SYMPOSIUM ARTICLE
UDC: 616.155.3:616.91:616-008.6

Treatment of a febrile neutropenic patient

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ABSTRACT

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KEY WORDS: *Neutropenia; Fever; Neoplasms; Infection; Antineoplastic Agents; Anti-Infective Agents*

Febrile neutropenia is a syndrome defined by the presence of fever (single oral temperature = 38,30C or >38 0C for = 1h) in a cancer patient with neutropenia (neutrophil count fewer than 0.5 x 109 /l, or fewer than 1.0 x 109 /l but predicted to decline to fewer than 0.5 x 109 /l over the next 48h), (1). Fever should not be caused by noninfectious causes such as cancer itself, drugs, blood product transfusion or graft versus host disease (GVHD). Febrile neutropenia is a syndrome we have created with cancer treatments (chemotherapy and/or radiotherapy).

BACKGROUND (1-3)

Infection is the main cause of fever in neutropenic cancer patient. Consequently, any fever that develops during the episode of neutropenia should be considered to be due to infection until proven otherwise. The frequency and severity of infection is primarily related to the depth and duration of neutropenia. Although the risk of infection is present when neutrophil count is below 1 x 109/l, it is really increased if neutrophil count is lower than 0.5 x 109/l ("standard" neutropenia). The risks of severe infection and bacteremia are greatest when neutrophil count falls below 0.1 x 109/l ("profound" neutropenia). Besides initial depth of neutropenia the duration of neutropenia is also critical for clinical outcome during febrile neutropenic episode: neutropenia lasting for more than 7 days is considered a "high risk" neutropenia. Neutropenia markedly alters the inflammatory response, making it difficult to detect the presence of infection. Fever is the earliest and commonly the only sign of an infection, other signs and symptoms being minimal or frequently absent. Since undetected and untreated infections can progress quickly in neutropenic patients, neutropenic fever should be considered a medical emergency. The most common sites of infection in neutropenic cancer patient are alimentary tract (i.e., mouth, pharynx, lower esophagus); lungs; perineum, including anus; and skin. Bacteria are responsible for the majority of initial infections. Until two decades ago, gram-negative bacilli, especially Pseudomonas aeruginosa, Escherichia coli, and Klebsiella species were the predominant bacteremic isolates. Nowadays, bacteremia is most frequently due to gram-positive bacteria, namely coagulase-negative staphylococci, Staphylococcus aureus, viridans group of streptococci and enterococci. Even if they become less frequent, gram-negative infections remain of major concern to clinicians since their mortality in neutropenic patients is still high and their course can be fulminant. Subsequent infections of the neutropenic patient are usually caused by fungi (mainly Candida and Aspergillus species) and viruses but also by antibiotic-resistant bacteria. Based both on the clinical course and microbiological data each febrile neutropenic episode is retrospectively classified as: (1) microbiologically documented infection, (2) clinically documented infection, or (3) infection without any microbiological or clinical documentation ("fever of unknown etiology").

EVALUATION (1,3,4)

Initial evaluation of febrile neutropenic patient is aimed at determining the potential sites of infection and causative organisms. Initial evaluation encompasses site-specific history; scrupulous physical examination; laboratory evaluation (a complete blood cell count, measurement of serum levels of creatinine, urea nitrogen, and transaminases); culture of blood samples; a chest radiograph for patients with respiratory signs and symptoms; as well as site-specific cultures and imaging studies (if signs and symptoms point to a specific site). In addition, the assessment of a risk for serious medical complications during the episode of febrile neutropenia should be performed. Recently a scoring system to identify, at the onset of febrile neutropenia, patients with a low risk for serious medical complications was developed and validated by MASCC (Multinational Association for Supportive Care in Cancer) Study Section of Infectious Diseases (MASCC score) (4).

This score allows us to split febrile neutropenic patients into low- and high-risk on the basis of the criteria easily assessable at the time of presentation: age, underlying malignancy in interaction with a history of fungal infection, inpatient status, burden of symptoms, presence of hypotension, of chronic obstructive disease or of dehydration. Carefully selected patients with a low risk for developing serious medical complications during the episode of febrile neutropenia are candidates for initial treatment outside traditional hospital setting or

an empiric therapy with oral antibiotics.

MANAGEMENT (1,3,5)

All neutropenic cancer patients should be considered to be at risk for infection and, once febrile, should be treated immediately with antimicrobials, without waiting for clinical and/or microbiological documentation of infection ("empirical antibiotic therapy"). In addition, afebrile patients who are neutropenic and have signs and symptoms suggesting an infection should also receive empirical antibiotic therapy.

Available clinical practice guidelines (CPGs) for the use of antimicrobial agents in neutropenic patients with cancer state that "no specific scheme, no specific drug or combination of drugs, and no specific period of treatment can be unequivocally applied to all febrile neutropenic patients".

Treatment with intravenous antibiotics

Traditional management of febrile neutropenic patients consists of hospitalization and treatment with intravenous, bactericidal, broad-spectrum antibiotics. Three antibiotic regimens for empirical treatment are equally recommended: (1) dual therapy with aminoglycoside in combination with antipseudomonal penicillin (ticarcillin-clavulanic acid, piperacillin-tazobactam); or with an extended spectrum antipseudomonal cephalosporin (cefepime, ceftazidime); or with a carbapenem (imipenem/cilastatin, meropenem); (2) monotherapy with carbapenem, cefepime, ceftazidime or piperacillin/tazobactam, and (3) the combination of dual therapy or monotherapy with vancomycin for specific indications.

