Antibacterial prophylaxis in neutropenic children with cancer

Angelica Barone

Pediatric Hematology and Oncology Unit, Department of Pediatrics, Azienda Ospedaliero-Universitaria di Parma, Italy

Abstract

During the period of neutropenia induced by chemotherapy, patients have a high risk of infection. The use of antibiotic prophylaxis to reduce neutropenia-related complications in patients with cancer is still disputed. Recent meta-analysis and clinical trials demonstrated that antibiotic prophylaxis with quinolones reduces febrile episodes, bacterial infections and mortality in adult oncological patients with neutropenia induced by chemotherapy in acute leukaemia. In paediatric patients, the only randomized, double-blind, prospective study until now suggests that amoxicillin/clavulanate may represent an effective prophylactic treatment in reducing fever and infections in oncological children with neutropenia, with an efficacy that is statistically demonstrated only in patients with acute leukaemia. Considering the risk of resistances, antibiotic-prophylaxis should be used only in selected patients.

Introduction

During the period of neutropenia induced by chemotherapy, patients have a high risk of infections, with a risk-rate related to the level and duration of neutropenia.[1] Bacterial infections, proved in a minority of cases, are a major cause of disease and death in neutropenic patients, with some differences according to the aggressiveness of chemotherapy.[2,3] The use of antibiotic prophylaxis to reduce neutropenia-related infectious complications in patients with cancer, mostly used in adults, is still disputed. These antimicrobial agents are given to patients at the beginning of neutropenia, without fever or other signs of infection.[4] Neutropenia is defined as an absolute neutrophil count lower than 500/mmc or under 1.000/mmc if rapidly decreasing.[5] The risk is higher if neutropenia lasts longer than 7 days. Fever is defined by body temperature equal to or higher than 38.5°C or a temperature of 38°C lasting for more than an hour or 38°C or more measured at least twice in 12 hours.[5,6]

Methods

The terms *neutropenia* & similar, *antibiotic* & similar, *prophylaxis* & similar, *cancer* & similar, *fever* & similar were crossed in the Cochrane Library, MEDLINE and EMBASE from January 1980 to October 2010.

Results

Considering that 80% of infections in neutropenic patients originate from endogenous bacterial flora, and about half of these are acquired in the hospital,[7] the first approach was the reduction of intestinal flora through the use of non-absorbable antibiotics. Intestinal decontamination was either total or partial, if anaerobic flora was preserved. Antibiotics mostly used were gentamicin, vancomycin, colistin or neomycin/polymyxin.[8] However, a poor patient compliance associated with the risk of resettlement by opportunistic or resistant bacteria led to the failure of the prophylaxis.[9] Selective decontamination required careful monitoring of the intestinal flora. Afterwards the drug of choice became TMP-SMX, frequently used in association with nystatin or amphotericin B, even if it sometimes lengthened neutropenia.[10] However the administration of TMP-SMX was a systemic prophylaxis, as far as it is an adsorbable antibiotic. Fluoroquinolones are interesting drugs for oral prophylaxis, due to their bioavailability, wide antibacterial spectrum, sparing of the anaerobic intestinal flora, bactericide action, good tolerance and absence of myelosuppressive effect.[11] However, their use is contraindicated for prophylaxis in patients under 18 years of age because of their possible interference with osteocartilagineous development.

Guidelines from the Infectious Diseases Society of America (IDSA) in 2002 recommended the use of antibiotic prophylaxis for a period as short as possible and in a small number of patients, in order to avoid the risk of ddeveloping bacterial resistance and beacuse of the unproven reduction in mortality despite the decreased rate of fever episodes.[5] However some meta-analysis and clinical trials showed that prophylaxis with fluoroquinolones reduces fever episodes, clinically and microbiologically proven bacterial infections, infection-related and overall mortality in adult patients with acute leukaemia.[2,12,13] A large clinical trial in adult patients with solid tumours undergoing standard chemotherapy did not show the same results.[14] Guidelines from ECIL (European Conference on Infections in Leukaemia) and NCCN (US-National Comprehensive Cancer Network) recommend prophylaxis with quinolones in adult patients undergoing chemotherapy for acute leukaemia.[15,16] According to other Authors, prophylaxis with quinolones should also be considered in patients with solid tumour or lymphoma at the first block of chemotherapy since it is frequently associated with a 4°-degree neutropenia.[17-19]

