Aztreonam and Vancomycin for Initial Treatment of Febrile Neutropenia in Penicillin-Allergic Patients During Hematopoietic Stem Cell Transplantation

STEVEN TRIFILIO, RPh, and JAYESH MEHTA, MD

From Northwestern Memorial Hospital and Robert H. Lurie Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, Illinois

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Steven Trifilio, RPh, Northwestern Memorial Hospital, 250 E. Superior, Chicago, IL 60611. E-mail: strifili@nmh.org

https://doi.org/10.6004/jadpro.2019.10.7.4

Abstract

Most patients who undergo hematopoietic stem cell transplantation develop neutropenic fever and are at high risk for developing potentially life-threatening infections. β-lactam antibiotics remain the cornerstone for initial empiric treatment of neutropenic fever. In cancer patients with allergy or intolerance to β-lactams, guidelines recommend using aztreonam with vancomycin (AV) for neutropenic fever treatment. To date, the efficacy of AV for the treatment of neutropenic fever during stem cell transplantation is unknown. A retrospective study was conducted to identify hematopoietic stem cell transplantation recipients who were initially treated with concomitant AV for neutropenic fever between 2007 and 2013. Febrile neutropenia was classified as neutropenia with unexplained fever, neutropenic fever with a local source of infection, or neutropenic fever with a microbiologically documented infection. Seventy-six patients were identified who received AV as initial treatment for neutropenic fever over the study period. Responses to AV for neutropenia with unexplained fever (n = 41), febrile neutropenia with local site of infection (n = 11 [pneumonia = 9, other = 2]), and neutropenic fever with microbiologically documented infection (n = 34) were 75%, 55% (45% pneumonia), and 46% respectively. Infection-related mortality was 5%. Aztreonam with vancomycin was effective in treating neutropenia with unexplained fever. For patients with neutropenic fever and local source or microbiologically documented infection, alternative antibiotic treatments should be considered.

J Adv Pract Oncol 2019;10(7):685–690

Infections that occur during episodes of neutropenic fever (NF) in patients who undergo hematopoietic stem cell transplantation (HSCT) can cause serious morbidity and mortality. Guidelines suggest initiating antibiotic coverage with a broad-spectrum β-lactam antibiotic as the backbone for initial treatment for NF. Aztreonam, a monobactam antibiotic, lacks cross-sensitivity with β-lactam antibiotics and is an alternative for those with allergy or intolerance to β-lactam antibiotics (Adkinson, 1990). Current guidelines recommend giving aztreonam with vancomycin (AV) in order to provide adequate coverage against gram-positive and gram-negative organisms (Freifeld et al., 2011). Aztreonam plus vancomycin has been used successfully to treat febrile neutropenia in patients with cancer (Bodey & Jones, 1986; Jones et al., 1986), yet the efficacy of AV during stem cell transplantation is largely unknown. We report the results of an observational study undertaken to determine the efficacy of AV as initial treatment of NF in patients who undergo HSCT.

METHODS

The Northwestern Memorial Hospital electronic database was used to collect data for all hematopoietic stem cell transplantation recipients who received concomitant AV for the initial treatment of NF between August 2008 and August 2014. Data were collected from the day of admission through hospital discharge. History of immediate IgE hypersensitivity reaction (hives) or previous intolerance to β-lactams was documented from patient interviews.

Patients received ciprofloxacin, an azole antifungal agent and acyclovir prophylaxis beginning day 0 of stem cell transplantation. Neutropenia was defined as absolute neutrophil count (ANC) < 500 cells/mL and febrile fever as 100.4°F measured twice over 1 hour or a single temperature of 101°F. Patients with NF were started on aztreonam at 2 g IV every 8 hours and dose-adjusted IV vancomycin per previously published guidelines (Hughes et al., 1992). All patients received at least 48 hours of AV concomitantly. Patients were classified as having neutropenia with unexplained fever only, NF with microbiologically documented infection, or NF with a clinically defined source but without a microbiologically documented infection according to the published guideline by Hughes and colleagues (1992).

Based upon the same guidelines, response to treatment was defined as defervescence within 96 hours, eradication of signs and symptoms without addition of antimicrobials, and no recurrence within 7 days. Cultures were obtained from urine and blood before AV was started, and a chest x-ray was obtained within the first 24 hours of treatment. Blood culture specimens were obtained daily while patients remained febrile. Isolates from bacteria commonly associated with colonization (e.g., coagulase-negative staphylococci, or CoNS) required two positive cultures. Fungal and viral cultures were excluded.

Chi-squared or Fisher's exact tests were used for difference in frequency counts of categorical variables. This study was approved by the Northwestern University Institutional Review Board.

RESULTS

Among 1,051 patients who underwent adult HSCT between August 2008 and August 2014, 76 patients were identified who received AV as initial treatment for febrile neutropenia. Table 1 shows patient characteristics. The majority of patients (65%) received autografts, most often for multiple myeloma. The number of patients who received either a full myeloablative or a reduced-intensity allogeneic regimen was the same. The median time for initiating AV was day +7 post HSCT transplantation and the median duration of treatment was 7 days.

