European Review for Medical and Pharmacological Sciences 2015; 19: 4105-4110

Use of proton pump inhibitors in hematopoietic stem cell transplantation does not increase the frequency of febrile neutropenia

M.C. OZKAN, A. DONMEZ, A. ARSLAN[1], S. AYDEMIR[2], M. TOMBULOGLU

Department of Hematology, [1]Internal Medicine, and [2]Microbiology; Ege University Medical School, Izmir, Turkey

Abstract. – OBJECTIVE: Despite the fact that proton pump inhibitor (PPI) use is a risk factor for infections in heterogeneous groups of patients, there are only a limited data related to PPI use and febrile neutropenic episodes (FNEs) in hematopoietic stem cell transplantation (HSCT) patients.

PATIENTS AND METHODS: In a 7-year period, we retrospectively reviewed 145 HSCT data to identify a risk factor for PPI use for febrile neutropenia. The follow-up process of 125 (86.2%) of the HSCTs was complicated with FNEs.

RESULTS: A multivariate analysis indicated that PPI use was not significantly associated with FNEs (Odds ratio [OR]: 0.46; 95% Confidence Interval [CI] 0.12-2.16; $p = 0.24$) or bacterial culture positivity (OR: 1.37; 95% CI 0.45-4.18; $p = 0.58$).

CONCLUSIONS: Our study revealed that PPI use does not appear to be a risk factor for FNE or bacterial culture positivity for HSCT patients but further studies are needed.

Key Words:
Febrile neutropenia, Hematopoietic stem cell transplantation, Proton pump inhibitor.

Introduction

The most common cause of mortality and morbidity in patients with chemotherapy-induced neutropenia remains infectious complications[1]. Although there are many studies that have examined the risk factors for febrile neutropenic episodes (FNEs) in heterogeneous patient groups with hematologic malignancies[2,3], studies in hematopoietic stem cell transplantation (HSCT) patients are limited[4].

Proton pump inhibitors (PPIs) have become one of the most commonly used medications worldwide[5]. The majority of patients required PPI's during the HSCT because of dyspeptic complaints due to stress and multi-drug usage. Although experts have generally viewed PPIs as safe[6], increased proclivity to infections[7-9] is a potential complication of this class of drugs. Available evidence for enhanced susceptibility to enteric infections by PPI use was described in a systematic review[10]. Other systematic review indicated that the overall risk of pneumonia was higher among people using PPI's[9].

PPI use was investigated as a risk factor for Gram-positive coccal infections and Gram-negative bacterial infections in a heterogeneous neutropenic patient population with hematologic malignancies which also consist transplanted patients[2,11]. The aim of this study was to investigate the effects of PPI use only on patients who underwent HSCT.

Patients and Methods

Patients

The data of 145 hematopoietic stem cell transplantations (autologous or allogeneic) from 139 patients who was underwent transplantation at the Hospital of Ege University School of Medicine, Adult Hematology Department, Transplant Center between January 2005 and July 2012 were analyzed retrospectively. The patient data and variables related to stem cell transplantation (diagnosis, age, sex, underlying disease, type of transplantation, proton pump use, febrile neutropenic episodes, G-CSF use, duration of neutropenia, viremia, fungal infections, culture results) were obtained from the standard charts which was belong to hematology clinic that stored in the files and records of clinical microbiology laboratory for a uniform time frame. The data provide only transplant related admissions, two weeks before and 30 day after transplantation (Table I).

Corresponding Author: Melda Comert Ozkan, MD; e-mail: zjdocchina@163.com

Table I. The main characteristics of the patients.

