Biol Blood Marrow Transplant 21 (2015) 1808–1814

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Impact of Prophylactic Levofloxacin on Rates of Bloodstream Infection and Fever in Neutropenic Patients with Multiple Myeloma Undergoing Autologous Hematopoietic Stem Cell Transplantation

Michael J. Satlin [1,2,*], Santosh Vardhana [3], Rosemary Soave [1,2], Tsiporah B. Shore [2,4], Tomer M. Mark [2,4], Samantha E. Jacobs [1,2], Thomas J. Walsh [1,2], Usama Gergis [2,4]

[1] *Transplantation-Oncology Infectious Diseases Program, Division of Infectious Diseases, Weill Cornell Medical College, New York, New York*
[2] *New York-Presbyterian Hospital, Weill Cornell Medical Center, New York, New York*
[3] *Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, New York*
[4] *Division of Hematology and Medical Oncology, Weill Cornell Medical College, New York, New York*

Article history:
Received 3 April 2015
Accepted 19 June 2015

Key Words:
Fluoroquinolone prophylaxis
Multiple myeloma
Autologous stem cell transplantation

A B S T R A C T

Few studies have evaluated the role of antibacterial prophylaxis during neutropenia in patients with multiple myeloma undergoing autologous hematopoietic stem cell transplantation (HSCT). At our center, levofloxacin prophylaxis was initiated in June 2006 in patients with myeloma who were undergoing autologous HSCT. We compared the incidence of bloodstream infection (BSI) and fever and neutropenia (FN) within 30 days of transplantation before (January 2003 to May 2006) and after (June 2006 to April 2010) the initiation of levofloxacin prophylaxis in patients undergoing autologous HSCT for myeloma. We also compared rates of BSI and FN during the same time periods in autologous HSCT recipients with lymphoma who did not receive antibacterial prophylaxis during either time period. After the initiation of levofloxacin prophylaxis, the BSI rate decreased from 41.2% (49 of 119) to 14.7% (23 of 156) and the rate of FN decreased from 91.6% to 60.9% in patients with myeloma ($P < .001$, for each). In contrast, rates of BSI (43.1% versus 47.3%; $P = .50$) and FN (98.8% versus 97.1%; $P = .63$) did not change in patients with lymphoma. Levofloxacin prophylaxis was independently associated with decreased odds of BSI (odds ratio, .27; 95% confidence interval, .14 to .51; $P < .001$) and FN (odds ratio, .18; 95% confidence interval, .09 to .36; $P < .001$) in multivariate analysis. Patients with myeloma had a nonsignificant increase in the risk of BSI due to levofloxacin-resistant Enterobacteriaceae (5% versus 1%, $P = .08$) and *Clostridium difficile* infection (7% versus 3%, $P = .12$) after the initiation of levofloxacin prophylaxis but did not have higher rates of BSI due to other resistant bacteria. Levofloxacin prophylaxis is associated with decreased risk of BSI and FN in patients with myeloma undergoing autologous HSCT.

INTRODUCTION

High-dose chemotherapy combined with autologous hematopoietic stem cell transplantation (HSCT) is an important component of the treatment of patients with multiple myeloma [1]. Neutropenia is a universal complication of autologous HSCT and combines with chemotherapy-induced mucositis to establish a high-risk setting for bacteremia [2,3]. To decrease the risk of bacterial infection, guidelines of the Infectious Diseases Society of America and American Society for Blood and Marrow Transplantation recommend considering the administration of antibacterial prophylaxis during chemotherapy-induced neutropenia in patients with anticipated neutropenic periods of at least 7 days [4,5].

These recommendations are largely based on 2 randomized, placebo-controlled trials of levofloxacin in patients with cancer and neutropenia that were conducted from 1999 to 2003 and demonstrated lower rates of fever and neutropenia (FN) and bacterial infections, but not decreased mortality, in patients receiving levofloxacin prophylaxis [6,7]. However, during the decade since these trials were conducted, fluoroquinolone resistance has become

Financial disclosure: See Acknowledgments on page 1813.