In paediatric patients, the only randomized, double-blind 2-year multicentric AIEOP (Italian Association of Pediatric Hematology and Oncology) prospective study on 173 children suggested that amoxicillin/clavulanate may be an effective prophylactic treatment in reducing fever and infections in neutropenic children with cancer, although its efficacy has been statistically demonstrated only in patients with acute leukaemia and lymphoma. In the general population a clinically significant reduction (12%) in fever and infections was observed, comparing to the placebo group, although not statistically significant. Authors concluded that, due to the risk of developing resistances, antibiotic prophylaxis should be used with caution in a selected group of patients and for short periods of time.[20] Another paediatric study assessed the use of ciprofloxacin in 69 children with acute lymphoblastic leukaemia during reinduction phases, observing a statistically significant reduction in the incidence of Gram-negative bacteraemias and related admissions to the hospital; however the design of the study considered previous patients as control group.[21] A retrospective study conducted by the St. Jude group on antibiotic prophylaxis in 78 consecutive paediatric patients with acute myeloid leukaemia undergoing chemotherapy showed a significant reduction in incidence and mortality by septicaemia after prophylaxis with

Correspondence: Angelica Barone, Pediatric Hematology and Oncology Unit, Department of Pediatrics, Azienda Ospedaliero-Universitaria di Parma, via Gramsci 14 - 43100 Parma, Italy.
Tel. +39.0521.702210 - Fax: +39.0521.702360.
E-mail: abarone@ao.pr.it

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intravenous cefepime or intravenous vancomycin associated with oral ciprofloxacin.[4]

There are few data on what concerns repeated neutropenic periods in the same patients. The positive effect of antibacterial prophylaxis reported in a meta-analysis considered randomized trials including only one neutropenic period per patient.[2] This beneficial effect of prophylaxis may disappear in patients with repeated neutropenic periods as shown by Castagnola[3,20] and Cullen.[14] In order to evaluate the efficacy of repeated cycles of antibiotic prophylaxis, the number of multicenter clinical trials with a very large number of oncological patients should be increased.

The prolonged administration of wide spectrum antibiotics can cause either the onset of bacterial resistance and toxicity. The onset of resistant strains is a justified concern, and has been reported by centres using prophylaxis with fluoroquinolones.[22-24] However a large and recent meta-analysis was not able to demonstrate a significant increase in colonization and infections caused by fluoroquinolone-resistant bacteria in patients undergoing prophylaxis.[25] However these results are limited by the lack of data reported in trials: in less than half of the studies microbiologic surveillance was assessed and data on resistant bacteria colonization were reported; less than a third reported data on quinolone-resistant bacteria infections. Observation length was not prolonged enough to properly evaluate the effect of antibiotic prophylaxis on resistances. Therefore, at the moment, long-term effects of antibiotic prophylaxis on microbiologic resistances are still unknown.[12,26]

Discussion

There are some patient groups that may benefit from antibiotic prophylaxis. However, the wide and prolonged use of antibiotic prophylaxis can lead to the onset of resistant bacteria, nullifying the effect of prophylaxis. Therefore, antibiotic prophylaxis in pediatric patients with cancer should be used only in selected cases of acute leukaemia, with amoxicillin/clavulanate (at a dose of 25 mg/kg twice a day), at the end of chemotherapy blocks, since quinolones are contraindicated in patients under 18 years of age. The choice of a prophylaxis policy for patients at higher risk of infections requires the adoption or the implementation of a microbiological surveillance program.

