ANTIMICROBIAL ACTIVITY AND SPECTRUM OF DAPTOMYCIN AND COMPARATOR AGENTS TESTED AGAINST GRAM-POSITIVE ORGANISMS COLLECTED FROM PATIENTS WITH CANCER

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ABSTRACT

PURPOSE: To evaluate the antimicrobial susceptibility patterns of Gram-positive organisms causing infections in cancer patients hospitalized in USA and European medical centers. We also evaluated the bactericidal activity of daptomycin, vancomycin and linezolid against methicillin-resistant *S. aureus* (MRSA).

METHODS: 3,590 Gram-positive isolates were collected (one per patient) from infections in cancer patients at 63 medical centers (33 in the USA and 30 in Europe [13 countries]) in 2002-2006. Strains were susceptibility tested by the reference broth microdilution method with appropriate broth Ca^{++} content (50 mg/L) for testing daptomycin. Susceptibility patterns of strains from patients with cancer were compared to those from bloodstream infections (BSI) of non-cancer patients collected in the same hospitals and time period (20,784 strains). The bactericidal activity of daptomycin, vancomycin and linezolid was evaluated in a subset of 72 MRSA from cancer and non-cancer patients. The lowest concentration of antimicrobial agent that killed ≥99.9% of the initial inoculum was defined as the minimum bactericidal concentration (MBC).

RESULTS: *S. aureus* (37.2%) ranked first among Gram-positive pathogens isolated from cancer patients, followed by coagulase-negative staphylococci (CoNS; 26.4%) and enterococci (25.7%). Enterococci were more commonly isolated in the USA (32.2%) compared to Europe (21.7%). Daptomycin was very active against all pathogens (99.9% susceptible) from cancer patients. MRSA rate was 34.0% and daptomycin was 2- to 4-fold more potent than vancomycin against *S. aureus*. Minimum inhibitory concentration $(MIC)_{50}$ (µg/ml), MIC_{90} (µg/ml) and %susceptible were 0.25 / 0.5 / 100.0% for daptomycin and 1 / 1 / 100.0% for vancomycin when tested against *S. aureus* and 1 / 2 / 99.8% for daptomycin and 2 / >16 / 74.9% for vancomycin against enterococci. Vancomycin-resistant enterococci (VRE) rates were 38.1% in the USA and 11.5% in Europe. The highest daptomycin MBC value was only 2 µg/ml (one strain) and 98.6% of results were at the MIC or two-fold greater. In *S. aureus*, 15.3% were tolerant to vancomycin (MBC/MIC at ≥16).

CONCLUSIONS: Daptomycin was active against 99.9% of Gram-positive strains collected from patients with cancer in USA and European hospitals. Vancomycin was only active against 87.7% of USA and 97.2% of European strains, and showed limited activity against enterococci, especially in the USA (61.7% susceptible). These in vitro results indicate that daptomycin has the appropriate spectrum and potency for Gram-positive isolates from cancer patients.

INTRODUCTION

Historically, Gram-negative bacilli originating from the gastrointestinal tract were the prominent cause of bloodstream infections in neutropenic patients. However, since the introduction of extended-spectrum ß-lactams, a continuous decrease in the frequency of Gram-negative bacilli and an increase in Gram-positive cocci has been observed. Gram-positive cocci now represent the majority of organisms recovered from bloodstream infections in cancer patients hospitalized in United States (USA) hospitals. Some of these organisms, such as viridians group streptococci and *Staphylococcus aureus*, may cause fulminant infections resulting in serious complications or death if not treated promptly. Furthermore, *Enterococcus* spp., particularly vancomycin-resistant enterococci (VRE), have emerged recently as an important cause of infection in this patient population.

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. This compound was approved by the USA Food and Drug Administration (USA-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 USA-FDA for treatment of *S. aureus* bacteremia and right-sided endocarditis at a higher 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 Daptomycin Surveillance Program, a total of 3,590 Gram-positive organisms were collected from infections in cancer patients at 63 medical centers (33 in the USA and 30 in Europe) 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 (20,784 strains).

Susceptibility testing: The strains were tested for susceptibility to daptomycin and numerous comparator agents by reference broth microdilution methods performed according to Clinical and Laboratory Standards Institute (CLSI, formerly the 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 USA-FDA and CLSI (M100-S18) were applied. The following quality control organisms were concurrently tested: *Enterococcus faecalis* ATCC 29212, *S. aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619.

