Outpatient management of febrile neutropenia in children with cancer

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Abstract

Optimizing the therapeutic strategies based on the results of randomized studies comparing different regimens led to a better prognosis of nearly all pediatric malignancies during the past four decades. Fever and neutropenia (FN) is a common complication in patients undergoing chemotherapy to treat cancer. There is no consensus on when standard therapy can be safely reduced; this lack of consensus leads to important variations in management of FN between different institutions, usually conducted according to local attitudes. To address this issue, the Infection working group of the Italian association for pediatric hematology oncology (AIEOP) organized a consensus meeting. This paper reports the agreement derived from this meeting.

Introduction

Optimizing the therapeutic strategies based on the results of randomized studies comparing different regimens led to a better prognosis of nearly all pediatric malignancies during the past four decades. While morbidity and mortality of the malignancy itself have been reduced, infections, with or without severe neutropenia, remain the most frequent potentially lethal complications of therapy.[1]

Fever and neutropenia (FN) is a common complication in patients undergoing chemotherapy to treat cancer. For decades empiric treatment with intravenous (IV) broad-spectrum antibiotics in an in-patient setting has been the mainstay of therapy for FN in pediatric patients.[2] With the advent of aggressive management of FN, the outcome of episodes in children improved dramatically. Mortality fell from 30-40% in the 1970s to 1% in the late 1990s.[3] To achieve those results, the standard of supportive care became very protective; yet, this probably led to the overtreatment of a substantial group of patients. All these measures have a potential to induce side effects, such as promoting microbial resistances in the case of antibiotics, reducing the patient's quality of life, and further increasing the treatment costs.[1,4] On the other hand, there is no consensus on when standard therapy can be safely reduced; this lack of consensus leads to important variations in management of FN between different institutions, usually conducted according to local attitudes.

To address this issue, the Infection working group of the Italian Association for Pediatric Hematology Oncology (AIEOP) organized a consensus meeting. This paper reports the agreement derived from this meeting.

Patient stratification

Large-scale adult studies have produced detailed scoring systems to identify episodes of low-risk febrile neutropenia within the first 24 h of initial presentation.[5,6] The ultimate goal of risk stratification is to identify patients at *low risk* in order to offer them less aggressive therapeutic approaches, such as shortened antimicrobial treatment, early hospital discharge, oral antibiotic therapy, and outpatient management.

In children with FN however, presenting characteristics and outcome differ significantly from those found in adult patients.[7] Models of risk prediction for FN-related morbidity and mortality and risk-based stratification of care including outpatient and oral antibiotics have been suggested in pediatic patients.[8-12] The generalization of these study results, however, is limited due to a variety of inconsistencies, including i) different definitions of outcome criteria; ii) missing data sets in retrospective studies and, and most importantly; iii) the high variability of patient cohorts including ethnic diversities, sample size, and center-to-center variations (single-center vs. multi-center trials).[13] However, only a selection of parameters have proven to have value in the various prospective intervention studies: good clinical condition, no comorbidity needing hospitalization, indication or evidence of bone marrow recovery/activity, being afebrile, control of local infection, negative BC, low inflammation laboratory parameters (IL-8, CRP), chemotherapy ≥7 days previous, neutropenia expected to prolong <10 days, stable disease or remission.[14] In this setting non-medical barriers (e.g language barriers, reliable family/caretakers, the possibility of being able to contact and come to the hospital within a short period of time), to outpatient treatment of Fever and Neutropenia in Children With Cancer[11,14] should be carefully considered. Finally, even among those patients who may be considered to do well enough to be eligible for an outpatient care, in many cases either the family or the treating physician did not find the prospect of outpatient care appealing enough.[9,15] In fact, according to data from Sung *et al*.,[16] only 53% of parents would choose outpatient oral antibiotic management for low-risk febrile neutropenia.

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Which treatment approach for patients considered at lower risk?