References

1. Pizzo PA. Management of fever in patients with cancer and treatment-induced neutropenia. N Engl J Med 1993;328:1323-32.
2. Gafter-Gvili A, Fraser A, Paul M, Leibovici L. Met-Analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. Ann Intern Med 2005;142:979-95.
3. Castagnola E, Fontana V, Caviglia I, et al. A prospective study on the epidemiology of febrile episodes during chemotherapy-induced neutropenia in children with cancer or after hemopoietic stem cell transplantation. Clin Infect Dis 2007;45:1296-304.
4. Kurt B, Flynn P, Shenep JL, et al. Prophylactic antibiotics reduce morbidity due to septicemia during intensive treatment for pediatric acute myeloid leukemia. Cancer 2008;113:376-82.
5. Hughes WT, Armstrong D, Bodey GP, et al. 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 2002;34:730-51.
6. Viscoli C, Castagnola E. Prophylaxis and empirical therapy of infection in cancer patients. In: Mandell, Douglas and Bennett'. Principles and Practice of Infectious Diseases. 6th ed. Churchill Livingstone; 2005; p. 3442-62.
7. Schimpff SC, Young V, Green E, et al. Origin of infection in acute non-lymphocytic leukemia: significance of hospital acquisition of potential pathogens. Ann Int Med 1972;77:707-15.
8. Hawthorn JW. Critical appraisal of antimicrobials for prevention of infections in immunocompromised hosts. Hematol Oncol Clin N Am 1993;7:1051-99.
9. Guiot HF, van der Broek J, van dee Meer JW, van Furth R. Selective antimicrobial modulation of the intestinal flora of patients with acute nonlymphocytic leukemia: a double blind, placebo-controlled study. J Infect Dis 1983;147:615-23.
10. Gualtieri RJ, Donowitz GR, Kaiser DL, et al. Double-blind randomized study of prophylactic trimethoprim/sulfametoxazole in granulocytopenic patients with hematologic malignancies. Am J Med 1983;74:934-40.
11. Engels EA, Lau J, Barza M. Efficacy of quinolone prophylaxis in neutropenic cancer patients: a meta-analysis. J Clin Oncol 1998;16:1179-87.
12. Bucaneve G, Micozzi A, Menichetti F, et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Engl J Med 2005;353:977-87.
13. Leibovici L, Paul M, Cullen M, et al. Antibacterial prophylaxis in neutropenic patients. Cancer 2006;107:1743-51.
14. Cullen M, Steven N, Billingham L, et al. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. N Engl J Med 2005;353:988-98.
15. Meunier F, Lukan C. The first European Conference on Infections in Leukaemia. Eur J Cancer 2008;44:2112-7.
16. Segal BH, Freifeld AG, Baden LR, et al. Prevention and treatment of cancer-related infections. J Natl Compr Cancer Netw 2008;6:122-74.
17. Cullen M, Billingham L, Gaunt C et al. Rational selection of patients for antibacterial prophylaxis following chemotherapy. J Clin Oncol 2007;25:4821-8.
18. Pascoe J and Steven N. Antibiotics for the prevention of febrile neutropenia. Curr Opinion Hematol 2009;16:48-52.
19. Cullen M and Baijal S. Prevention of febrile neutropenia: use of prophylactic antibiotics. British J Cancer 2009;101:S11-14.
20. Castagnola E, Boni L, Giacchino M, et al. A multicenter, randomized, double-blind placebo-controlled trial of amoxicillin/clavulanate for the prophylaxis of fever and infection in neutropenic children with cancer. Pediatr Infect Dis J 2003;22:359-65.
21. Yousef AA, Fryer CJH, Chedid FD, et al. A pilot study of prophylactic ciprofloxacin during delayed intensification in children with acute lymphoblastic leukaemia. Pediatr Blood Cancer 2004;43:637-43.
22. Castagnola E, Haupt R, Micozzi A, et al. Differences in the proportions of fluoroquinolone-resistant Gram-negative bacteria isolated from bacteraemic children with cancer in two Italian centres. Clin Microbiol Infect 2005;11:505-7.
23. Kern WV, Klose K, Jellen-Ritter AS. Fluoroquinolone resistance of Escherichia coli at a cancer centre: epidemiological evolution and effects of discontinuing and re-introducing quinolone use in neutropenic patients with leukaemia. Eur J Clin Microb Infect Dis 2005;24:111-8.
24. Ito JI, Tegtmeier BR, O'Donnell MR. Antibacterial prophylaxis in children with cancer and neutropenia. N Engl J Med 2006;354;1.
25. Gafter-Gvili A, Paul M, Fraser A, Leibovici L. Effect of quinolone prophylaxis in afebrile neutropenic patients on microbial resistance: systematic review and meta-analysis. J Antimicrobial Chemotherapy 2007;59:5-22.
26. Viscoli C. Antibacterial prophylaxis in neutropenic patients. Int J Antimicrobial Agents 2007;305:560-5.