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Levofloxacin to Prevent Bacterial Infection in Patients with Cancer and Neutropenia

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ABSTRACT

BACKGROUND

The prophylactic use of fluoroquinolones in patients with cancer and neutropenia is controversial and is not a recommended intervention.

METHODS

We randomly assigned 760 consecutive adult patients with cancer in whom chemotherapy-induced neutropenia (<1000 neutrophils per cubic millimeter) was expected to occur for more than seven days to receive either oral levofloxacin (500 mg daily) or placebo from the start of chemotherapy until the resolution of neutropenia. Patients were stratified according to their underlying disease (acute leukemia vs. solid tumor or lymphoma).

RESULTS

An intention-to-treat analysis showed that fever was present for the duration of neutropenia in 65 percent of patients who received levofloxacin prophylaxis, as compared with 85 percent of those receiving placebo (243 of 375 vs. 308 of 363; relative risk, 0.76; absolute difference in risk, -20 percent; 95 percent confidence interval, -26 to -14 percent; $P=0.001$). The levofloxacin group had a lower rate of microbiologically documented infections (absolute difference in risk, -17 percent; 95 percent confidence interval, -24 to -10 percent; $P<0.001$), bacteremias (difference in risk, -16 percent; 95 percent confidence interval, -22 to -9 percent; $P<0.001$), and single-agent gram-negative bacteremias (difference in risk, -7 percent; 95 percent confidence interval, -10 to -2 percent; $P<0.01$) than did the placebo group. Mortality and tolerability were similar in the two groups. The effects of prophylaxis were also similar between patients with acute leukemia and those with solid tumors or lymphoma.

CONCLUSIONS

Prophylactic treatment with levofloxacin is an effective and well-tolerated way of preventing febrile episodes and other relevant infection-related outcomes in patients with cancer and profound and protracted neutropenia. The long-term effect of this intervention on microbial resistance in the community is not known.

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BACTERIAL INFECTIONS ARE A MAJOR cause of complications and death in patients with hematologic cancers and chemotherapy-induced neutropenia. A number of randomized clinical trials and two meta-analyses^{1,2} have suggested that prophylaxis with fluoroquinolones may be better than placebo or trimethoprim-sulfamethoxazole in reducing bacteremic infections caused by gram-negative bacilli, with ciprofloxacin being the compound most widely used.³ However, the evidence provided by these studies is not seen as entirely convincing.

First, only three studies were placebo-controlled, double-blind, randomized clinical trials, and none were sufficiently large to provide conclusive evidence of the real efficacy of prophylaxis.⁴⁻⁶ Second, in most studies, the occurrence of fever requiring empirical antibiotic therapy was not considered or was not significantly reduced by prophylaxis.¹ Third, these studies did not address the important question of whether prophylaxis should be considered for all patients with cancer and neutropenia, since the risk of infection may differ among such patients. Fourth, in all studies, prophylaxis with fluoroquinolones did not reduce the risk of infections caused by gram-positive microorganisms. Finally, the routine use of fluoroquinolone prophylaxis in patients with cancer and neutropenia has been questioned, because it can increase bacterial resistance to these agents⁷⁻⁹ and thus limit their efficacy in reducing infection-related morbidity or mortality.

To clarify these issues, we conducted a large, double-blind, placebo-controlled clinical trial using levofloxacin, a fluoroquinolone with an extended spectrum against gram-positive bacteria, as a prophylactic agent in adult patients with cancer in whom profound and prolonged chemotherapy-induced neutropenia was expected to develop.

METHODS

PATIENTS

Consecutive adult patients with acute leukemia, solid tumors, or lymphoma who were hospitalized at participating centers and who were at risk for chemotherapy-induced neutropenia (absolute neutrophil count less than 1000 per cubic millimeter) lasting more than seven days were eligible for the study. Patients were enrolled only once in the study. Patients undergoing allogeneic stem-cell transplantation, patients with a history of hypersensitivity to

fluoroquinolones, those treated with antimicrobial therapy in the preceding five days, and those with fever of infectious origin or a documented infection at the time of enrollment were excluded.

All patients entered the study one to three days before the administration of cytotoxic chemotherapy. Among recipients of hematopoietic stem-cell transplants, prophylaxis was started within three days before or after the reinfusion of stem cells.

STUDY DESIGN

The study was designed as a prospective, multicenter, double-blind, randomized, placebo-controlled trial and was approved by the ethics committee at each participating center. The study was conducted between April 30, 2001, and March 18, 2003, at 35 centers in Italy by a committee that included all the authors. At entry, after having provided written informed consent, patients were assigned to receive 500 mg of levofloxacin orally, once daily, or an identical-appearing placebo, according to a computer-generated random-number program accessible 24 hours a day. Patients were stratified according to the center and the underlying disease (solid tumors or lymphoma vs. acute leukemia). Patients with acute leukemia were presumed to have longer and more profound neutropenia (fewer than 100 neutrophils per cubic millimeter) and thus were in the high-risk stratum, whereas patients with solid tumors and lymphoma who were undergoing hematopoietic stem-cell transplantation were in the stratum at low risk for infection. Prophylaxis was continued in all patients until neutropenia had resolved.