However, despite the lack of a single, validated risk-prediction system for paediatric from febrile neutropenia, many studies have compared differing approaches to treatment in febrile neutropenia episodes identified as low risk by local criteria. Useful approaches to reduced-intensity treatment include i) early discharge on ambulatory intravenous treatment; ii) step-down treatment (starting with intravenous antibiotics and moving to oral treatment after a period of 8-48 h); iii) oral antibiotics from the outset of the episode, given in the hospital or as an outpatient.

Heterogeneity of the therapeutic approaches

An international consensus on when and how to assess the risk of which kind of adverse events in pediatric FN is still lacking[14,17] and this induced major variations among the policies adopted among different centers participating to the AIEOP, as well as in other countries and cooperative groups. In this context Boracina *et al*. undertook a cross sectional survey of all Canadian tertiary pediatric centers in order to better understand the Canadian practices for the management of febrile neutropenic children and to determine the prevalence of alternatives to traditional treatment for patients at low risk of severe bacterial infection.[18] The authors reported that three out of seventeen Canadian centers carry out exclusively traditional management. The remaining 14 offer modified treatment for low risk chil-

dren, mostly they carry out an early discharge approach; only a few centers implement complete outpatient management.

The striking variation across the UK in the treatment of febrile neutropenia has been also reported from Phillips *et al.*; they documented that a child with acute lymphoblastic leukemia is with chemotherapy at the regional center, according to the national treatment protocol, regardless where he lives.[19] Yet, they report that the policies adopted by the different hematology-oncology centers participating in the United Kingdom Children's Cancer Study Group varied very widely, in almost all aspects, starting from the definitions of *febrile* and *neutropenic*, up to the use of risk stratification and duration of antibiotic therapy.[20]

Comparably, the results of a survey performed in 2007 on eleven italian centers, members of the AIEOP network, showed a large variability of treatment strategies adopted in episodes of febrile neutropenia.

How to select the therapeutic strategy?

After defining the best criteria to define the risk of each child to develop sepsis, the next step is how to harmonize the treatments and what therapeutic method to use: i) Home treatment or day-hospital every day? ii) Treatment with antibiotics orally or parenterally? iii) Which molecules to use? iv) How long should treatment last? The most convenient choice would be an oral product, since it improves compliance and, in a setting of low risk for sepsis, allows remote monitoring of the conditions of the child who may remain at home until the end of treatment. The timing and type of the controls during the treatment, depend on the clinical and logistic situation. However, in the presence of features such as incompletely low risk, or bad compliance to treatment, also according to the distance of the child's domicile from the caregiver site, single daily dose of parenteral antibiotics may be considered.

In the case of an oral therapy, third generation cephalosporin or amoxicillin/clavulanate seem to be the best choice; both drugs have a good spectrum and confortable formulations.

If parenteral drugs appear to be preferred, ceftriaxone might to be the first choice. The possibility of a single daily parenteral administration and the good spectrum are his characteristics. Yet, a good knowledge of the local epidemiology of bacterial isolates will be very helpful in order to select and then to update the empiric antibiotic therapy.[21] In particular situations, quinolones might represent the best choice, especially if the child experiences multiple infections or gram negative bacteria are prevalent. We have to consider that ciprofloxacin and levofloxacin, the more used quinolones, have a different spectrum and a different use.

In conclusion, many studies are published regarding the home-patient treatment, but they are not homogeneus in selection criteria, sample size and used drugs. Thus, they do not allow a conclusive comparison. In this document, the panel of expert of the Infection working group of the Italian association for pediatric hematology oncology (AIEOP) summarize the consensus achieved in the meeting. Given the obvious difficulties in organizing a prospective study at this stage, the panel suggest to address these issues within the AIEOP network by defining a pediatric score for definition of risk assessment; furthermore, the group expresses its interest in defining a common set of drugs to be tested in a prospective data recruitment. This might provide the basis for definition of a uniform approach to outpatient treatment.

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