Chemoprophylaxis of Bacterial Infections in Granulocytopenic Patients with Ciprofloxacin

D.		Dennig
H.H.		Fülle
K.P.		Hellriegel

2nd Department of Internal Medicine, Moabit Hospital, Berlin

Key Words

Ciprofloxacin
Infection prophylaxis
Selective decontamination
Granulocytopenia
Cancer patients

Summary

The trial was conducted to evaluate the antimicrobial prophylactic efficacy of ciprofloxacin in reducing the frequency of infections in granulocytopenic patients. The frequency of infections was evaluated in 34 patients with acute non-lymphoblastic leukemia, acute lympho-blastic leukemia, blast crisis of chronic myelogenous leukemia and other malignancies. 46 courses of oral prophylactic treatment with 500 mg ciprofloxacin twice daily were administered. While there was no infection in 61% of treatment courses, fever over 38°C (axillary) occurred in 39%. 6 patients had a fungal pulmonary infection, one patient a supposed viral pneumonia, and only two patients had a documented bacterial infection. There were no severe side effects. We conclude that ciprofloxacin is a potent drug in prophylaxis of bacterial infections in cancer patients with therapy-induced granulocytopenia.

Request for reprints to: Prof. Dr. med. K. P. Hellriegel, II. Innere Klinik, Krankenhaus Moabit, Turmstraße 21, D-1000 Berlin 21

Zusammenfassung und Schlüsselwörter

Ziel der Untersuchungen war die Frage, ob mit Ciprofloxacin die Häufigkeit bakterieller Infektionen bei granulozytopenischen Patienten verringert werden kann. In 46 Behandlungszyklen bei 34 Patienten mit akuter nicht-lymphatischer Leukämie, akuter lymphoblastärer Leukämie, Blastenschub einer chronischen myeloischen Leukämie und anderen bösartigen Erkrankungen wurde die Infektionshäufigkeit unter einer oralen Prophylaxe mit 2 × 500 mg Ciprofloxacin täglich ermittelt. 61% der Behandelten blieben fieberfrei. Von 18 Patienten mit Fieber über 38°C hatten sechs Patienten eine Pilzpneumonie, ein Patient eine Pneumonie vermutlich viraler Genese und zwei Patienten eine nachgewiesene bakterielle Infektion. Schwere Nebenwirkungen wurden nicht beobachtet. Ciprofloxacin erweist sich als zuverlässiges Medikament zur Prophylaxe bakterieller Infektionen bei Tumorpatienten mit therapieinduzierter Granulozytopenie.

Ciprofloxacin – Infektionsprophylaxe – Selektive Dekontamination -Granulozytopenie – Tumorpatienten

Cytotoxic chemotherapy of patients with neoplastic diseases requires different kinds of supportive treatment. Decreasing the rate of infections during prolonged granulocytopenia is one of the most important strategies in supportive care. There is a correlation between frequency and severeness of infections and duration and degree of granulocytopenia. Infections occurring in

granulocytopenic patients are caused by the potentially pathogenic aerobic flora of the intestinal tract. For prophylaxis antimicrobial drugs are applied to selectively reduce the aerobic flora of the intestinal tract without disturbing the less pathogenic anaerobic flora. In reducing the proliferation of potentially pathogenic microbials the anaerobic flora induces a colonisation resistance. The efficacy of cotrimoxazole in prophylaxis of bacterial infections was evaluated in several clinical trials leading to different and controversial results [1, 3–5, 8]. Cotrimoxazole seems to prolong granulocytopenia [2, 6, 7, 9]. Quinolones have shown to be bactericidal for the aerobic flora including *Pseudomonas aeruginosa*. Ciprofloxacin is superior to other quinolones in vitro and in vivo [10]. Ciprofloxacin has no cross-resistance to aminoglycosides, beta-lactam antibiotics and cephalosporins of third generation [10]. Therefore ciprofloxacin was evaluated in chemoprophylaxis of bacterial infections in granulocytopenic patients.

