Management of chemotherapy-induced febrile neutropenia among adult oncology patients: A review

by Audai Nader Saeed and Dr. Nijmeh Al-Atiyyat

ABSTRACT

The aim of this literature review is to investigate the safest and most appropriate actions for the management of chemotherapy-induced febrile neutropenia. A literature search was undertaken, including major computerized electronic databases (PUBMED, SPRINGER, and WILEY). All studies that discuss colony stimulating factor plus antibiotics versus antibiotics or colony stimulating factors alone for the treatment of febrile neutropenia in adult oncology patients were sought. A review of the selected studies was performed. Most studies focus on the prompt assessment and management for oncology patients who are experiencing febrile neutropenia by using appropriate antibiotics and highlight the importance of using antibiotics and colony stimulating factor in the management of chemotherapy-induced neutropenic fever.

Key words: febrile neutropenia, chemotherapy, management, oncology patients

INTRODUCTION

Chemotherapy-induced febrile neutropenia (CIFN) remains one of the most common complications that occurs as a consequence of administering myelosuppressive chemotherapy, and typically results in extended hospitalization and death for many patients (Weycker, Barron, Kartashov, Legg, & Lyman, 2014). It is considered one of the most serious oncology emergencies and mortality rates have been reported as ranging between 5% and 21% in adult oncology patients (National Institute for Health and Clinical Excellence, 2012). The highest incident rate is seen among patients with

hematological malignancies, reported as above 80%, while as many as 50% of patients with solid tumours are also prone to develop it (Mathew, 2012).

Neutropenia and fever are major dose-limiting effects of many cytotoxic drugs. The neutropenic fever incidence is directly related to the depth and duration of the neutropenia (Schouten, 2006). Despite major advances in prevention and treatment of chemotherapy side effects, CIFN remains one of the most concerning complications of cancer chemotherapy and is the major cause of morbidity (De Naurois, Novitzky-Basso, Gill, Marti, Cullen, & Roila, 2010). Progress has been made in this field, but the management of CIFN patients still remains a challenge (Biswal & Godnaik, 2013).

Prompt care and the initiation of empiric antibiotic therapy are critically important universal aspects of treatment decision-making for CIFN (Bhardwaj & Navada, 2013). Thus, the purpose of this literature review was to investigate the safest and most appropriate actions to be taken in the management of patients who are febrile and neutropenic, as a consequence of receiving chemotherapy as a cancer treatment modality.

METHODS

To critically examine the body of knowledge related to the management of CIFN among oncology patients, a literature review using a search of the main electronic databases of interest was conducted including PUBMED, SPRINGER, and WILEY. All studies that discuss colony stimulating factors plus antibiotics versus antibiotics or colony stimulating factors alone for the treatment of febrile neutropenia in adult oncology patients were sought. For studies published between 2010 and 2014, all references of any selected studies were scanned, and any additional studies of potential interest were retrieved for analysis.

For PUBMED, these authors used the advance methodological search strategy in search terms included: neutropenia [MeSH term] AND fever [MeSH term], AND neoplasms [MeSH term] OR lymphoma [MeSH term], AND drug therapy [MeSH term] OR drug therapy combination [MeSH term]. Overall, 19 studies appeared and were filtered by applying the inclusion criteria: studies written in the English language, research-based studies, published in the last five years, and free full text. Subsequently, five studies

ABOUT THE AUTHORS

Audai Nader Saeed, Senior Charge Nurse in Leukemia Unit at King Hussein Cancer Center
Audai_saeed1@yahoo.com

Dr. Nijmeh Al-Atiyyat, RN, PhD, The Hashemite University-Jordan
King Hussein Cancer Center

Tel 00962786183740 / 00962796178895

Jordan- Amman

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were identified and scanned, six studies were selected and retrieved for full text analysis. For SPRINGER, the same strategy was adopted resulting in two studies being identified. Finally, two studies were identified from WILEY by using febrile neutropenia, chemotherapy, management, and oncology patients as key words. These authors performed an additional search by reviewing the list of references within each of the identified studies. The exclusion criteria for those studies were: qualitative research, published more than five years ago, not written in English, and copies of studies required purchase.

Based on the application of the inclusion and exclusion criteria, eight studies published between 2010 and 2014 were selected and form the basis of this review.

Methodological characteristics

The eight studies composing this literature review were quantitative studies.

One study used a randomized clinical trial design and one used a questionnaire. Two studies used retrospective cohort study designs, another one used an experimental study design, and two used prospective designs. Although, the selected articles are only eight in number, they cover a wide variation in case situations. The method of data collection used in the studies was observational, and only one study used a questionnaire.