Number of patients	139
Sex (male/female)	84/61
Age (years), median (range)	51 (18-68)
Type of disease	
Multiple myeloma/primary amyloidosis	58
Lymphoma (non-Hodgkin's/Hodgkin's)	48
Acute leukemia (myeloblastic/lymphoblastic)	26
Other	7
Type of transplantation	
Autologous	105
Allogeneic	40
Conditioning regimen	
BEAM	44
Melphalan	57
BUCY	27
Reduced-intensity	6
Other	11
Catheter (yes/no)	90/55
Duration of neutropenia (days), median (range)	9.4 (3-39)
Culture positivity	
Blood	25
Urine	8
Catheter	17
Other	3

One hundred and five transplantations were autologous and 40 were allogeneic. The median age was 51 years (range, 18-68 years). The study subjects consisted of patients with multiple myeloma and primary amyloidosis (n = 58, 40.0%), lymphoma (Hodgkin's or non-Hodgkin's [n = 48, 33.1%]), acute leukemia (lymphoblastic or myeloid [n = 26, 17.9%]), and other diseases (chronic lymphocytic leukemia, chronic myeloid leukemia, mycosis fungoides, etc. [n = 7, 4.8%]). The patient population included 84 (57.9%) males and 61 (42.1%) females (Table I).

Six males were re-transplanted. Four of these patients had multiple myeloma and 2 of these patients had lymphomas. Ninety (62.1%) of the transplantations were performed using a central venous catheter (Table I). All of the transplantations were performed using peripheral blood stem cells.

PPI Use

Thirty-six (24.8%) patients used PPIs from the beginning of the transplantation conditioning regimen until the stem cell infusion, 14 (9.6%) patients used PPI's starting on any day of the conditioning regimen until +4 days after stem cell infusion, 10 (7.0%) patients used PPIs until +5 - +9 days after stem cell infusion, 2 (1.4%) patients used PPIs until +10 - +14 days after stem cell infusion and 1 (0.7%) patients used PPIs until > +14 days after stem cell infusion. Chronic PPI use (before hospitalization for transplantation, during the hospitalization and after the discharge) was recorded in 56 (38.6%) patients.

High-Dose Chemotherapy

In the autologous group, BEAM (BCNU 300 mg/m^2; etoposide 200 mg/m^2/day, 4 days; ARA-C 400 mg/m^2/day, 4 days; melphalan 140 mg/m^2) was administered to 44 (30.3%) patients. High-dose melphalan (200 mg/m^2) was administered to 57 (39.3%) patients (Table I). In the allogeneic group, BuCy (busulfan 4 mg/kg/day, 4 days and cyclophosphamide 60 mg/kg/day, 2 days) was administered to 27 (18.6%) patients. A reduced-intensity conditioning regimen (busulfan [oral: 4 mg/kg/day, 2 days; IV: 3.2 mg/kg/day, 2 days] + fludarabine [30 mg/m^2/day, 6 days] + ATG [10 mg/kg/day, 4 days]) was administered to 6 (4.1%) patients and other conditioning regimens was administered in 11 (7.6%) patients (Table I).

Patient Monitoring and Care

Out of 9 patients who underwent allogeneic HSCT, all of the patients received 5 μg/kg G-CSF per day, starting on the fifth day after the stem cell infusion. The irradiated blood components were infused to maintain hemoglobin and platelet levels above 8 g/dL and 20 × 10^9/L, respectively. All of the patients received antiviral and antifungal prophylaxis. Ninety-eight of 145 HSCT patients received antibiotic prophylaxis (levofloxacin or ciprofloxacin).

In patients with a neutrophil count below 500/mm^3 or a count expected to fall below 500/mm^3 within 48 hours, a measured one time oral or axillary temperature of at 38.3°C and higher or a measured oral or axillary temperature of 38.0-38.2°C for one hour was defined as febrile neutropenia. The day neutrophil and platelet engraftment was defined as the first day on which the neutrophil and platelet counts exceeded 0.5 × 10^9/L and 20 × 10^9/L (without a need for platelet transfusion) for three consecutive days, respectively.

The patients who developed neutropenic fever were treated according to the established guidelines. High-resolution computed tomography

(HRCT) was performed on the patients with uncontrolled fewer. We routinely tested patients for CMV viremia and galactomannan in blood twice a week after the transplantation until engraftment occurred.

