International Journal of Research in Medical Sciences
Peters J et al. Int J Res Med Sci. 2018 Jul;6(7):2479-2484
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20182839

Original Research Article

Prophylactic levofloxacin in cancer chemotherapy: a randomized controlled study

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Received: 12 April 2018
Accepted: 04 May 2018

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ABSTRACT

Background: The patients on cancer chemotherapy are at substantial risk of developing febrile episodes, bacteremia and infection related mortalities, yet the prophylactic use of antimicrobials continues to be a controversial issue. Hence, this study was designed to study the effect of antimicrobial prophylaxis in cancer chemotherapy.
Methods: The patients receiving the cancer chemotherapy were randomly divided into two groups. Group A patients received cancer chemotherapy and no prophylactic antimicrobials. Group B patients were given prophylactic levofloxacin with each cancer chemotherapy cycle. Patients were evaluated for febrile episodes, documented infections and hospitalizations. The Eastern Cooperative Oncology Group (ECOG) performance grade and culture sensitivity reports were also recorded.
Results: Demographic profile of patients was comparable in both groups. Absolute neutrophil count at 6 weeks was significantly higher with levofloxacin prophylaxis. Levofloxacin prophylaxis led to 92% reduction in risk of having neutropenia in first cycle, 78% reduction in clinically documented febrile episodes during the first chemotherapy cycle (36 % vs 8%, 95% confidence interval 0.08 to 0.56, $p<0.001$), 88% reduction in risk of developing infections, 63% reduction in risk of hospitalization and 30% decrease in average cost of treatment per patient per day (₹1269.80±220.32 vs. ₹372.21±99.23, $p<0.01$) as compared to control group. All documented infections were from gram negative bacteria, E. coli being the commonest.
Conclusions: Antimicrobial prophylaxis with levofloxacin is beneficial to patients receiving cancer chemotherapy as it decreases the morbidity, in terms of febrile episodes, neutropenia, infections, hospitalizations and it also reduces the cost of overall treatment.

Keywords: Cancer, Chemotherapy, Fluoroquinolones, Levofloxacin, Prophylaxis

INTRODUCTION

Bacterial infections are a major cause of morbidity and mortality in patients receiving cancer chemotherapy for malignancies.[1] The most important risk factor for infection is an absolute neutrophil count (ANC) of less than $0.5x10^9$/L and its duration.[2] In addition, disruptions of physical defense barriers of skin mucosa, secondary to chemotherapy, leads to increased exposure to potentially pathogenic organisms. In-dwelling venous access catheters further increase the risk of bacteremia.

Pooled results from randomized controlled trials show that antimicrobial prophylaxis when started during cancer chemotherapy or at onset of neutropenia reduces all-cause mortality.[3,4] Fluoroquinolones are currently the primary antimicrobials used for prophylaxis.[5,6] When quinolones are used as prophylaxis, the rate of gram negative

bacteremia is reduced.[5,7] Levofloxacin is one of the most widely used fluoroquinolone with an acceptable adverse effect profile and is administered once daily. Thus, it optimizes compliance, a major issue in prophylaxis. It is active against a wide range of gram negative pathogens as well as some gram positive bacteria and organisms causing atypical pneumonias.[8]

The role of prophylactic antimicrobial agents with cancer chemotherapy still remains controversial. The main argument against their use is the induction of antimicrobial resistance.[9,10] The emergence of multidrug resistant strains in the population of cancer patients who are given prophylactic quinolones for the prevention of gram-negative sepsis is of great concern.[11] The cost factor involved in prophylactic use of antibiotics along with cancer chemotherapy is another major deterrent in Third World countries like India. Extensive literature research shows no such study reporting the effectiveness of antibiotic prophylaxis with cancer chemotherapy and its cost analysis, in Indian population. Hence, this study was designed to evaluate the efficacy of antimicrobial prophylaxis given to the patients receiving cancer chemotherapy.