Bactericidal activity: The bactericidal activity of daptomycin, vancomycin and linezolid was evaluated in a subset of 72 methicillin-resistant *S. aureus* (MRSA) from cancer and non-cancer patients. Minimum bactericidal concentrations (MBC) experiments were performed by plating the broth onto appropriate growth media from the microdilution tray well (100 µl) and those from at least five $\log_2$ dilutions at and above the MIC for each organism. Quantitative colony counts were also performed on the starting inoculum. The lowest concentration of antimicrobial agent that killed ≥99.9% of the initial inoculum was defined as the MBC.

RESULTS

- *S. aureus* (37.2%) ranked first among Gram-positive pathogens isolated from cancer patients, followed by coagulase-negative staphylococci (CoNS; 26.4%) and enterococci (25.7%). Furthermore, enterococci were more commonly isolated in the USA (32.2%) compared to Europe (21.7%).
- Daptomycin was very active against Gram-positive organisms causing infections in patients with malignancies (99.9% susceptible) and daptomycin MIC distributions of isolates from cancer patients were very similar to those from control patients with BSI (non-cancer) collected in the same institution and the same period of time (Table 1).
- 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).
- Daptomycin was highly bactericidal and two- to four-fold more potent than vancomycin against *S. aureus*. The highest daptomycin MBC value was only 2 µg/ml (1 strain) and 98.6% of results were at the MIC or only two-fold greater. In contrast 15.3% of *S. aureus* were tolerant (MBC/MIC at ≥16) to vancomycin and all strains exhibit high linezolid MBC values (Table 3).

RESULTS

- Antimicrobial susceptibility rates of *S. aureus* strains isolated from cancer patients were very similar to those isolated from control patients (Table 2). Oxacillin resistance rates were 34.0% among isolates from cancer patients and 39.8% among isolates from non-cancer patients (Table 2).
- Daptomycin and linezolid, both with a MIC_{90} of 2 µg/ml and 99.8% susceptibility, were the most active compounds tested against *Enterococcus* spp. Resistance rates to vancomycin (25.5 vs. 14.7%, respectively), ampicillin (49.2 vs. 27.0%), and levofloxacin (64.8 vs. 49.7%) were higher among enterococcal isolates from patients having cancer when compared to those from the control group (Table 2).
- Vancomycin-resistant enterococci (VRE) rates were significantly higher in the USA (38.1%) compared to Europe (11.5%; data not shown).
- Susceptibility to levofloxacin was generally lower among organisms from cancer patients compared to the control group, except for *S. aureus* where levofloxacin susceptibility rates were slightly higher among isolates from cancer patients (64.9%) compared to the control group (60.7%; Table 2).
- Higher resistance rates among *Enterococcus* spp. (ampicillin, levofloxacin and vancomycin), CoNS (levofloxacin and trimethoprim) and viridans group streptococci (erythromycin and levofloxacin) isolated from cancer patients may reflect previous use of antimicrobial prophylaxis and/or extended hospital exposures of these patients.

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 (µg/ml) of:						
Organism (no. tested)	≤0.12	0.25	0.5	1	2	4	8
S. aureus							
Cancer (1,335)	72 (5.4)	939 (75.7)	316 (99.4)	8 (100.0)	-	-	-
Non-cancer[a] (10,362)	426 (4.1)	7,226 (69.7)	2,630 (99.2)	77 (>99.9)	3 (100.0)	-	-
CoNS							
Cancer (946)	53 (8.1)	516 (62.7)	341 (98.7)	10 (99.8)	2 (100.0)	-	-
Non-cancer[a] (3,630)	313 (8.6)	1,900 (61.0)	1,275 (96.1)	136 (99.8)	5 (>99.9)	1 (100.0)	-
Enterococci							
Cancer (923)	10 (1.1)	34 (4.8)	257 (32.6)	295 (64.6)	239 (90.5)	86 (99.8)	2 (100.0)
Non-cancer[a] (4,000)	35 (0.9)	185 (5.5)	1,351 (39.3)	1,502 (76.8)	676 (93.7)	246 (99.9)	5 (100.0)
Viridans group streptococci							
Cancer (157)	38 (24.2)	47 (54.1)	58 (91.1)	13 (99.4)	1 (100.0)	-	-
Non-cancer[a] (586)	197 (33.6)	176 (63.7)	166 (92.0)	44 (99.5)	3 (100.0)	-	-
ß-haemolytic streptococci							
Cancer (131)	96 (73.3)	33 (98.5)	2 (100.0)	0 (100.0)	-	-	-
Non-cancer[a] (1,290)	974 (75.5)	286 (97.4)	30 (100.0)	0 (100.0)	-	-	-

a. Bacterial isolates from patients with BSI hospitalized in the same institutions at the same time period as the cancer patients.
b. Underlined values are those at the susceptible breakpoint concentration.