Fungal infections were defined as possible, probable or proven. Possible fungal infections included only cases with the appropriate host factors and with sufficient clinical evidence consistent with fungal infection but for which there was no mycological support. The cases of probable fungal infections required that a host factor, clinical features, and mycological evidence were present. The category of proven fungal infections required demonstration of fungal elements in the diseased tissue.

Sterility Testing and Microbial Sampling

Bacteriological culture of the specimens: Sterile specimens were transported to the Ege University Medical Faculty Microbiology Laboratory. Two or three mL blood samples were inoculated into blood culture bottles of a commercially available bacterial detection system (BacT/ ALERT 3D automated system, bioMerieux, Durham, NC), and they were incubated in the BacT/ALERT 3D system for a minimum of 7 days or until considered positive. The midstream urine samples were taken for quantitative culture. Stool samples of the patients were cultured for enteropathogens such as *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., *Yersinia enterocolitica, Vibrio cholerae* and Enterohemorrhagic *E. coli*.

All isolated microorganisms were identified using conventional biochemical procedures and an automated bacterial identification system (VITEK 2, bioMerieux, Marcy-l'Etoile, France). In addition, the antimicrobial susceptibility testing was performed for each isolate according to the Clinical and Laboratory Standards Institute guidelines. Antibiotic susceptibility patterns were used to confirm that the organisms that were recovered from the products and the patients were identical.

CMV Viremia Tests

For CMV viremia, the CMV antigenemia test (CINAkit Argene Biosoft, France) was performed in cases before November 2010 and the CMV real-time PCR test that targets the gB gene (CMV QNP 2.0 kit, Fluorion Iontek, Turkey) was performed after November 2010. Blood samples (with EDTA) were collected and tested on the same day. CMV antigenemia was reported quantitatively when positive pp65 cells were > 2/200 000 leucocytes, and the limit of detection for the CMV DNA PCR assay was 37 iu/ml.

Clostridium Difficile Tests

Clostridium difficile toxin A+B was investigated in stool samples using an immunoassay test (ELFA, Biomerieux, VİDAS, France).

Galactomannan Testing

The galactomannan test was performed using The Platelia™ *Aspergillus* Ag, which is a one-stage immunoenzymatic sandwich microplate assay that detects galactomannan in human serum and bronchoalveolar lavage□(BAL) fluid. The assay uses rat EBA-2 monoclonal antibodies that are directed against *Aspergillus* galactomannan. Blood samples (with EDTA) were collected and tested on the same day. The presence or absence of the galactomannan antigen in the test sample was determined by the calculation of an index for each patient specimen. Sera/BAL fluid with an index < 0.50 was considered to be negative for galactomannan antigen.

Statistical Analysis

We analyzed the relationship between PPI use and febrile neutropenic episodes, culture results, CMV viremia and fungal infections. For this purpose, the described variables were examined using a multivariate test (logistic regression). *p* values less than 0.05 were considered significant. The data were analyzed using computer software (SPSS 16.0, SPSS, Inc., Chicago, IL, USA).

Results

The data from 145 hematopoietic stem cell transplantations from 139 patients were analyzed. The follow-up process for 125 (86.2%) of the transplantations was complicated with FNEs, and in 20 (13.8%) transplantations, FNEs were not observed. Granulocyte colony-stimulating factor (G-CSF) was used in 136 (93.8%) transplantations. The median neutropenia period was 9.4 days.

The bloodstream culture positivity was 14.5%, urine culture positivity was 5.5%, catheter blood culture positivity was 11.0% and some patients had more than one type of culture positivity. No positivity was detected in stool culture. Blood cultures were positive in 23 samples. Nine (39.1%) of these cultures were Gram-negative,

and fourteen (60.9%) were Gram-positive microorganisms. Urine culture positivity was detected in 8 samples. All of them were Gram-negative microorganisms. Catheter cultures were positive in 18 samples. Three (16.7%) of them were Gram-negative, and 15 (83.3%) were Gram-positive microorganisms. Some patients had more than one type of culture positivity. There was no statistically significant difference between Gram-positive and Gram-negative microorganism positivity with PPI use in any culture type. Isolated microbiological pathogens and the relationship between the uses of PPI are presented in Table II.

