays is neutropenia, a life-threatening condition that results from the destruction of infection-fighting white blood cells. Patients who have both fever and neutropenia, called febrile neutropenia, must be treated aggressively, usually with IV antibiotics and hospitalization. If neutropenia occurs, an oncologist may lower the chemotherapy dose, delay the time between treatment cycles, and/or provide colony-stimulating factor (CSF), which
will stimulate the bone marrow to make more white blood cells.

Lyman believes that lenient physicians—those who are too willing to decrease the dose to make the patient feel better—may actually be doing their patients a disservice. “Far too many patients are not receiving the chemotherapy doses they need in order to have the best chance of remission or cure,” said Lyman.

Charles Bennett, M.D., Ph.D., associate director of the Midwest Center for Health Services Policy Research, Chicago VA/Lakeside Division in Chicago, has a different take on this point. “You need to accept the realities of the patient’s busy life. I believe that when clinicians make these important decisions, they consider all the issues,” said Bennett.

He explained that the decision to use CSFs or modify the treatment regimen must take into consideration the patient’s lifestyle and tolerance of the protocol, the physician’s resources and familiarity with protocols, and the health care system’s insurance reimbursement as well as the support structure of the oncology practice. This complexity is why there are variations in regional and practice patterns and why many patients will travel great lengths for optimal treatment, Bennett said.

Bennett and colleagues conducted two separate surveys on behalf of the American Society of Clinical Oncology (ASCO) on physician practice patterns with respect to CSF treatment. They found that physicians in a fee-for-service setting are more likely to support the use of granulocyte and granulocyte-macrophage CSF over reducing the chemotherapy dose, whereas their colleagues at academic medical centers and in health maintenance practices are more likely to use a dose-reduction strategy.

**High Costs**

If given prophylactically, CSFs could allow patients to receive treatment on time and at full doses by preventing complications before they occur. But treating a patient with CSF as a preventive measure adds approximately $2,000 to the cost of each chemotherapy cycle. In addition, few studies show that pretreatment with CSFs has any effect on overall or disease-free survival. Thus, it is not surprising that Lyman and colleagues found that of the one-quarter of all patients who received CSF treatment, 97% received it in reaction to neutropenia rather than prophylactically.

On the other hand, two economic analyses have reported that the average length of stay in the hospital for febrile neutropenia is 10 days, with costs totaling more than $20,000 and rising. “We need to find better ways to identify patients at risk [for neutropenia] in order to provide optimal supportive care,” said Lyman, stressing that physicians should not wait until after their patients experience toxicity but instead implement CSF therapy early so the dose intensity needed for potential cure can be reached and maintained.

Lyman and colleagues have decided to systematically look for such strategies. They are in the midst of developing a nationwide prospective registry of five major cancers from more than 100 oncology practices.

The goal of the registry is to identify predictive factors that will help physicians make more rational decisions regarding the use of supportive medications as preventive measures. They will also uncover whether under-dosing is common in other tumor types, and they will be able to analyze why a chemotherapy dose was reduced or delayed—an issue of toxicity, physician disagreement over effective strategy, or the patient’s wish.

Ozer and colleagues are also forming a registry similar to Lyman’s that will cover the same disease categories, but they will attempt to determine precisely how much of a dose reduction is associated with worsened outcomes.

“It is possible that some physicians decrease dose or extend schedules because they are not convinced that these factors affect cure rates,” said Larry Norton, M.D., deputy physician-in-chief, director of breast cancer programs, Memorial Sloan-Kettering Cancer Center, New York, “but we now know that dose and dosing schedule are very important determinants for cure rate. We hope this will encourage oncologists.”

—Tracy Webb