

# Empirical oral and IV antibiotics had similar effects for febrile neutropenia during chemotherapy in low-risk patients with cancer

Freifeld A, Marchigiani D, Walsh T, et al. A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy. *N Engl J Med.* 1999 Jul 29;341:305-11.

## QUESTION

For low-risk hospitalized cancer patients with febrile neutropenia during cancer chemotherapy, are oral empirical broad-spectrum antibiotics (ciprofloxacin and amoxicillin-clavulanate) as safe and effective as monotherapy with intravenous (IV) ceftazidime?

## DESIGN

Randomized (unclear allocation concealment\*), blinded (patients and clinicians),\* controlled trial with follow-up to resolution of neutropenia.

## SETTING

2 hospitals in the United States.

## PATIENTS

163 patients (mean age 42 y, range 5 to 74 y, 78% women) had 284 episodes of febrile neutropenia during cancer chemotherapy. Patients had fever with neutropenia that was expected to resolve within 10 days; were hemodynamically stable; and had no gastrointestinal, neurologic, or pulmonary complications. They had no neurologic or mental status changes; no intravascular,

catheter, or catheter-tunnel infection; and no new pulmonary infiltrate. Patients were able to swallow medications, had not received antibiotics other than trimethoprim-sulfamethoxazole within 72 hours, had adequate hepatic and renal function, had no allergies to study medications, and had no serious comorbid conditions. 82% of episodes were followed up.

## INTERVENTION

Analysis included 84 patients who were allocated to oral ciprofloxacin, 30 mg/kg of body weight (maximum 750 mg/8 h), and amoxicillin-clavulanate, 40 mg/kg (maximum dose 500 mg/8 h), and 79 patients who were allocated to IV ceftazidime, 90 mg/kg (maximum dose 2 g/8 h). All medication was given in 3 divided doses/d until neutropenia resolved. Changes in medication were based on pre-defined criteria.

## MAIN OUTCOME MEASURES

Successful therapy defined as survival with no change in drug regimen plus resolution of neutropenia with no evidence of active infection. Adverse events were also analyzed.

## MAIN RESULTS

After adjustment for treatment assignment, the groups did not differ for rate of episodes of successful therapy (71% in the oral group vs 67% in the IV group,  $P = 0.5$ ). More episodes were considered treatment failures in the IV group because of need for change in treatment (32% for IV vs 13% for oral,  $P < 0.001$ ), and more episodes failed in the oral group because of patients' inability to tolerate the treatment (16% for oral vs 1% for IV,  $P < 0.001$ ). No deaths occurred.

## CONCLUSION

Oral ciprofloxacin plus amoxicillin-clavulanate and intravenous ceftazidime were equally safe and effective for hospitalized patients with febrile neutropenia after cancer chemotherapy.

*Source of funding:* Not stated.

*For correspondence:* Dr. A. Freifeld, University of Nebraska Medical Center, Infectious Diseases Section, 985400 Nebraska Medical Center, Omaha, NE 68198-5400, USA. FAX 301-402-0172. ■

\*See Glossary.

## COMMENTARY

Febrile neutropenia is a common dose-limiting complication of cancer chemotherapy for which the standard treatment has been prompt hospitalization and institution of empirical broad-spectrum IV antibiotics. It has recently become apparent that patients with febrile neutropenia differ for risk for medical complications and death. Talcott and colleagues (1, 2) validated the identification of lower-risk outpatients with febrile neutropenia and tumors who had responded to cancer chemotherapy and had no associated medical comorbid conditions. Medical complications occurred in < 2% of patients, and no deaths occurred. The potential of identifying a lower-risk group of patients with febrile neutropenia has prompted investigators to study such alternative modes of treatment as ambulatory IV and oral therapy. Published studies have been limited by their design and small sample sizes.

The studies by Freifeld and Kern and their colleagues provide evidence that broad-spectrum oral antibiotics are safe and effective when given in a hospital setting to appropriately identified low-risk patients, such as those with solid tumors and short-lived neutropenia without associated medical comorbid conditions.

Freifeld and colleagues report the first large study comparing inpatient oral with IV therapy to use a double-blind design, thus eliminating the inherent bias toward an early change in treatment in the oral therapy group. However, 52 of 284 randomized episodes (18%) of febrile neutropenia were not followed (evenly distributed in the oral and IV groups) and were excluded from analysis for various reasons. A separate analysis that included this group was not done, and this introduces uncertainty as to whether the differences present in this group of episodes could affect the overall outcome of the study. Treatment was considered to have failed because 16% of patients in the oral antibiotic group and 1% in the IV group were unable to tolerate the regimen. The unusually high doses of ciprofloxacin (30 mg/kg up to 750 mg every 8 h) probably contributed to this intolerance.

Kern and colleagues also compared inpatient oral with IV treatment in low-risk patients with febrile neutropenia, but their study differs from the study by Freifeld and colleagues in that it was open-label, used ceftriaxone plus amikacin as the IV arm, used a  
(continued on page 53)

# Empirical oral and IV antibiotics had similar effects for febrile neutropenia during chemotherapy in low-risk patients with cancer

Kern WV, Cometta A, de Bock R, et al., for the International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer. Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. *N Engl J Med.* 1999 Jul 29;341:312-8.