METHODS

The study was approved by Institutional Research committee. All patients signed written informed consent before enrolment into study.

Study design and sample

This was a prospective, randomized and controlled study. A total of 100 patients receiving cancer chemotherapy were enrolled. Patients 18 years of age and above with a diagnosis of solid tumors and lymphomas were included in the study. Patients with leukemia, hypersensitivity to fluoroquinolones, patients treated with antibiotic therapy in the previous four weeks, patients with fever of infectious origin, a documented infection at the time of enrolment or pregnant/lactating subjects were excluded from the study.

Evaluation parameters

The evaluation included primary and secondary parameters. Primary parameters included number of febrile episodes, number of documented infections and number of hospitalizations. Patient's temperature was recorded daily and oral temperature of 38.3ºC (101ºF) single reading or temperature of 38ºC (100.4ºF) for one hour was defined as a febrile episode.[8] Secondary parameters included development of resistance as per culture/sensitivity reports, Eastern Cooperative Oncology Group (ECOG) Performance grade and cost analysis in both groups.[12]

ECOG performance scale are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient. Literacy and socio-economic status of subjects was evaluated using class III of Modified Kuppuswamy socio-economic scale.[13]

The type of cancer, other modalities for treatment, existence of comorbid conditions, use of bone marrow stimulating strategies and absolute neutrophil count (ANC) was recorded. Patients were followed up, until the completion of chemotherapy and six weeks after the last cycle. A patient on cancer chemotherapy, received an average of 4-6 cycles of chemotherapy. ANC was recorded for all patients in each cancer chemotherapy cycle and at end of follow up to find out neutropenia ($ANC<2000/mm^3$). Antibiotic sensitivity test for levofloxacin was done for all cultures sent for group B patients.

Study procedure

The patients were randomly assigned to two groups A and B using computer generated randomization. The group A patients received the cancer chemotherapy and no antimicrobials were given prophylactically. The group B patients were given levofloxacin 500mg once a day for a total of seven days with each cycle of cancer chemotherapy. Complete blood count was done before each cycle of chemotherapy to monitor the neutrophil counts. If infection was suspected, samples were obtained for microbiologic cultures and empirical antibacterial therapy was initiated, according to judgment of the treating physician pending culture/sensitivity reports. Isolated bacteria were identified with the use of standard methods and susceptibility was evaluated according to the Kirby-Bauer method.[14]

Statistical analysis

The data was analyzed using Fisher exact test and Kruskal Wallis test for non-parametric data. Parametric data was analyzed by ANOVA for comparing two different groups and a paired 't-test' for comparison within the group. p value <0.05 was considered as statistically significant.

RESULTS

Demographic profile of patients was comparable in both groups and is depicted in Table 1. There was female predominance in both groups (68% in group A and 60% in group B). Majority of patients were illiterate (34 vs. 36%) and mainly came from rural area (62 vs. 68%) in group A and B respectively. Half of the patients (44%) belonged to lower middle class (class III of modified Kuppuswamy socio-economic scale).[13] The biochemical and hematological investigations of patients done at enrollment were comparable. One fourth of the patients had carcinoma breast (30% in group A and 20% in group B).

Table 1: Demographic profile and socio-economic status of patients in both groups at baseline.

Characteristics	Group A (n=50)	Group B (n=50)
Age (years) (Mean±SE)	55.76±1.71	57.04±1.77
Sex (M:F)	16:34 (32%:68%)	20:30 (40%:60%)
Weight (kg)	55.77±1.92	57.29±2.03
Height (cm)	160.94±1.35	159.94±2.31
Body surface area (m^2)	1.52±0.03	1.56±0.28
Co-morbid conditions		
Diabetes	4 (8%)	3 (6%)
Hypertension	4 (8%)	8 (16%)
CAD	0	2 (4%)
Rural/Urban	31:19 (62%:38%)	34:16 (68%:32%)
Education		
Illiterate	18 (36%)	17 (34%)
Primary education	7 (14%)	9 (18%)
Middle School	7 (14%)	4 (8%)
Matric	8 (16%)	10 (20%)
Intermediate	2 (4%)	4 (8%)
Graduate	6 (12%)	5 (10%)
Post-Graduate	2 (4%)	1 (2%)
Socio-Economic Status*		
Upper	1 (2%)	3 (6%)
Middle	11 (22%)	12 (24%)
Lower middle	22 (44%)	22 (44%)
Lower middle lower	15 (30%)	11 (22%)
Lower	1 (2%)	2 (4%)

