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ORIGINAL ARTICLE

Addition of doxycycline to ciprofloxacin for infection prophylaxis during autologous stem cell transplants for multiple myeloma

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Abstract

Background The most commonly used antibacterial prophylaxis during autologous stem cell transplants (ASCT) for multiple myeloma (MM) involves a fluoroquinolone, such as ciprofloxacin or levofloxacin. We assessed the impact of adding doxycycline to ciprofloxacin as routine antibacterial prophylaxis in these patients.

Methods We retrospectively reviewed electronic medical records and our ASCT database to analyze rates and types of bacterial infections in MM patients who underwent ASCT in our institution.

Results Among 419 patients, 118 received ciprofloxacin alone (cipro group), and 301 ciprofloxacin and doxycycline (cipro-doxy group). Neutropenic fever (NF) developed in 63 (53%) and 108 (36%) patients of the cipro and cipro-doxy groups, respectively ($p = 0.010$). The number of documented bacteremic episodes was 13 (11%) and 14 (4.7%) in the two groups, respectively ($p = 0.017$). Antimicrobial resistance and *Clostridium difficile* infections were uncommon. Transplant-related mortality was 1% in both groups.

Conclusions The addition of doxycycline to standard prophylaxis with ciprofloxacin seems to reduce the number of NF episodes and documented bacterial infections in patients with MM undergoing ASCT, without increasing rate of serious complications.

Keywords Doxycycline · High-dose melphalan · Autologous stem cell transplant · Infection prophylaxis · Multiple myeloma

Introduction

Infection is a leading cause of morbidity and mortality in patients with multiple myeloma (MM), contributing to nearly 50% of early deaths [1]. Risk factors for infections in MM are multiple, and they may be related to the patients, the disease, or its treatment. Patient-related risk factors include advanced age, poor performance status, comorbidities, and presence of central venous or urinary catheters. MM can impair immunity because of hypogammaglobinemia (which increases susceptibility to encapsulated bacteria) and renal insufficiency (which impairs neutrophil function and cell-mediated immunity). The chemotherapy agents used in the treatment of MM suppress immunity with various mechanisms. For example, some agents like melphalan and cyclophosphamide commonly induce neutropenia. Corticosteroids, like prednisone and dexamethasone, are lymphocytolytic and impair the cell-mediated immunity. The proteasome inhibitor bortezomib, one of the most commonly used novel agents, typically decreases T cell proliferation [1–4]. Recently, bortezomib exposure has been linked to increased risk of bacterial infections in one analysis, but in another, the attribution was linked to the use of corticosteroids instead of bortezomib [3, 4].

High-dose melphalan (HD-Mel), followed by autologous stem cell transplant (ASCT), is considered the standard therapy for eligible patients with symptomatic MM, after completion of the induction therapy [5, 6]. The toxicities induced by HD-Mel include pancytopenia, oral and intestinal mucositis, alopecia, and others, but the most important are febrile infections due to severe neutropenia, because they are the leading cause of death in these patients [7, 8]. Factors that predispose the development of neutropenic fever (NF) are the disruption of the normal mucosal barrier by oral mucositis and the widespread use of central venous catheters (CVCs), which can induce central line-associated bloodstream infections

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(CLABSI) [9, 10]. According to published studies, NF develops in approximately 60–90% of patients undergoing ASCT, and bloodstream infections can be documented in as many as 41% of patients receiving HD-Mel without prophylaxis. Even with the use of broad-spectrum antibacterial prophylaxis, clinically documented infections occur in approximately 15–20% of these patients [5, 11–14].

Fluoroquinolones are the most commonly used antibacterial drugs for prophylaxis of NF in ASCT, resulting in a reduced incidence of gram-negative bacteremias and decreased mortality in one meta-analysis [14, 15]. Fluoroquinolone use is recommended by the Infectious Diseases Society of America (IDSA) guidelines in regimens expected to cause severe neutropenia, defined as an absolute neutrophil count (ANC) < 100/μL for > 7 days [16]. The most common microorganisms isolated in blood cultures during NF are gram-positive cocci, particularly coagulase-negative staphylococci (CoNS) and viridans group streptococci (VGS) [11, 14–17]. Notably, these have remained the most commonly identified microorganisms with ciprofloxacin prophylaxis alone, along with fluoroquinolone-resistant *E. coli* [14, 17]. Despite its improved gram-positive coverage compared to ciprofloxacin, the use of levofloxacin did not lead to a consistent reduction in these organisms [11, 14]. Nonetheless, it is currently not recommended to add gram-positive coverage routinely in these patients [16]. In the experience of another group, the addition of doxycycline to a fluoroquinolone was able to reduce the incidence of CLABSI in patients undergoing ASCT [18]. In view of those data, we decided to add doxycycline to our standard prophylaxis regimen with ciprofloxacin, in the attempt to improve the incidence of NF and hospital-acquired CLABSI during ASCT in our patients with MM. In this study, we retrospectively compared rates of NF and bloodstream infections in this patient population with and without the addition of doxycycline to standard prophylaxis with ciprofloxacin.

