A Phase II Prospective Randomized Study to Assess Ceftolozane-Tazobactam in the Management of Febrile Neutropenia in Patients with Hematological Malignancies

#1257

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ABSTRACT

Introduction

Despite the implementation of successful antibiotic stewardship programs, antibiotic resistance continue to emerge particularly against gram-negative bacteria. With the increase use of antibiotics in high risk patients with hematological malignancies, the empiric therapy with standard antibiotic could be inappropriate. New antibiotics may be useful to cover potential resistant pathogens. We evaluated the role of a new cephalosporin/β-lactamase inhibitor ceftolozane-tazobactam (C/T) in comparison to standard of care (SOC) antibiotics in the empiric treatment of febrile neutropenic cancer patients with hematological malignancies.

Methods

We conducted a prospective randomized open label comparative study to evaluate the safety and efficacy of C/T vs SOC antibiotics consisting of cefepime, piperacillin-tazobactam or meropenem when used in combination with gram positive antibacterial agents. Between May 2018 and March 2020, we enrolled 88 febrile neutropenic patients with hematological malignancies who presented to our emergency center. Patients received at least 72 hours of intravenous study drugs and were followed through end of IV therapy and for up to 42 days.

Results

A total of 88 patients were analyzed of whom 42 received C/T and 46 SOC antimicrobial agents. The rate of documented bloodstream infections was similar in both groups (C/T 21% vs SOC 26%, p=0.61). Favorable clinical response at end of IV therapy was significantly better in the C/T arm compared to SOC therapy (88% vs 72%, p=0.039), at test of cure (21 days), and last follow-up (42 days). In patients with documented infections, the rate of microbiological eradication was similar in both groups. Drug-related adverse events that led to drug discontinuation was similar in both groups (7%). Similarly overall mortality was similar in both groups.

Conclusions

The empiric use of C/T to cover gram negative organisms in high risk febrile neutropenic patients with hematological malignancies is safe and associated with better clinical outcome than SOC antimicrobial agents. The emergence of resistant pathogens should be further evaluated.

INTRODUCTION

Despite the implementation of successful antibiotic stewardship programs, antibiotic resistance continue to emerge particularly against gram-negative bacteria. With the increase use of antibiotics in high risk patients with hematological malignancies, the empiric therapy with standard antibiotic could be inappropriate. New antibiotics such as ceftolozane-tazobactam (C/T) that consists of a novel cephalosporin and an established β-lactamase inhibitor that is being developed to address antimicrobial resistance in serious infections caused by gram-negative pathogens is warranted. Ceftolozane/tazobactam is approved in the United States for the treatment of complicated intra-abdominal infections (administered with metronidazole) (cIAI), complicated urinary tract infections (cUTI) including pyelonephritis, and ventilated nosocomial pneumonia in adults. We therefore in this study evaluated the role of this new cephalospoine/β-lactamase inhibitor (C/T) in comparison to standard of care (SOC) antibiotics in the empiric treatment of febrile neutropenic cancer patients with hematological malignancies.

METHODS

We conducted a prospective randomized open label comparative study to evaluate the safety and efficacy of C/T vs SOC antibiotics consisting of cefepime, piperacillin-tazobactam or meropenem. If indicated, patients could receive gram positive antibacterial agents consisting of vancomycin, linezolid or daptomycin.

Inclusion Criteria:

- Patients ≥ 18 years old, with hematological malignancies, presenting to our emergency center for neutropenic fever.
- Requires hospitalization for IV empiric antibiotic therapy

Exclusion Criteria:

- Allergic reaction to any cephalosporin antibiotic
- Patient has received > 24 hours of IV antibiotics at the time of enrollment

Definitions:

- Neutropenic fever was defined as an absolute neutrophil count (ANC) < 500 cells/mm3 within 48 hours of trial entry
- Fever was defined as either a single oral temperature measurement of ≥ 101°F (38.3°C) or a temperature of ≥ 100.4°F (38.0°C) sustained over a 1-hour period

❖ Between May 2018 and September 2020, 100 patients were randomized on a 1:1 ratio to receive either C/T or SOC antibiotics for at least 72 hours.

❖ Patients were followed through end of IV therapy and for up to 42 days.

