C2-290

Potency and Susceptibility for Six Gram-Positive Antimicrobials Tested Against Prevalent Gram-Positive Bacteria Isolated in the Chemotherapy Alliance for Neutropenics and Control of Emerging Resistance (CANCER) Program

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ICAAC 2002

AMENDED ABSTRACT

Background: The CANCER Program was founded in 2001 to monitor resistance (R) in antimicrobial and antifungal therapies used for oncology patients.

Methods: More than half of 1,992 isolates from bloodstream, respiratory, urinary and cutaneous infections submitted by 32 oncology centers in North America (NA) were Gram-positives (GP). Several potent GP-focused antimicrobials were tested including an investigational fluoroquinolone.

Results: *S. aureus* (SA; n=361, 18.1%), Coagulase-negative staphylococci (CoNS;282, 14.1%), *Enterococcus* spp. (ESP;197, 9.9%), viridans group streptococci (VGS;n=70, 3.5%), and *S. pneumoniae* (SPN; n=52, 2.6%) were the top 5 GP pathogens during the initial year. Linezolid (LZD) showed no R among the GP pathogens. With the exception of ESP, vancomycin (VAN) and quinupristin/dalfopristin (Q/D) had complete susceptibility (S) rates. The novel desfluoroquinolone, garenoxicin (GXN) compared exceptionally to gatifloxacin (GATI) with S rates of 81 – 90% versus 71%, respectively. VAN (MIC_{90}, 1 µg/ml), LZD (2), Q/D (0.5), and teicoplanin (TEI; 1) provided high, near complete S rates (99.7 – 100%) against SA. Versus CoNS (% S, MIC_{90} in µg/ml), LZD (100%, 1), VAN (99.6%, 2), Q/D (98.9%, 0.5), and TEI (94.3%, 8) were most active. Only LZD (99.5% S, 2 µg/ml) provided satisfactory coverage (no R) against the ESP. Each cited agent demonstrated 100% S against VGS and SPN, with the exception of GATI (80% S against VGS). The overall rank order of spectrum was: LZD (100%) > TEI (97) > VAN (96) > GXN (90 at ≤ 4) > Q/D (88) > GXN (81 at ≤ 2) > GATI (78).

Conclusions: VAN continues to provide acceptable S rates (95.6%) against common GP isolates obtained from the CANCER Program patients. Additionally, LZD provides excellent activity (0% R) including ESP strains exhibiting R to glycopeptides. Based on the initial year of results, GATI and GXN provide superior Gram-positive coverage as compared to older agents of their class.

INTRODUCTION

During the last two decades a significant change has occurred in the prevalence of bacterial organisms in oncology patients with neutropenia. The spectrum has changed from one previously dominated by Gram-negative pathogens to one where Gram-positive pathogens dominate.

Current reports describing reduced morbidity and mortality in febrile patients with neutropenia, focus attention on the introduction of many broad-spectrum antibacterial, antifungal, and antiviral agents. Though these agents have favorably influenced the epidemiology of infections within this high-risk patient group, diligence is still required to minimize the development of resistance.

The concerns for penicillin-resistant streptococci, vancomycin-resistant enterococci and methicillin-resistant staphylococci are still present, and have been supplemented by the emergence of newer and novel resistance mechanisms such as: extended-spectrum ß-lactamases (ESBL), macrolide-lincosamide-streptogramin B (MLSB) resistance, glycopeptide-resistant staphylococci, efflux pump mechanisms, and metallo ß-lactamases.

The CANCER Surveillance Program is a three-year program intended to monitor broad-spectrum antimicrobial agents in haematology-oncology centers from diverse geographic regions in North America. The following report represents the experience with six Gram-positive active antimicrobials tested against bacteria during the benchmark year of this innovative longitudinal surveillance program.

MATERIALS AND METHODS

Thirty-two oncology centers, hospitals and clinics in North America submitted 2,042 isolates (1,992 bacterial and 50 yeast isolates) to a central monitoring laboratory (JMI Laboratories, North Liberty, IA) for testing. More than half of 1,992 isolates from bloodstream, skin and soft tissue, respiratory tract, and urinary tract were Gram-positives. Confirmation of organism identification was performed using Vitek® Automated Microbial Identification System (bioMerieux, Hazelwood, MO) or other standardized methods, as necessary.

All strains were tested and interpreted at the monitoring laboratory using reference broth microdilution methods as described by the National Committee for Clinical Laboratory Standards (NCCLS). MIC values were determined using validated, dry-form panels inoculated with the appropriate broth suspension of organisms delivered by automated inoculators (TREK Diagnostics, Westlake, OH). Organisms were suspended in cation-adjusted Mueller Hinton broth (MHB) or MHB enriched with 5% lysed horse blood for *Streptococcus* spp. or Haemophilus Test Medium (HTM) for *Haemophilus* spp. testing. The final concentration of inoculum present in each well of the microdilution tray was equivalent to ca. 5 X 10^5 CFU/ml.

RESULTS

- Gram-positive pathogens represented more than 50% of all bacterial isolates obtained during the initial year of the program. Rank order for the top 5 Gram-positive pathogens was: *S. aureus* (18.1%) > CoNS (14.1%) > *Enterococcus* spp (9.9%) > viridans group streptococci (VgS; 3.5%) > *S. pneumoniae* (2.6%) (Table 1).