Randomized patients were examined daily for clinical signs of infection. When axillary temperature exceeded 38.5°C once or 38°C at least twice during a period of 12 hours and an infection was suspected, samples were obtained for microbiologic cultures, including at least two separate blood specimens, and empirical antibacterial therapy was initiated, according to the judgment of the investigator. Isolated bacteria were identified with the use of standard methods, and susceptibility was evaluated at each center according to the Kirby-Bauer method.¹⁰ Infections were classified according to the definitions of the European Organization for Research and Treatment of Cancer.¹¹ Compliance was monitored by counting pills. The primary end point of the study was the occurrence of fever requiring empirical antibacterial therapy during neu-

tropenia. Secondary end points were the type and number of documented infections, the use of parenteral antimicrobial agents during neutropenia, survival at the resolution of neutropenia, compliance, and tolerability. The costs of antimicrobial agents used during neutropenia excluding prophylaxis were calculated according to the Italian National Drug Formulary.¹²

STATISTICAL ANALYSIS

We assumed that fever of infectious origin occurs in approximately 80 percent of patients with chemotherapy-induced neutropenia who are not receiving antibacterial prophylaxis.^{13,14} We estimated that at least 300 patients (150 in each group) would be needed in each stratum to detect an absolute difference of at least 15 percent between levofloxacin and placebo with a statistical power of 80 percent and a 5 percent significance level. Because we also assumed that 20 percent of patients would not be included in the efficacy analysis, we set an enrollment goal of at least 750 patients (375 in each group).

All case-report forms were centrally reviewed and statistical analysis was carried out at the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) Infection Program Data Center with the use of the SAS software package (SAS Institute). All evaluations were made in a blinded fashion with respect to the assigned treatment. An analysis that included all eligible patients was conducted according to the intention to treat by considering that treatment was successful in all patients without fever during the study whose response could not be assessed because they were lost to follow-up. A per-protocol analysis was conducted that included all assessable patients, and a subanalysis of this group that included only patients with neutropenia lasting at least seven days was also performed. Efficacy with respect to the primary and secondary end points was expressed as the absolute difference in rates between treatment groups (the rate with levofloxacin minus the rate with placebo). The 95 percent confidence interval for the difference between proportions is given, as is the relative risk of the primary end point. The chi-square test with a correction for continuity was used to compare proportions. The Wilcoxon rank-sum test was used to compare the means, and a logistic-regression model was used to assess the relative importance of the various prognostic factors assessable at the time of random-

ization (the types of prophylaxis, the duration of neutropenia, the underlying disease, and the presence or absence of protective isolation and a central venous catheter). Kaplan–Meier estimates of survival without fever were also determined. Differences in survival without fever were assessed with a log-rank test at the 5 percent significance level.

The study was designed and the article was written by Drs. Del Favero, Bucaneve, Menichetti, Martino, and Micozzi, coordinators of the GIMEMA Infection Program. The data were collected, held, and analyzed by the coordinators with the help of the data-review committee (see the Appendix) at the GIMEMA data center. All the authors helped write the article and reviewed the manuscript. The two companies that helped support the study did not have any involvement in the conduct of the trial and had no role with respect to the project design, conduct of the study, data analysis, or writing of the manuscript, all of which were carried out exclusively by the investigators at the GIMEMA data center at Perugia University (Italy). During the study period, the only communication between the sponsors and investigators was related to the monitoring of enrollment and the reporting of adverse events.

RESULTS

A total of 760 patients with neutropenia were enrolled: 384 were randomly assigned to receive oral levofloxacin, and 376 to receive placebo. The outcomes are shown in Figure 1. The characteristics of the 675 patients whose response to therapy could be assessed are provided in Table 1. There were no significant differences between the two groups within each stratum of disease.

FEBRILE EPISODES

An intention-to-treat analysis showed that fever developed in 65 percent of patients in the levofloxacin group, as compared with 85 percent of those in the placebo group (243 of 375 vs. 308 of 363; relative risk, 0.76; absolute difference in risk, –20 percent; 95 percent confidence interval, –26 to –14 percent; $P=0.001$). A per-protocol analysis of patients whose response to treatment could be assessed as well as a subanalysis of this group including only the patients with neutropenia lasting at least seven days yielded similar results (Fig. 2). The number of patients who needed to be treated with levofloxacin