Advantages of duo therapy with an aminoglycoside are broad coverage, potential synergistic effects against gram-negative bacilli and protection of the patient, in case the infecting organism is resistant to one of the empirically administered drugs (usually beta-lactam). Dual therapy with aminoglycoside is recommended for patients with a history of P. aeruginosa colonization or invasive disease. The major disadvantages are the lack of activity against some gram-positive bacteria (now predominant), and the nephrotoxicity, ototoxicity, and hypokaliemia associated with the use of amynoglycosides. More recently, there is a trend towards monotherapy of febrile neutropenia with carbapenems, cefepime, ceftazidime or piperacillin/tazobactam. In fact, most patients with solid tumors can be safely and effectively treated with monotherapy, and certainly those who are clinically stable with "standard" neutropenia and expected duration of further neutropenia less than 7-10 days. Patient should be closely monitored for no response: modifications of the initial monotherapy regimen may be necessary according to clinical / microbiological data. The increased frequency of beta-lactam resistant gram-positive pathogens and the fulminant clinical course of certain gram-positive infections made the rationale for the inclusion of vancomycin into empirical antibiotic regimen. Nevertheless, clinical trials have shown that vancomycin is not a necessary part of the initial empirical regimen. Empiric use of vancomycin is justified only in patients at high risk for serious gram-positive infections in following clinical situations: clinically documented serious catheter-related infection; substantial mucosal damage; prophylaxis with TMP-SMZ or quinolone antibiotics; known colonization with penicillin and cephalosporin resistant pneumococci or meticillin-resistant S. aureus; blood culture positive for gram-positive bacteria; and hypotension or septic shock without an identified pathogen.

To conclude, many antibiotic regimens are effective for initial, empirical treatment of presumed infection in patients with febrile neutropenia. The following factors can assist clinicians in antibiotic selection: local epidemiological situation (local patterns of infection and susceptibility of local bacterial isolates), patient clinical condition at the onset of fever, the risk for developing infection-related, serious medical complications, previous antibiotic therapy, patient medication allergy, as well as preexisting organ dysfunction.

Treatment with oral antibiotics

Carefully selected patients, determined to be at a low risk for developing infection-related complications during the course of neutropenia (see above) may be treated with oral antibiotic therapy as an alternative for intravenous monotherapy. Oral antibiotic are as safe as standard intravenous approach in terms of success rate and complications development at least when patients are managed in a hospital setting. The reference regimen is a combination of oral ciprofloxacin plus amoxicillin-clavulanate. For patients who are allergic to penicillin, the combination of oral clindamicin with oral ciprofloxacin is recommended.

Use of hematopoietic colony-stimulating factors

Colony stimulating factors are not recommended for routine use to treat febrile or afebrile neutropenic patients. The use of colony stimulating factors in neutropenic cancer patients should be guided by the recommendations given in the valid CPGs (5).

MONITORING (1,3)

Daily evaluation of febrile neutropenic patient is essential. In general, it includes site-specific history and examination, review of all previous culture, laboratory and imaging results, culturing of additional blood samples and specimens of specific sites of infection and diagnostic imaging of any organ suspected of having an infection. At least 3 to 5 days of antibiotic treatment are usually required to determine efficacy of the initial regimen. From this point, in general, further management is dictated by the patient's clinical condition, new clinical and /or microbiologic findings identifying the site of infection and /or the causative pathogen (patients with clinically or microbiologically documented infection versus patients with fever of unknown etiology), fever response to antibiotic treatment (patients afebrile within first 3-5 days of treatment versus patients with persistent fever), along with the recovery of neutrophils. The treatment with vancomycin should be considered if clinical or microbiological findings supporting its use are met (see above). The initiation of empiric antifungal therapy is warranted in neutropenic patient who remains febrile after 5-7 days of broad-spectrum antibiotics (persistent or recurrent fever), in whom no bacterial infection can be documented, and neutropenia is expected to last for longer than 5-7 more days. Amphothericin B deoxycholate has traditionally been the drug of choice, however, clinical studies also support the use of less toxic alternatives such as lipid formulations of amphotericin B, fluconasole, itraconazole, voriconazole, and caspofungin.

No specific period of treatment can be unequivocally recommended for all febrile neutropenic patients. The most important determinants of the duration of treatment are the documentation of infection and recovery of patient's neutrophil count. Recommendations for determining the duration of antibiotic treatment under various clinical conditions in patients with febrile neutropenia are provided in valid CPGs (1,3).

PREVENTION OF INFECTION (1,3)

The routine prophylaxis with antibacterial (TMP-SMZ or quinolones), antifungal (fluconazole, itraconazole) or with antiviral drugs in all afebrile neutropenic patients is not recommended.

In conclusion, febrile neutropenia has been a changing syndrome over past years. Empirical antibiotic treatment of all neutropenic patients at the onset of fever remains the cornerstone of infection management. The specific composition of the empirical antibiotic regimen remains subject to change, due to changing pattern of pathogens, the emergence of antibiotic-resistant organisms, the appearance of the new clinical entities, the availability of new drugs and the improved models for patient's infection risk categorization. No specific antibi-

otic, combination of antibiotics or period of treatment can be universally recommended for all febrile neutropenic patients. Evidence based clinical practice guidelines related to the management of febrile neutropenia are developed to assist practitioners and patients in their decision making (1,3,6,7).

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