Growth Factor Therapy May Have a Clinical Benefit for Patients With Cancer With Established Febrile Neutropenia

A recent study has shown decreased mortality when granulocyte–colony-stimulating factor (G-CSF) is used therapeutically for patients diagnosed with febrile neutropenia (FN) (Support Care Cancer [published online ahead of print December 7, 2013]. doi: 10.1007/s00520-013-2067-1). Although the use of G-CSF is well established for prophylaxis of FN among patients receiving chemotherapy, studies concerning its use for patients with established FN have demonstrated mixed results.

The authors note that it is an important question. Even with appropriate broad-spectrum antibiotics and supportive care, the mortality rate for patients with FN and established infection is approximately 10%.

“Although these data are observational in nature, they do provide some evidence that the use of adjunctive G-CSF in critically ill febrile neutropenic patients is beneficial,” says lead author Alexandre Chan, PharmD, MPH, associate professor in the department of pharmacy at the National University of Singapore.

Currently, the National Comprehensive Cancer Network guidelines do not recommend the routine use of G-CSF in patients with FN unless they are at high risk of infectious complications or have prognostic factors that put them at risk of poor outcomes. Risk factors include the development of FN as an inpatient; the presence of sepsis syndrome; age older than 65 years; prior fungal infection; and severe, long-lasting neutropenia. Although some patients with FN typically have already received prophylactic G-CSF according to guidelines at their institution, the decision to prescribe G-CSF for the treatment of FN is made by the treating oncologist on an individualized basis.

Study Details
Dr. Chan and colleagues performed a single-center, prospective cohort study of adult patients with cancer who had solid tumors or lymphoma, had received chemotherapy, and developed FN between January 2009 and January 2012. A total of 437 patients were identified with FN, 430 of whom were included in the analysis. The majority of malignancies were lymphoma (36.7%), breast cancer (25.6%), and genitourinary cancers (8.2%). Nearly one-half of the patients who developed FN had received prophylactic G-CSF, including some who received pegfilgrastim, the long-acting G-CSF. In all, 335 patients (78%) were treated with G-CSF after FN developed, whereas 95 patients (22%) did not receive therapeutic G-CSF. The majority of patient characteristics were similar between the 2 groups, as was the percentage of patients with poor prognostic risk factors.

“About half of the patients had received G-CSF prophylactically in this study,” says Jeffrey Crawford, MD, codirector of the Solid Tumor Therapeutics program at the Duke Cancer Institute in Durham, North Carolina. “It would be important to know how many had received pegfilgrastim.
There would likely be no benefit to further adjunctive G-CSF, as therapeutic serum concentrations of pegfilgrastim should already be present in these patients. In the United States, the majority of patients getting prophylactic growth factor receive pegfilgrastim.”

At the time of presentation, patients treated with adjunctive G-CSF were found to have a significantly lower absolute neutrophil count (ANC) nadir than those who did not receive therapeutic G-CSF. However, the Multinational Association of Supportive Care in Cancer (MASCC) score was not found to be statistically significantly different between groups, the authors note. The MASCC score is a validated risk index incorporating multiple factors to identify a patient’s risk of complications from FN (J Clin Oncol. 2000;18:3038-3051). In the current study, the majority of patients (81%) were considered to be low risk based on MASCC scoring.

Complications from FN, specifically duration of grade 4 neutropenia (ANC < 0.5 × 10^9/L) and mortality, were significantly different between patient groups. The duration of grade 4 neutropenia was longer for those who received G-CSF (2.5 days vs 2 days; P = .011), but the mortality rate was lower for the group that received G-CSF (2.4% vs 8.4%; P = .006).

No significant differences were noted between groups with regard to length of hospital stay, duration of antibiotic use, duration of fever, time to neutrophil recovery, or incidence of documented infections. A statistically nonsignificantly shorter length of hospitalization (3.5 days vs 3.7 days), fewer days to fever resolution (3.5 days vs 4.2 days), and fewer days to neutrophil recovery (3.4 days vs 3.5 days) were noted among patients who received G-CSF.

“This study was not a randomized study, so conclusions that can be drawn are limited,” says Dr. Crawford. “Most randomized studies investigating therapeutic G-CSF do show a modest decrease in time to ANC recovery, as well as fewer days of hospitalization, but a mortality benefit has not been established in these randomized trials.”

The presence of an invasive fungal infection and a low ANC nadir were found to be significant predictors of poor outcomes. Patients with invasive fungal infections were 4 times more likely to have a prolonged hospitalization, and a 1-unit (1 × 10^9/L) decrease in the ANC nadir conferred a 12.5-fold increase in the risk of prolonged hospitalization.

Clinical Implications
Although the outcomes demonstrated a decrease in mortality with the use of G-CSF for the treatment of patients with FN, other outcomes were not affected. The authors note that in their review of the literature, mortality benefit was not often chosen as a study endpoint.

“In my study, we have chosen mortality prior to ANC recovery, which is not a commonly adopted endpoint in most studies,” says Dr. Chan. “Most studies utilize either overall mortality or infection-related mortality.”

One meta-analysis that examined overall mortality as an endpoint did not demonstrate a lower mortality with the use of therapeutic G-CSF, and only reported a borderline mortality benefit for infection-related mortality (J Clin Oncol. 2005;23:4198-4214).

“Overall mortality is hard to gauge as it may be confounded by other events (such as fatal bleeding or death from cancer) that many highly myelosuppressed patients would face,” Dr. Chan adds.

The authors suggest further study is needed to confirm that a mortality benefit is accomplished with the use of therapeutic G-CSF. They acknowledge that the variety of tumors and chemotherapy regimens used among the study patients hindered their ability to define characteristics that can identify which patients with FN should receive G-CSF. However, these researchers also note that the patients with a low ANC nadir and invasive fungal infections fare particularly poorly and may likely benefit from treatment with G-CSF.

Limitations of the study are acknowledged by the authors. Because of the variety of malignancies, chemotherapy regimens, and FN-related risks, each patient had a different risk profile. In general, patients with solid tumors had a lower risk of FN and subsequent complications than patients with hematologic malignancies. Despite the heterogeneity, a mortality reduction was still documented with therapeutic G-CSF.

“These data remind clinicians that adjunctive G-CSF is clinically important in critically ill FN patients,” says Dr. Chan. “I think further analysis would be useful to evaluate which subset of patient population would benefit most from adjunctive G-CSF in treatment of FN.”

“This study does not change guidelines, which currently state that G-CSF be used for the treatment of febrile neutropenia with poor prognostic risk factors,” adds Dr. Crawford. “This study showed benefit in those subgroups, but is not a strong enough study to draw further conclusions.”

doi: 10.3322/caac.21222