The types of interventions used in the studies were Granulocyte-Colony Stimulating Factor (G-CSF) plus antibiotics versus antibiotics or G-CSF alone. Outcome measures included mortality-related infection, time to antibiotic withdrawal, time of hospitalization, treatment side effects, time to neutrophil recovery, and time to defervescence.

Sample characteristics

The sample sizes for the eight studies ranged between 44 to 25,000 oncology patients. There were no significant differences noted in the management of CIFN between male and female in these studies. However, some chemotherapy induced severe neutropenia (i.e., CHOP regimen) when compared with other regimens and need specific interventions. Most cancer types were covered in this review (i.e., lymphoma, breast cancer, leukemia, and other solid tumours). The participants in the selected studies were receiving chemotherapy at the time the studies were conducted. The studies were carried out in many different countries, including United States, England, Wales, Spain, Pakistan, Canada, and Brazil.

FINDINGS

Despite advances in the management of CIFN, there is evidence that the number of deaths from neutropenic sepsis is increasing at a rather fast rate. The most likely explanation for this is the increase in the amount of chemotherapy administered in recent years (National Chemotherapy Advisory Group, 2009). Up to 25% of patients treated with chemotherapy are likely to develop a CIFN episode, although this percentage could increase up to 96% in any particular type of tumours (Doshi et al., 2012). Current treatment for CIFN includes: evaluation by hospitalization, G-CSF, broad-spectrum empirical antibiotics, and other supportive care.

According to analysis of the selected studies, most of studies (62.5%) focus on the importance of a combination of G-CSF and antibiotics; the rest of the studies (37.5) focus on the initiation of antibiotics. Gupta et al. (2010) was concerned with determining the efficacy and feasibility of G-CSF as secondary prophylaxis when used with full dose of chemotherapy that induced febrile neutropenia. These investigators used a randomized clinical trial design with 52 patients. They focused on using antibiotics as primary prophylaxis and G-CSF as secondary prophylaxis for patients receiving chemotherapy. The researchers found that using G-CSF led to shortening the neutrophil recovery time, resulting in significant reduction in the incidence of CIFN, hospitalization, and use of broad spectrum antibiotics. They concluded that G-CSF is safe and effective as a secondary prophylaxis with full-dose chemotherapy in patients who developed febrile neutropenia following cycles of chemotherapy.

Villafuerte-Gutierrez, Villalon, Losa, and Camacho (2014) provided an overview of management guidelines for CIFN in the setting of hematologic malignancies. They found that prophylaxis antibiotics are not necessary for all patients, and should be used only in high-risk patients to avoid the emergence of resistant pathogens. Empiric broad-spectrum antibiotics should be initiated immediately after blood cultures have been obtained in high-risk patients with CIFN, and should be started within 60 minutes of presentation in all patients presenting with neutropenic fever. They added that pre-emptive antifungal therapy seems to be similar to the empirical approach in low-risk patients with CIFN. Selecting antimicrobial agents for prophylaxis and/or empirical therapy should be based on the local susceptibility and resistance patterns of microorganisms.

Simmons (2012) used a questionnaire to develop guideline recommendations for CIFN by providing a description of the current burden of neutropenic sepsis and service provision in England and Wales. He distributed 80 questionnaires via the cancer networks in England and Wales asking that one questionnaire be completed for each policy. He identified that almost all centres had a door-to-needle time of one hour or less, when giving intravenous antibiotics to patients who were suspected of having neutropenic sepsis. Different centres had a policy where lower risk patients are given oral antibiotics instead of intravenous ones. Most of the patients were discharged immediately if started on this treatment plan.

Mahmood and Tariq (2014) focused on pediatric patients to evaluate if G-CSF with empirical antibiotic therapy accelerates CIFN resolution when compared with antibiotics without G-CSF. He used an experimental study with 56 children with CIFN. The investigators found there is a significant difference in duration of hospitalization in G-CSF with an empirical antibiotic group compared with antibiotics alone. By using G-CSF, we can decrease the cost of hospitalization and antibiotics by decreasing duration, and that is approved in different tumour types (Leukemia, Wilm's tumour, and Rhabdomyosarcoma). Twenty-eight patients were given only antibiotics and 28 patients were given G-CSF plus antibiotics. Adding of G-CSF significantly reduced neutropenia and febrile neutropenia recovery times. The median number of days for febrile

neutropenia resolution was 4.3 days earlier with G-CSF (5.3 versus 9.6 days respectively). Resolution of fever was one day earlier in patients who were given G-CSF. Hospitalization was 2.1 days shorter with G-CSF (6.1 versus 8.2 days respectively). There was a difference of 2.2 days in the duration of intravenous and oral antibiotic treatment.