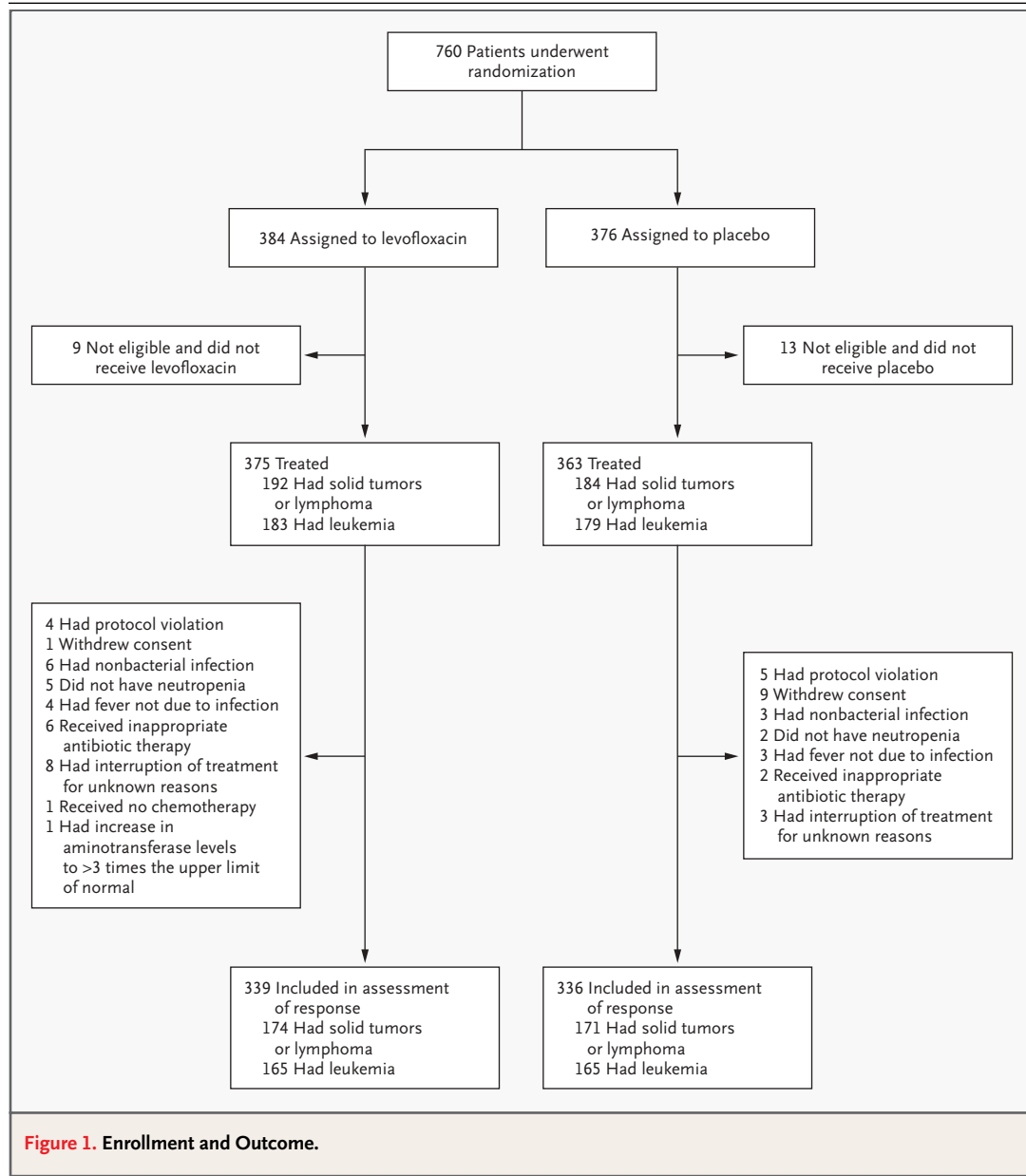


Figure 1. Enrollment and Outcome.

to avoid a single episode of febrile neutropenia was five.

A multivariate analysis that used multiple logistic regression identified the use of antibacterial prophylaxis and a duration of profound neutropenia of at least seven days as the only factors capable of influencing the development of febrile episodes. Kaplan–Meier estimates of survival free of fever during prophylaxis showed a clear advantage of levofloxacin both overall (Fig. 3A) and among patients with

acute leukemia (Fig. 3B) and patients with solid tumors or lymphoma (Fig. 3C).

MICROBIAL ISOLATES AND RESISTANCE TO LEVOFLOXACIN

Patients receiving prophylactic levofloxacin had a significantly lower rate of microbiologically documented infections, gram-negative bacteremias, and polymicrobial bacteremias than did those receiving placebo. The number of bacteremias caused by a

Table 1. Characteristics of the 675 Patients Whose Response to Therapy Could Be Assessed.