The CMV viremia frequency was 18.6% (PPI use: 21.0%, No PPI use: 7.7%, Table III). Fungal infection frequency was 5.5% (PPI use: 5.0%, No PPI use: 7.7%, Table III). Six (75.0%) of them were probable fungal infections and 2 (25.0%) of them were possible fungal infections. The pneumonia frequency was 6.2% (PPI use: 5.9%, No PPI use: 7.7%, Table III). Four patients had both diarrhea and pneumonia. There was no statistically significant difference between the frequency of pneumonia and PPI use.

The diarrhea frequency was 23.5% (PPI use: 21.0%, No PPI use: 34.6%, Table III). Twenty-five cases (73.5%) were in autologous recipients and 9 (26.5%) were in allogeneic recipients. There was no statistically significant difference between the frequency of diarrhea and PPI use. *Clostridium difficile* toxin testing was performed to 11 of 34 patients who had diarrhea. Positive results were detected in only one of the autologous patient who did not use PPIs.

Table II. Isolated microbiological pathogens and the relationship between the uses of PPI.

	PPI use	No PPI use
Blood		
Gram negative	8	1
Gram positive	11	3
Urine		
Gram negative	6	2
Gram positive	0	0
Catheter		
Gram negative	3	0
Gram positive	14	1
Other		
Gram negative	1	0
Gram positive	1	1

Based on the multivariate analysis, PPI use was not significantly associated with febrile neutropenic episodes (Odds ratio [OR]: 0.46; 95% Confidence Interval [CI] 0.12-1.68; $p = 0.24$), viral infections (OR: 0.49; 95% CI 0.95-2.53; $p = 0.39$), fungal infections (OR: 0.86; 95% CI 0.20-17.31; $p = 0.58$) and culture positivity (OR: 1.37; 95% CI 0.45-4.18; $p = 0.58$, Table IV).

Discussion

Our study revealed that in the patient group which was consist of majorly using chronic PPIs did not propose any additional risk for FNE (OR: 0.46; $p = 0.24$), CMV viremia (OR: 0.49; $p = 0.39$) or fungal infections (OR: 0.86; $p = 0.58$)

Table III. Viremia, fungal infections, diarrhea, pneumonia frequency and the relationship between the uses of PPI.

	All patients (%)	PPI use (%)	No PPI use (%)
CMV Viremia	18.6	21.0	7.7
Fungal infections	5.5	5.0	7.7
Pneumonia	6.2	5.9	7.7
Diarrhea	23.5	21.0	34.6

Table IV. Multivariate analysis of the use of PPI relationship with the variables.

	OR	95% CI	*p* value
FNE	0.46	0.12-2.16	0.24
Culture positivity	1.37	0.45-4.18	0.58
Viremia	0.49	0.95-2.53	0.39
Fungal infections	0.86	0.20-17.31	0.58

on hematopoietic stem cell transplanted patients (Table III).

PPI use was not determined to be a risk factor for Gram-positive and Gram-negative infections in the patient group consisting of only transplanted patients in our study. PPI use was investigated as an statistically borderline independent risk factor (OR: 1.7; $p = 0.05$) for Gram-positive coccal infections in Cordonnier et al. study[2]. In another study of this group PPI use was not determined to be a risk factor (OR 0.59; $p = 0.24$) for Gram-negative bacterial infections in a heterogeneous group of patients with hematologic malignancies which also consists transplanted patients[11]. Unlike our study, the number of transplanted patients was low (n: 44) in one of these studies[11] and there was no a subgroup analysis for PPI use in transplanted patients in both studies[2,11].

No difference was detected in pneumonia frequency with PPI use in our study. Eom et al. reported in a meta-analysis that the overall risk of pneumonia was higher among people using PPIs (OR: 1.27) who were hospitalized, regardless of circumstances[9]. Unlike in this meta-analysis, the relationship between PPI use and pneumonia frequency was investigated in only the transplanted homogenous patient group in our study.