No significant difference between group A and B was observed (p>0.05), *Modified Kuppuswamy's Socioeconomic Status Scale, CAD - Coronary artery disease

Other common cancers were lung and ovarian carcinoma (Table 2). The comorbid conditions like diabetes, hypertension and coronary artery disease were seen in 21 patients. Thirty eight patients (23 group A vs. 15 group B) received other treatment modalities like radiotherapy or surgery. Adjuvant biological agents comprising colony stimulating factors were used in 15 patients. Most of the patients received two cancer chemotherapy drugs (68% group A vs. 56% group B).

The intergroup analysis showed that ANC was comparable in both groups at baseline and in all the chemotherapy cycles (Figure 1). However, ANC done at 6 weeks follow-up was significantly higher in group A (p<0.05).

Figure 2 shows incidence of neutropenia, febrile episodes, hospitalizations and documented infections**.** Incidence of neutropenia in first cycle was significantly higher in group A as compared to group B (12 vs. 1, Relative risk 0.08, 95% Confidence interval 0.01- 0.62, p<0.05). It indicates 92% reduction in risk of having neutropenia in first cycle with levofloxacin prophylaxis.

Table 2: Diagnostic and therapeutic profile of patients in both groups.

Characteristics	Group A (n=50)	Group B (n=50)
Cancer types		
Carcinoma breast	15 (30%)	10 (20%)
Carcinoma lung	8 (16%)	7 (14%)
Carcinoma ovary	10 (20%)	5 (10%)
Others	17 (34%)	28 (56%)
Treatment modalities		
Chemotherapy only	27 (54%)	35 (70%)
Combined treatment	23 (46%)	15 (30%)
No. of chemotherapy drugs used		
1	9 (18%)	4 (28%)
2	34 (68%)	28 (56%)
3	6 (12%)	7 (14%)
4	1 (2%)	1 (2%)
Adjuvant agents	6 (12%)	9 (18%)
Previous chemotherapy	18 (36%)	22 (44%)
Previous radiotherapy	4 (8%)	4 (8%)
Previous surgery	23 (46%)	26 (52%)
Adjuvant chemotherapy	15 (30%)	12 (24%)
Neo-adjuvant chemotherapy	8 (16%)	3 (6%)

A clinically documented febrile episode occurred during the first chemotherapy cycle in four patients (8%) in the levofloxacin group as compared with 18 patients (36%) in the control group (Relative risk 0.22, 95% confidence interval 0.08 to 0.56, p<0.001), indicating a 78% reduction in the risk. Fever in other cycles was seen in 14% patients in group B and in 40% patients in group A (Relative risk 0.35, 95% Confidence interval 0.16-075, p<0.05) indicating 65% reduction in the risk. There was 63% reduction in risk of hospitalization in group B patients as compared to group A (Figure 2). Average duration of hospital stay was less than half of the average duration for patients of group A.

In group A, 9 (18%) patients had documented infections and in group B, only one patient had documented infection (relative risk 0.11, 95% confidence interval 0.01-0.84, p<0.05), indicating 88% reduction in risk of developing infections. All documented infections were from gram negative bacteria. The most common bacteria isolated was *Escherichia coli* (*E. coli)* in 60% of samples. Other bacteria isolated were *Acinetobacter* (20%), *Klebsiella* (10%) and *salmonella* (10%). Resistance to levofloxacin was reported in one patient in group B. All cultures were reported to be normal, but urine culture showed significant growth of *E. coli*. Patient became afebrile within first 48 hours and was discharged after receiving 5 days of parenteral antimicrobials.

