

The Use of Fluoroquinolones as Prophylaxis in Neutropenia



From left to right

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Febrile neutropenia, one of the most serious adverse events encountered by physicians caring for cancer patients, results in lengthened hospital stays and an increased mortality rate. Thus, efficacious antibiotic prophylaxis should produce significant benefits. We performed a meta-analysis of randomized, blinded, placebo-controlled trials of fluoroquinolone prophylaxis in neutropenic patients using a random effects model for pooling dichotomous data. A total of 2,721 patients were randomized in 8 eligible trials. Results exhibited a consistent trend in reduction of all-cause mortality thus favoring the use of fluoroquinolone prophylaxis (relative risk [RR]: 0.76; 95% confidence interval [CI]: 0.54–1.08; $p = 0.13$). Analyses also favored fluoroquinolone prophylaxis for the prevention of febrile episodes (RR: 0.76; 95% CI: 0.55–1.03; $p = 0.08$); however, substantial inconsistencies in the results prevent a meaningful interpretation of the pooled data. Results of the subgroup analyses showed a significant reduction in febrile episodes with fluoroquinolone prophylaxis in outpatients with solid tumors including lymphoma compared with the inpatient hematology and stem cell transplant population included in these trials (RR: 0.34 [95% CI: 0.14–0.80] and 0.90 [95% CI: 0.70–1.16], respectively [$p < 0.001$]). The results also suggested a different effect with levofloxacin prophylaxis when trials that used levofloxacin were compared with trials of other fluoroquinolones (RR: 0.60 [95% CI: 0.33–1.10] and 0.89 [95% CI: 0.65–1.22], respectively [$p = 0.01$]). We also reviewed the recommendations by the National Comprehensive Cancer Network panel (1) which advises that fluoroquinolone prophylaxis be considered in patients with an expected duration of neutropenia of more than 7 days. The panel also believes that the benefit of prophylaxis in patients with hematologic malignancies on overall survival outweighs the events related to adverse effects and the development of resistance. This panel suggests levofloxacin as the preferred agent. With regard to surveillance for the emergence of resistant pathogens, fluoroquinolone prophylaxis should be considered in selected adult populations receiving cancer chemotherapy.

Introduction

Despite continuing improvements in health care, infectious complications remain the major source of morbidity and mortality in cancer patients receiving chemotherapy worldwide. Febrile neutropenia is one of the most serious adverse events encountered by physicians caring for this population. An absolute neutrophil count (ANC) of $< 1,000$ cells/mm³ is associated with an increased susceptibility to infection and profound (ANC ≤ 100 cells/mm³) or protracted neutropenia car-

ries an even greater risk (2–5).

The incidence of febrile episodes in neutropenic patients undergoing cancer chemotherapy and hematopoietic stem cell transplantation ranges from < 10 –85% (6–10). Febrile episodes involving bacteremia, which have been documented in up to 34% of these patients (11), result in lengthened hospital stays and an increased mortality rate.

Because of their broad antimicrobial coverage, bactericidal activity, high tissue concentrations and good tolerability and safety profiles, several

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fluoroquinolones have been used extensively for prophylaxis in neutropenic patients in many countries (12–15). A previously published pooled analysis of both open-labeled, placebo-controlled trials of fluoroquinolone prophylaxis in cancer patients, in addition to a reduction in febrile episodes, suggested there was a reduction in all-cause mortality (16). In this paper, we review the results of the meta-analysis in which we only included randomized, blinded, placebo-controlled trials of single agent fluoroquinolone prophylaxis in neutropenic patients. There is also a discussion of the limitations associated with the routine use of fluoroquinolone prophylaxis and the added benefit of levofloxacin compared with other fluoroquinolones.

Materials and Methods

The methods for this systematic review and meta-analysis have previously been described in detail elsewhere (17). Structured forms were used to collect data regarding febrile episodes and all-cause mortality. Missing data were complemented through correspondence with authors. Two articles, one published in French and the other in Spanish, were translated into English. For more generalizable results, a random effects model was used as the primary model for pooling dichotomous data across trials. To investigate the inconsistency between the results of the studies, I^2 was estimated and pre-specified subgroup analyses were performed if the value was $> 50\%$ (18).