Khalafallah et al. (2012) conducted a retrospective study to assess the impact of early antifungal therapy on outcomes during induction chemotherapy. Forty-four patients whose ages ranged from 18–81 years were included. The researchers found that early empirical antifungal treatment was associated with significantly lower treatment-related mortality during the induction therapy for acute leukemia in neutropenic fever patients. Fifteen patients were treated with voriconazole and 12 patients with caspofungin. There were no significant differences between the two groups of patients for either regimen regarding the resolution of fever and improvement of radiological findings in the further follow-up. The 120-day mortality rate after the induction therapy was 2.2%, without any incidence of invasive fungal disease. Furthermore, there was no indication that any of patients had progressed to severe invasive fungal infection, particularly in high-risk patients with prolonged episodes of neutropenia after chemotherapy.

Recently, Rosa and Goldani (2014) focused on the time of antibiotic administration and proposed quality-of-care measures in patients with CIFN. Few data regarding the impact of time in antibiotic administration on mortality of adult cancer patients with CIFN are available. These investigators used a prospective cohort study with a sample size of 169 patients with febrile neutropenia. The time to antibiotic administration was assessed as a predictive factor for 28-day mortality. In total, 169 subjects were evaluated during the study period and there were 29 deaths. The time to antibiotic administration was independently associated with 28-day mortality; each increase of one hour in the time to antibiotic administration raised the risk of 28-day mortality by 18%. The CIFN episodes with time to antibiotic administration ≤ 30 minutes had lower 28-day mortality rates compared with those with time to antibiotic administration between 31 minutes and 60 minutes. At the end of their study, they summarized that early antibiotic administration is associated with higher survival rates in patients with CIFN. Efforts should be made to ensure that patients with CIFN receive effective antibiotic therapy as soon as possible.

The same result was recommended by Perron, Emara, and Ahmed (2014) using a retrospective cohort study with 105 CIFN patients with median age of 60 years. Thirty-five per cent of patients were in high-risk groups. The median time

to antibiotic administration was 2.5 hours and median length of hospital stay was six days. This retrospective cohort study revealed a positive relationship between time to antibiotic administration and prolonged hospital stay. They conclude that delay in antibiotic administration is associated with a longer hospital stay.

Wright et al. (2013) used a prospective study with 25,231 patients admitted with CIFN. Guideline-based antibiotics, which included all antibiotics that have been recommended by consensus groups, were given within 48 hours of hospital admission. The antibiotics included: cefepime, ceftazidime, imipenem, meropenem, piperacillin /tazobactam, and an aminoglycoside in combination with any of the aforementioned agents or ciprofloxacin or ticarcillin/clavulanate. Guideline-based antibiotics were administered to 19,897 patients (79%), vancomycin to 37%, and G-CSF to 63%. Patients managed by hospitalists were more likely to receive guideline-based antibiotics. Vancomycin use increased from 17% in 2000 to 55% in 2010, while G-CSF use only decreased from 73% to 55%. Among low-risk patients with CIFN, prompt initiation of guideline-based antibiotics decreased mortality rate. In concluding, the authors reported high use of guideline-based antibiotics, but that use of the non-guideline-based treatments, vancomycin and G-CSF, is also high. Hospital factors and physician are the strongest predictors of both guideline- and non-guideline-based treatment.

CONCLUSIONS

Hospitalization with CIFN continues to be associated with significant mortality, as well as possible detrimental effects on patients' clinical outcomes, because of the discontinuation of chemotherapy or substantial delays or reductions in its delivery. Clinical practice guidelines for the effective management of CIFN are widely recommended.

Appropriate prophylactic antibiotics should be implemented before the first cycle of treatment in oncology patients, and the use of G-CSF after chemotherapy treatment and before the patients develop CIFN. This approach is more effective than using it after the development of neutropenia. Prophylactics are the first line of management.

Adoption of standardized protocols to lower the time to antibiotic administration in the setting of an episode of CIFN is helpful. Protocols ought to identify the selected type of antibiotic, time to administer, dose, use of combination antibiotics, use with or without G-CSF in order to have effective patient outcomes and to relieve CIFN among cancer patients. Additionally this topic area requires further future investigations.

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