* Correspondence and reprint requests: Dr. Michael J. Satlin, 1300 York Avenue, A-421, New York, NY 10021.
E-mail address: mjs9012@med.cornell.edu (M.J. Satlin).

http://dx.doi.org/10.1016/j.bbmt.2015.06.017
1083-8791/

increasingly common [8,9] and a new virulent strain of fluoroquinolone-resistant *Clostridium difficile* has emerged [10]. These developments merit a reassessment of the role of levofloxacin prophylaxis in patients with neutropenia. Furthermore, the applicability of results from these landmark trials to patients with multiple myeloma undergoing autologous HSCT is unclear, as very few of these patients were evaluated in these trials. Two subsequent, single-center, randomized trials have been conducted to assess the role of fluoroquinolone prophylaxis in patients receiving autologous HSCT, but these studies are limited by small sample sizes and/or the use of multiple prophylactic antimicrobial agents [11,12].

Before June 2006, antibacterial prophylaxis was not administered to patients undergoing autologous HSCT at our center. In response to 2 deaths in patients with multiple myeloma from septic shock due to fluoroquinolone-susceptible Gram-negative bacteria, levofloxacin prophylaxis was initiated in June 2006 in patients with myeloma undergoing autologous HSCT but not in patients receiving autologous HSCT for other indications, such as lymphoma. This selective intervention established a unique setting to evaluate the efficacy and adverse effects related to the use of levofloxacin prophylaxis in patients undergoing autologous HSCT.

MATERIALS AND METHODS

Study Design

This is a single-center, retrospective, cohort study at New York-Presbyterian Hospital/Weill Cornell Medical Center that consists of 2 study periods. In period 1 (January 2003 to May 2006), neither patients with multiple myeloma nor patients with lymphoma received antibacterial prophylaxis during their autologous transplantation admission. In period 2 (June 2006 to April 2010), patients with myeloma who underwent autologous HSCT received 500 mg of oral levofloxacin daily from 1 day before their stem cell infusion until recovery from neutropenia. Patients with lymphoma who underwent autologous HSCT continued not to receive antibacterial prophylaxis during period 2. Multiple transplantations involving individual patients were eligible for analysis, provided that the patient did not have a prior transplantation within the previous 90 days.

The primary objective of the study was to compare the incidence of (1) bloodstream infection (BSI) and (2) FN within 30 days of transplantation in period 1 versus period 2 in patients with myeloma and in patients with lymphoma. We also assessed the incidence of BSI and FN during each year of the study in both patient populations. Secondary objectives of the study were to compare rates of BSIs due to specific bacteria, including multidrug-resistant (MDR) pathogens, and rates of *C. difficile* infection within 90 days of transplantation between time periods in both patient groups.

Furthermore, for autologous HSCT recipients with multiple myeloma, we reviewed medical records to compare the following variables between patients who received and did not receive levofloxacin prophylaxis: demographics, myeloma characteristics, comorbidities [13], baseline serum albumin and creatinine levels, recent *C. difficile* infection, conditioning regimen, central venous catheter type, number of CD34 cells infused, and duration of neutropenia. We then conducted multivariate analyses to determine whether levofloxacin prophylaxis was independently associated with the risk of BSI or FN in patients with myeloma. Finally, we compared the following additional outcomes for myeloma patients who received and did not receive levofloxacin prophylaxis: developing a BSI that was associated with severe sepsis or an intensive care unit (ICU) admission, a microbiologically documented infection other than bacteremia or an invasive fungal infection, duration of hospitalization, readmission within 90 days of the transplantation, mortality within 30 and 90 days of the transplantation, and mortality related to sepsis.

Definitions and Study Procedures

Fever was defined as a temperature $\geq$ 38.0°C and neutropenia was defined as an absolute neutrophil count $\leq$ 500 cells/μL. Common skin commensals (coagulase-negative staphylococci, *Bacillus* and *Corynebacterium* spp. other than *C. jeikeium*) were only considered causes of BSI if isolated from at least 2 sets of blood cultures collected on the same day or on consecutive days.

