The role of prophylaxis of bacterial infections in children with acute leukemia/non-Hodgkin lymphoma

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Abstract

Infections represent a well-known complication of antineoplastic chemotherapy that may cause delay of treatment, with alteration of the antineoplastic program and dose-intensity, or even the death of a patient that could heal from his/her neoplasia. Bacterial infections are a major cause of morbidity and mortality in patients who are neutropenic following chemotherapy for malignancy. Therefore a program of antibiotic prophylaxis for febrile neutropenia may be considered in the management strategy of cancer patients.

Comments

When such a program is planned some questions have to be asked.1 The first should be which disease we want to prevent: febrile neutropenia, bacteremia or other bacterial invasive infections, or death from bacterial disease, and the efficacy of the prophylaxis against the specific disease we chosen. The frequency of the disease to prevent and the effectiveness of prophylaxis will condition the number to treat (NNT), i.e. the number of patients that will receive prophylaxis to prevent 1 of the event we want to avoid. The lower the NNT, the higher is the probability that prophylaxis will be effective (i.e. low NNT yes prophylaxis, high NNT no prophylaxis). The NNT depends on frequency of the disease in the controls, consequences of the treatments (efficacy vs toxicity and/or drug interactions), costs (of prophylaxis and the treatment of the disease if not prevented), and selection of resistances and there is no standardization to decide if the NNT is satisfactory, i.e. in a disease with highly severe consequences also a high NNT could be acceptable.2 Many clinical trials have demonstrated the efficacy of different antibiotics (mainly cotrimoxazole, ciprofloxacin, amoxicillin-clavulanate) as prophylaxis of febrile neutropenia both in children and adults with leukemia,3,4 with different NNT according to the type of disease that should be prevented: the lowest for fever, the highest for death.5

However in the absolute majority of these studies patients were enrolled only once (for statistical reasons) and the effectiveness of prophylaxis during repeated neutropenic periods has been studied only in one, very questionable clinical trial in adults solid tumors (by the way the effect of prophylaxis was could be observed only during the neutropenic period following the first cycle of chemotherapy, but not in the subsequent ones).6,7 Therefore the effectiveness of prophylaxis during repeated neutropenic periods (i.e. the normal course of antineoplastic chemotherapy) must still be demonstrated, especially in leukemic patients. In this sense, the analysis of epidemiological data in neutropenic children with cancer shows that the risk of repeated febrile episodes during subsequent neutropenic periods is influenced by the aggressiveness of chemotherapy in acute leukemia/non-Hodgkin lymphoma and the level of neutropenia at onset in solid tumors, with no effect estimated for antibacterial prophylaxis in both cases.9

The second question to be answered planning a prophylactic program is if the even we want to prevent it a severe one (Yes: prophylaxis, No: no prophylaxis), and, if it could be easily treated in case of occurrence. The most frequent infectious event in neutropenic children is fever of unknown origin, which occurs in near 50% of neutropenic periods following aggressive treatment for acute leukemia/non-Hodgkin lymphoma or conditioning regimen for hemopoietic stem cell transplant, and in less than 1/3 of neutropenic periods following less aggressive chemotherapy for acute leukemia/non-Hodgkin lymphoma or any type of treatment for solid tumors.10 Gram-negative bacteremia that is the most severe (and feared) complications and one of the major targets of prophylaxis is diagnosed in no more than 15% of episodes of febrile neutropenia in children.10 The majority of episodes of febrile neutropenia is treated quite easy, with a reasonably low rate of failure (i.e. the need to change the initial treatment treatment or mortality) and the most recent pediatric guidelines indicates monotherapy with a beta-lactam active against Pseudomonas as the most reasonable choice for initial empirical treatment.11

However, in presence of infection due to resistant strains the risk of failure increases, with a significant reduction of patients’ survival.12,13 Selection of resistant strains is probably the worst adverse event induced by widespread use of antibacterial prophylaxis in neutropenic cancer patients.14,15 In spite of many inferences from clinical trials and meta analyses suggest that administration of prophylaxis had no impact on he selection of resistant bacteria,1,5,16 the search for colonization by resistant strains is generally absent in randomized clinical trials on antibacterial prophylaxis of febrile neutropenia. Indeed, only in one recent randomized clinical trial of antibiotic prophylaxis for febrile neutropenia in children the risk of selection of resistant strains during antibacterial prophylaxis was addressed in a satisfactory way with evaluation of intestinal flora colonizing the patients before and after the administration of prophylaxis.6

In general, only epidemiological studies analyzing bacterial infections/colonization when a prophylactic program is adopted in a specific patients’ population may give a correct evaluation of the risk of selecting resistant bacteria induced by antibiotic prophylaxis. In this sense, data from a pediatric epidemiological study clearly show that the widespread use of antibacterial prophylaxis causes ecological changes, with acquisition of resistant pathogens also in patients who did not receive antibiotics for preventing febrile neutropenia.19

As specifically regards antibacterial prophylaxis of febrile neutropenia in children with acute leukemia/non-Hodgkin lymphoma, only 2 randomized, double-blind, placebo-controlled clinical trials have been performed in this setting so far.4,6 In the first one, the administration of amoxicillin-clavulanic acid significantly reduced, ~21%, the incidence of fever in neutropenic children with acute leukemia/lymphoma, while no effect could be demonstrated in solid tumors. In the second one performed in acute leukemia, administration of ciprofloxacin determined a 23% reduction of febrile episodes compared with placebo. In both cases the NNT to prevent one episode of febrile neutropenia was very similar, 5 in the first and 4 in the second (no NNT could be calculated for bacteremia or death since the studies were not planned to analyze the effect of

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Infections in immunocompromised patients

...and Gram-negative bacteremia, absence of effect during repeated neutropenic periods and increasing in severe infections due to antibiotic-resistant strains, it is my personal opinion that now is the time when antibacterial prophylaxis in neutropenic children with cancer should be abandoned at least during chemotherapeutic regimens.

References