

Antibacterial prophylaxis reduced the incidence of fever in patients receiving chemotherapy for solid tumors or lymphoma

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.

Clinical impact ratings: Hospitalists ★★★★★☆☆ Hematol/Thrombo ★★★★★☆☆ Infectious Disease ★★★★★☆☆ Oncology ★★★★★☆☆

QUESTION

In patients receiving chemotherapy for solid tumors or lymphoma who are at risk for bacterial infection, does antibacterial prophylaxis reduce the incidence of fever?

METHODS

Design: Randomized placebo-controlled trial (Simple Investigation in Neutropenic Individuals of the Frequency of Infection after Chemotherapy ± Antibiotic in a Number of Tumours [SIGNIFICANT] Trial).

Allocation: Concealed.*

Blinding: Blinded [clinicians, patients, data collectors, outcome assessors, and microbiologists]†.*

Follow-up period: Up to 6 cycles of chemotherapy (mean 4.4 cycles).

Setting: 60 cancer centers in the United Kingdom.

Patients: 1565 patients 16 to 83 years of age (median age 55 y, 56% women) who were starting cytotoxic chemotherapy for solid tumors (including breast cancer 35%, lung cancer 23%, and testicular cancer 14%) or lymphoma (13%) and were at risk for bacterial infection because of anticipated cyclic neutropenia.

Intervention: Levofloxacin 500 mg ($n = 781$) or placebo ($n = 784$) once daily for 7 days in each chemotherapy cycle, with start day

determined by type of chemotherapy and cycle length.

Outcomes: Febrile episode (core temperature $> 38^{\circ}\text{C}$) attributed to infection. Secondary outcomes were probable infection, hospitalization for infection, and severe infection (including death from infection).

Patient follow-up: 97% in first cycle (100% included in intention-to-treat analysis).

MAIN RESULTS

45% of patients completed 6 cycles of chemotherapy and 79% received the study drug for the duration of chemotherapy. Patients in the levofloxacin group had lower rates of febrile episodes, probable infection, and hospitalization for infection than did those in the placebo group, both in the first cycle and at least once in any cycle (Table).

The groups did not differ for severe infection (Table).

CONCLUSION

In patients receiving chemotherapy for solid tumors or lymphoma who were at risk for bacterial infection, antibacterial prophylaxis reduced the incidence of fever, both in the first cycle and throughout the duration of chemotherapy.

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*See Glossary.

†Information provided by author.

Levofloxacin vs placebo to prevent infection after chemotherapy in patients with solid tumors or lymphoma†

Cycle	Outcomes	Levofloxacin	Placebo	RRR (95% CI)	NNT (CI)
During first cycle	Febrile episode	3.5%	7.9%	56% (32 to 72)	23 (15 to 46)
	Probable infection	14%	19%	28% (10 to 43)	19 (11 to 58)
	Hospitalization	6.7%	10%	36% (10 to 54)	28 (16 to 109)
During any cycle	Febrile episode	11%	15%	29% (8.1 to 45)	23 (13 to 91)
	Probable infection	34%	41%	18% (6.3 to 27)	14 (9 to 41)
	Hospitalization	16%	22%	27% (9.9 to 41)	18 (11 to 52)
	Severe infection	1.0%	2.0%	50% (-14 to 78)	Not significant

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

COMMENTARY

Cullen and colleagues had to administer 23 000 doses of levofloxacin to 781 patients to prevent 54 febrile episodes, with no effect on mortality. At the same time, they achieved a significant 29% relative risk reduction in febrile episodes. A concurrent study involving a different patient population had similar findings (1). A recent meta-analysis suggested that prophylactic fluoroquinolones reduce the number of infections during neutropenia and decrease mortality (2). Should levofloxacin prophylaxis be routinely recommended during chemotherapy?

In this sample, 85% of placebo recipients did not develop fever. If one were to give levofloxacin in this manner, most patients would not benefit and would be exposed to the toxicity (both immediate effects and long-term bacterial resistance) of the antibiotic. This approach hardly seems sensible. The subgroup of patients actually at risk should be identified.

Could one give levofloxacin better? Interestingly, of the 97 febrile episodes in the levofloxacin group, 66 of them occurred during the days the patients were *not* taking prophylaxis, but in 56 of them the neutrophil count was $< 1000/\mu\text{L}$. In other words, many patients were not taking the antibiotic when they were neutropenic. It might be possible to improve the results by obtaining neutrophil counts more frequently and timing the prophylaxis during actual neutropenia, instead of at

fixed intervals. Regarding which subgroups of patients with solid tumors, if any, should receive prophylaxis, the article is not illuminating. Rapidly developing, profound neutropenia, as well as uncontrolled cancer, age, and serious comorbid conditions, are known risk factors for both neutropenic fever and poor outcome and should be considered.

The dangers of bacterial resistance from giving broad-spectrum antibiotics to thousands of patients who do not need them cannot be overemphasized (3). Levofloxacin prophylaxis may be a successful intervention to use only in carefully selected situations.

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