Materials and methods

After obtaining permission from our Institutional Review Board, we performed a systematic retrospective review of all medical charts in our ASCT database of MM patients treated at our institution between January 2004 and December 2016. Our standard conditioning regimen for these patients changed over time: it first consisted of Bu/Cy with busulfan at a dose of 1 mg/kg PO or 0.8 mg/kg IV every 6 h for 16 doses, and cyclophosphamide 60 mg/kg per day IV for 2 doses [19]. In October 2006, we changed the conditioning regimen to HD-Mel, initially given as 100 mg/m^2 IV infusion over 20 min in two divided doses on days − 1 and − 2, then as a single dose of 200 mg/m^2 on day − 2, and finally as a single dose of 200 mg/m^2 on day − 1 [20]. The dose of melphalan was 200 mg/m^2, but it was reduced to 140 mg/m^2 if the creatinine clearance (CrCl) was < 50 mL/min or patient's age > 70. One patient received BEAM as conditioning regimen due to concurrent MM and non-Hodgkin's lymphoma, and she was excluded from the analysis [21, 22]. Autologous stem cells were infused on day 0, followed by G-CSF 5 μg/kg/day starting on day + 6 until neutrophil engraftment, defined as an ANC > 500/μL. Dual lumen apheresis catheters (Bard® GlidePath) were placed prior to stem cell mobilization. Our standard institutional guidelines for oral antimicrobial prophylaxis for ASCT included ciprofloxacin 500 mg twice a day, fluconazole 200 mg once a day, and acyclovir 400 mg three times a day. Doses were appropriately reduced according to the CrCl, when necessary. These drugs were started on day 0 (day of transplant) and stopped upon neutrophil engraftment. In the case of NF of undetermined source, our empiric antibiotic therapy consisted of cefepime 2 g IV every 8 h, with dose adjusted according to CrCl. In May 2010, we decided to use doxycycline 100 mg orally twice a day in addition to the ciprofloxacin as routine antibacterial prophylaxis. Bacteremias associated with commensal skin flora were assessed to be central line associated as per 2009 IDSA guidelines, with single positive isolates excluded from analysis [6]. Time to engraftment was measured from the day of transplant (day 0). Statistical analysis was performed using the software program SAS® System, version 9.1 (SAS Institute, Cary, NC). Dichotomous variables were compared using chi-squared test, or Fisher's exact test with small sample size (< 5). For continuous variables, Mann-Whitney *U* test was used given non-normal distribution of the data. In all statistical tests, a p value < 0.05 was considered as significant. Multivariate analysis was performed using a logistic regression model for risk factors, where only factors with p values < 0.1 in the univariate analysis were examined. In the subgroup analyses, we chose the cutoff values for numerical data according to the median values.

Results

Among a total of 419 patients who underwent ASCT for MM, 118 received prophylaxis with ciprofloxacin alone (cipro group), whereas 301 received both ciprofloxacin and doxycycline (cipro-doxy group). Median age at the time of ASCT was 58 and 60 years in the cipro and cipro-doxy groups, respectively ($p = 0.043$). Gender, chemotherapy drugs used in the induction phase pre-ASCT, median number of stem cells infused, and type of ASCT conditioning regimens for the two groups are summarized in Table 1.

NF developed in 63 (53%) and 108 (36%) patients of the cipro and cipro-doxy groups, respectively, and the difference reached statistical significance ($p = 0.010$). A univariate analysis performed examining disease state and treatment-related