Methods

Ciprofloxacin was administered to 34 patients in 46 treatment courses. The patients had previously been treated with cytotoxic drugs, and a prolonged granulocytopenic phase was expected. The median age of the patients was 51 years (range 19–88 years). The courses were performed in patients with acute non-lymphoblastic leukemia (n=22), acute lymphoblastic leukemia (n=8), blast crisis of chronic myelogenous leukemia (n=2) and other malignancies (n=14). 18 patients suffering from acute leukemia received the first remission induction therapy. In 28 treatment courses at least one intensive cytotoxic treatment had previously been performed. Patients with symptoms of infection, antibiotic treatment in the past two weeks, creatinine clearance below 30 ml/min, increase of serum GOT, GPT, alkaline phosphatase or bilirubin to more than twice the normal range were excluded from the study.

Ciprofloxacin was applied when WBC count decreased below 1,000/ μ l or the granulocyte count below 500/ μ l. Ciprofloxacin was given orally in a dose of 500 mg twice daily. In addition nystatin, ketoconazole or amphotericin B were given to prevent fungal infection. The drug administration was discontinued after white blood cells had increased over 1,000/ μ l. In the case of an axillary temperature over 38°C the continuation of ciprofloxacin was determined individually.

Results

The median duration of treatment with ciprofloxacin was 17 days (range 4–60 days) with a median granulocytopenic phase of 15 days (range 5–97 days). There was no fever in 28 granulocytopenic phases (61%). Fever over 38°C occurred in 18 treatment courses (39%). In 9 episodes of fever (50% of febrile episodes) the origin of fever remained unknown. In 6 patients fever was due to fungal pulmonary infection with *Aspergillus fumigatus* in 5 cases and *Torulopsis glabrata* in one case. In one patient the origin of fever was a supposed viral pulmonary infection, in one patient there was a gram negative septicemia with *Enterobacter cloacae* and in another patient a urinary tract infection with *Klebsiella pneumoniae*.

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The median duration of granulocytopenia was 28 days (range 8–97 days) in patients with fever and 12 days (range 5–33 days) in patients without fever. The onset of fever occurred after a median treatment duration of 9 days (range 3–18 days). With the onset of fever ciprofloxacin was discontinued in 10 cases and replaced by intravenous broad-spectrum antibiotic therapy. In 8 patients ciprofloxacin was continued in addition to intravenous broad-spectrum antimicrobial therapy. In 35 treatment courses ciprofloxacin was discontinued after an increase of white blood

cells over 1,000/ μ l without respect to fever. One patient died from fungal pulmonary infection during the treatment with ciprofloxacin. During the application of ciprofloxacin, serum GOT, GPT, γ T, alkaline phosphatase were elevated alone or in combination in 5 patients. In 3 of these cases there was also an increase of serum creatinine or urea. These side effects went down to normal when simultaneously applied ketoconazole or amphotericin B were discontinued even when ciprofloxacin was further administered.

Discussion

In this study the oral administration of 500 mg ciprofloxacin twice daily reduced the frequency of bacterial infections in granulocytopenic cancer patients. Only in 4% of the patients were bacterial infections documented. A fungal pulmonary infection was seen in 13%. In 20% of the patients the origin of fever remained unknown. Fever of more than 38°C occurred in only 39% of treatment courses.

Selective decontamination with cotrimoxazole alone or in combination with other antimicrobial drugs has shown a rate of 50–70% of infections [5, 6]. Only when fever of unknown origin was not included was the rate of infection less than 50–70%. It was also below 50–70% when the granulocytopenic phase included patients with a granulocyte count between 500 and 1,000/ μ l. In accordance with other authors [9, 11, 12] there is an increase in fungal infections during an antibacterial prophylaxis. While there is a decrease of infections by *Candida* spp during additional antifungal prophylaxis, a decrease of infections by *Aspergillus* spp is not observed [13]. In 46 treatment courses we found no single *Candida* spp infection, but 5 infections by *Aspergillus* spp.

