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ANTIMICROBIAL ACTIVITY OF DAPTOMYCIN TESTED AGAINST GRAM-POSITIVE ORGANISMS COLLECTED FROM PATIENTS WITH CANCER HOSPITALIZED IN THE UNITED STATES MEDICAL CENTERS

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ABSTRACT

BACKGROUND: Prompt initiation of appropriate antimicrobial therapy is a crucial factor to improve outcomes of infected immunocompromised patients (PT). Daptomycin (DAP) is a rapidly bactericidal drug with a broad-spectrum against Gram-positive (GP) organisms. We evaluated the antimicrobial susceptibility (S) patterns of GP causing infections in patients with cancer.

METHODS: As part of the USA DAP Surveillance Program, 1,374 GP were collected (one per patient [PT]) from infections in PTs with cancer at 33 medical centers in 2002-2006. Strains were S tested against DAP and various comparators by the CLSI broth microdilution method with appropriate broth Ca^{++} content (50 mg/L) for testing DAP. S patterns of strains from PTs with cancer were compared to those from bloodstream infections (BSI) of non-cancer PTs collected in the same hospitals and time period (11,081 strains).

RESULTS: *S. aureus* (SA; 42%) ranked first among GP pathogens from cancer PTs, followed by *Enterococcus* spp. (ESP; 32%). DAP was very active against all pathogens and only 3 DAP non-S isolates were observed, all with MIC value at one doubling dilution above S breakpoint. Only 55% of SA were S to oxacillin, and DAP was 2- to 4-fold more potent than vancomycin (VAN) against SA. Resistance (R) to VAN was high among ESP (39%). S patterns of strains from cancer PTs were very similar to those of non-cancer PT controls.

	MIC_{50}/MIC_{90} (µg/ml)/%S	
Organism (no. tested)	DAP	VAN
SA (573)	0.25 / 0.5 / 100.0	1 / 1 / 100.0
ESP (444)	1 / 2 / 99.8[a]	2 / >16 / 61.3
CoNS (254)	0.25 / 0.5 / 99.6[a]	1 / 2 / 100.0
β-haemolytic streptococci (59)	0.12 / 0.25 / 100.0	0.25 / 0.5 / 100.0
viridans group streptococci (44)	0.25 / 0.5 / 97.7[a]	0.5 / 0.5 / 100.0

a. One non-S strain.

CONCLUSIONS: DAP was active against 99.8% of GP strains collected from PTs with cancer at USA hospitals, but VAN was only active against 80.2% of strains and showed limited activity against ESP (61% S). These results indicate that DAP has appropriate spectrum and potency to be used for empirical coverage of GP infections in PTs with cancer in the USA 21 hospitals surveyed in the USA.

INTRODUCTION

There has been important progress in the treatment of patients with neoplastic disease over the past several decades. New therapeutic approaches, such as bone marrow and stem cell transplantation, have been introduced into clinical practice and have significantly decreased death rates. Unfortunately, neutropenia remains the most prominent chemotherapy-induced immune defect, rendering patients susceptible to infections. Thus, despite improvements in long-term cancer-related survival, infection remains a common complication of therapy and accounts for the majority of chemotherapy-associated deaths, especially when the administration of proper antimicrobial treatment is delayed.

Daptomycin is a novel lipopeptide with potent in vitro activity against Gram-positive cocci. Daptomycin has a unique mechanism of action and has demonstrated rapid in vitro bactericidal activity against a wide spectrum of Gram-positive organisms, including multidrug-resistant (MDR) strains of staphylococci, enterococci and streptococci. Furthermore, daptomycin monotherapy was shown to be superior to vancomycin monotherapy in the treatment of experimental endocarditis due to methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA).

Daptomycin was approved by the United States (USA) Food and Drug Administration (US-FDA) and by the European Medicine Agency (EMEA) for the treatment of complicated skin and skin structure infections (cSSSI) using a dose of 4 mg/kg every 24 hours. More recently, daptomycin was approved by the US-FDA for treatment of *S. aureus* bacteremia and right-sided endocarditis at a dose of 6 mg/kg every 24 hours.

