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Efficacy and Safety of Ciprofloxacin for Prophylaxis of Polyomavirus BK Virus–Associated Hemorrhagic Cystitis in Allogeneic Hematopoietic Stem Cell Transplantation Recipients

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Polyoma virus BK–induced hemorrhagic cystitis is an important cause of morbidity after hematopoietic stem cell transplantation (HSCT). Fluoroquinolones have been shown in vitro to inhibit BK viral replication by direct inhibition of the BK-encoded DNA gyrase. We hypothesized that extended prophylaxis with ciprofloxacin may decrease the incidence of severe (grades 3 and 4) BK virus–associated hemorrhagic cystitis (sBKHC) after HSCT. We retrospectively collected patient and transplant data, as well as incidence of sBKHC, for all consecutive patients undergoing allogeneic HSCT between June 2006 and August 2010 at our institution. Prophylaxis for sBKHC with ciprofloxacin 500 mg orally twice daily from day 0 until day 60 had been instituted in March 2009, delimiting a group receiving ciprofloxacin prophylaxis (CP) or no prophylaxis (NP). We compared the cumulative incidence of sBKHC in CP and NP, including death in absence of sBKHC as a competing risk. Ninety-two consecutive patients were included in the analysis, 44 in CP and 48 in NP. Median age of patients was 50 years (range: 19-70), and 47% received a myeloablative conditioning regimen. The cumulative incidence of sBKHC was significantly reduced in CP (2.6% versus 20.9%, $P = .01$). Multivariate Cox regression analysis revealed that assignment to CP and concomitant acute graft-versus-host disease (GVHD) were the only factors independently associated with the occurrence of sBKHC. Patients in CP did not experience a higher risk of *Clostridium difficile* diarrhea and were less likely to develop episodes of bacteremia. Ciprofloxacin prophylaxis appears safe and effective in reducing the incidence of severe BKHC after allogeneic HSCT.

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BACKGROUND

BK virus-associated hemorrhagic cystitis (BKHC) is a potentially serious complication that occurs in 12% to 40% [1-7] of allogeneic hematopoietic stem cell transplantation (HSCT) recipients. Clinical manifestations of BKHC can be minor, with asymptomatic hematuria, but can be severe, causing massive blood loss, pain, urinary obstruction, renal failure, and even death [2,6,7].

Polyomavirus hominis 1, the BK virus, is present in the urinary tract of >80% of adults and not linked to any significant morbidity in immunocompetent individuals [8,9]. In allogeneic HSCT patients, the chemotherapy and irradiation from the conditioning regimen cause damage to the urothelium cooperating with the iatrogenic immunosupresive state to trigger viral replication and shedding, alloimmune attack to the urothelium, and finally bleeding [6,10-12].

Even though BKHC occurs typically beyond 30 days after transplantation [1,2,7,13], most of the events implicated occur early, during an asymptomatic phase. Indeed, the level of asymptomatic urinary shedding of BK virus during the first 2 to 3 weeks after HSCT is linked to the likelihood of development of symptomatic BKHC at a latter time [6,14].

Most cases of BKHC are mild and self-limited, but there are no treatments proven to be effective in decreasing the morbidity or the duration of severe

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episodes of BKHC. However, the intense viral replication and viral shedding occurring in the asymptomatic phase of the disease provides opportunity to establish an effective prophylactic intervention.

The antibacterial fluoroquinolone ciprofloxacin carries inhibitory activity against the prokaryotic DNA gyrase subunit A, can prevent BK virus replication in vitro, and decrease the magnitude of BK virus shedding following HSCT [14-16]. Because of preliminary evidence that prolonged use of fluoroquinolones can prevent episodes of severe BKHC [14], we instituted universal prophylaxis with ciprofloxacin until day 60 after allogeneic HSCT. This report compares the incidence of severe BKHC with and without prophylaxis and provides confirmation of the safety and efficacy of ciprofloxacin prevention for BKHC after allogeneic HSCT.