Results

Eight trials met the eligibility criteria for this meta-analysis (6, 19–25).

Characteristics of the included trials

A total of 2,721 adult patients were enrolled in

these trials spanning the period 1987–2005. Trials included patients with acute leukemia, other hematologic malignancies, solid tumors including lymphomas and those who underwent autologous or allogeneic stem cell transplantation. All studies that included patients with hematologic malignancies or stem cell transplantation were conducted in an inpatient setting (6, 20–22, 24, 25). In contrast, all studies of patients with solid tumors including lymphomas were conducted in an outpatient setting (19, 23). The smallest trial included 18 patients while the largest trial had 1,565 patients.

The duration of neutropenia as described in 4 studies ranged from 2 to 55 days (6, 20, 21, 23). It was defined either as an ANC $< 500/\text{mm}^3$ or $< 1,000/\text{mm}^3$. The duration and timing of prophylaxis varied among studies but, for most patients, it was started around the time of the initiation of chemotherapy until the resolution of neutropenia or at least covering the expected duration of neutropenia. The fluoroquinolones used in these studies included levofloxacin (6, 19), norfloxacin (20), ciprofloxacin (21, 22), ofloxacin (23), enoxacin (24) and pefloxacin (25). Compliance was reported to be good or excellent in 6 out of 8 trials (6, 19, 20, 24, 25). As summarized in Table 1, data regarding one or two methodology criteria were not accessible for 3 trials. Nonetheless, the majority of the trials did not have serious methodologic concerns and the number of patients lost to follow-up was minimal.

Quantitative results

The mortality rate was 4.5% for the placebo group and 3.9% for the fluoroquinolone prophylaxis group. There was a consistent trend in the reduction of all-cause mortality thus favoring the use of fluoroquinolone prophylaxis (relative risk [RR]: 0.76; 95% confidence interval [CI]: 0.54–1.08; $p =$

Table 1. Quality assessment of the included trials according to the components proposed by reference (26)

Study, year	Allocation concealment	Method of randomization	Outcome ascertainment	ITT analysis	Lost to follow-up, N (%) ^a
Karp et al. (20)	Adequate	Adequate	Adequate	Yes	0
Rafecas et al. (22)	Adequate	Adequate	Adequate	Yes	0
Lew et al. (21) ^b	Unknown	Adequate	Adequate	No	8 (44)
Schroeder et al. (23)	Unknown	Unknown	Adequate	Yes	5 (7)
Talbot et al. (24)	Unknown	Unknown	Adequate	Yes	0
Thomas et al. (25)	Adequate	Adequate	Adequate	Yes	11 (7) ^c
Cullen et al. (19)	Adequate	Adequate	Adequate	Yes	0
Bucaneve et al. (6)	Adequate	Adequate	Adequate	Yes ^d	22 (3)

N = total number of participants who were lost to follow-up, % = proportion of participants who were lost to follow-up.

^a Patients found ineligible or inevaluable after randomization before the first dose of the assigned treatment was given.

^b This study did not contribute to the meta-analysis due to the equal number of events in each group for both mortality and febrile episode data.

^c 7% of the total study population that included another arm of fluoroquinolone and vancomycin that was not included in our analysis.