No difference was detected in stool culture and *Clostridium difficile* toxin positivity with PPI use in our study. Our facilities are limited to detect enteropathogens that are defined in methods. Since there is huge numbers of bacteria in the intestinal microbiota in humans, we did not intend to determine enteric microbiota. Obviously, any bacteria can be a risk for FEN in immuncomprimised patients. Recent data suggest that diarrhea complicates 79% of allogeneic HSCT[12] and 83% of both allogeneic and autologous transplantations[13]. In a study by Dial et al[14] *C. difficile* diarrhea was significantly associated with the use of PPIs (OR: 2.1) in a large number of hospitalized patients, regardless of circumstance. *C. difficile*-associated disease during HSCT has been reported to affect 10.3% of HSCT patients in recent papers[13]. The cause of our low *C. difficile* frequency was the toxin test was not able to perform all patients with diarrhea, because the test was not used routinely in the early years of our study.

Invasive fungal infections were detected in 8 (5.5%) of HSCTs and no significant difference was detected in fungal infection frequency with PPI use in our study. The occurrence of invasive mycoses was 19.1% with a 23.2% frequency in allogeneic HSCT recipients and 10.9% in autologous HSCT recipients[15]. Our fungal infection frequency is lower than what has been reported in previous studies due to the fact that bronchoscopy was not routinely used in our patient population.

CMV viremia was detected in 27 (18.6%) transplantations in our study. No difference was detected in viral infection frequency with PPI use. In allogeneic HSCT patients who received myeloablative-conditioning regimens and preemptive ganciclovir therapy, the reported prevalences of early CMV disease was 3.5% to 10.5%[16]. The probability of detection of CMV DNA was 48.3% and the probability of CMV disease was 6% at 100 days after BMT[17]. A large cohort of 278 patients could be monitored with the tetramers, and 198 (71%) actually developed detectable cytomegalovirus-specific $CD3^+CD8^+$ T cells following HSCT[18].

Because our study was retrospective, HRCT was not used for all patients in the earlier years examined. In addition, *C. difficile* tests were not performed on all patients with diarrhea.

Conclusions

PPI use does not appear to be a risk factor for febrile neutropenia, viremic or fungal infections in HSCT. Further prospective studies with a larger number of patients may confirm the role of PPI use in FNEs experienced after HSCT.

Acknowledgements

We are deeply grateful to Professor Mehmet Orman for his statistical evaluation from department of biostatistics and medical informative.

Conflict-of-Interest Disclosure

The authors declare no competing financial interests. The authors declare that no form of grants and/or equipment and drugs are used.

References

1) Kjellander C, Björkholm M, Cherif H, Kalin M, Giske CG. Hematological: Low all-cause mortality and low occurrence of antimicrobial resistance in hematological patients with bacteremia receiving no antibacterial prophylaxis: a single-center study. Eur J Haematol 2012; 88: 422-430.

2) Cordonnier C, Buzyn A, Leverger G, Herbrecht R, Hunault M, Leclercq R, Bastuji-Garin S; Club de Réflexion sur les Infections en Onco-Hématologie. Epidemiology and risk factors for gram-positive coccal infections in neutropenia: toward a more targeted antibiotic strategy. Clin Infect Dis 2003; 36: 149-158.

3) Poon LM, Jin J, Chee YL, Ding Y, Lee YM, Chng WJ, Chai LY, Tan LK, Hsu LY. Risk factors for adverse outcomes and multidrug resistant Gram-negative bacteraemia in haematology patients with febrile neutropenia in a Singaporean university hospital. Singapore Med J 2012; 53: 720-725.

4) Mendes ET, Dulley F, Basso M, Batista MV, Coracin F, Guimarães T, Shikanai-Yasuda MA, Levin AS, Costa SF. Healthcare-associated infection in hematopoietic stem cell transplantation patients: risk factors and impact on outcome. Int J Infect Dis 2012; 16: 424-428.