Table 1 Patient and treatment characteristics

	Ciprofloxacin group ($n = 118$)	Ciprofloxacin + doxycycline group ($n = 301$)	p value
Median age (range) (years)	58 (37–74)	60 (35–77)	0.043
Gender	Male = 62	Male = 184	0.11
	Female = 56	Female = 117	
ISS stage			
I	37 (31%)	90 (30%)	
II	28 (24%)	59 (20%)	*n.s.*
III	28 (24%)	95 (32%)	
n/a	25 (21%)	57 (19%)	
Drugs used in induction therapy pre-ASCT			
Thalidomide	51 (43%)	11 (4%)	
Lenalidomide	28 (24%)	164 (54%)	< 0.001
Bortezomib	28 (24%)	268 (89%)	
Corticosteroids	113 (96%)	289 (96%)	
Anthracyclines	22 (19%)	4 (1%)	
Other	19 (16%)	67 (22%)	
Disease status pre-ASCT			
PD or SD	21 (18%)	56 (19%)	*n.s.*
PR or VGPR	70 (59%)	182 (60%)	
CR or sCR	21 (18%)	61 (20%)	
n/a	6 (5%)	2 (1%)	
Median CD34+ cells (range), $\times 10^6$ cells/kg	14.5 (1.8–118)	4.8 (1.8–23.3)	< 0.001
Type of conditioning regimen			
Mel200	83	235	< 0.001
Mel140	15	55	
Mel100	4	11	
Bu/Cy	16	0	
Median day to ANC > 500/μL (range)	+ 12 (6–21)	+ 12 (7–19)	> 0.05

Percentages may not total 100 due to rounding. N.B.: response criteria (PD, SD, PR, VGPR, CR, and sCR) have been defined according to the 2006 International Uniform Response Criteria published by the International Myeloma Working Group [23]

ASCT autologous stem cell transplant, *Bu* busulfan, *Cipro* ciprofloxacin, *CR* complete response, *Cy* cyclophosphamide, *Doxy* doxycycline, *ISS* International Staging System, *Mel* melphalan, *PD* progressive disease, *PR* partial response, *sCR* stringent complete response, *SD* stable disease, *VGPR* very good partial response

variables demonstrated doxycycline to be the only statistically significant predictor of NF risk (Table 2). The total number of documented bacteremic episodes was 13 (11%) and 14 (4.7%) in the two groups, respectively ($p = 0.017$).

Antimicrobial resistance was uncommon, with only two cases of fluoroquinolone-resistant *Escherichia coli* reported in the cipro-doxy group. Table 3 describes the specific bacterial infections documented in our patients. In the overall cohort, viral infections were observed in 12 patients (3%), and they included cytomegalovirus (CMV) reactivation ($n = 3$), HHV-6 infection ($n = 5$), herpes zoster ($n = 2$), adenovirus ($n = 1$), and rhinovirus ($n = 1$). Fungal infections were seen in 11 patients (1%), and they consisted of mucocutaneous infections ($n = 10$) and fungemia with *Candida glabrata* ($n = 1$). The fungemia, which was catheter associated, occurred in the cipro monotherapy group. No statistically significant differences between groups were seen in viral and fungal infections (data not shown). *Clostridium difficile* infection (CDI) within 60 days of the ASCT was observed in three (2.5%) and two (0.7%) patients of the cipro and cipro-doxy groups, respectively ($p = 0.13$). Four patients (three in the cipro group and one in the cipro-doxy group, $p = 0.0638$) developed urinary tract infection with cultures positive for vancomycin-resistant *Enterococcus* (VRE).

Rash was the most common documented reason for discontinuing prophylaxis early, occurring in two patients (2%) in the cipro group and seven patients (2%) in the cipro-doxy group. The addition of doxycycline did not compromise post-ASCT hematologic recovery, as the median day of neutrophil engraftment and platelets > 20,000/μL (unsupported

Table 2 Univariable analysis of risk factors for neutropenic fever

Characteristics	No NF	NF	*p* value
Age at transplant (years)			
≤ 60	128 (60%)	87 (40%)	0.882
> 60	120 (59%)	84 (41%)	
Gender			
Male	141 (53%)	106 (47%)	0.294
Female	107 (62%)	65 (38%)	
Time from diagnosis to SCT (months)			
≤ 6	139 (61%)	88 (39%)	0.355
> 6	109 (57%)	83 (43%)	
ISS stage			
I	75 (59%)	52 (41%)	0.972
II	51 (59%)	36 (41%)	
III	74 (60%)	49 (40%)	
Prior lenalidomide therapy			
No	105 (56%)	84 (44%)	0.171
Yes	143 (62%)	87 (38%)	
Prior bortezomib therapy			
No	33 (58%)	24 (42%)	0.831
Yes	215 (59%)	147 (41%)	
Prior cyclophosphamide therapy			
No	193 (59%)	135 (41%)	0.784
Yes	55 (60%)	36 (40%)	
Number of prior lines of therapy			
1	198 (59%)	140 (41%)	0.605
2–5	50 (62%)	31 (48%)	
Use of novel agents before the SCT			
No[a]	20 (61%)	13 (39%)	0.863
Yes[b]	228 (59%)	158 (41%)	
Disease status at transplant			
PR, VGPR, CR	197 (58%)	140 (42%)	0.503
DS, PD	47 (63%)	28 (37%)	
Conditioning regimen			
Mel 100–140 mg/m^2	54 (64%)	31 (36%)	0.652
Mel 200 mg/m^2	185 (58%)	133 (42%)	
Bu/Cy	9 (56%)	7 (44%)	
Number of CD34+ cells/kg infused, × 10^6			
≤ 3.7	121 (59%)	85 (41%)	0.891
> 3.7	120 (59%)	82 (41%)	
Oral mucositis, grade > 1			
No	170 (59%)	118 (41%)	0.128
Yes	54 (50%)	53 (50%)	
Doxycycline prophylaxis			
No	55 (47%)	63 (53%)	0.001
Yes	193 (64%)	108 (36%)	