Ciprofloxacin has proved to be a well tolerated drug without severe side effects. In contrast to cotrimoxazole there seems to be no prolongation of granulocytopenia. The necessary addition of *Pseudomonas aeruginosa* active drugs to cotrimoxazole causes gastrointestinal side effects like nausea, vomiting and diarrhea and may reduce patients' compliance [9]. These side effects did not occur in our study. Ciprofloxacin is a suitable drug for chemoprophylaxis of bacterial infections in granulocytopenic cancer patients.

References

- EORTC International Antimicrobial Therapy Project Group: Trimethoprim-sulfamethoxazole in the prevention of infection in neutropenic patients. *J. infect. Dis.* 150: 372–379 (1984).
- Henry, S. A.: Chemoprophylaxis of bacterial infections in granulocytopenic patients. *Am. J. Med.* 76: 645–651 (1984).
- Gualtieri, R. J.; Donowitz, G. R.; Kaiser, D. L.; Hess, C. E.; Sande, M. A.: Double-blind randomized study of prophylactic trimethoprim/sulfamethoxazole in granulocytopenic patients with hematologic malignancies. *Am. J. Med.* 74: 934–940 (1983).
- Gurwith, M.; Truog, K.; Hinthorn, D.; Lui, C.: Trimethoprim-sulfamethoxazole and trimethoprim alone for prophylaxis of infection in granulocytopenic patients. *Rev. Infect. Dis.* 4: 593–601 (1982).
- Kurrle, E.; Krieger, D.; Vanek, E.; Heimpel, H.: Selektive Dekontamination als Verfahren einer Infektprophylaxe bei Patienten mit akuten Leukämien. *FAC Bd.* 3–6 (1984).
- Kurrle, E.; Bhaduri, S.; Krieger, D.; Pflieger, H.; Heimpel, H.: Antimicrobial prophylaxis in acute leukaemia: Prospective randomized study comparing two methods of selective decontamination. *Klin. Wschr.* 61: 691–698 (1983).
- Bow, E. J.; Louie, T. J.; Riben P. D.; McNaughton, R. D.; Harding, G. K.; Ronald, A. R.: Randomized controlled trial comparing trimethoprim/sulfamethoxazole and trimethoprim for

infection prophylaxis in hospitalized granulocytopenic patients. *Am. J. Med.* 76: 223–233 (1984).

Henry, S. A.: Chemoprophylaxis of bacterial infections in granulocytopenic patients; in Brown, Armstrong, Infectious complications of neoplastic disease. Controversies in management (Yorke Medical Books, New York 1984).

Pizzo, P. A.; Robichaud, K. J.; Edwards, B. K.; Schumaker, C; Kramer, B. S.; Johnson, A.: Oral antibiotic prophylaxis in patients with cancer. A double-blind randomized placebo-controlled trial. *J. Pediat.* 102: 125–133 (1983).

Zeiler, H. J.; Retzger, K. G.; Schacht, P.; Grohe, K.: Assessment of the in vitro and in vivo activity of ciprofloxacin measured against current standards of therapy. *Drugs exp. clin. Res.* XI: 343–350 (1985).

Seeliger, H. P. R.: Spektrum der Diagnose von Pilzinfektionen beim abwehrgeschwächten Patienten. *FAC Band 3–6*: 919–933 (1984).

Pizzo, P. A.; Conners, J.; Cotton, D.; Gress, J.; Hathorn, J.; Hienieur, J.; Longo, D.; Marshall, D.; Robichaud, K. J.: Approaching the controversies in antibacterial management of cancer patients. *Am. J. Med.* 76: 436–449 (1984).

Reunier-Carpentier

F.: Chemoprophylaxis of fungal infections; in Brown Armstrong

Infectious complications of neoplastic disease. Controversies in management (Yorke Medical Books

New York 1984).