Table 2 shows treatment results. Overall AV response was 62%. Reasons for treatment failure included failure to defervesce within the appropriate time period (27%), recurrent fever (23%), and antibiotic change (38%).

Neutropenia with unexplained fever alone occurred in 41 patients (55%). Aztreonam plus vancomycin treatment successfully resolved fever within 96 hours, with no change or addition of antibiotics in 31 patients (74%). One patient (2%) died from an unrelated cardiac event. Response was significantly lower in patients who received an allogeneic transplant.

Eleven patients had NF with a clinically defined source of infection but without a microbiologically documented infection. Hospital-acquired

Table 1. Patient Characteristics

Characteristic	
N	76
Age, mean (range)	54 (24–77)
Gender (female)	44 (58)
Diagnosis, no. (%)	
Myeloma	34 (45)
Acute myeloid leukemia	18 (24)
Non-Hodgkin lymphoma	16 (21)
Transplant type, no. (%)	
Autologous	51 (67)
Allogeneic	25 (33)
Full myeloablative	14 (56)
Reduced intensity	11 (44)
Aztreonam treatment duration, d (range)	7 (2–33)
Aztreonam initiation day post-HSCT	7 (-6–+33)
Vancomycin duration, d (range)	7 (2–32)
Vancomycin initiation day post-HSCT	7 (-6–+38)

Table 2. Aztreonam/Vancomycin Treatment Results

	Success (%)	*p* value
Number treated (n = 76)	48 (62)	
Failed to defervesce within 72 hr	21 (27)	
Recurrent fever after defervescence	18 (23)	
Antibiotic regimen change	30 (38)	
Overall mortality	5 (6)	
Indications for use		
FN with unexplained fever (n = 41)	32 (78)	
Autograft (n = 29)	23 (79)	
Allograft (n = 11)	8 (73)	.6831
Mortality	1 (3)	
FN with local source (n = 11)	6 (55)	
Autograft	8	
Allograft	3	.99
Lungs (n = 9)	4 (44)	
GI tract (n = 1)	1 (100)	
Skin and soft tissue (n = 1)	1 (100)	
Mortality	2 (18)	
Microbiologically documented infection (n = 24)	15 (63)	
Autograft (n = 12)	10 (83)	
Allograft (n = 12)	5 (42)	.0894
Mortality	2(8)	

Note. FN = febrile neutropenia.

pneumonia was the most frequently observed source (9 of 11, or 82%). Treatment failure due to persistent fever and lack of clinical response requiring antibiotic change occurred in 5 of 9 patients (55%), two (22%) of whom died. The other two cases (cellulitis and typhlitis) were successfully treated with AV.

Twenty-four patients (32%) had microbiologically documented infection (Table 3). Forty organisms were isolated. Treatment failure from persistent fever, failure to clear microorganisms from their source, or lack of clinical response requiring antibiotic change occurred in 13 cases (54%). The bloodstream was the major source of infection (76%), and gram-positive organisms were the most frequently identified microorganisms (80%). Gram-negative organisms occurred in 5 patients (12%), of whom 2 (40%) were multidrug resistant. Seven patients had polymicrobic infection, of whom 2 patients (28%) died.

Clostridium difficile developed in 8 patients (10%). Fifteen cases (20%) had vancomycin-resistant enterococci (VRE)-positive rectal surveillance cultures prior to AV therapy, while another 9 patients (11%) converted positive after 48 hours of AV treatment. The most frequently prescribed rescue antibiotics were an aminoglycoside (n = 16), echinocandin (n = 13), linezolid (n = 13), and a carbapenem (n = 5).

DISCUSSION

β-lactam antibiotics remain the drugs of choice for high-risk cancer patients who develop NF. In patients with immediate-type IgE-mediated hypersensitivity reactions or intolerance to β-lactams, management of NF can be challenging. Current guidelines recommend AV for patients with allergy, yet within the HSCT transplant setting, there is little evidence to support this recommendation.

The current observational study is the first recent study to report the efficacy of AV treatment for episodes of NF during stem cell transplanta-

Table 3. Isolated Microorganisms

Organism	Number	Source
Streptococcus viridans	11	Blood
Clostridium difficile	8	Stool
Coagulase-negative staphylococci	8	Blood
Enterococcus faecalis	4	Blood
Escherichia coli[a]	3	Blood(1[a])/ urine (2)
Staphylococcus aureus	2	Blood
Enterococcus faecium (VRE)	2	Blood
Enterobacter cloacae	1	Urine
Burkholderia mallei[a]	1	Blood

Note. VRE = vancomycin-resistant enterococci.
[a]Extended-spectrum β-lactamase producer.

tion. The results show most patients treated for neutropenia with unexplained fever (no local or documented infection) responded well to AV treatment without antibiotic modification. There was no difference in response between autologous and allogeneic stem cell recipients and no treatment-related mortality. Weakening the results from this group, however, include those patients whose fever may have been caused by drugs or an engraftment syndrome. Conversely, more than half the NF cases accompanied by either microbiologically documented infection or infection with a local source were treatment failures. Infection-related mortality was 11%.