## QUESTION

For low-risk hospitalized cancer patients with febrile neutropenia during cancer chemotherapy, are oral empirical broad-spectrum antibiotics (ciprofloxacin and amoxicillin-clavulanate) as effective and safe as intravenous (IV) antibiotics (ceftriaxone and amikacin)?

## DESIGN

Randomized (concealed allocation\*), blinded (outcome assessors)\*, controlled trial with 30-day follow-up.

## SETTING

25 hospitals in Europe and the Middle East.

## PATIENTS

370 patients were enrolled, and 353 (median age 52 y, age range 5 to 85 y, 55% women) were analyzed. Patients had cancer (solid tumors, lymphoma, or chronic leukemia), fever, and neutropenia (defined as  $< 1000$  granulocytes/mm<sup>3</sup>) that was expected to resolve within 10 days. Exclusion criteria were allogeneic bone marrow or stem-cell transplantation; recent antibiotic use; allergy to study drugs; renal failure; shock; respiratory

insufficiency; need for IV supportive therapy; inability to swallow; high likelihood of dying within 48 hours; HIV infection; catheter or central nervous system infection; pregnancy; lactation; or known bacterial, fungal, or viral disease.

## INTERVENTION

Randomization was stratified on the basis of study site, type of cancer, and granulocyte count. 185 patients were allocated to oral ciprofloxacin, 750 mg 2 times/d, and amoxicillin-clavulanate, 625 mg every 8 hours. Children's doses were based on body weight. 185 patients were allocated to IV ceftriaxone, 2 g/d, and amikacin, 20 mg/kg of body weight.

## MAIN OUTCOME MEASURES

Successful therapy defined as no change in drug regimen plus normal temperature for  $\geq 3$  days, clinical resolution at infection sites, eradication of primary pathogen, and no recurrence of infection within 1 week of end of treatment.

## MAIN RESULTS

At the second interim analysis, equivalency was shown and the study was stopped.

The groups did not differ for rates of successful therapy according to per-protocol analysis (86% for oral vs 84% for IV therapy, absolute difference 2%, 95% CI -6.3% to 9.6%, not significant) or intention-to-treat analysis (80% vs 77%, absolute difference 3%, CI -5.7% to 11.6%, not significant); 30-day mortality (8 vs 9 deaths); time to resolution of fever (2 d for both), first change in regimen (3.5 vs 3.0 d), and discontinuation of therapy (6 d for both); any adverse event (36% vs 31%); or serious adverse events (9% vs 7%).

## CONCLUSION

Oral therapy with ciprofloxacin and amoxicillin-clavulanate was as effective as intravenous therapy with ceftriaxone and amikacin for hospitalized cancer patients who had developed febrile neutropenia.

*Source of funding:* Bayer.

*For correspondence:* Dr. W.V. Kern, Medizinische Universitätsklinik und Poliklinik, Sektion Infektiologie und Klinische Immunologie, D-89070 Ulm, Germany. FAX 49-731-502 44 88. ■

\*See Glossary.

## COMMENTARY (continued from page 52)

more standard dose of ciprofloxacin (750 mg twice/d) in the oral arm, allowed patients to be enrolled only once, and included an intention-to-treat analysis. 19 patients (11%) in each group had absolute neutrophil counts  $> 500/\text{mm}^3$  at enrollment. In 25 of these patients, neutrophil counts remained  $> 500/\text{mm}^3$ , which lowered the overall success rates in both the IV and oral groups when these patients were excluded.

Oral antibiotic treatment for febrile neutropenia offers many potential benefits related to avoiding or shortening hospitalization: improved quality of life, reduced costs, and decreased acquisition of nosocomial organisms. The studies by Freifeld and Kern and their colleagues suggest that oral antibiotics will be useful in the outpatient treatment of patients with febrile neutropenia. However, the efficacy, safety, and feasibility of outpatient oral antibiotic treatment of patients with febrile neutropenia are separate questions, which should be addressed in large, well-designed, random-

ized trials. Successful outpatient treatment of febrile neutropenia will involve the careful selection of low-risk patients on the basis of medical, personal, and social factors, which could not be addressed by the above studies (3).

Elizabeth Phillips, MD  
University of Toronto  
Toronto, Ontario, Canada

## References

1. Talcott JA, Finberg R, Mayer RJ, Goldman L. The medical course of cancer patients with fever and neutropenia. Clinical identification of a low-risk subgroup at presentation. *Arch Intern Med.* 1988;148:2561-8.
2. Talcott JA, Siegel RD, Finberg R, Goldman L. Risk assessment in cancer patients with fever and neutropenia: a prospective, two-center validation of a prediction rule. *J Clin Oncol.* 1992;10:316-22.
3. Uzun O, Anaissie EJ. Outpatient therapy for febrile neutropenia: who, when, and how? *J Antimicrob Chemother.* 1999;43:317-20.