METHODS

Study Design

Prior to March 2009, all adult patients undergoing allogeneic HSCT at the Medical University of South Carolina (MUSC) received prophylaxis for opportunistic bacterial infections from the day of transplantation until neutrophil engraftment (typically, the third consecutive day of neutrophils $>500/mm^3$) consisting of ciprofloxacin 500 mg orally every 12 hours. In the event of the patient developing fever and neutropenia, ciprofloxacin was discontinued upon initiation of broader spectrum parenteral antimicrobial coverage. Motivated by preliminary evidence in the literature of the impact of fluoroquinolones in preventing BKHC, we changed our practice in March 2009 to institute prophylaxis with ciprofloxacin from day 0 until day 60 after transplantation in all allograft recipients (except patients allergic to ciprofloxacin). Patients unable to take oral medication received the equivalent dose of ciprofloxacin intravenously. We subsequently obtained approval from the MUSC institutional review board to retrospectively collect patient- and transplant-related data and perform the present analysis. All consecutive patients undergoing allogeneic HSCT at MUSC between January 2006 and August 2010 are included in the analysis.

Definitions

BKHC was defined as the presence of hematuria, concomitant urinary excretion of BK virus (as detected by real-time polymerase chain reaction (PCR) for a 72-nucleotide sequence from the *VP-1* gene, with a limit of detection of 10,000 copies/mL), and absence of any other known cause for hematuria. Episodes of BKHC were graded as follows: grade 1, microscopic hematuria; grade 2, macroscopic hematuria; grade 3, macroscopic hematuria with small blood clots; grade 4, massive macroscopic hematuria requiring instrumentation of the urinary tract or causing urinary retention [12]. Most episodes of grades 1 and 2 hemorrhagic cystitis are self-limited and associated with minimal morbidity. Therefore, we only utilized the occurrence of grades 3 and 4 BKHC, hereafter called severe BKHC, as an endpoint for the study.

With the intent to assess other disease and patient characteristics associated with BKHC, we extracted demographic data along with conditioning regimen, type of donor, that is, sibling HLA matched donor or alternative donor (matched and mismatched unrelated, cord blood, or partially matched related donors), and occurrence of clinically significant acute graft-versus-host disease (aGVHD). Conditioning regimens were defined as fully myeloablative if containing melphalan ≥ 140 mg/m^2 and/or total-body irridiation (TBI) >500 cGy (single fraction) or 800 cGY (multiple fractions) and/or busulfan >8 mg/kg (oral or intravenous equivalent) [17]. All remaining conditioning regimens were categorized as reduced intensity (RIC). The incidence and severity of aGVHD had been prospectively recorded according to IBMTR standards [18].

Statistics

The main endpoint of the study was to compare the cumulative incidence of severe BKHC between the group of patients receiving prophylaxis with ciprofloxacin (PC) and the group not receiving prophylaxis (NP). For this comparison, we utilized competing risk analysis with development of severe BKHC and death in absence of severe BKHC as competing events.

Because several factors influence the incidence of severe BKHC [3,7], and to account for the possible disproportionate frequency of these factors in PC and NP, we performed a multivariate analysis for the endpoint of cumulative incidence of severe BKHC employing Cox proportional hazard regression analysis. This analysis included use of ciprofloxacin prophylaxis, intensity of conditioning regimen (myeloablative versus RIC), donor type (sibling matched versus alternative donor), age of the patient, occurrence of grades B-D GVHD, and the use of a uroprotective agent during conditioning (mesna) as covariables. Variables to be included in the final model were selected utilizing the forward stepwise method.

Extended use of antibacterial drugs can lead to the development of *Clostridium difficile* diarrhea in HSCT patients and emergence of infections caused by antibiotic-resistant bacteria [19,20]. Therefore, we compared the incidence of bacteremia and *C. difficile* diarrhea during the 100 days after transplantation in PC and NP. Because the groups had dissimilar duration of follow-up, incidence of bacteremia and *C. difficile* diarrhea were normalized and presented as episodes/100 days at risk. All comparisons between

rates utilized Fisher's exact test. All inferential analyses were done for $\alpha < 0.05$.

