BRIEF CLINICAL UPDATE

Should G-CSFs be used with Antibiotics to Treat Established Neutropenic Fever?

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With the continued treatment of many types of cancers with myelosuppressive chemotherapy, the risk of febrile neutropenia remains significant and potentially detrimental. Febrile neutropenia is usually identified by examining a patient's temperature and absolute neutrophil count (ANC). The Infectious Disease Society of America (IDSA) defines fever as a temperature of 38 degrees Celsius or above for one hour or more. There is some variation on the definition of neutropenia, but it is typically recognized as an ANC of 1500 or less, with mild neutropenia being an ANC of 1000-1500, moderate neutropenia being an ANC of 500-1000, and severe neutropenia being an ANC less than 500. There is widespread agreement that management of neutropenic fever should involve rapid initiation of broad spectrum antibiotics. However, though commonly seen implemented in addition to antibiotics in clinical practice, the use of granulocyte colony stimulating factors (G-CSFs) for established neutropenic fever remains controversial. This update seeks to evaluate the existing guidelines and data on the use of G-CSFs in established neutropenic fever and discuss how this evidence can be applied to current clinical practice.

Official guidelines from multiple clinical societies recommend against the routine use of G-CSFs in febrile neutropenia. The American Society of Clinical Oncology states, "CSFs should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, CSFs should be considered in patients with fever and neutropenia who are at high risk for infection-associated complication or who have prognostic factors predictive of poor clinical outcomes" and offers this as a strong recommendation.[1] Similarly, the IDSA writes simply, "CSFs are not generally recommended for treatment of established fever and neutropenia"[2] and presents this as a grade B-II recommendation. From these guidelines alone, it would appear that the answer to this clinical question is relatively straightforward. However, the suggestion made by both of these sets of guidelines contradicts what is often seen in actual clinical practice.

This may be because the data available to evaluate these recommendations is not clear cut. No large randomized-controlled trials have been conducted to answer this question. A Cochrane review was done by Mhaskar et al in 2014[3] to analyze the smaller published randomized trials addressing this issue. The review suggests that the consensus from these trials is that the use of G-CSFs in conjunction with antibiotics for neutropenic fever does not reduce mortality in a statistically significant way. For example, Garcia-Carbonero et al conducted a multicenter randomized trial in 1997-1999.[4] In their trial, 210 patients with documented temperature above 38 degrees Celsius and ANC less than 500 were randomized to receive antibiotics or antibiotics with G-CSF. There were no statistically significant differences in treatment outcomes or in serious medical complications (such as congestive heart failure, respiratory failure, renal failure) between the two treatment arms, and no statistically significant difference in mortality as 5 patients died in each study arm. These results and similar results in other small studies indicate that use of G-CSFs as adjunctive treatment with antibiotics in neutropenic fever does not significantly reduce mortality.

However, this does not mean that there are no clinical benefits to using G-CSFs in these cases. The analysis done by Mhaskar, et al., also showed that use of G-CSFs led to fewer prolonged hospitalizations, and faster recovery of neutrophil count. For example, Mitchell et al conducted a placebo-controlled, randomized trial to examine the use of G-CSFs in pediatric patients with chemotherapy-related neutropenic fever.[5] In that study, 112 patients, aged 17 or younger, with documented fever greater than equal to 38.5 degrees Celsius once or 38 degrees Celsius twice were randomized to receive antibiotics and G-CSF or antibiotics alone. The study found that hospital stays were significantly shorter in the group that received antibiotics with G-CSF (median of 5 days) compared with the group that received antibiotics alone (median of 7 days). They also found that patients who received G-CSF had a statistically significant decrease in overall duration of neutropenia. This research illustrates that although use of G-CSFs does not seem to lead to a significant difference in mortality, there may be other clinical benefits to administering G-CSFs in neutropenic fever.

Another factor to consider when deciding whether to use G-CSFs in these situations is how well the drug is tolerated and the incidence of adverse effects. In these studies, the adverse effects tended to be mild to moderate, such as bone pain or flu-like symptoms. In general, it was felt that G-CSFs were reasonably well-tolerated overall.

Examining these studies on whether G-CSFs should be used in conjunction with antibiotics for the treatment of established neutropenic fever remains a difficult question to answer. While the existing studies do not indicate a mortality benefit to using G-CSFs, other endpoints such as shorter hospitalizations merit consideration. Shorter hospitalizations not only can have clinical benefits for patients, but can have economic benefits to hospitals as well. For example, a decision tree model was used by Wang et al in a cost-effectiveness analysis of the use of G-

CSFs in neutropenic fever.[6] They found from their modeling that from a hospital perspective, there was a significant cost benefit to using G-CSFs (a cost saving of $125 per patient). The rising cost of medical care continues to be a huge issue in modern medicine, so areas where costs can be saved should not be overlooked.

The decision to use G-CSFs with antibiotics in cases of established chemotherapy-induced neutropenic fever is not straightforward. Only small randomized-controlled trials of varying quality have been published to investigate this issue. Although the current data would suggest that the use of G-CSFs do not have a significant impact on mortality, their findings do indicate that there are secondary benefits such as decreased duration of neutropenia and shorter hospital stays. These benefits suggest that using G-CSFs may be cost effective from a hospital perspective. However, the outcomes of shorter hospitalizations are likely influenced by hospital policies regarding neutrophil count before discharge, and it is not clear whether returning to a certain neutrophil count confers clinical benefits. It is obvious that further research needs to be undertaken with larger, more robust studies in order to decide definitively whether G-CSFs should be used with antibiotics in the treatment of neutropenic fever.

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