RESULTS

Table 1. Characteristics of patients treated with ceftolozane-tazobactam and those treated with standard care

Characteristics	Ceftolozane-Tazobactam	Standard Care	p-value
	(n=47)	(n=50)	
	N (%)	N (%)	
Age (years), median (range)	60 (25-84)	55 (18-79)	0.12
Sex, male	28 (60)	32 (64)	0.65
Type of hematological malignancy			0.32
ALL	9 (19)	12 (24)	
AML	19 (40)	22 (44)	
CML	3 (6)	0	
Lymphoma	9 (19)	6 (12)	
Others	7 (15)	10 (20)	
History of BMT within 1 year prior to fever	6 (13)	9 (18)	0.48
Autologous	2/6 (33)	4/9 (44)	
Allogeneic	4/6 (67)	5/9 (56)	
Type of allogeneic			
Matched unrelated donor (MUD)	0	1/5 (20)	
HLA matched related	4/4 (100)	4/5 (80)	
GVHD	1/6 (17)	1/8 (13)	> .99
Temperature at baseline (°C), median (IQR)	37.3 (36.9 - 38.2)	37.5 (37.0 - 38.3)	0.31
Organism of positive culture			
Entereococcus faecalis	2	2	
E. coli	1	2	
Klebsiella pneumoniae	1	0	
MRSA	1	1	
Pseudomonas aeruginosa	2	0	
Rothia mucilaginosa	1	0	
Streptococcus spp.	5	5	
Staphylococcus epidermidis	0	1	
Bacteremia	10 (21)	13 (26)	0.58
CVC being the source of bacteremia isolation	6/10 (60)	7/13 (54)	> .99
Duration of hospital stay (days), median (IQR)	6 (4-9)	6 (4-10)	0.92
ICU admission	2 (4)	3 (6)	> .99

Table 2. Outcomes of patients treated with ceftolozane-tazobactam and those treated with standard care

Outcomes	Ceftolozane-Tazobactam	Standard Care	p-value
	(n=47)	(n=50)	
	N (%)	N (%)	
Microbiological documentation (positivity)	11 (23)	11 (22)	0.87
Microbiology response at end of therapy (EOIV)			0.48
Eradication	11/11 (100)	9/11 (82)	
Microbiology response at test of cure (TOC)			> .99
Eradication	3/11 (27)	2/11 (18)	
Microbiology response at last follow-up			> .99
Eradication	3/11 (27)	3/11 (27)	
Clinical outcome at end of therapy (EOIV)			0.051
Favorable clinical response	41 (87)	36 (72)	
Clinical outcome at test of cure (TOC) *			0.034
Clinical cure	34/46 (74)	29/49 (59)	
Clinical outcome at last follow up (LFU) **			0.041
Clinical cure	33/46 (72)	26/48 (54)	
Clinical failure	6/46 (13)	17/48 (35)	
Indeterminate	7/46 (15)	5/48 (10)	
Notes:			
* The study is still going on for clinical outcome evaluation at time point of TOC for 2 patients.			
** The study is still going on for clinical outcome evaluation at time point of LFU for 3 patients.			

Table 3. Adverse events of patients treated with ceftolozane-tazobactam and those treated with standard care

Adverse events	Ceftolozane-Tazobactam	Standard Care	p-value
	(n=47)	(n=50)	
	N (%)	N (%)	
Adverse events	38 (81)	37 (74)	0.42
Serious adverse events (SAE)	33 (70)	33 (66)	0.66
Drug related adverse events	8 (17)	3 (6)	0.09
ALT elevation	1	1	
Bilirubin increased	1		
Rash	3	1	
Rash maculo-papular	1	1	
Alanine aminotransferase increased	1		
Alkaline phosphatase increased	1		
Headache	1		
Drug related serious adverse events	7 (15)	3 (6)	0.19
Drug related adverse events leading to drug discontinuation	3 (6)	3 (6)	> .99

CONCUSIONS

❑ The empiric use of C/T to cover gram negative organisms in high risk febrile neutropenic patients with hematological malignancies is safe. The numbers of patients experiencing adverse events were comparable in both groups.

❑ Patients who received C/T had a better clinical outcome than patients treated with SOC antimicrobial agents.