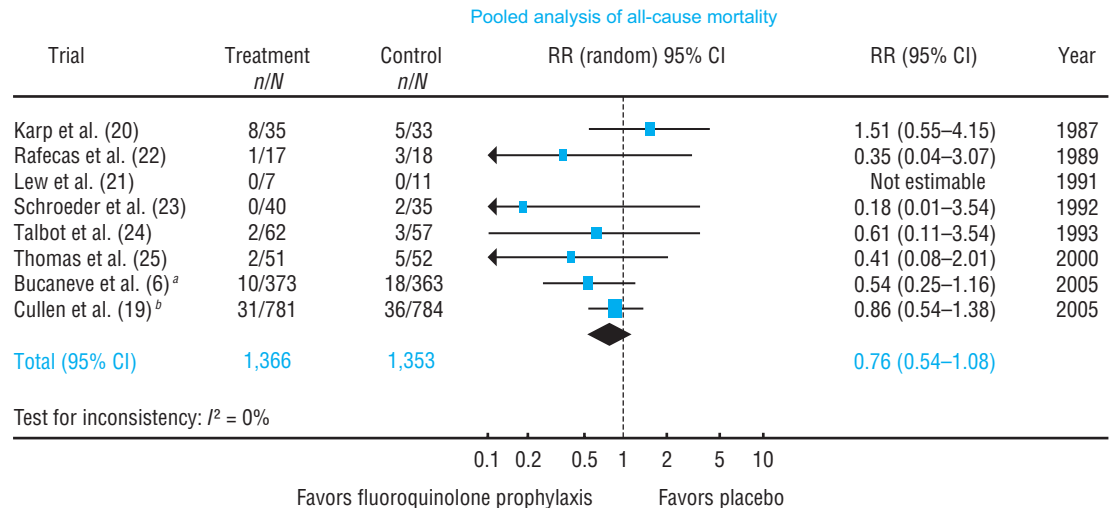
^d Treatment was considered successful for the ITT analysis for 2 patients who were lost to follow-up.

Abbreviation: ITT =intent-to-treat.

0.13; $I^2 = 0\%$) (Figure 1). The rate of febrile episodes was 39% for the placebo group and 31% for the fluoroquinolone prophylaxis group. Analyses favored the use of fluoroquinolone prophylaxis for the prevention of febrile episodes (RR: 0.76; 95% CI: 0.55–1.03; $p = 0.08$) (Figure 2); however, the test for evaluating inconsistency exhibited substantial variation in the results between studies ($I^2 = 95.8\%$) preventing a meaningful interpreta-

tion of the pooled febrile episodes data. Nevertheless, the subgroup analyses performed to investigate the inconsistencies showed a significant reduction in febrile episodes with fluoroquinolone prophylaxis in 2 trials in outpatients compared with 6 trials conducted in an inpatient setting (RR: 0.34 [95% CI: 0.14–0.80] and 0.90 [95% CI: 0.70–1.16], respectively [$p < 0.001$]). The results also favored levofloxacin when 2 trials that

Figure 1. Pooled relative risk for the reduction in all-cause mortality with fluoroquinolone prophylaxis in neutropenic patients compared with placebo



n = total number events, N = total number of participants.

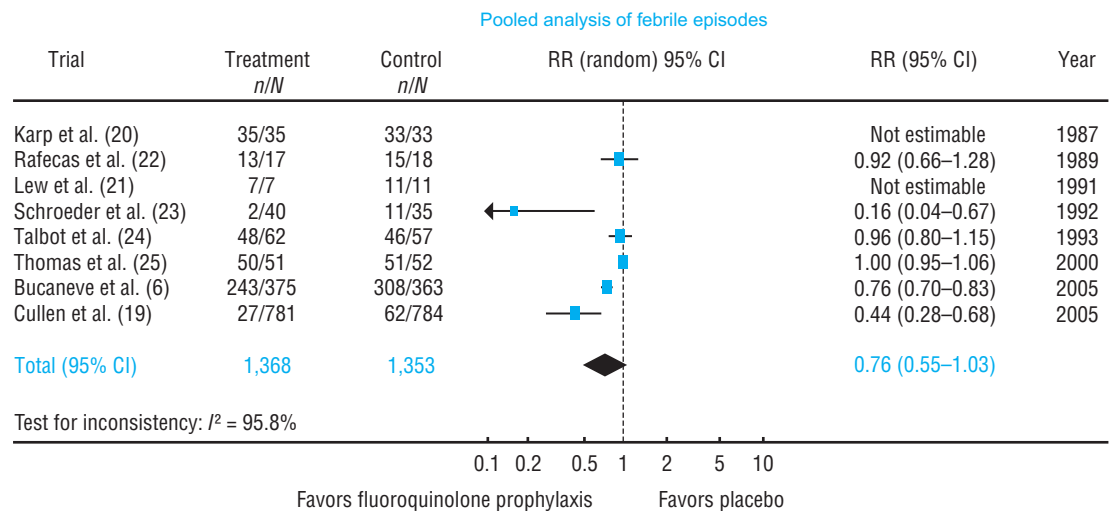
^a Data on mortality was not available for 2 patients who were lost to follow-up as published by the author.