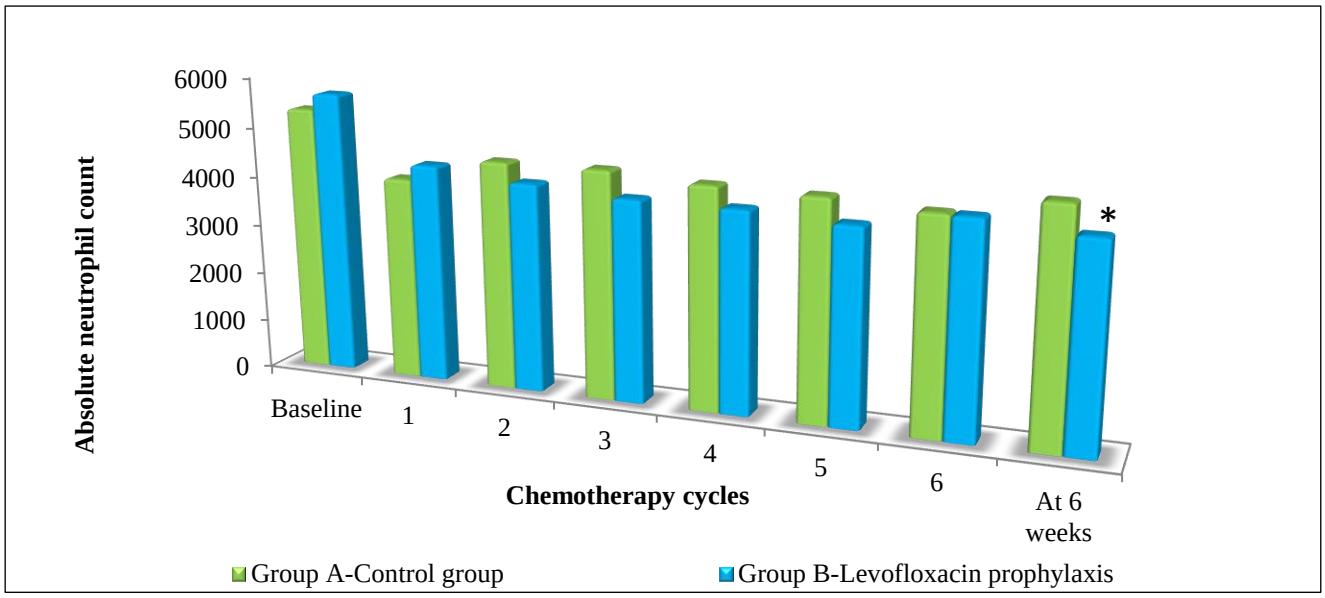

Figure 1: Absolute neutrophil count at various time intervals and in various chemotherapy cycles in both groups.