Characteristic	Patients with Solid Tumors or Lymphoma		Patients with Leukemia	
	Levofloxacin (N=174)	Placebo (N=171)	Levofloxacin (N=165)	Placebo (N=165)
Age — yr				
Mean	47	49	48	49
Range	19–72	18–70	18–75	18–75
Sex — no. (%)				
Male	102 (59)	93 (54)	88 (53)	87 (53)
Female	72 (41)	78 (46)	77 (47)	78 (47)
Underlying cancer — no. (%)				
Acute leukemia	—	—	164 (99)	163 (99)
Lymphoma and Hodgkin's disease	112 (64)	100 (58)	—	—
Solid tumor	24 (14)	22 (13)	—	—
Other hematologic cancers	38 (22)	49 (29)	1 (1)	2 (1)
Chemotherapy — no. (%)				
First remission or induction	—	—	80 (48)	79 (48)
Reinduction	—	—	37 (22)	32 (19)
Augmentation	—	—	47 (28)	47 (28)
Stem-cell transplantation — no. (%)				
Single room	43 (25)	42 (25)	46 (28)	47 (28)
Reverse isolation	28 (16)	27 (16)	19 (12)	18 (11)
Laminar airflow room	25 (14)	26 (15)	11 (7)	13 (8)
Other	19 (11)	21 (12)	9 (5)	7 (4)
Intravenous catheter in situ — no. (%)				
Antifungal prophylaxis — no. (%)	148 (85)	155 (91)	154 (93)	152 (92)
Antiviral prophylaxis — no. (%)	107 (61)	110 (64)	29 (18)	38 (23)
Duration of prophylaxis — days				
Mean	14	15	27	25
Range	4–36	5–61	9–65	6–70
Median	14	14	25	24
Duration of neutropenia (<1000 neutrophils/mm ³) — days				
Mean	9	9	20	18
Range	4–28	2–51	3–54	3–67
Median	8	8	19	15
Duration of severe neutropenia (<100 neutrophils/mm ³) — days				
Mean	6	6	11	10
Range	0–20	0–49	0–47	0–38
Median	6	5	10	8

single gram-positive organism was also reduced among patients who received levofloxacin, but this reduction only approached significance (Fig. 2).

The pathogens responsible for bacteremia and those resistant to levofloxacin are listed in Table 2. Data were available for 90 percent of infections caused by a single agent in the levofloxacin group (47 of 52) and 74 percent of such infections in the placebo group (68 of 92).

Patients receiving prophylactic levofloxacin had a striking decrease in gram-negative bacteremias, especially those due to *Escherichia coli* (Table 2). Three percent of patients given levofloxacin had levofloxacin-resistant gram-negative bacilli, as compared with 1 percent of those receiving placebo (10 of 337 vs. 4 of 322; absolute difference in risk, 2 percent; 95 percent confidence interval, -0.4 to 3 percent; $P=0.10$), even though among gram-negative isolates from patients with bacteremia, a greater percentage of levofloxacin-resistant gram-negative bacilli were documented in the former group than in the latter (77 percent vs. 17 percent [10 of 13 vs. 4 of 24]).

There were fewer bacteremias due to *Staphylococcus aureus* and streptococcus species in the levofloxacin group than in the placebo group (Table 2). Among the gram-positive isolates tested, 91 percent of those in the levofloxacin group and 64 percent of those in the placebo group were resistant to levofloxacin (31 of 34 and 28 of 44, respectively). Methicillin-resistant, coagulase-negative staphylococci, all of which were also resistant to levofloxacin, were the most frequent gram-positive isolates in both groups.

CLINICALLY DOCUMENTED INFECTIONS, FEVER OF UNKNOWN ORIGIN, AND ANTIBIOTIC THERAPY

The numbers of clinically documented infections and episodes of fever of unknown origin were similar in the two groups (Fig. 2). The lung was the most frequent site of origin of these infections (13 of 30 such infections among patients receiving levofloxacin and 16 of 33 among those receiving placebo), also accounting for the most severe infections.

Empirical antibacterial therapy was administered according to the protocol guidelines. An analysis of the initial antibiotic regimens showed that the most frequently used regimen consisted of a broad-spectrum beta-lactam with an aminoglycoside (117 of 221 regimens in the levofloxacin group and 159 of 290 regimens in the placebo group). The second

Figure 2 (facing page). Rates and Absolute Differences in the Risk of Primary and Secondary End Points.

The overall analysis of death among all treated patients excludes two patients in the levofloxacin group who were lost to follow-up. CI denotes confidence interval.

choice was monotherapy with an antipseudomonas beta-lactam (56 of 221 regimens and 72 of 290 regimens, respectively). Combination therapy including a glycopeptide and a beta-lactam with or without an aminoglycoside was the least frequently used regimen (48 of 221 regimens and 59 of 290 regimens, respectively). There was no significant difference in the rates of use of preferred regimens between the two groups.

The total cost of antibiotics, on the basis of the acquisition cost, was lower in the levofloxacin group than in the placebo group. The mean cost per patient of antibiotics was €1,953 in the levofloxacin group, as compared with €2,841 in the placebo group ($P<0.001$).