Bu/Cy busulfan and cyclophosphamide, *CR* complete response, *ISS* International Staging System, *Mel* melphalan, *NF* neutropenic fever, *PR* partial response, *SCT* stem cell transplant, *VGPR* very good partial response

[a] In this group, patient received regimens with traditional chemotherapy agents, such as VAD (vincristine, doxorubicin, and dexamethasone), VD-PACE (bortezomib, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide), liposomal doxorubicin, and oral melphalan

[b] In this group, patients received induction chemotherapy with regimen containing IMiDs (thalidomide, lenalidomide, and pomalidomide) and/or proteasome inhibitors (bortezomib, carfilzomib, and ixazomib)

by transfusions) occurred on days + 12 and + 14 in both groups, respectively ($p > 0.05$). In the overall cohort, transplant-related mortality was seen in four patients (1%), with two patients in each group.

Discussion

The standard antibacterial prophylaxis used during ASCT involves the use of a single-agent fluoroquinolone antibiotic, such as levofloxacin or, more commonly, ciprofloxacin [18]. However, despite the use of fluoroquinolone prophylaxis, published data show that documented bacterial infections develop in 15–20% of patients undergoing high-dose chemotherapy and ASCT, both with BEAM and HD-Mel [11, 14–18, 20]. Our data show that the addition of doxycycline to our antimicrobial prophylaxis regimen was associated with a statistically significant reduction in gram-positive bacterial bloodstream infections and microbiologically confirmed bacterial infectious episodes. We decided to select doxycycline as an additional agent to ciprofloxacin prophylaxis because our historical internal data suggested that gram-positive bacteria were the most common cause of documented infections in this patient population (data not shown). Moreover, data regarding the relative benefit for other antibacterial strategies, such as the use of levofloxacin over ciprofloxacin, provided controversial results [11, 24, 25].

The addition of doxycycline in this setting seems to be cost-effective: while inexpensive, the wholesale

Table 3 Transplant-related neutropenic fever and documented bacterial infections in 419 patients with multiple myeloma

	Ciprofloxacin group ($n = 118$)	Ciprofloxacin + doxycycline group ($n = 301$)	p value
Neutropenic fever	63 (53%)	108 (36%)	0.010
Gram-pos. bacteremia	13 (11%)	12 (4%)	< 0.001
Methicillin-resistant CoNS	5	5	
Vancomycin-resistant *E. faecium*	2	3	
Viridans group streptococci	2	2	
MRSA	2	0	
MSSA	1	0	
E. faecalis	1	0	
Gemella	0	1	
Micrococcus	0	1	
Gram-neg. bacteremia	0 (0%)	2 (< 1%)	*n.s.*
Fluoroquinolone-resistant *E. coli*	0	2	

CoNS coagulase-negative Staphylococcus, *E. coli Escherichia coli*, *E. faecalis Enterococcus faecalis*, *E. faecium Enterococcus faecium*, *MRSA* methicillin-resistant *Staphylococcus aureus*, *MSSA* methicillin-sensitive *Staphylococcus aureus*, *S. aureus Staphylococcus aureus*

acquisition cost of doxycycline has increased since initiation of this regimen, from approximately $0.10 to $2.13 for a 100 mg dose. With this, the associated cost of preventing an episode of NF and a gram-positive bacteremia would be approximately $320 and $770, respectively, assuming 15 days of prophylaxis per patient. This compares favorably to published data examining rapid identification of coagulase-negative staphylococci (as a contaminant) and the impact of antimicrobial stewardship, where treatment costs for hospital stay were reduced by $17,844 and infection-related treatment costs reduced by $8338 in one analysis [26]. For severe CLABSIs, the estimated cost is substantially higher, about $34,000–56,000 per episode [27].