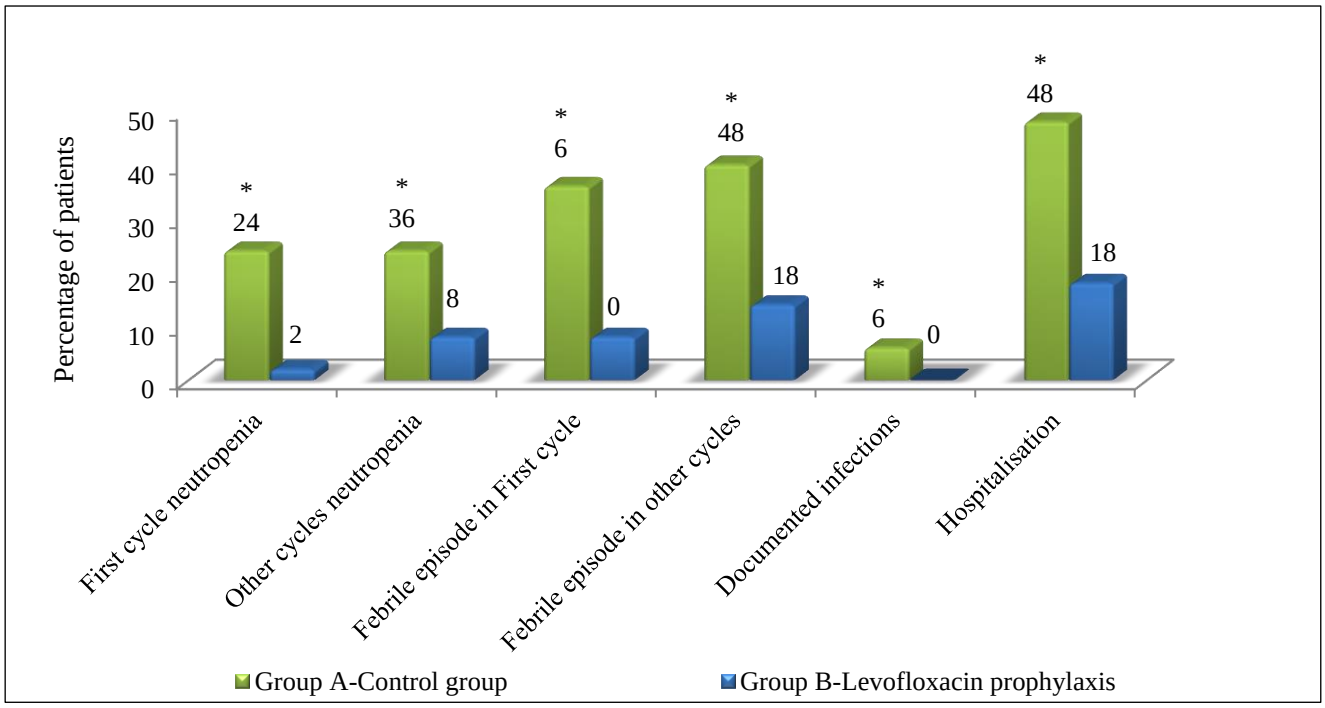

Figure 2: Incidence of neutropenia, febrile episodes, documented infections and hospitalizations in both groups.

Fifty four percent (44%) patients in group A and 20% in group B received antibiotic treatment. The most common antibiotic used was cefipime combined with amikacin in both groups (36% vs. 18%). There was no serious adverse event reported with levofloxacin. The mild adverse effects reported were headache, insomnia, nausea, anorexia and loose stools. The grades were comparable at enrollment and at the end of follow up in both groups. The total cost of treatment in group A was ₹4.41 lakhs and in group B was ₹1.45 lakhs. There was significant difference in the average cost of treatment per patient per day in two groups (₹1269.80±220.32 vs. ₹372.21±99.23, $p<0.01$).

DISCUSSION

Demographic and clinical profile of patients was comparable in both groups. The commonest cancer was

carcinoma breast in our study. This is comparable to other studies with carcinoma breast being most common cancer reported.[3,15,16] A decline in ANC from baseline is seen in both groups. Neutropenia was seen less after first cycle when levofloxacin was given, and this was statistically significant. Levofloxacin showed a protective role in first cycle neutropenia. It indicates 92% reduction in risk of having neutropenia in first cycle with levofloxacin prophylaxis. It has been proven that the risk of the initial episode of severe neutropenia or febrile neutropenia is greatest during the first cycle of treatment.[11,17] It is the major cause of dose reductions and delays resulting in reduced relative dose intensity that may compromise disease-free and overall survival. Thus, levofloxacin prophylaxis by preventing neutropenia may decrease the morbidity in cancer patients.