The epidemiology of microbiologically confirmed infections in the current study is similar to that of those treated with β-lactams reported from other transplant centers (Wingard, Hsu, & Hiemenz, 2010). Gram-positive organisms isolated from the blood and urine were the leading cause of infections. The incidence of gram-negative infections was low (6%); however, 2 of 5 cases had polymicrobic infections, which included extended-spectrum β-lactamase (ESBL)-producing organisms resistant to aztreonam. Both patients died.

Our treatment results are very similar to those reported in a recent study of nontransplant neutropenic cancer patients treated with an aztreonam-based regimen (McCullough et al., 2014). In that study, 40 patients had 18 documented cases of infection, mostly from gram-positive organisms (> 70%). Overall response to aztreonam combination therapy was 47% according to Hughes criteria, and infection-related mortality was 12.5% (McCullough et al., 2014). What remains puzzling is the low rate of response to bloodstream infections caused by gram-positive organisms, which are normally sensitive to vancomycin.

Infections caused by ESBL-producing organisms have increased dramatically over the past 10 to 20 years. Extended-spectrum β-lactamases confer resistance to β-lactams and aztreonam, and clinical outcomes are poor despite susceptibility studies that report good sensitivity. Meropenem or imipenem are recommended as the agents of choice for treating ESBL-producing infections (Paterson et al., 2001, 2004; Perez, Adachi, & Bonomo, 2014). The last trial that directly compared aztreonam to a carbapenem (imipenem) for febrile neutropenia was conducted in 1996 in nontransplant patients. The results showed imipenem improved overall response and success in treating polymicrobic infection (Raad et al., 1996).

With high treatment failure rates and increased mortality from ESBL infections reported from the general population and poor responses observed in neutropenic patients, albeit from small numbers of patients, a case could be made to use a carbapenem as the drug of choice for initial treatment of NF in high-risk patients with a β-lactam allergy (e.g., allograft patients, patients colonized with multidrug-resistant organisms, or those with a high index of suspicion for sepsis or pneumonia). Cross-allergenicity between β-lactams and carbapenems is low (< 1%), and they are generally safe to give once immediate hypersensitivity has been ruled out (Romano et al., 2010). In order to minimize the overuse of carbapenems and avoid the risk for emergence of resistant organisms, treatment should be tailored once localized or documented infection has been ruled out. Local hospital patterns of drug resistance should be used to guide antibiotic treatment.

Although we observed high rates of VRE rectal surveillance culture positivity both before and after AV was started, only two VRE infections occurred (8%). Reports from other transplant centers show similar rates of colonization, but are more discordant with respect to the rates of VRE conversion from colonization to bacteremia, depend-

ing largely upon patient risk factors. Interestingly, others have found VRE colonizers are not only at higher risk for VRE bacteremia, but also possibly bacteremia from other organisms (Benamu & Deresinski, 2018; Ford et al., 2017; Webb et al., 2017).

Our study results show that the percentage of patients who developed *C. difficile* infection during AV therapy was nearly identical (10% vs. 10.3%) to the percentage of patients who developed *C. difficile* infection while receiving β-lactam antibiotics during stem cell transplantation over the same time period. This highlights the need for optimizing pathogen-directed antibiotic treatment and early antibiotic discontinuation (Trifilio, Pi, & Mehta, 2013).

IMPLICATIONS FOR THE ADVANCED PRACTITIONER

At many institutions, advanced practitioners are often the first responders to patients who develop NF. Ideally, all patients with a reported β-lactam allergy should have been screened by the allergy service to rule out an IgE-mediated type allergic reaction; however, in our experience, many are not. Our approach to patients with suspected or true IgE-mediated allergy is to initiate aztreonam at 1 g IV every 8 hours and dose-adjusted vancomycin with drug level monitoring. Additionally, patients who present with signs and symptoms consistent for sepsis or pneumonia are given an extended interval dosed aminoglycoside, in our case amikacin at 15 mg/kg/day, dose adjusted for body weight and renal function, and continued for 24 to 48 hours only (1–2 doses only) based upon results from blood cultures and chest CT. The allergy service is consulted to determine which other antibiotics are safe for use. Aztreonam and vancomycin are usually continued until neutropenia is resolved or deescalated to oral therapy based upon the patient's clinical response to treatment.

In conclusion, AV was successful in treating neutropenia with unexplained fever following stem cell transplantation. Alternative treatment should be considered for patients with a high level of suspicion for microbiologically confirmed or locally advanced infection.

Disclosure

The authors have no conflicts of interest to disclose.

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