Klastersky. Int J Crit Care Emerg Med 2016, 2:016
Volume 2 | Issue 2
ISSN: 2474-3674

International Journal of
Critical Care and Emergency Medicine

Commentary: Open Access

How to Deal With Febrile Neutropenia in Chemotherapy - Treated Cancer Patients? A Comprehensive Approach to Prevention and Therapy

Jean A Klastersky*

Institut Jules Bordet, Centre des Tumeurs de l'Université Libre de Bruxelles, Brussels, Belgium

***Corresponding author:** *Jean A Klastersky, Institut Jules Bordet, Centre des Tumeurs de l'Université Libre de Bruxelles, Brussels, Belgium, E-mail: jean.klastersky@bordet.be*

Chemotherapy-induced neutropenia in patients with cancer were comprehensively discussed recently by Bennett *et al.* [1]. While similar appraisals are available in the literature [2,3], evaluation of the problem on a national basis is useful for practicing physicians as it take into consideration local aspects relating to microbiological epidemiology and general medical practice that can modulate international guidelines.

To understand the importance of assessing the strategies for the prevention and treatment of the morbid consequences of neutropenia in chemotherapy-treated cancer patients, the non-expert reader has to take into account both the historical evolution as well as the impacts of the most recent achievements.

The relationship between neutropenia and infection has been clearly established by Bodey *et al.* [4] early in the 1960's, in patients receiving chemotherapy for the treatment of acute leukemia. It was then shown that the severity of neutropenia and its duration predispose to infection by Gram negative bacilli and fungal pathogens, respectively. Because empirical therapy with antibiotics [5] or antifungal agents [6] results in defervescence in most patients with neutropenia and fever, it can be concluded that most febrile episodes in neutropenic patients are indeed due to an infectious process.

As a matter of facts, infection in neutropenic patients can be manifested only by fever, as inadequate neutrophil response attenuates the usual clinical signs and symptoms associated with infection in non-neutropenic patients [7]; this led to the concept of "febrile neutropenia" (FN), a syndrome recognized as a surrogate for potentially severe infection in chemotherapy-treated cancer patients. Because the infection in neutropenic patients can have a fulminant course, it has become accepted to treat those patients empirically with broad spectrum antibiotics (and antifungals) [8]. This paradigm of therapy has never been validated in a prospective controlled trial, but it gained wide acceptance based on its obvious efficacy.

FN complicates about 10% of the chemotherapy treatments and is associated approximately with 10% mortality [1]; therefore, FN remains a medical emergency, as early empirical therapy is the major factor for a favorable outcome. The most significant recent advance in the field has been the possible stratification of the management according to risk factors and the development of effective prophylaxis thru the use of GCSF.

The heterogeneity of the population of patients with FN, resulting from the increasing numbers of patients with solid tumors who are receiving chemotherapy, led to the concept of risk evaluation to tailor the therapeutic approach to these patients. The most effective scoring system for the evaluation of the risk of severe complications and death in patients with FN has been developed by the MASCC (Multinational Association for Supportive Care in Cancer) Infection Study Group [9] and has been validated in many studies, both in patients with solid and hematological tumors [10]. Its use has been recommended by international organizations such as ESMO (European Society of Medical Oncology) and IDSA (Infectious Diseases Society of America) [4,5]. Indeed, the calculation of the MASCC score, upon the presentation of the patient with FN, can separate between those patients with low risk of complications (< 5%) and death (< 1%) and those with an increased risk, leading to the different therapeutic options. However, it should be emphasized that FN is always a medical emergency, as the progression from a relatively stable condition into overwhelming sepsis may be fulminant; this is why it is recommended that the administration of antibiotics to a patient presenting with FN should not be less than 60 minutes [11]. In addition, as resistant bacteria are common in many places, the choice of empirical antimicrobial therapy should be based on local epidemiological data relative to bacterial resistance.

Patients with a low risk of complications (MASCC score ≥ 21) can probably be treated safely with oral antibiotics, provided there is no contra-indication to the oral route of administration and no like hood of resistance to the planned therapy. The most common regimens include amoxicillin-clavulanate plus ciprofloxacin or moxifloxacin [12]; obviously, patients receiving prophylactic fluoroquinolones should be treated with other regimens. The next question is whether those low-risk patients on oral antimicrobial therapy could be discharged early from the hospital. Although there are potential disadvantages with early hospital discharge (e.g. the risk of non-compliance and limited supervision) for low-risk patients with FN, overall there are many positive aspects, including enhanced quality of life for patients and lowered costs of care. The management of outpatients receiving oral antimicrobial therapy has been proven to be safe and effective, provided the patients are carefully selected [13].