5) Klastersky J, Paesmans M, Rubenstein EB, Boyer M, Elting L, Feld R, Gallagher J, Herrstedt J, Rapoport B, Rolston K, Talcott J. The multinational association for supportive care in cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. J Clin Oncol 2000; 18: 3038-3051.

6) Moayyedi P, Leontiadis GI. The risks of PPI therapy. Nat Rev Gastroenterol Hepatol 2012; 9: 132-139.

7) Vanderhoff BT, Tahboud RM. Proton pump inhibitors: an update. Am Fam Physician 2002; 66: 273-280.

8) Laine L, Ahmen D, McClain C, Solcia E, Walsh JH. Review article: potential gastrointestinal effects of long-term acid supression and supression with proton pump inhibitors. Aliment Pharmacol Ther 2000; 14: 651-668.

9) Eom CS, Jeon CY, Lim JW, Cho EG, Park SM, Lee KS. Use of acid-supressive drugs and risk of pneumonia: a systematic review and meta-analysis. Canadian Med Ass 2011; 183: 310-319.

10) Bavishi C, DuPont HL. Systematic review: the use of proton pump inhibitors and increased susceptibility to enteric infection. Aliment Pharmacol Ther 2011; 34: 1269-1281.

11) Cordonnier C, Herbrecht R, Buzyn A, Leverger G, Leclercq R, Nitenberg G, Bastuji-Garin S; Club de Réflexion sur les Infections en Onco-Hématologie group. Risk factors for Gram-negative bacterial infections in febrile neutropenia. Haematologica 2005; 90: 1102-1109.

12) Roddie C, Paul JPW, Benjamin R, Gallimore CI, Xerry J, Gray JJ, Peggs KS, Morris EC, Thomson KJ, Ward KN. Allogeneic hematopoietic stem cell transplantation and norovirus gastroenteritis: a previously unrecognized cause of morbidity. Clin Infect Dis 2009; 49: 1061-1068.

13) Trifilio SM, Pi J, Mehta J. Changing epidemiology of Clostridium difficile-associated disease during stem cell transplantation. Biol Blood Marrow Transplant 2013; 19: 405-409.

14) Dial S, Alrasadi K, Manoukian C, Huang A, Menzies D. Risk of Clostridium difficile diarrhea among hospital inpatients prescribed proton pump inhibitors: cohort and case-control studies. CMAJ 2004; 171: 33-38.

15) Popova MO, Zubarovskaia LS, Klimko NN, Vavilov VN, Volkova AG, Ziuzgin IS, Ignat'eva GM, Alianski AL, Paina OV, Babenko EV, Blagodarova-Smirnova MS, Smirnov BI, Afanas'ev BV. Invasive mycoses during hematopoietic stem cell transplantation. Ter Arkh 2012; 84: 50-57.

16) Junghanss C, Boeckh M, Carter RA, Sandmaier BM, Maris MB, Maloney DG, Chauncey T, McSweeney PA, Little MT, Corey L, Storb R. Incidence and outcome of cytomegalovirus infections following nonmyeloablative compared with myeloablative allogeneic stem cell transplantation, a matched control study. Blood 2002; 99: 1978-1985.

17) Ljungman P, Loré K, Aschan J, Klaesson S, Lewensohn-Fuchs I, Lönnqvist B, Ringdén O, Winiarski J, Ehrnst A. Use of a semi-quantitative PCR for cytomegalovirus DNA as a basis for pre-emptive antiviral therapy in allogeneic bone marrow transplant patients. Bone Marrow Transplant 1996; 17: 583-587.

18) Borchers S, Bremm M, Lehrnbecher T, Dammann E, Pabst B, Wölk B, Esser R, Yildiz M, Eder M, Stadler M, Bader P, Martin H, Jarisch A, Schneider G, Klingebiel T, Ganser A, Weissinger EM, Koehl U. Sequential anti-cytomegalovirus response monitoring may allow prediction of cytomegalovirus reactivation after allogeneic stem cell transplantation. PLoS One 2012; 7: e50248.