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PALLIATIVE MEDICINE (A JATOI, SECTION EDITOR)

Optimizing Symptoms and Management of Febrile Neutropenia among Cancer Patients: Current Status and Future Directions

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Abstract Febrile neutropenia (FN) is a common and serious complication among cancer patients undergoing myelosuppressive chemotherapy. FN should be treated as a medical emergency because it can lead to life-threatening complications if appropriate treatment is not initiated immediately. This study provides a critical review on the current management of FN and identifies possible directions to optimize FN management.

Keywords Febrile neutropenia · Management · Optimization · Economic evaluation · Biomarker · Patient-reported outcome

Introduction

Febrile neutropenia (FN) is defined as a single oral temperature of ≥38.3°C or a temperature of ≥38.0°C sustained over 1 hour, together with an absolute neutrophil count (ANC) of <500/mm^3, or an ANC of <1000/mm^3 with an expected decrease below 500/mm^3 within the next 48 hours [1]. This definition has been well accepted by other major medical societies [2–5], with only some minor variations.

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FN is a serious and common complication among cancer patients undergoing myelosuppressive chemotherapy. One recent study revealed that despite prescribing appropriate granulocyte colony-stimulating factor (G-CSF) prophylaxis support, up to 16% of cancer patients would experience at least one FN episode during their chemotherapy [6]. FN can lead to life-threatening complications and the inpatient mortality rate of FN was reported as 6.6% by a recent audit study among FN patients with solid tumors and lymphomas [7]. Furthermore, FN is often associated with chemotherapy dose reductions or treatment delays, which could potentially affect patients' long-term clinical outcomes [8, 9]. In addition to the clinical burden, FN leads to a significant economic burden on patients, payers, and general society, especially when the FN patient was hospitalized and managed inpatient [10]. In the USA, the average cost of FN inpatient management was conservatively estimated to be around US$18,880 per episode [11].

Considering the substantial disease and economic burden of FN, it is imperative to identify patients who are at high-risk for FN, so that interventions could be implemented to appropriately manage their FN risk. The National Comprehensive Cancer Network (NCCN) guideline has classified chemotherapy regimens into high (>20%), intermediate (10–20%), and low risk (<10%) of developing FN [5]. Besides, it has recommended to assess the patient-related risk factors in order to fully evaluate the overall risk of FN [5]. One recent systematic review focused on identifying risk factors for febrile neutropenia has revealed that older age, poor performance status, advanced disease, presence of comorbidities, low baseline blood cell counts, and low body surface area/body mass index correlated with an increased FN risk [12]. With a better understanding on FN risk factors, those patients with a high-risk of developing FN can be identified more accurately, so that prophylactic interventions can be introduced to appropriately manage their FN risk.

In this review, we will discuss a number of strategies, based on current literature that a multidisciplinary care team for cancer patients could implement to control the symptoms associated with FN and to improve the management strategies. We will also discuss the potential gaps in the current management and how management of FN can be optimized through further research.

Treatment of FN

Initial Assessment and Investigations

Initial assessment and investigations should be performed before applying empirical broad-spectrum antimicrobial therapy. A comprehensive history should be taken, which includes information with the nature of administered chemotherapy, prior antimicrobial prophylaxis, concomitant steroid use, recent surgical procedures, presence of allergies, infection exposures, prior documented infections or pathogen colonization, coexistence of non-infectious causes of fever, and underlying comorbidities [1, 5]. After that, physical examination, blood tests, microbiologic cultures, and radiographic tests should be further investigated [1, 5]. Based on the Infectious Disease Society of America (IDSA) guideline, tests on complete blood cell counts, serum creatinine levels, and urea nitrogen levels are recommended to be performed at least every 3 days during the antibiotic therapy, in order to monitor and manage possible drug toxicity [1].

In recent years, a number of studies have investigated the use of biomarkers for infections, such as C-reactive protein (CRP), interleukins-6 (IL-6), and procalcitonin (PCT), among cancer patients with febrile neutropenia [13, 14, 15••]. One meta-analysis investigated the performance of CRP, IL-6, and PCT as biomarkers for bacterial infections and identified that the positive likelihood ratios, IL-6, and PCT were 1.82 (95%CI: 1.42–2.33), 3.68 (95%CI: 2.41–5.60), and 5.49 (95%CI: 4.04–7.45), respectively, suggesting that PCT had the best performance on predicting bacterial infections [15••]. In addition, one recent review has indicated that serial PCT evaluations can be more accurate at the diagnostic stage, and the use of PCT in combination with other clinical and laboratory tests is promising to identify early infectious complications among FN patients and guide the antibiotic usage [16].