In non-low-risk patients, with a lower than 21 MASCC score, the vital prognosis is much less favorable and most of the complications

ClinMed International Library

Citation: Klastersky JA (2016) How to Deal With Febrile Neutropenia in Chemotherapy - Treated Cancer Patients? A Comprehensive Approach to Prevention and Therapy. Int J Crit Care Emerg Med 2:016

Received: February 25, 2016: **Accepted:** May 31, 2016: **Published:** June 03, 2016

and deaths are due to sepsis [14]. These patients should be rapidly treated with intravenous antibiotics (piperacillin-tazobactam, meropenem) and hospitalized; those with an unstable condition or predictive factors for sepsis such as thrombocytopenia, elevated CRP and/or lactate, high fever (> 40 C), low granulocyte count (< 100) or clinical evidence of focal infection, should be admitted to intensive care units and closely monitored.

Patients with persistent neutropenia and prolonged fever in spite of broad spectrum antibiotic administration (most often patients with aggressively treated hematological diseases) are at risk of occult fungal infections, as already mentioned. Those patients might benefit from empirical or pre-emptive antifungal therapy [6].

Although a systematic approach to therapy of FN has been instrumental in decreasing the morbidity and mortality associated with it, it is important to stress that prophylaxis of infection in neutropenic patients is definitely possible today. The use of prophylactic antibiotics (quinolones) or antifungals (posaconazole) can lower substantially the risk of bacterial or fungal infections, respectively, in predisposed neutropenic patients. However, the use of chemoprophylaxis is limited by the risk of emergence of resistant bacterial or fungal strains.

The use of granulocyte colony stimulating factors (GCSF) provides a much more physiological way to prevent infection in neutropenic patients, thru more rapid recovery of a normal granulocyte count after chemotherapy. Comprehensive guidelines for the use of GCSF are available [15]. The use of GCSF decreases the morbidity related to infection and increases the overall quality of life of the patients; moreover, it makes chemotherapy more effective and the overall management of the patients less expensive.

To conclude, the most significant recent advance in the field has been the possible stratification of the management according to risk factors and the development of effective prophylaxis thru the use of GCSF.

Further progress will require continuing dedicated research.

References

1. Bennett CL, Djulbegovic B, Norris LB, Armitage JO (2013) Colony-stimulating factors for febrile neutropenia during cancer therapy. N Engl J Med 368: 1131-1139.
2. Freifeld A, Bow E, Sepkowitz K, Boeckh MJ, Ito JI, et al. (2011) Executive summary: clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by infectious disease society of America. Clin Infect Dis 52: e56-e93.
3. de Naurois J, Novitzky-Basso I, Gill MJ, Marti FM, Cullen MH, et al. (2010) Management of febrile neutropenia: ESMO Clinical Practice Guidelines. Ann Oncol 21 Suppl 5: v252-256.
4. Bodey GP, Buckley M, Sathe Y, Freireich EJ (1996) Quantitative relationship between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 64: 328-340.
5. Schimpff S, Satterlee W, Young VM, Serpick A (1971) Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. N Engl J Med 284: 1061-1065.
6. Klastersky J (2004) Antifungal therapy in patients with fever and neutropenia – more rational and less empirical? N Engl J Med 351: 1445-1447.
7. Sickles EA, Greene WH, Wiernik PH (1975) Clinical presentation of infection in granulocytopenic patients. Arch Intern Med 135: 715-719.
8. Klastersky J, Awada A, Paesmans M, Aoun M (2011) Febrile neutropenia: a critical review of the initial management. Crit Rev Oncol Hematol 78: 185-194.
9. Klastersky J, Paesmans M, Rubenstein EB, Boyer M, Elting L, et al. (2000) The Multinational Association for Supportive Care in Cancer Risk Index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. J Clin Oncol 18: 3038-3051.
10. Klastersky J, Paesmans M (2013) The Multinational Association for Supportive Care in Cancer (MASCC) risk index score: 10 years of use for identifying low-risk febrile neutropenic cancer patients. Support Care Cancer 21: 1487-1495.
11. Burry E, Punnett A, Metha A, Thull-Freedman J, Robinson L, et al. (2012) Identification of educational and infrastructural barriers to prompt antibiotic delivery in febrile neutropenia: a quality improvement initiative. Pediatr Blood Cancer 59: 431-435.
12. Kern WV, Marchetti O, Drgoina L, Akan H, Aoun M, et al. (2013) Oral antibiotics for fever in low-risk neutropenic patients with cancer: a double-blind, randomized, multicenter trial comparing single daily moxifloxacin with twice daily ciprofloxacin plus amoxicillin/clavulanic acid combination therapy-EORTC infectious diseases group trial XV. J Clin Oncol 31: 1149-1156.
13. Innes H, Lim SL, Hall A, Chan SY, Bhalla N, et al. (2008) Management of febrile neutropenia in solid tumors and lymphomas using the Multinational Association for Supportive Care in Cancer (MASCC) risk index: feasibility and safety in routine clinical practice. Support Care Cancer 16: 485-491.
14. Ahn S, Lee YS, Chun YH, Kwon IH, Kim W, et al. (2011) Predicitive factors of poor prognosis in cancer patients with chemotherapy-induced febrile neutropenia. Support Care in Cancer 19: 1151-1158.
15. Aapro MS, Bohlius J, Cameron DA, Dal Lago L, European Organization for Research and Treatment of Cancer, et al. (2011) 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumors. Eur J Cancer 47: 8-32.