RESULTS

Patient Characteristics

Ninety-two consecutive patients were included in the analysis, of which 44 received ciprofloxacin prophylaxis. Median age of patients was 50 years (range: 19-70), and 38% were female. All living patients had at least 30 days of follow-up. Median follow-up for patients in the ciprofloxacin and control groups were, respectively, 175 (range: 16-549) and 515 days (range: 29-1706). Characteristics of patients included in both groups are displayed in Table 1. Patients in the PC group were, in general older, more likely to receive a transplant from an alternative (non-HLA matched sibling) donor, and less likely to receive a myeloablative regimen than patients in the NP group. Only 1 patient in the entire study received a conditioning regimen containing thymoglobulin, a known risk factor for BKHC [21].

Incidence of Severe BKHC

Among the 48 patients in the NP group, 4 never received ciprofloxacin because of allergy. Of the remaining 44 patients, 36 discontinued ciprofloxacin because of fever and neutropenia requiring broader antibiotic coverage, and 8 patients discontinued ciprofloxacin at the time of neutrophil engraftment. The median number of days of exposure to ciprofloxacin in the NP cohort was 8 (interquartile range: 5.5-12). All surviving patients in the PC cohort completed 60 days of ciproprofloxacin prophylaxis.

There were 11 cases of severe BKHC in the NP group and 1 case in the PC group, occurring after a median of 68.5 (range: 30-118) days after transplantation. The long-recognized intrinsic relationship between aGVHD and BKHC [7,11] was also verified in the current series. Severe BKHC occurred in 9 of 38 (23.7%, 95% confidence interval [CI] 10.2%-37.2%) patients with and in 3 of 54 (6.1%, 95% CI 0%-11.7%) patients without clinically significant (grades B-D) aGVHD ($P = .024$). We also verified an association between intensity of the conditioning regimen and risk of severe BKHC. Overall, 11 of 43 (25.6%, 95% CI 12.5%-38.6%) patients receiving a myeloablative conditioning regimen developed severe BKHC compared to only 1 of 49 (2%, 95% CI 0%-6%) patients receiving a reduced intensity conditioning ($P < .001$).

Using competing risk analysis (with death in absence of severe BKHC as a competing risk), the cumulative incidence of severe BKHC was 20.9% (±5.9%) in NP and 2.6% (±2.6%) in PC (Figure 1; $P = .01$). By the same analysis, there was no statistically significant difference between cumulative incidence of death in absence of severe BKHC between NP and PC (Figure 2; $P = .62$). There was no difference in overall survival (OS) between patients without and with severe BKHC ($P = .07$). Estimated OS rates at day 100 were 82.8% (±4.3%) and 83.3% (±10.8%), whereas survival rates at 1 year were 66.1% (±5.9%) and 40% (±14.6%).

In order to clarify whether the differences in incidence of severe BKHC between the groups could be linked to the exposure to ciprofloxacin and not only to differences in prevalence of known risk factors for BKHC, we performed Cox regression analysis for the endpoint of incidence of severe BKHC. As displayed in Table 2, among the 5 variables integrating the final model, only the use of a myeloablative regimen, the occurrence of grades B-D aGVHD, and the lack of ciprofloxacin prophylaxis were independently associated with higher risk of severe BKHC.