Risk Assessment for Complications

Patients with FN are at risk of developing serious medical complications. Classification of FN patients into low-risk or high-risk for serious complications can guide the subsequent management decision-making, such as the necessity for inpatient admission, antibiotic usage, and length of stay in hospital.

Currently, the most widely used risk assessment model is the Multinational Association for Supportive Care in Cancer (MASCC) score which allows the identification of low-risk FN patients for serious medical complications [17]. Existing guidelines, such as the European Society for Medical Oncology (ESMO) [2], European Organization for Research and Treatment of Cancer (EORTC) [4], American Society of Clinical Oncology (ASCO) [3], NCCN [18], and IDSA [1], have also advocated the implementation of the MASCC score in clinical practice to identify low-risk FN patients. The MASCC score consists of a number of weighted factors, which include elderly patient (age ≥60 years); outpatient or inpatient status; burden of illness; presence of hypotension; presence of chronic obstructive pulmonary disease; presence of dehydration; and presence of solid tumor or, among patients with hematological malignancies, the absence of previous fungal infection [17]. Patients with a cumulative MASCC score ≥21 points are defined as low-risk for experiencing serious complications [17]. For those low-risk FN patients, a simpler and cost-effective management option can be considered, such as oral antibiotics, outpatient management, and early discharge [1]. However, there are some inherited limitations with the MASCC score. For example, there is a lack of clear definition on how one defines the burden of illness; hence, the severity of the disease burden is normally subjected to a clinician's judgment which may lead to confusion and inconsistency in the application of the MASCC score [1]. Furthermore, the specificity of the MASCC score still needs to be improved [19], so that false positive results (patients developed serious complication while predicted as low-risk patients) can be reduced and safe management can be promoted among those FN patients predicted as low-risk in the risk assessment tool.

In recent years, several studies have investigated the value of other clinical and biological parameters that may improve the risk stratification of FN patients. One modified MASCC model was proposed by incorporating additional investigation on the presence of a "complex infection" [20], and this model has shown a better performance in identifying low-risk patients than using the MASCC score alone, although the model requires rigorous validation before it can be widely used. Similarly, one study developed a scoring system, by combining patients' initial body temperature, presence of hypotension, presence of infection, presence of central venous catheter, initial ANC, and CRP levels, to predict the bacteremia among low-risk FN patients classified by the MASCC score [21]. However, its model performance was not compared with that of the MASCC model. In addition, one study evaluated the predictive value of PCT, CRP, serum amyloid, IL-1β, IL-6, IL-8, and IL-10 for prediction of FN complications and identified that none of those laboratory markers can be useful

as an independent predictor, although PCT was most strongly associated with the MASCC score [22]. In another study, it was revealed that the addition of PCT to the MASCC score resulted to a better performance on risk stratification of FN patients than using the MASCC score alone [23]; however, validation was needed for that proposed model.

It should be noted that the MASCC score was initially developed for identifying low-risk FN patients, although identification on high-risk FN patients was also important in the clinical practice, and the cut-off on 21 in the MASCC model seemed unsatisfactory in predicting high-risk FN patients [19]. The Clinical Index of Stable Febrile Neutropenia (CISNE) was the most recently developed and validated model for predicting serious complications among patients with FN [24••]. In this model, a number of weighted factors were identified, which included the Eastern Cooperative Oncology Group performance status ≥2, the presence of chronic obstructive pulmonary disease, the presence of chronic cardiovascular disease, mucositis of grade ≥2, monocytes <200/μL, and the presence of stress-induced hyperglycemia [24••]. When compared with that of the MASCC score, the CISNE model showed a better performance in predicting high-risk FN patients (areas under the receiver operating characteristic curves: 0.868 vs. 0.721; $P = 0.002$) [24••].

Antibiotics Treatment

FN is treated as a medical emergency, as infections among FN patients can rapidly progress and lead to life-threatening complications, particularly when empirical antibiotics are not promptly initiated [1]. The antibiotics treatment should normally be given to FN patients immediately after the collection of blood culture and before the completion of any other investigations [25]. Delay in the antibiotics treatment can result in increased mortality [26] and prolonged hospitalization [27]. The optimal empirical antibiotic regimen remains controversial and could change over time due to the development of resistant bacteria. Based on the IDSA guideline, for high-risk FN patients, hospitalization with intravenous antibiotics treatment is needed, and initial antibiotics should cover *Pseudomonas aeruginosa* and other severe gram-negative pathogens [1]. The IDSA guideline also recommends monotherapy with an antipseudomonal β-lactam agent (cefepime, piperacillin-tazobactam) or a carbapenem (imipenem or meropenem) as the first-line treatment [1]. In addition, the monotherapy with β-lactam agent was found superior than a combination therapy of β-lactam agent plus aminoglycoside, due to lower infection-related mortality, fewer adverse events, and fewer fungal super-infections [28].