^b Data on mortality provided by the author.

Abbreviations: RR = relative risk, CI = confidence interval.

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Figure 2. Pooled relative risk for the reduction in febrile episodes with fluoroquinolone prophylaxis in neutropenic patients compared with placebo



n = total number events, N = total number of participants.

Abbreviations: RR = relative risk, CI = confidence interval.

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used levofloxacin were compared with 6 trials that used other fluoroquinolones (RR: 0.60 [95% CI: 0.33–1.10] and 0.89 [95% CI: 0.65–1.22], respectively [$p = 0.01$]). The results exhibited a trend towards significance when the trial that used levofloxacin in patients with hematologic malignancies and stem cell transplant recipients was compared with trials of other fluoroquinolones conducted in the same patient population (RR: 0.76 [95% CI: 0.70–0.83] and 0.99 [0.94–1.05], respectively [$p = 0.08$]).

Discussion

In agreement with the findings of a previously published meta-analysis (16) and its updated results (27), we found a clinically important and consistent trend towards a reduction in mortality in neutropenic patients receiving fluoroquinolone prophylaxis. Our findings support the concept of risk-based prophylactic therapy as proposed by other investigators (27, 28). Outpatients with solid tumors, including lymphomas, a low-risk population with an 8–31% risk of febrile episodes in placebo-controlled subjects, were found to be more responsive to prophylaxis. Conversely, hematology inpatients and stem cell transplant recipients, a high-risk population with an 83–100% risk of febrile episodes in placebo-controlled subjects, were less responsive to prophylaxis. One of many plausible explanations might be that factors other than bacterial infections are a significant cause of fever in this population. With the caveat that the results between studies varied significantly, a subgroup analysis produced significantly different estimates favoring levofloxacin. Although this was a between-study subgroup analysis, the results are supported by the fact that levofloxacin has a broader antimicrobial coverage than the earlier used fluoroquinolones (29).

The most recent Infectious Disease Society of America (IDSA) guidelines that were published in 2002 do not recommend the routine use of antimicrobial prophylaxis in neutropenic patients (30). Their conclusions stem from two basic concerns: 1) emerging drug-resistant pathogens due to extensive antibiotic use, and 2) prophylaxis has not been shown consistently to reduce mortality rates despite adequate evidence that supports its efficacy in reducing febrile episodes. With the new evidence emerging from the two recent randomized controlled trials (6, 19) and meta-analyses addressing this topic (16, 17, 27), the guidelines are outdated and will probably be changed in the updated version due to appear in the spring of 2009.

The first trial by Bucaneve et al. evaluated levofloxacin prophylaxis in adult patients with

cancer in whom chemotherapy-induced neutropenia ($ANC < 1,000/mm^3$) was expected to occur for more than 7 days (6). Levofloxacin recipients had a lower rate of microbiologically documented infections, bacteremias, and single-agent Gram-negative bacteremias than placebo recipients. The effects of prophylaxis were similar between patients with acute leukemia and those with solid tumors or lymphoma. Mortality and tolerability were similar in the two groups. It is noteworthy that a high percentage of resistance was reported in this trial. In the control group from that trial, 47% of 68 isolates were resistant to levofloxacin, and the resistance rate among Gram-negative aerobic bacteria was 17%.

The second trial by Cullen et al. evaluated levofloxacin prophylaxis after chemotherapy for solid tumors and lymphomas for patients anticipated to have a brief duration of neutropenia and categorized as low-risk (19). During the entire chemotherapy course, 10.8% of patients in the levofloxacin group had at least one febrile episode compared with 15.2% of patients in the placebo group ($p = 0.01$). Hospitalization was required for the treatment of infection (suspected and documented) in 15.7% of patients in the levofloxacin group and 21.6% of patients in the placebo group ($p = 0.004$). The incidence of severe infections, infection-related mortality, and overall mortality was similar in both groups.