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]

Organism/antimicrobial agent (no. tested)	Cancer MIC_{90} (µg/ml)	Cancer % susceptible	Non-cancer[a] MIC_{90} (µg/ml)	Non-cancer[a] % susceptible
S. aureus	(1,335)		(10,362)	
Daptomycin	0.5	100.0	0.5	>99.9
Linezolid	2	100.0	2	>99.9
Vancomycin	1	100.0	1	>99.9
Oxacillin	>2	66.0	>2	60.2
Clindamycin	>8	80.1	>8	73.5
Levofloxacin	>4	64.9	>4	60.7
Trimethoprim/sulfamethoxazole	≤0.5	97.5	≤0.5	97.4
CoNS	(946)		(3,360)	
Daptomycin	0.5	99.8	0.5	99.8
Linezolid	1	100.0	1	99.8
Vancomycin	2	100.0	2	100.0
Oxacillin	>2	13.5	>2	22.7
Clindamycin	>8	65.1	>8	63.6
Levofloxacin	>4	30.9	>4	42.9
Trimethoprim/sulfamethoxazole	>2	44.6	>2	62.0
Enterococcus spp.	(923)		(4,000)	
Daptomycin	2	99.8	2	99.9
Linezolid	2	99.8	2	99.6
Vancomycin	>16	74.5	>16	85.3
Ampicillin	>16	50.8	>16	73.0
Levofloxacin	>4	35.2	>4	50.3
Gentamicin (HL)[b]	>1000	66.3	>1000	69.0
Viridans group streptococci	(131)		(586)	
Daptomycin	0.5	99.4[c]	0.5	99.5[c]
Linezolid	1	100.0	1	100.0
Vancomycin	0.5	100.0	1	100.0
Penicillin	2	68.8	1	77.1
Ceftriaxone	1	90.4	0.5	97.6
Erythromycin	>2	43.9	>2	61.9
Clindamycin	2	85.4	≤0.25	90.3
Levofloxacin	2	93.6	1	97.6
ß-haemolytic streptococci	(157)		(1,290)	
Daptomycin	0.25	100.0	0.25	100.0
Linezolid	1	100.0	1	100.0
Vancomycin	0.5	100.0	0.5	100.0
Penicillin	0.06	100.0	0.06	100.0
Ceftriaxone	≤0.25	100.0	≤0.25	100.0
Erythromycin	>2	74.8	>2	79.3
Clindamycin	≤0.25	90.1	≤0.25	91.2
Levofloxacin	1	97.7	1	99.1

a. Bacterial isolates from patients with bloodstream infections hospitalized in the same institutions at the same time period as the cancer patients.
b. High level (>500 µg/ml) resistance.
c. Percentage inhibited at ≤1 µg/ml. No daptomycin breakpoints have been established for viridans group streptococci.

Table 3. Distribution of isolates according to MBC/MIC ratios for daptomycin, vancomycin and linezolid among 72 selected MRSA strains.

MBC/MIC ratio	No. of isolates (%): Daptomycin		Vancomycin		Linezolid	
1	55	(76.4)	30	(41.7)	-	
2	16	(22.2)	15	(20.8)	-	
4	1	(1.4)	8	(11.1)	-	
8	-		8	(11.1)	1	(1.4)
≥16[a]	-		11	(15.3)	71	(98.6)

a. MBC/MIC ≥16 and MBC ≥16 µg/ml; tolerance.

CONCLUSIONS

- Daptomycin was active against 99.9% of Gram-positive strains collected from cancer patients in USA and European hospitals, while vancomycin was active against 93.5% of strains and showed a more limited activity against *Enterococcus* spp. (74.5% susceptible).
- Daptomycin has the appropriate spectrum and potency to be used for empirical coverage of Gram-positive infections in patients with cancer in USA and European hospitals, in contrast to other agents (vancomycin, ampicillin, fluoroquinolones) that exhibited greater resistance rates among these at-risk population of patients.

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