For low-risk FN patients, outpatient management with oral antibiotics treatment can be considered among carefully selected patients [2]. A combination therapy of fluoroquinolones (ciprofloxacin or levofloxacin) plus amoxicillin-clavulanate is proposed as the oral empirical treatment [1, 3, 18]. If the low-risk FN patients have presented documented infections, especially for the cases of infection by bacteria resistant to fluoroquinolones and β-lactam, the IDSA [1] and ASCO [3] recommend inpatient management, so that intravenous antibiotics, such as meropenem or piperacillin-tazobactam, can be administered.

Adjunctive Treatment with G-CSF

The benefit of using therapeutic G-CSF as an adjunctive treatment for established FN remains controversial. One recent meta-analysis evaluated the safety and efficacy of adding therapeutic G-CSF to antibiotics treatment for FN [29] and identified that the addition of G-CSF has no significant impact on overall mortality (G-CSF plus antibiotics vs. antibiotics alone: hazard ratio = 0.74; 95%CI: 0.47–1.16; $P = 0.19$) and infection-related mortality (hazard ratio = 0.75; 95%CI: 0.47–1.20; $P = 0.23$). However, the use of therapeutic G-CSF in established FN has been demonstrated to reduce a patient's likelihood for prolonged hospitalization of over 10 days (relative risk = 0.65; 95%CI: 0.44–0.95; $P = 0.03$), duration of antibiotic usage (standardized mean difference = −1.50 days; 95%CI: −2.83 to −0.18; $P = 0.03$), and duration of neutropenia (standardized mean difference = −1.70 days; 95%CI: −2.65 to −0.76; $P = 0.0004$) [29]. Although these benefits are statistically significant, the IDSA guideline considers the benefit is too minimal to be clinically important [1]. After taking into account the high cost of G-CSF at that time and its possible associated adverse effects, therapeutic use of G-CSF is not recommended by the IDSA guideline [1]. However, it should be noted that this recommendation is mainly based on the economical factor concerning the high cost of G-CSF (the IDSA guideline was last updated in 2010). With the availability of less expensive biosimilar G-CSF in recent years, it is necessary to reconsider whether the therapeutic use of G-CSF should be advocated. In fact, the recent updated NCCN guideline has recommended that therapeutic G-CSF can be considered in certain circumstances during the treatment of FN [5]: (i) if patients received short-acting G-CSF (such as filgrastim) as prophylaxis but developed FN, the short-acting G-CSF should be continued during the treatment of FN; (ii) if patients did not receive any G-CSF as prophylaxis and developed FN, for those patients who presented risk factors for serious complications, therapeutic G-CSF should be considered. The risk factors for serious complications include the presence of sepsis syndrome, age over 65 years, ANC lower than 100 cells/mm^3, neutropenia duration expected to be over 10 days, presence of pneumonia or other clinically documented infections, presence of invasive fungal infection, inpatient fever, and prior episode of FN [5].

Prevention of FN

Antibiotic Prophylaxis

Both ASCO [3] and IDSA [1] guidelines recommend that antibacterial prophylaxis with fluoroquinolone should be considered for high-risk patients who were expected to have prolonged neutropenia over 7 days. A Cochrane review included 109 trials with 13,579 cancer patients with chemotherapy-induced neutropenia and has demonstrated that antibiotic prophylaxis could significantly reduce the all-cause mortality (relative risk = 0.66; 95%CI: 0.55–0.79) and infection-related mortality (relative risk = 0.61; 95%CI: 0.48–0.77), when compared with those of the placebo group or no intervention group [30]. It was also shown that antibiotic prophylaxis could significantly reduce the incidence of fever (relative risk = 0.80; 95%CI: 0.74–0.87), clinically documented infections (relative risk = 0.65; 95%CI: 0.56–0.76), and microbiologically documented infections (relative risk = 0.51; 95%CI: 0.42–0.62) [30]. However, as bacterial resistance continues to remain a public health issue [31–33], the concern on the emergence of resistant bacteria has restricted the routine use of prophylactic antibiotics, and the IDSA guideline recommends not to provide routine antibiotic prophylaxis to those low-risk patients for developing prolonged neutropenia [1].