As part of the Daptomycin Surveillance Program, we evaluated the antimicrobial susceptibility patterns of Gram-positive organisms causing infections in patients with cancer.

MATERIALS AND METHODS

Bacterial isolates: As part of the USA Daptomycin Surveillance Program, 1,374 Gram-positive were collected from infections in patients with cancer at 33 medical centers in 2002-2006. Only one isolate per patient was included. Control strains from bloodstream infections (BSI) of non-cancer patients were collected in the same hospitals and time period (11,081 strains).

Susceptibility testing: The strains were susceptibility tested against daptomycin and numerous comparator agents by reference broth microdilution methods performed according to Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) documents. All strains were processed in validated broth microdilution panels manufactured by TREK Diagnostics (Cleveland, OH). Mueller-Hinton broth adjusted to contain physiological levels of calcium (50 mg/L) was used when testing daptomycin. Daptomycin susceptible breakpoint approved by US-FDA and CLSI were applied. The following quality control organisms were concurrently tested: *Enterococcus faecalis* ATCC 29212, *S. aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619.

RESULTS

- Daptomycin was very active against Gram-positive organisms causing infections in patients with malignancies.
- Daptomycin MIC distributions of isolates from patients with cancer were very similar to those from control patients with bloodstream infections (non-cancer) collected in the same institution and the same period of time (**Table 1**).

Table 1. Daptomycin MIC distributions among bacterial isolates from patients with cancer in comparison to non-cancer patients[a].

	No. of isolates (cumulative % inhibited) at daptomycin MIC of:						
Organism (no. tested)	≤0.12	0.25	0.5	1	2	4	8
S. aureus							
Cancer (573)	35 (6.1)	392 (74.5)	142 (99.3)	4 (100.0)	-	-	-
Non-cancer[a] (6,018)	238 (4.0)	4,122 (72.4)	1,616 (99.3)	40 (>99.9)	1 (100.0)	-	-
Enterococci							
Cancer (444)	4 (0.9)	18 (5.0)	122 (32.4)	149 (66.0)	110 (90.8)	40 (99.8)	1 (100.0)
Non-cancer[a] (2,429)	20 (0.8)	118 (5.7)	825 (39.6)	916 (77.4)	415 (94.4)	131 (99.8)	4 (100.0)
CoNS							
Cancer (254)	23 (9.1)	162 (65.0)	83 (97.6)	5 (99.6)	1 (100.0)	-	-
Non-cancer[a] (1,281)	114 (8.9)	663 (60.7)	447 (95.6)	54 (99.8)	3 (100.0)	-	-
β-haemolytic streptococci							
Cancer (59)	43 (72.9)	16 (100.0)	0 (100.0)	0 (100.0)	-	-	-
Non-cancer[a] (764)	548 (71.7)	744 (97.4)	20 (100.0)	0 (100.0)	-	-	-
Viridans group streptococci							
Cancer (44)	9 (20.5)	16 (56.8)	15 (90.9)	3 (97.7)	1 (100.0)	-	-
Non-cancer[a] (192)	59 (30.7)	56 (59.9)	58 (90.1)	19 (100.0)	-	-	-

Shaded values are those at the susceptible breakpoint concentratio

a. Bacterial isolates from patients with bloodstream infections hospitalized in the same institutions at the same time period as the cancer patients.

RESULTS

- Daptomycin (MIC_{90}, 0.5 µg/ml), linezolid (MIC_{90}, 2 µg/ml) and vancomycin (MIC_{90}, 1 µg/ml) were active against 100.0% of *S. aureus* strains from cancer patients and >99.9% of the control group strains (**Table 2**). Oxacillin resistance rates were high in both groups (45.0-47.7%; **Table 2**).
- Antimicrobial susceptibility rates of *S. aureus* strains isolated from cancer patients were very similar to those isolated from control patients (**Table 2**).
- Daptomycin and linezolid, both with a MIC_{90} of 2 µg/ml and >99.9% susceptibility, were the most active compounds tested against *Enterococcus* spp. (**Table 2**). Resistance rates to vancomycin (38.7 vs. 21.2%), ampicillin (52.1 vs. 28.0%), and levofloxacin (82.9 vs. 52.4%) were higher among enterococcal isolates from patients having cancer when compared to those from the control group (**Table 2**).
- Resistance to levofloxacin was generally higher among organisms from patients with cancer compared to the control group, except for *S. aureus* where levofloxacin susceptibility rates
- Higher resistance rates among *Enterococcus* spp. (ampicillin, levofloxacin and vancomycin), CoNS (levofloxacin and trimethoprim) and viridans group streptococci (erythromycin and levofloxacin) from cancer patients may reflect previous use of antimicrobial prophylaxis and/or extended hospital stay of these patients.