Febrile episodes were significantly less in first cycle of cancer chemotherapy and other cycles also when levofloxacin was given. Reduction in relative risk was similar to another study done but much higher as compared to other studies which reported relative risk reduction ranging from 4-56%.[3,16-18]

The reason could be that these studies were conducted in western countries with a much lower incidence of infections. Emerging and re-emerging zoonotic diseases, foodborne and waterborne diseases and diseases caused by multi-resistant organisms constitute the major threats in India.[19] Similarly the number of documented infections was significantly less with levofloxacin as compared to group not given levofloxacin. The most common bacteria isolated was Escherichia coli in 10% of patients. This finding is also similar to previously reported studies in which gram-negative bacilli, especially *E. coli* and *Klebsiella species*, were prominent causes of infection.[20,21]

There is 63% reduction in risk of hospitalization with levofloxacin prophylaxis. The reduction in hospitalization rate is high as compared to other studies.[3,18] It is probably because of lower incidence of neutropenia, febrile episodes and documented infections.

Thus, levofloxacin prophylaxis significantly reduces the rate of hospitalization and its duration also. American Society of Clinical Oncology clinical practice guideline suggest that fluoroquinolone prophylaxis should be considered for high risk patients with prolonged and profound neutropenia.[22]

Resistance to levofloxacin was reported in one patient. The presence of fluoroquinolone resistance did not seem to affect clinical outcomes, such as infection-related morbidity or mortality.[18] Furthermore, there is some evidence that fluoroquinolone resistance is a multiclonal and reversible phenomenon and is not a reason to avoid the prophylactic use of these compounds.[10,18] 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. Levofloxacin is an important anti tubercular drug and especially in Indian subcontinent, with new emerging cases of multidrug resistant tuberculosis, it becomes necessary to avoid its unnecessary use. Careful monitoring of this phenomenon is mandatory.[23,2] Eastern Cooperative Oncology Group performance grade of patients were comparable at enrollment and at the end of follow up in both groups ($p>0.05$). The overall performance grade does not change much in short span of 4-6 months. A long-term study is required to prove improvement in performance grade.

Another major advantage of antimicrobial prophylaxis is cost-effectiveness. The overall cost of treatment decreased approximately by 30% with levofloxacin prophylaxis. Antimicrobial prophylaxis can reduce the cost of treatment by decreasing the number of hospitalizations and infections.[24] In our study, the average duration of hospital stay was also reduced with levofloxacin prophylaxis. As seen in our study, majority of patients belonged to lower middle socioeconomic strata. The cost factor involved in prophylactic use of antibiotics along with cancer chemotherapy is a major deterrent in developing countries like India where major portion of population is below poverty line. Thus, antimicrobial prophylaxis in patients receiving cancer chemotherapy is economical because it reduces the number of patients who become febrile during periods of neutropenia and therefore reduces the need for antibiotic therapy.

CONCLUSION

There is a statistically significant reduction, in first cycle neutropenia, febrile episodes, documented infections, hospitalizations and cost of treatment. This impact on decreasing the morbidity in cancer patients is considerable. The findings of past reviews do not support withholding quinolone prophylaxis from patients, for fear of resistance induction. But vigilant use of antimicrobials is the need of the hour in Indian population where tuberculosis is emerging as a dreadful disease. A careful selection of patients for prophylactic use of antimicrobial should be considered. Validation of country/region specific risk assessment models is required. A long-term study should be carried out to prove the mortality benefit and improvement in quality of life. To conclude, our study provides ample evidence that antimicrobial prophylaxis is beneficial to patients receiving cancer chemotherapy as it decreases the morbidity, in terms of febrile episodes, neutropenia, infections, hospitalizations and it also reduces the cost of treatment.

ACKNOWLEDGEMENTS

Authors would like to thank Ms. Himani Khattar, Biostatistician, Christian Medical College, Ludhiana in helping with analysis.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Peters J, Badyal DK, John JM. Prophylactic levofloxacin in cancer chemotherapy: a randomized controlled study. Int J Res Med Sci 2018;6:2479-84.