Outcomes of levofloxacin prophylaxis in obese versus non-obese patients with hematologic malignancies

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ABSTRACT

Background: Levofloxacin given at a standard dose of 500 mg daily is recommended for antibacterial prophylaxis in patients receiving myelosuppressive chemotherapy. Obese patients have been shown to exhibit enhanced clearance of levofloxacin and may be at risk for prophylactic failure.
Methods: This was a single center, retrospective cohort study evaluating the infectious outcomes of obese (BMI >30 kg/m^2) and non-obese (BMI ≤30 kg/m^2) adult patients who received standard dose levofloxacin as primary prophylaxis after chemotherapy. Patients were included if they were treated at our institution from June 1, 2014 through May 31, 2017 and had National Comprehensive Cancer Network (NCCN) defined intermediate infection risk. Patients were excluded if they were lost to follow-up, treated at another institution for febrile neutropenia (FN), or had renal impairment (estimated creatinine clearance (CrCL) less than 50 mL/min). The primary endpoint was incidence of FN as defined by NCCN guidelines. Secondary endpoints included 30-day mortality and the correlation between estimated levofloxacin AUC and rates of FN. Levofloxacin AUC was estimated from CrCL using the method of Pai, et al.
Results: A total of 98 patients met the inclusion criteria (34 obese and 64 non-obese). Estimated CrCL was similar between obese and non-obese patients (mean 84.5 vs 81.6 mL/min, *P* = 0.61), as was estimated levofloxacin AUC (mean 115.1 mg*h/L versus 107.8 mg*h/L, *P* = 0.25). FN occurred in 26 patients: 12 (35.3%) obese and 14 (21.9%) non-obese (*P* = 0.16). Bivariate comparisons between patients who did and did not experience FN found no significant associations with the weight-related variables total body weight (mean 84.7 vs 82.0 kg, *P* = 0.56), BMI (mean 28.8 vs 28.0 kg/m^2, *P* = 0.51), or body surface area (1.99 vs 1.96 m^2, *P* = 0.62). Multivariate analysis identified presence of mucositis and diagnosis of multiple myeloma as variables independently associated with FN. No patients died within 30 days of the FN event.
Conclusion: There were no significant associations between body weight-related variables and FN in this cohort of patients with similar renal function. Obesity should not be a justification for more aggressive levofloxacin dosing schemes when used for FN prophylaxis.

BACKGROUND

- FN is an oncological emergency associated with increased morbidity and mortality in patients with cancer.[1]
- Levofloxacin 500 mg daily is recommended by IDSA and NCCN guidelines for infection prophylaxis.[1,2]
- For fluoroquinolones, the pharmacodynamic target associated with killing effect is the AUC:MIC.[3]
- Obese patients with unimpaired renal function exhibit enhanced clearance of levofloxacin.[4,5,6]
- Obese patients may be predisposed to treatment failure due to enhanced clearance of levofloxacin.

METHODS

Definitions:[1,2]

- **Fever:** single temperature ≥ 38.3°C OR temperature of 38.0°C sustained over one hour without an obvious cause
- **Neutropenia:** ANC <500 cells/mcL OR less than 1,000 cells/mcL and expected to decline below 500 cells/mcL within 48 hours)
- **Intermediate Risk:** autologous HSCT, purine analog therapy, neutropenia anticipated to last 7-10 days, lymphoma, multiple myeloma or chronic lymphocytic leukemia

METHODS Continued

- Single-center, retrospective, descriptive cohort
- First cycle myelosuppressive chemotherapy from 6/2014-5/2017
- **Inclusion criteria:** adults ≥ 18 years of age and prophylaxis with levofloxacin 500 mg daily
- **Exclusion criteria:** lost to follow-up, FN treated at another institution, NCCN defined low or high risk, and renal impairment (estimated CrCL < 50 mL/min calculated using CG and IBW)
- Patients identified through EDW by searching for intermediate risk chemotherapy regimens and levofloxacin administration
- **Statistical analysis:** Bivariate comparisons were assessed using Chi-square or Fisher exact tests, or Mann-Whitney, as appropriate. Multivariate logistic regression was used to identify variables independently associated with FN

RESULTS

Figure 1. BMI and FN

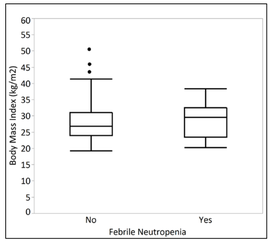


Figure 2. BSA and FN

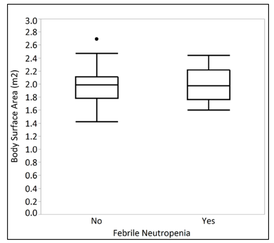


Figure 3. IBW and FN

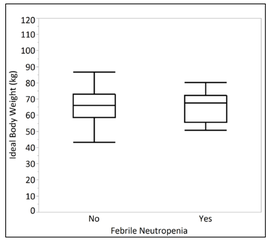
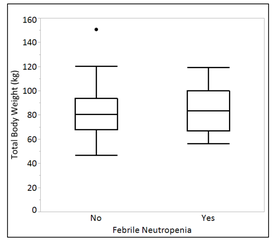