Table 1. Characteristics of the Patients

	NP	PC	
	n = 48	n = 44	*P*
Age*	44 (31-56)	55 (44-62)	.001
Sex (female)	20 (42%)	15 (34%)	.455
Diagnosis			
AML	18 (37%)	19 (43%)	
MDS	9 (19%)	5 (11%)	
ALL	7 (15%)	3 (7%)	
NHL	6 (13%)	7 (16%)	
CLL	1 (2%)	2 (5%)	
Other	2 (4%)	7 (16%)	
CML	5 (10%)	1 (2%)	
Donor			
HLA matched sibling	24 (50%)	11 (25%)	.014†
Unrelated volunteer donor	24 (50%)	27 (61%)	
Partially matched sibling (haploidentical)	0 (0%)	3 (7%)	
Unrelated cord blood	0 (0%)	3 (7%)	
Conditioning regimen			
Fully myeloablative	27 (56%)	16 (36%)	.056
Reduced intensity	21 (44%)	28 (64%)	
GVHD prophylaxis			
CSA + MMF	47 (98%)	34 (77%)	
Sirolimus +tacrolimus	1 (2%)	7 (16%)	
Tacrolimus + MMF	0 (0%)	3 (7%)	

AML indicates acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; CLL, chronic lumphocytic leukemia; CML, chronic myeloid leukemia; CSA, cyclosporine; MDS, myelodysplastic syndrome; MMF, mycophenolate mofetil; NHL, non-Hodgkin lymphoma.
*Median (interquartile range).
†HLA matched sibling versus alternative donor.

Complications

There is concern that the prolonged use of antibiotic prophylaxis after transplantation may lead to increased risk for infection by antibiotic-resistant pathogens and *Clostridium difficile* diarrhea [19,20]. There were 28 episodes of bacteremia in NP (0.61

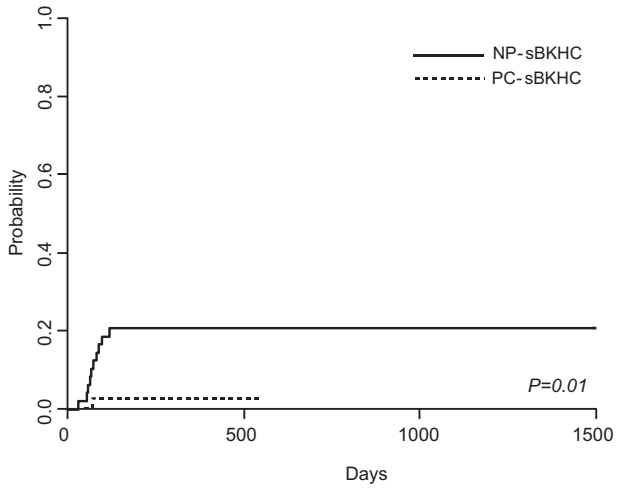

Figure 1. Cumulative incidence of severe BK polyomavirus–associated hemorrhagic cystitis (sBKHC) among patients receiving no prophylaxis (NP) or prophylaxis with ciprofloxacin (PC).

episodes/100 days at risk) versus 7 episodes of bacteremia in PC patients (0.19 episodes/100 days at risk; $P = .003$). Only 1 of 10 episodes of Gram-negative bacteremia in the NP group (*Escherichia coli*) and 3 of 4 in the PC group (2 cases of *Escherichia coli* and 1 case of *Citrobacter freundii*) were caused by a fluoroquinolone-resistant pathogen ($P = .04$). Table 3 display the pathogens implicated in episodes of bacteremia for both groups.

There was no significant difference in occurrence of episodes of *Clostridium difficile* diarrhea among the groups with 3 episodes (0.07 episodes/100 days at risk) in NP and 5 episodes (0.13 episodes/100 days at risk) in PC ($P = .48$). All 8 episodes of *Clostridium difficile* diarrhea were treated successfully with oral metronidazole or vancomycin. Only 1 patient later had a recurrence of the diarrhea and was successfully retreated with metronidazole.