Based on the results of these two large randomized clinical trials (6, 19), the National Comprehensive Cancer Network (NCCN) panel (1) advises that fluoroquinolone prophylaxis be considered in patients with an expected duration of neutropenia ($ANC < 1,000/mm^3$) of more than 7 days (1). The panel believes that the benefit of prophylaxis in patients with hematologic malignancies on overall survival outweighs the events related to adverse effects and development of resistance. The NCCN panel suggests levofloxacin as the preferred agent (1). Another expert group suggests that practitioners may choose between fluoroquinolones based on the theoretical advantage of ciprofloxacin against *Pseudomonas aeruginosa* or the theoretical advantage of levofloxacin against Gram-positive bacteria, according to the local distribution of pathogens in neutropenic patients (27).

Among patients with neutropenia who are at lower risk of infectious complications (a category that includes most patients with solid tumors), the main benefit of antibiotic prophylaxis relates to a reduction in fever rather than in documented infections. In patients with neutropenia expected to last less than 7 days who are not receiving immunosuppressive regimens (e.g., systemic corticosteroids), the NCCN panel suggests no antibiotic

prophylaxis (1). An important consideration for low-risk patients with a short duration of neutropenia is whether fluoroquinolone prophylaxis is of greater benefit than the option of outpatient treatment for fever and neutropenia, should it occur. Both the NCCN panel (1) and old IDSA guidelines (30) recommend oral fluoroquinolone-based regimens as outpatient empiric therapy for neutropenic fever in adults who meet the criteria for a low risk of complications. The use of fluoroquinolone prophylaxis may preclude their later use as empiric therapy for neutropenic fever in the same patient. In a pooled analysis of trials that reported resistance data (27), of all infections that developed among patients who received fluoroquinolone prophylaxis, 30% were fluoroquinolone-resistant; thus, fluoroquinolones cannot be used for the treatment of febrile neutropenia in patients who receive prophylaxis.

The decision whether to use antibiotic prophylaxis and the selection of the specific agent requires a balance between the expected benefits and risks. The concept of risk applies to the potential for selection for resistant pathogens that can harm the individual receiving prophylaxis, and the hazard of resistant organisms to a specific population of patients (e.g., those being treated at a cancer center). The recent link between fluoroquinolone use and severe *Clostridium difficile* (31–33) as well as MRSA (34) infections provides an additional cautionary note regarding the excessive use of fluoroquinolones. Several observational studies have also documented the emergence of bacteria resistant to fluoroquinolones in units in which prophylaxis is practiced (35–38). However, in the population at large, the quantity of fluoroquinolones to be given as prophylaxis in the neutropenic cancer population is insignificant compared with the consumption of fluoroquinolones for

other infections (e.g., involving the urinary and respiratory tracts). To assess the effect of fluoroquinolone prophylaxis on the emergence of resistant bacteria in neutropenic patients, a systematic review and meta-analysis of randomized controlled trials were conducted comparing fluoroquinolone prophylaxis with placebo or no intervention, or another antibiotic, for the prevention of bacterial infections in afebrile neutropenic patients (39). The search yielded 56 trials, 22 compared fluoroquinolones with placebo or no intervention. Data on colonization by resistant organisms could be extracted from 27 trials (48%). When compared with placebo or no intervention, there was a non-significant increase in colonization with organisms resistant to fluoroquinolones (RR: 1.68; 95% CI: 0.71–4.00). There was no difference between the two groups in the number of patients developing infections caused by resistant pathogens (RR: 1.04; 95% CI: 0.73–1.50). However, these trials lacked adequate length of follow-up to assess resistance development and did not report on the effect of prophylaxis on resistance to β -lactam antibiotics used for the treatment of febrile neutropenia.

In conclusion, the available data suggest that fluoroquinolone prophylaxis is beneficial in neutropenic cancer patients. Prophylaxis with a fluoroquinolone is associated with a favorable effect involving a reduction in overall mortality of these patients. In selected adult populations receiving cancer chemotherapy, fluoroquinolone prophylaxis should be considered with surveillance for emergence of resistant pathogens. Monitoring local pathogen prevalence and susceptibilities should facilitate the use and type of fluoroquinolone prophylaxis; however, based on the available supporting evidence, extended Gram-positive coverage and once-daily administration make levofloxacin a better choice.

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