Figure 4. TBW and FN



RESULTS Continued

Table 1. Bivariate Associations with FN

Variable	FN (n=26)	No FN (n=72)	P-value
Male sex, n (%)	17 (65.4)	49 (68.1)	0.80
Race/ethnicity, n (%)			**0.02**
White/Caucasian	**26 (100.0)**	**60 (83.3)**	
Hispanic	**0 (0.0)**	**5 (6.9)**	
Asian	**0 (0.0)**	**2 (2.8)**	
American Indian or Alaska Native	**0 (0.0)**	**1 (1.4)**	
Other	**0 (0.0)**	**2 (2.8)**	
Unknown	**0 (0.0)**	**2 (2.8)**	
BMI > 30 kg/m^2, n (%)	14 (53.8)	50 (69.4)	0.16
Cancer diagnosis, n (%)			**<0.0001**
Lymphoma	**3 (11.5)**	**48 (66.7)**	
Multiple myeloma	**23 (88.5)**	**24 (33.3)**	
GCSF administration, n (%)	26 (100.0)	70 (97.2)	0.26
Presence of mucositis, n (%)	**18 (72.0)**	**11 (15.9)**	**<0.001**
Other antimicrobial prophylaxis, n (%)	**26 (100.0)**	**57 (79.2)**	**0.01**
Antiviral prophylaxis, n (%)	**26 (100.0)**	**55 (76.4)**	**0.006**
Antifungal prophylaxis, n (%)[a]	**25 (96.2)**	**39 (54.2)**	**0.0001**
Albumin < 3.5 g/dL, n (%)	4 (15.4)	25 (35.2)	0.06
Inpatient management, n (%)	**26 (100.0)**	**0 (0.0)**	**<0.0001**
Age, years, median (IQR)	62 (55.8-65.3)	59 (51.3-68)	0.66
TBW, kg, median (IQR)	83.4 (66.8-100.1)	80.6 (67.8-93.6)	0.51
ABW, kg, median (IQR)	73.5 (63.1-83.8)	73.9 (64.4-79.8)	0.71
IBW, kg, median (IQR)	67.6 (55.7-72.2)	66.1 (58.8-73.0)	0.83
BMI, kg/m^2, median (IQR)	29.6 (23.5-32.6)	26.8 (24.0-31.0)	0.35
BSA, m^2, median (IQR)	1.98 (1.76-2.22)	1.99 (1.78-2.11)	0.68
SCr, mg/dL, median (IQR)	0.93 (0.73-1.06)	0.85 (0.70-1.06)	0.32
CrCL, mL/min, median (IQR)[b]	105.5 (72.4-130.0)	89.3 (65.3-113.9)	0.13
Estimated levofloxacin AUC, mg*hr/L, median (IQR)[c]	79.1 (64.1-115.1)	93.4 (73.2-127.6)	0.13

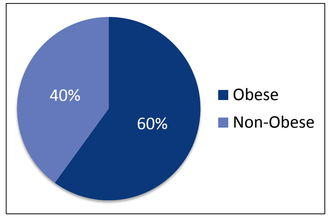
[a] All patients who received antifungal prophylaxis received fluconazole
[b] Measured CrCL included when available (n = 45), otherwise estimated by CG
[c] Estimated using measured CrCL when available and estimated CrCL otherwise

Multivariate analysis: Mucositis (OR 7.6, 95% CI 2.4-26.0) and multiple myeloma (OR 8.9, 95% CI 2.4-42.8) were independently associated with FN

Secondary Endpoints:

- 30-day mortality: 0 patients
- Delayed or modified cycle of next chemotherapy: 1 patient (4%)
- FN requiring ICU care: 6 patients (23%)
- Median hospital LOS for patients with FN: 5 days (range: 4-9 days)
- Median ICU LOS for patients with FN: 2.5 days (range 1.0-5.3 days)

Figure 5. Patients with Positive Microbiological Results (n=10)



3 patients with isolates resistant to fluoroquinolones:
- 1 obese patient with *E. coli*
- 1 non-obese patient with *Rhodococcus equi*
- 1 non-obese patient with *E. coli*

CONCLUSION

- There were no significant associations between weight-related variables and FN in this cohort of intermediate-risk patients with similar renal function.
- Obesity should not be used as a justification for more aggressive levofloxacin dosing schemes when used for FN prophylaxis in this population.
- Further analysis of the effect of obesity in patients with NCCN defined high infection risk may be warranted.

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DISCLOSURE

Authors of this presentation have nothing to disclose concerning possible financial or personal relationship with commercial entities that may have a direct or indirect interest in the subject of this presentation.

ABW= adjusted body weight, ANC= absolute neutrophil count, AUC= area under the curve, BMI= body mass index, BSA= body surface area, CG= Cockcroft-Gault equation, CI= confidence interval, CrCL= creatinine clearance, EDW= enterprise data warehouse, FN= febrile neutropenia, GCSF= granulocyte colony stimulating factor, HCI= Huntsman Cancer Institute, HSCT= hematopoietic stem cell transplant, IBW= ideal body weight, ICU= intensive care unit, LOS= length of stay, mcL=microliter, MIC= minimum inhibitory concentration, NCCN= National Comprehensive Cancer Network, OR= odds ratio, SCr= serum creatinine, TBW= total body weight

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