Because of the retrospective nature of our study, our data do not include types and rate of toxicity secondary to doxycycline. Only a randomized study could clarify that due to the multitude of drugs typically used in ASCT. Possible adverse effects from the addition of doxycycline include rash, anaphylaxis, diarrhea, nausea, anorexia, phototoxicity, blistering, and headache. Given the possible photosensitivity associated with this drug, patient education/counseling for this side effect may be warranted. Importantly, we did not observe a significant emergence of episodes of CDI or bacterial resistance, which were the two potential microbiological adverse consequences we feared with the routine administration of a second broad-spectrum antibacterial drug. These possible consequences have discouraged the use of gram-positive agent prophylaxis in NF guideline recommendations [16]. It is worth mentioning, however, that there is some evidence that doxycycline is not associated with CDI, and may actually be protective against it [28–30]. Two meta-analyses found that tetracyclines were not associated with an increased risk of CDI (OR 0.91, 95% CI 0.57–1.4) or potentially protective against it compared to other antibiotics (OR 0.62, 95% CI 0.47–0.81, $p < 0.001$), and another recent study found that doxycycline was protective against the development of CDI in hospitalized patients receiving ceftriaxone [28–30]. While the vast majority of patients undergoing ASCT for MM experience diarrhea as a result of melphalan-induced intestinal mucositis, CDI remains in the differential diagnosis of diarrhea in this setting, and therefore, the potential protective effect of doxycycline is intriguing.

Our study has several limitations. The most important is its retrospective nature, which predisposes to the occurrence of collection and confounding biases. Moreover, the two groups were treated in temporal sequence, and other factors associated with supportive care and nursing competence and practices may have changed over time, thus potentially affecting the results. For example, disinfectant methods and care of central catheters may have included different approaches over the study period. The use of ethanol impregnated caps (Curos®) vs "scrubbing the hub" or the use of chlorhexidine wipes/baths for pilot projects could have also influenced lower CLABSI rates [25]. Only a prospective randomized strategy can eliminate these confounding variables. However, it is important to note that the same practices did not lead to a similar reduction of NF and CLABSI rates in our patients receiving only ciprofloxacin prophylaxis for BEAM conditioning during the same time period (data not shown).

There are significant imbalances in patient characteristics between the cipro and cipro-doxy groups. The median age of the cipro group was younger (58 vs 60 years). This

is presumably related to our decision to increase the age threshold for ASCT in our institution over time, but the 2-year difference, albeit statistically significant, hardly represents a clinically relevant difference. The difference in the drugs used for the induction therapy reflects the change of the chemotherapy regimens for MM, with VAD (vincristine, Adriamycin® [doxorubicin], and dexamethasone) now being obsolete and VRD (bortezomib, lenalidomide, and dexamethasone) or CyBorD (cyclophosphamide, bortezomib, and dexamethasone) representing the current standards of care. The higher median number of stem cells infused in the cipro group (14.5 vs 4.8 million CD34+ cells/kg) reflects a more efficient strategy of stem cell collection, because we initially used chemotherapy mobilization with cyclophosphamide, then abandoned this practice over time, and replaced it with the use of granulocyte colony-stimulating factor (G-CSF) only. Collection of stem cells with G-CSF only provides a reduced yield as compared to mobilization chemotherapy [31]. All these factors and the evolution of the therapeutic approaches in the treatment of MM over time have induced imbalances in the characteristics of our two groups, and therefore, the validity of our results and conclusions could be compromised. In any case, among the factors chosen for our multivariate analysis, only the use of doxycycline reached a statistical significance, and this finding is biologically plausible. Of note, a recent publication by another group analyzed bacteremia and infection in MM patients receiving ASCT, and it suggested beta-2-microglobulin levels at diagnosis and use of bortezomib as risk factors [32]. However, our study, which included a larger number of patients, did not confirm the association between those two factors and the NF incidence.

In summary, based on our retrospective study, we believe that the addition of oral doxycycline to standard prophylaxis with ciprofloxacin may lead to a significant reduction of NF and bacteremia rates in patients with MM undergoing ASCT. We are currently studying the feasibility of a prospective randomized study to establish the validity of our results. If findings are confirmed, the routine antimicrobial prophylaxis strategy for these patients may need to be changed.

Author contributions Jeffrey M. Sivik, PharmD: primary/corresponding author—responsible for drafting article, concept/design, data analysis/interpretation, critical revision of article, and final approval of article

Jo Ann Davidson, CRNP: responsible for data collection/analysis/interpretation, critical revision of article, and approval of article

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Giampaolo Talamo, MD: senior author, responsible for concept/design, statistics, data collection/analysis/interpretation, critical revision of article, and approval of article

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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