SUBGROUP ANALYSIS

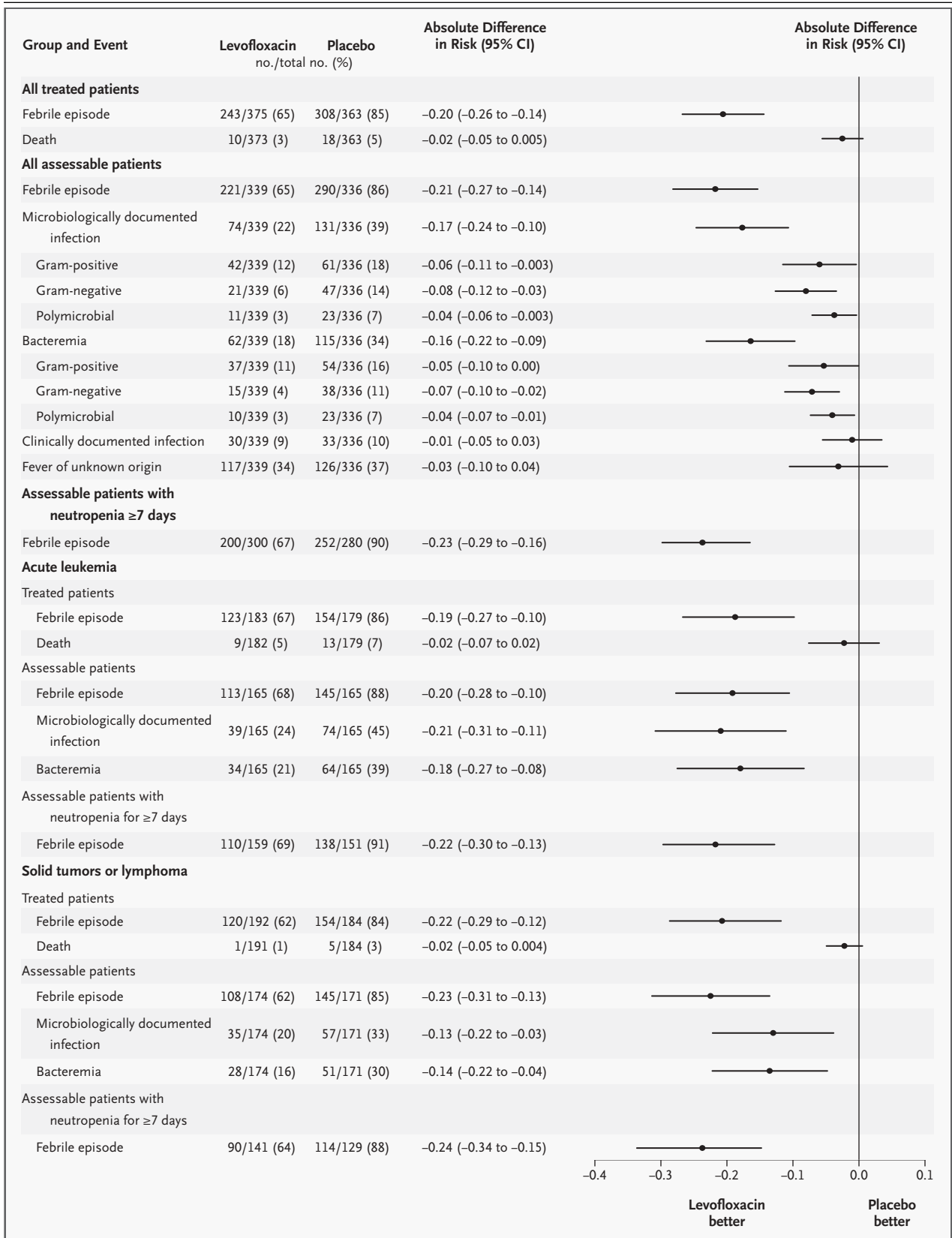
As compared with the patients with solid tumors or lymphoma who were undergoing hematopoietic stem-cell transplantation, the patients with acute leukemia had more sustained neutropenia (19 vs. 9 days with a neutrophil count of no more than 1000 per cubic millimeter) and more profound neutropenia (11 vs. 6 days with a neutrophil count of no more than 100 per cubic millimeter). Nonetheless, the efficacy of prophylaxis was similar in the two subgroups. Moreover, a subanalysis confined to the patients who had neutropenia for at least seven days did not show any significant difference in response rates between the two subgroups (Fig. 2).

COMPLIANCE AND ADVERSE EVENTS

Compliance was good, and it was similar in the two groups. There was a similar frequency of interruption of prophylaxis owing to adverse events in the two groups: three patients with gastrointestinal disturbances, three with rash, and one with seizure in the levofloxacin group and two patients with rash and one with rhabdomyolysis in the placebo group.