G-CSF Prophylaxis

Numerous studies and meta-analysis suggested that prophylactic use of G-CSF can reduce the incidence of FN, infection-related mortality, and all-cause mortality [34–36]. The IDSA [1] and NCCN [5] guidelines suggest primary prophylaxis with G-CSF throughout all cycles of chemotherapy for high-risk patients of developing FN (>20%); while for the low-risk patients for FN (<10%), routine use of prophylactic G-CSF is not advocated. If a patient experiences an episode of FN from his previous cycle of chemotherapy, the ASCO guideline recommends to initiate a secondary prophylaxis with G-CSF (for those who did not receive primary G-CSF prophylaxis) [37]. Due to the high cost of G-CSF and its potential for being overused, many studies have been conducted in recent years to investigate the appropriate G-CSF prophylaxis strategy [38–40]. One study conducted in the UK has compared the cost-effectiveness of primary prophylaxis, secondary prophylaxis, and no prophylaxis with G-CSF and indicated that the most cost-effective strategy mainly depended on the patient's risk of developing FN [38]. In addition, novel strategies including minimizing the number of G-CSF injections have also been explored, and it was identified that prophylactic use of G-CSF during just the first two cycles of chemotherapy was associated with a lower cost (€17,168 vs. €20,658) but a higher risk of FN (36% vs. 10%), when compared to primary prophylaxis with G-CSF throughout all cycles of chemotherapy [40]. If a patient's FN risk is over 20%, the ASCO guideline suggests that G-CSF prophylaxis should be used based on clinical considerations rather than by cost [37]. However, if a patient is at an intermediate risk of developing FN (10%-20%), appropriate G-CSF prophylaxis strategy remains uncertain, and the decision normally depends on clinician's preference. In this case, the cost-effectiveness analysis can be useful to guide appropriate G-CSF prophylaxis strategy.

Over the last decade, several studies have shown that biosimilar G-CSF is as good as the originator product in reducing the incidence of FN [41–44]. Hence, current guidelines, including the ASCO [37], NCCN [5], and ESMO [2], have recommended the use of biosimilar G-CSF as a prophylactic agent for FN. In addition, the ASCO suggests that the choice of prophylactic agent among the biosimilar G-CSF and the originator G-CSF should depend on a number of factors, such as the cost, convenience, and clinical situation [37].

Possible Directions for Optimizing FN Management

Encouraging Appropriate Use of G-CSF by Using Economic Evaluation

FN management, especially in the inpatient setting, is associated with a substantial economic burden [45]. One recent review reported that the estimated cost of FN varied from US$5,819 to US$34,756 per episode mainly due to the various healthcare system and patient population in different countries, and the medication cost was a main factor associated with higher FN management cost [46]. Therefore, health economics should play an essential role with regard to the rational medication usage for managing FN, especially to those high-cost medications such as G-CSF.

With the emergence of biosimilar G-CSF in the commercial market, the price of the originator product of G-CSF has been gradually decreased in recent years [47••]. This has provided an opportunity to review the ground on providing appropriate prophylaxis, in order to strike a balance between cost and effectiveness. Evaluation on this balance can guide the decision-makers to understand whether the broader use of G-CSF is beneficial, and the economic evaluation analysis, such as cost-effectiveness analysis and cost-utility analysis, can provide a solution on it. In fact, one systematic review on the economic evaluation studies of G-CSF in the prevention and treatment of FN has illustrated the cost-saving potential of G-CSF [48]. In that review, the therapeutic use of G-CSF was found to be cost-saving, which is surprising since it varies from the suggestion made in the IDSA guideline [1]. Although this result is limited by the small number of studies, it has already revealed a need for some rigorously designed economic evaluation studies in guiding the appropriate G-CSF usage in the prevention and treatment of FN [48].

Economic evaluation can be useful to select appropriate G-CSF and encourage its diffusion within the healthcare system. For example, as a prophylactic agent for FN, there could be many types of G-CSF available in the market, such as pegfilgrastim, filgrastim, and biosimilar G-CSFs. Economic evaluation can also inform the policy-makers about which type of G-CSF is the most cost-effective choice for preventing FN, so that they can consider to include the most cost-effective agent into the national formulary or provide government subsidy on it [49], and broaden its usage.