Table 2. Antimicrobial activity of daptomycin and selected comparator agents tested against bacterial strains isolated from cancer patients in comparison to those from a cancer-free control group.[a]

	Cancer		Non-cancer[a]	
Organism/antimicrobial agent (no. tested)	MIC_{90}	% susceptible	MIC_{90}	% susceptible
S. aureus		(573)		(6,018)
Daptomycin	0.5	100.0	0.5	>99.9[b]
Oxacillin	>2	55.0	>2	52.3
Clindamycin	>8	70.5	>8	67.8
Levofloxacin	>4	56.0	>4	54.7
Trimethoprim/sulfamethoxazole	≤0.5	97.4	≤0.5	97.1
Linezolid	2	100.0	2	99.9
Vancomycin	1	100.0	1	>99.9[c]
Enterococcus spp.		(444)		(2,429)
Daptomycin	2	99.8	2	99.8
Ampicillin	>16	47.9	>16	72.0
Levofloxacin	>4	27.1	>4	47.6
Gentamicin (HL)	>1000	70.8	>1000	70.1
Streptomycin (HL)	>2000	56.1	>2000	65.7
Linezolid	2	99.5	2	99.4
Vancomycin	>16	61.3	>16	78.8
CoNS		(254)		(1,281)
Daptomycin	0.5	99.6[d]	0.5	99.8
Oxacillin	>2	12.2	>2	16.6
Clindamycin	>8	58.7	>8	54.6
Levofloxacin	>4	30.3	>4	40.9
Trimethoprim/sulfamethoxazole	>2	48.8	>2	62.5
Linezolid	1	99.6[e]	1	99.6
Vancomycin	2	100.0	2	100.0
β-haemolytic streptococci		(59)		(764)
Daptomycin	0.25	100.0	0.25	100.0
Penicillin	0.06	100.0	0.06	100.0
Ceftriaxone	≤0.25	100.0	≤0.25	100.0
Erythromycin	>2	72.9	>2	76.3
Clindamycin	≤0.25	94.9	0.25	90.0
Levofloxacin	1	96.6	1	97.1
Linezolid	1	100.0	1	100.0
Vancomycin	0.5	100.0	0.5	100.0
Viridans group streptococci		(44)		(192)
Daptomycin	0.5	97.7[d]	0.5	100.0
Penicillin	2	75.0	1	82.3
Ceftriaxone	1	93.2	0.5	96.4
Erythromycin	>2	36.4	>2	52.1
Clindamycin	>2	86.4	≤0.25	92.2
Levofloxacin	>4	79.5	1	95.8
Linezolid	1	100.0	1	100.0
Vancomycin	0.5	100.0	1	100.0

a. Bacterial isolates from patients with bloodstream infections hospitalized in the same institutions at the same time period as the cancer patients.
b. Two isolates with daptomycin MIC at 2 µg/ml.
c. Two isolates with vancomycin MIC at 4 µg/ml.
d. One isolate with daptomycin MIC at 2 µg/ml.
e. One isolate with linezolid MIC at 8 µg/ml.

CONCLUSIONS

- Daptomycin was active against 99.8% of Gram-positive strains collected from cancer patients in USA hospitals, but vancomycin was only active against 80.2% of strains and showed limited activity against *Enterococcus* spp. (61% susceptible).
- Daptomycin has appropriate spectrum and potency to be used for empirical coverage of Gram-positive infections in patients with cancer in the USA hospitals, in contrast to other agents (vancomycin, ampicillin, fluoroquinolones) that exhibited greater resistance rates among these at-risk patients.

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