MORTALITY

Data on mortality at the end of follow-up were available for 736 of 760 patients (Table 3). The overall mortality rate was 4 percent (28 of 736 patients),



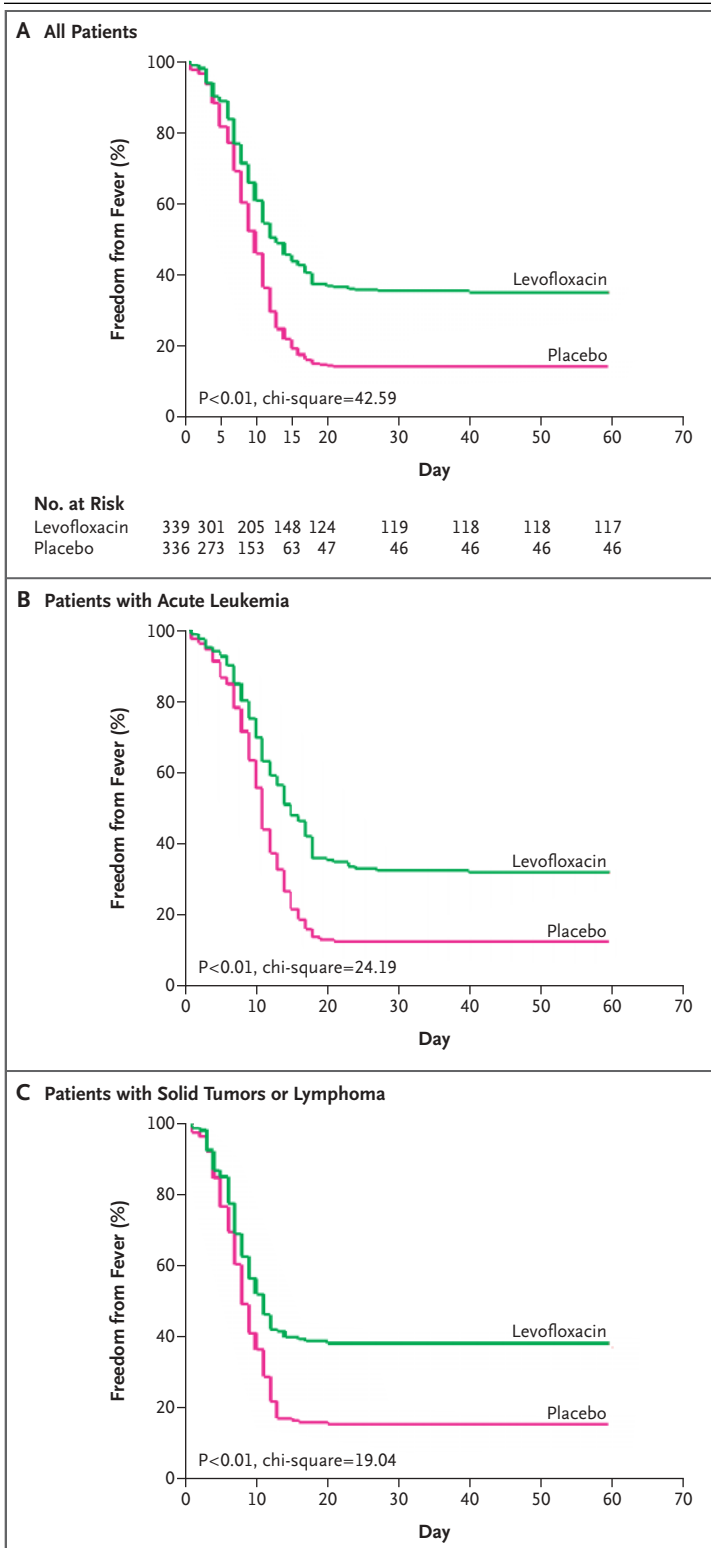


Figure 3. Kaplan–Meier Estimates of Survival Free from Fever among All Patients (Panel A), Patients with Acute Leukemia (Panel B), and Patients with Solid Tumors or Lymphoma (Panel C).

The log-rank test was used to determine the chi-square values.

and death was more frequent among patients with acute leukemia (accounting for 22 of 28 deaths) than among patients with solid tumors or lymphoma. Three percent of patients died in the levofloxacin group, as compared with 5 percent in the placebo group (10 of 373 vs. 18 of 363; absolute difference in risk, –2 percent; 95 percent confidence interval, –5 to 0.5 percent; $P = 0.15$). Also, the infection-related mortality rate was similar in the two groups, being 2 percent in the levofloxacin group and 4 percent in the placebo group (9 of 373 and 14 of 363, respectively; absolute difference in risk, –2 percent; 95 percent confidence interval, –4 to 1 percent; $P = 0.36$). Among the eight deaths occurring among patients with single-agent bacteremias, two were caused by gram-negative bacilli and both were in the placebo group. The survival rate among patients with single-agent bacteremias due to levofloxacin-resistant strains was similar in the two groups: 95 percent in the levofloxacin group (39 of 41) and 97 percent in the placebo group (31 of 32).