Biomarker-Guided Rational Antibiotic Usage

For all the patients with FN, it is still strongly recommended to administer empiric therapy with antibiotics, in order to prevent the rapid progress of infections [1]. However, the antibiotics treatment duration for most infections is likely to be inappropriately long and lead to the serious issue of antibiotic resistance [50]. The risk of infections with resistant gram-positive and gram-negative bacteria has a trend of increase in the past few years [51–53]. The emerging antibiotic resistant pathogens are associated with a high mortality rate in cancer patients [54–56]. In addition, for those with persistent fever and manifesting nonsevere infections, the early discontinuation of antibiotics treatment is also needed, in order to control antibiotic resistance. Although blood cultures remain the gold standard for the diagnosis of bacterial infection and to guide antibiotic therapy, a long turnaround time of blood culture results may possibly delay the initiation of appropriate antibiotics. In contrast, a number of serum biomarkers, including CRP, PCT, IL-6, and lipopolysaccharide-binding protein, have demonstrated their potential to differentiate between infectious fever and non-infectious fever and recognize severe infections [57]. Specifically, PCT has been most widely studied as a marker of infection and was demonstrated to possess the best performance on predicting for bacterial infections [13–15]. In addition, PCT can be detected within several hours since fever onset [58] and has the advantage of providing clinicians immediate and meaningful information to guide appropriate antibiotic usage. Several studies have revealed that there was a significant reduction on the antibiotic consumption among those patients who were treated based on PCT-guided approach, when compared to those who were treated with conventional approach [59–63]. Therefore, it is valuable to further explore the use of biomarkers, such as PCT, in differentiating the sources of fever, and develop a validated algorithm to guide appropriate antibiotic usage among FN patients.

Improving the Risk Assessment for Serious Complications Using Patient-Reported Outcome Tools

Clinical profiles of patients manifesting FN are generally heterogeneous, with subsets of patients possessing varying risks of developing serious medical complications. Identification of low-risk FN patients can promote the application of simpler and cost-effective management approaches, such as the early discharge from hospital and outpatient management [19]. To serve the purpose of identifying low-risk FN patients, the MASCC score was developed and published in 2000 [17] and has been well accepted by the existing guidelines [1, 2, 18]. However, it was revealed that the MASCC score has a weak specificity, and an improved model for safely predicting patients with an acceptably low-risk of developing serious complications is still expected [19]. In addition, one study observed that among those low-risk FN patients defined by the MASCC score who are eligible for early discharge and outpatient management, a proportion of them were still managed inpatient due to patient's reluctance for early discharge [64]. This implies that the current MASCC score did not capture factors from patient's perception of their health status.

Patient-reported outcome (PRO) describes the impact of health conditions and treatments on patient lives from the perspective of patients. PRO measure allows patients to report how they feel, function, and perceive their health-related quality of life (HRQoL) directly, without interpretation by another individual including the healthcare professional [65]. The Functional Assessment of Cancer Therapy-Neutropenia (FACT-N) is a profile-based instrument to provide a targeted assessment of HRQoL among patients with neutropenia based on their self-report and has been validated in the USA [66]. Several studies have reported that PRO can provide unique prognostic information for patients' survival [67, 68]. Considering the prognostic value of PRO, it is of interest to explore the possibility to use PRO elements from neutropenia-specific instrument, such as the FACT-N, as adjunctive to the MASCC score for identifying low-risk FN patients. In this way, patient's engagement in the FN management can be promoted and this may possibly improve patients' satisfaction in the treatment of FN.

Conclusions

FN is a medical emergency and can be life-threatening if appropriate treatment is not initiated promptly. Antibiotic prophylaxis should be limited to high-risk patients of developing FN in order to avoid the emergence of antibiotic-resistant bacteria. With the reduced price of G-CSF, it is necessary to update the indications on both prophylactic and therapeutic use of G-CSF by the implementation of economic evaluations, such as cost-effectiveness analysis. Empirical antibiotics treatment should be initiated immediately for all the FN patients in order to prevent rapid progress of infections. If patients experienced persistent fever, antifungal therapy should be considered. Inclusion of biomarkers, such as the PCT, into the initial investigation is promising to reduce antibiotics overuse by

differentiating fever from bacterial infections and fever from other sources. Risk assessment for serious complications is imperative to identify low-risk FN patients for a simpler and cost-effective treatment. A combination of the MASCC score with PRO would be interesting to explore in order to improve the model performance and promote patients' engagement in the treatment.

Compliance with Ethical Standards

Conflict of Interest Xiao Jun Wang and Alexandre Chan declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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