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Original article

Results of high-risk neutropenia therapy of hematology–oncology patients in a university hospital in Uruguay

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ABSTRACT

Background: Febrile neutropenia is an important cause of mortality and morbidity in hematology–oncology patients undergoing chemotherapy. The management of febrile neutropenia is typically algorithm-driven. The aim of this study was to assess the results of a standardized protocol for the treatment of febrile neutropenia.
Methods: A retrospective cohort study (2011–2012) was conducted of patients with high-risk neutropenia in a hematology–oncology service.
Results: Forty-four episodes of 17 patients with a median age of 48 years (range: 18–78 years) were included. The incidence of febrile neutropenia was 61.4%. The presence of febrile neutropenia was associated with both the duration and severity of neutropenia. Microbiological agents were isolated from different sources in 59.3% of the episodes with bacteremia isolated from blood being the most prevalent (81.3%). Multiple drug-resistant gram-negative bacilli were isolated in 62.5% of all microbiologically documented infections. Treatment of 63% of the episodes in which the initial treatment was piperacillin/tazobactam needed to be escalated to meropenem. The mortality rate due to febrile neutropenia episodes was 18.5%.
Conclusion: The high rate of gram-negative bacilli resistant to piperacillin/tazobactam (frontline antibiotics in our protocol) and the early need to escalate to carbapenems raises the question as to whether it is necessary to change the current protocol.

Introduction

Febrile neutropenia (FN) is among the leading causes of mortality and morbidity in hematology-oncologic patients undergoing intensive cytotoxic chemotherapy. It implies a large economic and social burden on the health system[1,2] as it represents the most frequent complication in these patients.[3] Infectious complications are the main cause of death not related to cancer progression.

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The incidence of FN was reported in around 10–50% of patients with solid tumors and up to 80% of those with hematologic malignancies.[4] In the pre-empiric antibiotics era, mortality due to infectious complications in patients receiving intensive chemotherapy was as high as 70%.[5] Nowadays, this figure has dropped to between 1% and 18%,[4,6,7] but still represents a serious problem that must be addressed actively using a multidisciplinary approach.

FN is a potentially life-threatening situation that requires prompt medical intervention. As neutropenic patients have an impaired inflammatory response, infection can occur with minimal signs and symptoms and progress rapidly, evolving with hypotension, renal failure, acidosis, or other life-threatening complications that lead to sepsis with multiorgan failure.[2] As fever may constitute the isolated sign in these patients, it should be considered a real emergency. Early recognition of FN is critical to initiate broad-spectrum, empiric systemic antibacterial therapy promptly in order to avoid progression to sepsis and possible death.[8]

The prophylactic use of granulocyte colony-stimulating factor (G-CSF) to reduce the incidence of FN, as well as to enhance antibiotic therapy, has been widely studied in the last few years with conflicting results.[9] In 2004 a Cochrane collaboration review concluded that the use of growth factors combined with antibiotic therapy in established FN caused by chemotherapy reduced the hospital stay and the duration of neutropenia, but the overall mortality was not influenced significantly.[9] Furthermore, a meta-analysis in 2011 concluded that the use of G-CSF as primary prophylaxis reduced the incidence of FN in patients receiving chemotherapy for solid tumors and lymphoma.[10]

The management of FN is typically algorithm-driven. The effectiveness of the antibacterial protocol proposed by international guidelines to reduce FN-related mortality has already been reported.[4,7] Thus, the aim of this study was to assess the impact of the implementation of international recommendations as the standardized protocol of local guidelines in 2011.[11] One of the specific objectives of this study was to assess whether the protocol was correctly followed in each case.

Methods

This is an analytic observational, retrospective, cohort study conducted from July 2011 to August 2012. The data were collected from the medical charts preserving the confidentiality of each patient.

Patients

The inclusion criteria were patients older than 18 years, undergoing intensive chemotherapy in the Hematology–oncology Department of the Hospital de clínicas Dr. Manuel Quintela in Montevideo, Uruguay, for whom high-risk neutropenia was expected. Patients treated in this service that, because of their personal risk factors and comorbidities, suffered high-risk neutropenia but did not receive intensive chemotherapy were excluded.

Definitions

Intensive chemotherapy was defined as chemotherapy regimens that cause high-risk neutropenia such as those used to treat acute myeloid leukemia, acute lymphoid leukemia, Burkitt lymphoma, and second lines for Hodgkin's and Non-Hodgkin's lymphoma. High-risk neutropenia was defined as one that is expected to last more than seven days.

Neutropenia was defined as a neutrophil count under 0.5×10^9/L or under 1.0×10^9/L when it was expected to reach under 0.5×10^9/L within the following 48 h. Severe neutropenia was defined as a neutrophil count under 0.1×10^9/L. Patients diagnosed with acute leukemia were considered to have functional neutropenia even though they had neutrophil counts above 1.0×10^9/L. Fever was defined as an oral temperature above 38 °C or a persistent temperature above 37.8 °C.

Alarm signs were defined in the protocol as the presence of at least one of the following: heart rate above 100 beats per minute, respiratory frequency above 20 breaths per minute, low carbon dioxide under 35 mmHg, oxygen under 100 mmHg or oxygen saturation under 93% while receiving supplementary oxygen, capillary refill longer than eight seconds, low pH, base excess under 5 meq/L, serum lactate above 2 mmol/L, systolic blood pressure under 90 mmHg, confusion, or oliguria.

Clinical and laboratory studies

When a febrile episode was diagnosed, a detailed physical examination was made and repeated daily. Additionally, samples of blood, and urine and samples from other suspected infection sites were taken before the initiation of empirical antibiotic treatment. If the patient had a central venous catheter, at least one blood culture was prepared for each lumen of the catheter and one of a peripheral vein. A chest radiograph was obtained and urinalysis performed within the first 24 h. Computed tomographies (CT) of the lung, head, sinuses, abdomen, and pelvis were performed as clinically indicated. Routine hematological investigations and biochemical analysis were carried out before treatment was started and every three days thereafter during the course of the therapy.

Additionally, C-reactive protein and procalcitonin levels were determined. A sinus and lung CT and serial galactomannan antigen test were performed prior to the initiation of antifungal therapy when a fungal infection was suspected in patients who remained febrile after 6–7 days of broad-spectrum antibiotic treatment.

Antibiotic treatment protocol

The protocol consisted in the use of a broad-spectrum antimicrobial (Figure 1).[11] Piperacillin–tazobactam therapy (4.5 g every 6 h) was started in patients without one of the following: alarm signs, more than one week of hospital stay, or having received ciprofloxacin or third-generation cephalosporin as prophylaxis within the previous 30 days. The other patients received meropenem (1 g every 8 h). Prophylactic antiviral (acyclovir) and antifungal (fluconazole) medications were given in all cases.

The initial empirical treatment was modified by changing the medication to meropenem, if there was: (a)