DISCUSSION

The prophylactic use of fluoroquinolones in patients with cancer and neutropenia is controversial and is not recommended.¹⁵ This double-blind, placebo-controlled trial was sufficiently large to provide clear evidence of the efficacy of bacterial prophylaxis with a fluoroquinolone, as reflected by a substantial reduction in the number of patients with fever requiring empirical antibiotic therapy (number needed to treat to avoid one episode of fever, five) as well as in the number of microbiologically documented infections, including bacteremias due to a single gram-negative isolate and polymicrobial bacteremias. The reduction in microbiologically documented infections was not accompanied by an increase in the incidence of clinically documented infections or fever of unknown origin, confirming that the reduction was not simply due to a lower

rate of documented infections as a result of prophylaxis.

Our study provides important information on the patients who may benefit most from prophylaxis. The study population was stratified into two groups, defined a priori at different risk for infection on the basis of the presumptive duration of neutropenia and the underlying disease. We found that the efficacy of prophylaxis was similar in the two subgroups. A possible explanation for this finding is that the majority of patients with solid tumors or lymphoma, but not of those with leukemia, underwent hematopoietic stem-cell transplantation, and this aggressive approach may account for adjunctive risk factors for bacterial infections other than neutropenia.

Our study does not provide data on low-risk patients with cancer. We did not include such patients in our study because the combination of a fluoroquinolone with amoxicillin and clavulanate represents the standard empirical treatment among febrile “low-risk” patients with neutropenia.^{16,17} The prophylactic use of fluoroquinolones would have precluded their empirical use in these patients.

Our study provides evidence that prophylaxis is economical because it reduces the number of patients who become febrile during periods of neutropenia and therefore reduces the need for antibiotic therapy. However, our study has some limitations. Two main criticisms have been made with respect to the policy of the routine use of fluoroquinolones as prophylaxis. First, their extensive use has been blamed on the increase in resistance to these agents, an effect that can limit their clinical efficacy. Second, no study has yet demonstrated a survival advantage from prophylaxis.

Although our study was not designed to monitor the emergence of resistance to fluoroquinolones, we noted a greater number of levofloxacin-resistant gram-negative strains among patients receiving levofloxacin than among those receiving placebo. However, the prevalence of gram-negative fluoroquinolone-resistant bacteremia did not differ significantly between the two groups, and the presence of fluoroquinolone resistance did not seem to affect clinical outcomes, such as infection-related morbidity or mortality. Furthermore, there is some evidence that fluoroquinolone resistance is a multiclonal¹⁸ and reversible^{19,20} phenomenon and is

Table 2. Characteristics of Bacterial Isolates and Number with Resistance to Levofloxacin.

Characteristic	Levofloxacin (N=339)	Placebo (N=336)
Microbiologically documented infection	74	131
No. with bacteremia	62	115
Single gram-positive isolate	37	54
<i>S. aureus</i>	0	10
Coagulase-negative staphylococcus	31	32
Streptococcus species	5	9
Other gram-positive organisms	1	3
Single gram-negative isolate	15	38
Pseudomonas species	6	8
<i>E. coli</i>	7	22
Other gram-negative organisms	2	8
Polymicrobial isolate	10	23
Gram-positive organisms only	5	5
Gram-positive and gram-negative organisms	5	18
No. without bacteremia	12	16
Single gram-positive isolate	5	7
Single gram-negative isolate	6	9
Polymicrobial isolate	1	0
Levofloxacin resistance in single-agent bacteremias — no. resistant/total no. available for analysis	41/47	32/68
Gram-positive isolate	31/34	28/44
<i>S. aureus</i>	0	1/7
Coagulase-negative staphylococcus	27/30	26/31
Streptococcus species	4/4	1/3
Other gram-positive organisms	0	0/3
Gram-negative isolate	10/13	4/24
Pseudomonas species	4/6	1/4
<i>E. coli</i>	5/5	2/16
Other gram-negative organisms	1/2	1/4

not a reason to avoid the prophylactic use of these compounds. On the other hand, the selective pressure exerted by the use of fluoroquinolone prophylaxis may be counterbalanced largely by the decreased use of empirical antibacterial therapy, thus limiting the risk of emergence of resistance to the drugs used as empirical therapy. Careful monitoring of this phenomenon is mandatory.

Although the absolute number of deaths was lower in the levofloxacin group than in the placebo

Table 3. Mortality Rates in the Treated Population.

