

Levofloxacin prevented fever and infection during prolonged chemotherapy-induced neutropenia

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.

Clinical impact ratings: Hospitalists ★★★★★☆ Infectious Disease ★★★★★☆ Oncology ★★★★★☆

QUESTION

In patients at risk for prolonged neutropenia after chemotherapy, does antibiotic prophylaxis with levofloxacin prevent fever and bacterial infection?

METHODS

Design: Randomized placebo-controlled trial.

Allocation: {Concealed}†.*

Blinding: Blinded {clinicians, patients, data collectors, outcome assessors, data analysts, and data safety and monitoring committee}†.*

Follow-up period: Until resolution of neutropenia: median 15 to 19 days in patients with leukemia and 8 days in patients with solid tumors or lymphoma.

Setting: 35 centers in Italy.

Patients: 760 patients 18 to 75 years of age with acute leukemia (49%), lymphoma (44%), or solid tumors (7%) who were at risk for prolonged neutropenia after chemotherapy. Exclusion criteria included allogeneic stem-cell transplantation and fever or infection at enrollment.

Intervention: Oral levofloxacin, 500 mg daily ($n = 384$), or placebo ($n = 376$), starting 1 to 3 days before chemotherapy (patients with leukemia) or within 3 days of hematopoietic stem-cell transplantation (patients

with solid tumors or lymphoma), and continuing until neutropenia resolved.

Outcomes: Fever, infection, and death.

Patient follow-up: 675 patients (89%) (mean age 48 y, 55% men). 97% of patients were included in the intention-to-treat analysis for fever and death.

MAIN RESULTS

Fewer patients developed fever during neutropenia with levofloxacin than with placebo (Table). The degree of benefit was similar in subgroup analysis by type of cancer (acute leukemia vs solid tumors or lymphoma). Fewer patients in the levofloxacin group had microbiologically documented infection and bacteremia (Table), and results were similar for gram-positive, gram-negative, and poly-

microbial infections. Rates of clinically documented infection, febrile neutropenia without infection, and death did not differ between groups (Table).

CONCLUSION

In patients at risk for prolonged neutropenia after chemotherapy, antibiotic prophylaxis with levofloxacin reduced the rates of fever and bacterial infection.

Sources of funding: GlaxoSmithKline and Aventis Pharma.

For correspondence: Dr. A. Del Favero, Università di Perugia, Perugia, Italy. E-mail delfa@unipg.it. ■

*See Glossary.

†Information provided by author.

Levofloxacin vs placebo to prevent fever and bacterial infection in patients at risk for prolonged neutropenia after chemotherapy at median 8 to 19 days†

Outcomes	Levofloxacin	Placebo	RRR (95% CI)	NNT (CI)
Fever	65%	85%	24% (17 to 30)	5 (4 to 8)
Microbiologically documented infection	22%	39%	44% (29 to 56)	6 (5 to 10)
Bacteremia	18%	34%	47% (30 to 59)	7 (5 to 11)
Clinically documented infection	8.8%	9.8%	10% (-44 to 44)	Not significant
Death	2.7%	5.0%	46% (-13 to 74)	Not significant

‡Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

Forty years ago, infection risk was related to the leukocyte count and the duration of neutropenia. In the 1970s, empirical antibacterial therapy was shown to reduce mortality from infection in febrile neutropenic patients, and this strategy has continued. Recently, it has been recognized that some febrile neutropenic patients are at low risk for serious complications. A scoring system for identifying low-risk, febrile, neutropenic patients has been developed (1) and is being used to select patients for testing therapeutic strategies that may be more cost-effective than hospitalization and empirical intravenous antibacterial therapy.

The strategy of early antimicrobial therapy was extended in the 1980s to prophylactic administration of antimicrobial agents in patients expected to become neutropenic because of therapy. A recent meta-analysis of antibiotic prophylaxis in cancer patients, most of whom had hematologic malignancy, showed that antibiotic prophylaxis reduced mortality (2).

In this trial, Bucaneve and colleagues evaluated prophylactic levofloxacin in 675 hospitalized adult patients (46 had nonhematologic cancer) in whom profound and prolonged chemotherapy-induced neutropenia was expected. Indeed, the rate of febrile episodes in the placebo group was 85%, and the median duration of prophylactic levofloxacin use was 14 and 25 days in patients with lymphoma and leukemia, respectively. Fewer patients developed fever, positive blood

cultures, and infection with gram-negative rods with levofloxacin than with placebo, and the number needed to treat to avoid a single episode of febrile neutropenia was 5. The rates of clinically documented infection and death did not differ between the 2 groups.

The widespread use of prophylactic fluoroquinolones in cancer patients is not supported by these results. The results do not apply to the large number of patients with solid tumors who develop transient neutropenia following chemotherapy. In low-risk patients, antibiotics early in the course of infection may be preferred to prophylactic fluoroquinolones. The results do support the use of prophylactic fluoroquinolones in patients with leukemia or those having high-dose chemotherapy requiring stem-cell support. But even in these high-risk patients, prolonged use of prophylactic levofloxacin is likely to lead to emergence of resistant organisms in hospital environments that adopt this approach.

Martin Tattersall, MD
University of Sydney
Sydney, New South Wales, Australia

References

1. Klastersky J, Paesmans M, Rubenstein EB, et al. *J Clin Oncol.* 2000; 18:3038-51.
2. Gafter-Gvili A, Fraser A, Paul M, Leibovici L. *Ann Intern Med.* 2005; 142:979-95.