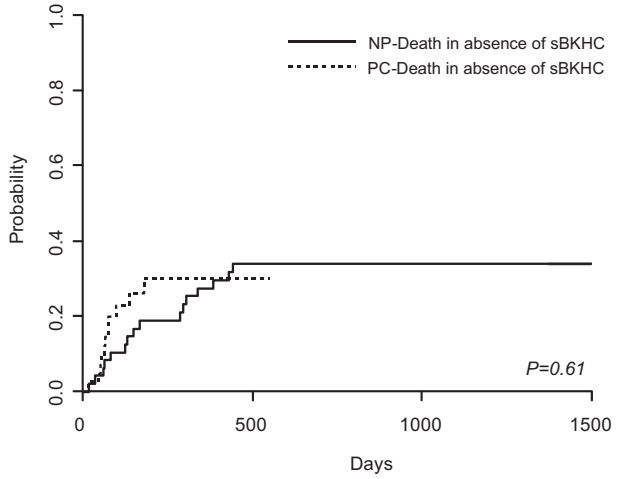

Figure 2. Cumulative incidence of death in absence of severe BK polyomavirus–associated hemorrhagic cystitis (sBKHC) among patients receiving no prophylaxis (NP) or prophylaxis with ciprofloxacin (CP).

Table 2. Multivariate Analysis for Incidence of Severe BKHC

Factor	HR	*P*
Sex (female)	0.35 (0.09-1.32)	.12
Conditioning (myeloablative)	12.63 (1.46-109.0)	.02
Mesna	4.99 (0.95-26.3)	.58
Grades B-D aGVHD	6.87 (1.48-31.9)	.01
Ciprofloxacin prophylaxis	0.03 (0.002-0.38)	.007

HR indicates hazard ratio; aGVHD, acute graft-versus-host disease; BKHC, BK virus-associated hemorrhagic cystitis.

DISCUSSION

Polyomavirus BK–associated hemorrhagic cystitis can be distinguished from the hemorrhagic cystitis caused by urothelial damaged from cytotoxic chemotherapy (particularly acrolein, a metabolite of cyclophosphamide) on the basis of the latter onset, and presence of high copy numbers of BK virus in the urine and, less frequently, serum [1,2,6,12,13].

Even though BKHC and conditioning regimen-induced HC have long been regarded as distinct entities, they are likely interconnected. Urothelial damage from the conditioning regimen triggers viral replication and generation of an alloimmune reaction [6,10,11,14], events known to be associated with the development and sustainability of BKHC. In fact, it is now recognized that the use of more intense conditioning regimens, leading to more extensive urothelial damage, is associated with higher incidence of BKHC [3-5]. Leung et al. [14] have demonstrated a correlation between the extent of BK virus urinary shedding in the first 2 to 3 weeks after transplantation and subsequent development of BKHC. Similarly, a recent report including 209 patients successfully correlated the presence of BK in the urine prior to

Table 3. Episodes of Bacteremia

	NP	PC
Pathogen	n = 28	n = 7
Gram positives		
Enterococcus spp	9	2
Staphylococcus aureus	3	1
Coagulase-negative *Staphylococcus*	4	0
Streptococcus mutans	1	0
Gram negatives		
Acinetobacter baumannii	3	1
Klebsiella pneumoniae	3	0
Escherichia coli	0	2
Citrobacter freundii	1	1
Enterobacter spp	1	0
Burkholderia cepacia	1	0
Stenotrophomonas maltophilia	1	0
Others		
Mycobacterium fortuitum	1	0

initiation of the conditioning regimen with subsequent development of symptomatic BKHC [3]. These findings imply that strategies aiming at preventing the development of BKHC would need to be instituted early in the posttransplantation setting, particularly during the first 60 days.

Currently, there is no established treatment for BKHC. Its management consists mostly of transfusion support, hydration, and in more severe cases, continuous bladder irrigation or even cystectomy [12,21,22]. There have been many reports of the use of antiviral agents, particularly cidofovir (intravenous and/or intravesical), with the intent to improve or reverse episodes of BKHC [4,23-26]. These reports, however, are limited by small sample sizes and lack of appropriate control groups.