Variable	Levofloxacin (N=373)*	Placebo (N=363)	P Value
	<i>no. of patients</i>		
Death	10	18	0.15
Death due to infection	9	14	0.36
Microbiologically documented infection	4	7	0.25
Microbiologically documented infection with bacteremia	3	5	0.34
Single gram-positive isolate	2	2	
Single gram-negative isolate	0	2	
Polymicrobial (gram-positive and gram-negative) isolate	1	1	
Microbiologically documented infection without bacteremia	1	2	0.48
Single gram-positive isolate	0	1	
Single gram-negative isolate	1	1	
Clinically documented infection	2	4	0.33
Lung	1	2	
Other site	1	2	
Fever of unexplained origin	3	3	0.64
Death from noninfectious causes	1	4	0.17

* Two patients were lost to follow-up.

group, we were not able to document a significant effect of levofloxacin in the reduction of mortality. Worldwide, the reported mortality rate due to bacterial infection in patients with cancer and neutropenia is approximately 5 percent^{21,22}; thus, the

demonstration of a significant reduction in mortality owing to the use of bacterial prophylaxis would have required a trial with a much larger sample size than ours. Furthermore, the mortality rate among patients with neutropenia is influenced by factors unrelated to prophylaxis, such as the response to empirical antibiotic therapy, the severity of underlying disease, and the presence of comorbidity. Moreover, a recent observational trial performed at a single center in a small number of patients with hematologic cancers and neutropenia even suggests that patients receiving fluoroquinolone prophylaxis, despite high rates of fluoroquinolone resistance, had a survival advantage over patients who did not receive prophylaxis.²⁰

In conclusion, our study provides evidence that prophylaxis with levofloxacin in high-risk patients with neutropenia is effective, well tolerated, and cost-effective but has no effect on the risk of death. The observed reversibility of fluoroquinolone resistance and the absence of a negative effect on clinical outcomes are sufficient reasons to support the use of fluoroquinolone prophylaxis in patients with neutropenia. The decreased rate of complications related to infection associated with the use of prophylaxis can counterbalance the potential threats of emerging resistance to levofloxacin. This conclusion contrasts with the lack of consensus in some guidelines on the prophylactic use of fluoroquinolones in patients with neutropenia.¹⁵ Our results indicate that there is a need to reassess the role of fluoroquinolones for this indication.

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APPENDIX

The GIMEMA Infection Program includes the following: *Investigators and Centers* — S. Ballanti (Policlinico Monteluce, Università di Perugia, Perugia), G. Gentile (Università La Sapienza, Roma), S. Cinieri (Istituto Europeo di Oncologia, Milano), A. Levis (Ospedale San Antonio e Biagio, Alessandria), G. Fioritoni (Ospedale Civile Santo Spirito, Pescara), T. Barbui (Ospedali Riuniti di Bergamo, Bergamo), E. Morra (Ospedale Niguarda, Milano), E. Brusa (Ospedale San Luigi, Orbassano-Torino), A. Zaccaria (Ospedale Santa Maria delle Croci, Ravenna), A. Peta (Azienda Ospedaliera Pugliese-Ciaccio, Catanzaro), V. Liso (Università di Bari, Bari), L. Cudillo (Ospedale Sant' Eugenio, Roma), S. Mirto (Azienda Ospedaliera Cervello, Palermo), C. Annaloro (Istituto di Ricovero e Cura a Carattere Scientifico [IRCCS], Ospedale Maggiore, Università di Milano, Milano), M. Tozzi (Università di Siena, Policlinico Le Scotte, Siena), M.E. Mitra (Policlinico Universitario, Palermo), A. De Blasio (Ospedale Santa Maria Goretti, Latina), F. Rossini (Università di Milano, Monza), G. Milone (Ospedale Ferrarotto, Catania), A. Cortellezzi (Università di Milano, Milano), G. Landonio (Ospedale Niguarda Ca' Granda, Milano), M. Offidani (Ospedali Riuniti-Università Politecnica delle Marche, Ancona), P. Servida (Divisione di Ematologia, Ospedale S. Raffaele, Milano), R. Invernizzi (Università di Pavia, IRCCS, Policlinico San Matteo, Pavia), L. Castagna (Istituto Humanitas di Rozzano, Milano), N. Cascavilla (Ospedale Casa Sollievo delle Sofferenze, IRCCS, San Giovanni Rotondo), M.A. Capucci (Ospedale Civile, Brescia), G. Trapè (Università Cattolica, Roma), D. Derudas (Università di Sassari, Sassari), M. Picardi (Università di Napoli, Napoli), D. Mattei (Azienda Ospedaliera Santa Croce Carle, Cuneo), R. Sancetta (Ospedale Umberto I Mestre, Venezia), A. D'Emilio (Ospedale San Bortolo, Vicenza), and C. Romani (Ospedale Oncologico Businco, Cagliari); *Data-Review Committee* — C. Cenci, C. Santeusano, F. Mearelli, and I. Nicoletti (Università di Perugia, Policlinico Monteluce, Perugia).

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