During both study periods, HSCT recipients with myeloma and lymphoma were placed in private rooms on the same inpatient transplant unit until neutrophil engraftment. They were cared for by the same medical staff and received the same supportive care practices (other than antibacterial prophylaxis), including infection control practices recommended by the Centers for Disease Control and Prevention [14]. Intravenous melphalan was administered as a conditioning regimen at a dose of 200 mg/m^2, divided into 2 doses on days −2 and days −1. The melphalan dose was reduced to 140 mg/m^2 in frail elderly patients and in patients with a creatinine clearance < 60 mL/minute.

For initial work-up of FN, blood cultures (1 aerobic and 1 anaerobic bottle per set) were obtained from peripheral blood and each central venous catheter lumen. Subsequent blood cultures were drawn daily for persistent fever. Piperacillin-tazobactam was the primary agent used for FN during both time periods and broad-spectrum β-lactam therapy was typically continued until resolution of FN. All patients received prophylactic fluconazole and valacyclovir and daily filgrastim injections until resolution of neutropenia. All patients had central venous catheters that were typically placed on the day of admission for transplantation and removed upon discharge from the transplantation admission, unless intravenous medications were required after discharge.

BacT/ALERT 3D (BioMérieux Inc., Durham, NC) was the automated blood culture system used during both study periods. Species identification and antimicrobial susceptibility testing of bloodstream isolates were primarily performed by Vitek II (BioMérieux Inc.), according to Clinical and Laboratory Standards Institute recommendations [15]. From 2003 to 2009, the Wampole *Clostridium difficile* Tox A/B Microplate Assay (Alere, Orlando, FL) was used to detect *C. difficile* toxin from stool. In 2010, more sensitive assays were employed to detect *C. difficile* toxin, and thus patients who received a transplant in 2010 were excluded from the analysis of *C. difficile* infection rates.

Statistical Analysis

Proportions were compared using 2-tailed chi-squared or Fisher exact tests and $P \leq .05$ was considered statistically significant. Continuous variables were expressed as median values with interquartile ranges and compared by the Wilcoxon rank-sum test. Factors associated with developing a BSI or FN in patients with multiple myeloma were evaluated in univariate and multivariate logistic regression models. All variables with a P value $\leq .10$ in the univariate model, as well as age, years since myeloma diagnosis, prior HSCT, and duration of neutropenia, were included in the multivariate model. STATA, version 12.0 (StataCorp, College Station, TX) was used for statistical analysis.

RESULTS

Patients and Rates of BSI and FN in Period 1 and Period 2

Four hundred seventy-five autologous HSCTs were performed during the study period. Of these, 275 transplantations for multiple myeloma and 190 transplantations for lymphoma were eligible for analysis. None of the 119 patients with myeloma and none of the 88 patients with lymphoma in period 1 received antibacterial prophylaxis. In period 2, 148 of the 156 myeloma patients received levofloxacin prophylaxis (eight patients had a levofloxacin allergy or prior intolerance) and none of the 102 lymphoma patients received antibacterial prophylaxis.

The incidence of BSI within 30 days of transplantation in patients with myeloma decreased from 41.2% in period 1 (before levofloxacin prophylaxis) to 14.7% in period 2 (after levofloxacin prophylaxis; $P < .001$) (Table 1). Patients with lymphoma who did not receive antibacterial prophylaxis during either time period had no significant change in BSI incidence (43.1% in period 1 versus 47.3% in period 2; $P = .50$). Similarly, the incidence of FN in patients with myeloma decreased from 91.6% in period 1 to 60.9% in period 2 ($P < .001$). The incidence of FN did not change in patients with lymphoma (98.8% versus 97.1%; $P = .63$). The decreases in rates of BSI and FN in patients with myeloma occurred immediately after the intervention of fluoroquinolone prophylaxis and were sustained during each subsequent study year (Figure 1A and B).