Fluoroquinolones inhibit prokaryotic DNA gyrase subunit A and are active in a plethora of Gram-negative and Gram-positive infections. Fluoroquinolones also inhibit in vitro the DNA gyrase produced as a consequence of BK infection of mammalian cells, making them promising agents for BKHC prophylaxis [14-16]. Leung et al. [14] tested the impact of ciprofloxacin treatment in a cohort of 68 patients undergoing allogeneic HSCT in Hong Kong. This study noted markedly lower loads of BK urinary excretion in patients receiving ciprofloxacin for bacterial prophylaxis when compared to patients receiving cephalosporins, translating into lower frequency of BKHC. Even though this series provided strong rationale for ciprofloxacin prophylaxis, it suffers from inconsistencies in the use and duration of treatment with ciprofloxacin, small sample size, and insufficient comparisons between ciprofloxacin and nonciprofloxacin groups in terms of patient and transplant-related characteristics.

Until March, 2009, our program routinely administered ciprofloxacin as prophylaxis of bacterial infection during the pre-engraftment phase. Given the strength of the preliminary data, the importance of BKHC and the relative ease in implementing this intervention, we decide to extend ciprofloxacin prophylaxis until day 60. The current analysis suggests that this intervention is both safe and effective, with a near 90% reduction in the risk to develop severe BKHC. Despite the inevitable differences between groups, the impact of prophylaxis remained significant even in multivariate analysis, along with factors demonstrated in prior series to be implicated in BKHC, namely, GVHD and myeloablative conditioning. To our knowledge, this is one of the first comparative series, and the largest one, to confirm the effectiveness of any pharmacological intervention in preventing severe BKHC after allogeneic HSCT. Similar analysis in cohorts of patients undergoing renal transplantation have shown that prolonged exposure to fluoroquinolones are associated with reduced risk of BK viremia and BK nephropathy [27]. Even though the present study addresses the effect of ciprofloxacin in BKHC, its proposed mechanism of action is shared by other fluroquinolones, such as levofloxacin, and is likely class-specific instead of drug-specific. In fact, there is preliminary evidence that levofloxacin also can be effective in preventing BK virus–associated complications after kidney transplantation [27].

It is important to emphasize that ciprofloxacin prophylaxis was in general safe, with none of the patients in the PC cohort discontinuing therapy prior to day 60 after transplantation. Extended use of ciprofloxacin did not seem to increase the incidence of *C. difficile* diarrhea. Interestingly, there was a marked reduction in the risk of bacteremia during the first 100 days after transplantation in the PC group. However, bacteremias developing in the setting of ciprofloxacin prophylaxis were more likely to be caused by a fluoroquinolone-resistant pathogen. These observations demand caution, as they are preliminary and retrospective. Further studies are needed to properly assess the safety of extended prophylaxis with ciprofloxacin after HSCT.

The main limitation of this report is its retrospective nature, only partially overcome by the multivariate analysis. Even though unaccounted differences in supportive care between cohorts may have affected the outcome, this is unlikely to be the case, because all the transplants in both cohorts occurred during a relatively short period of time (56 months) with no other interim substantial change in supportive care practices.

Another caveat is the possibility that the apparent reduction in incidence of severe BKHC may be in fact a result of regression to the mean and not truly an impact of the institution of ciprofloxacin prophylaxis [28]. In this scenario, an unusual, "by chance," high incidence of severe BKHC during a determined period (covered by the NP cohort) would have triggered the institution of ciprofloxacin prophylaxis. The subsequent reduction in severe BKHC would be an expected regression toward average rates instead of a true effect of the intervention. Although possible, this hypothesis is unlikely, considering the marked differences observed between PC and NP and the rate of severe BKHC seen in the NP group are comparable to those reported in the literature [1-6].

In summary, ciprofloxacin prophylaxis appears safe and effective in reducing the incidence of severe BKHC after allogeneic HSCT, with potential concomitant reduction in the risk of bacteremias. This finding requires confirmation with a prospective randomized trial. Such trial may focus on high-risk patients and should ideally be accompanied by prospective monitoring of BK virus urinary shedding and viremia.

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