Table 1. Frequency of occurrence of Gram-positive bacterial pathogens from medical centers participating in the 2001 CANCER Program (Species with ≥ 1.0% prevalence).

Rank	Organism	No. of occurrences (%)
1	*Staphylococcus aureus*	361/(18.1)
3	Coagulase-negative staphylococci[a]	282/(14.1)
4	*Enterococcus* spp.[b]	197/(9.9)
7	Other streptococci[c]	111/(5.6)
10	*S. pneumoniae*	52/(2.6)
14	*Corynebacterium* spp.[d]	20 (1.1)

a. Includes *S. auricularis* (three strains), *S. capitis* (three strains), *S. epidermidis* (55 strains), *S. haemolyticus* (six strains), *S. hominis* (four strains), *S. lugdunensis* (one strain), *S. warneri* (one strain), and coagulase-negative staphylococci (not speciated; 209 strains).
b. Includes *E. casseliflavus* (one strain), *E. faecalis* (109 strains), *E. faecium* (68 strains), *E. gallinarium* (two strains), and enterococci (not speciated; 17 strains).
c. Includes ß-haemolytic streptococci (41 strains) and viridans group streptococci (70 strains).
d. Includes *C. jeikeium* (seven strains); *C. xerosis* (one strain), diptheroides (four strains), and *Corynebacterium* spp. (not speciated; eight strains)

- Linezolid provided excellent potency against the most prevalent Gram-positive isolates and demonstrated susceptibilities of 99.5 and 100.0% with no resistant strains (Table 2).
- Vancomycin and quinupristin/dalfopristin paralleled linezolid activity against most Gram-positive isolates and demonstrated susceptibilities ranging from 98.9 to 100% with no resistant isolates amongst *S. aureus*, CoNS, VgS, and *S. pneumoniae* (Table 2).
- The prevalence of vancomycin-resistant enterococci (VRE) was 21.3%, and the number of *Enterococcus* spp. exhibiting resistance to quinupristin/dalfopristin approached 60% (Table 2). The Van A resistance pattern was present in more than 90% (38 isolates) of the VRE (Table 2).
- The incidence of *S. aureus* resistant to oxacillin or methicillin during the first year of the CANCER Program was 29.4% (data not shown).
- Garenoxicin, the novel desfluoroquinolone, at a recommended breakpoint of ≤ 4 µg/ml, provided superior activity versus gatifloxacin and other fluoroquinolones (data not shown) for the top 5 Gram-positive pathogens; while providing comparable or higher susceptibilities at a breakpoint of ≤ 2 µg/ml (Table 2).

Table 2. Activities and spectrum for activity of six potent antimicrobial agents tested against the five most prevalent causes of Gram-positive infections in the CANCER Program.

	Cummulative % inhibited at MIC (µg/ml)										MIC (µg/ml)		% by category:[a]	
Organism (no. tested)	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	50%	90%	Susceptible	Resistant
S. aureus (361)														
Garenoxacin	65.1	68.1	68.4	68.4	70.9	80.1	90.3	96.4[b]	-[c]	-	≤0.03	2	96.4[d]	-
Gatifloxacin	11.1	50.4	66.8	68.4	68.4	69.0	76.7	86.7	-	-	0.06	>4	76.7	13.3
Linezolid	-	0.0	0.0	0.3	0.6	13.9	97.5	100.0	100.0	-	2	2	100.0	0.0
Quinupristin/dalfopristin	-	0.0	3.3	61.2	95.6	99.7	100.0	100.0	100.0	-	0.25	0.5	99.7	0.0
Teicoplanin	-	-	0.6	6.9	60.7	97.0	98.9	100.0	100.0	100.0	0.5	1	100.0	0.0
Vancomycin	-	-	0.0	0.6	9.1	95.8	99.7	100.0	100.0	100.0	1	1	100.0	0.0
Coagulase-negative staphylococci (282)														
Garenoxacin	22.7	28.0	29.4	29.4	36.9	53.9	76.2	87.9	-	-	1	>4	87.9[d]	-
Gatifloxacin	4	12.1	27.7	29.4	29.8	38.3	78.4	86.2	-	-	2	>4	78.4[b]	13.8
Linezolid	-	0.0	0.4	0.4	13.8	91.1	100.0	100.0	100.0	-	1	1	100.0	0.0
Quinupristin/dalfopristin	-	1.1	40.4	85.1	95.0	98.9	100.0	100.0	100.0	-	0.25	0.5	98.9	0.0
Teicoplanin	-	-	0.0	10.3	19.1	36.5	59.9	80.9	94.3	98.9	2	8	94.3	1.1
Vancomycin	-	-	0.0	0.4	4.6	39.0	98.9	99.6	100.0	100.0	2	2	99.6	0.0
Enterococcus (197)														
Garenoxacin	0.0	0.5	11.2	33.7	38.8	40.3	58.2	74.5	-	-	2	>4	74.5[d]	-
Gatifloxacin	0.0	0.0	1	12.2	34.7	38.3	40.3	43.4	-	-	>4	>4	40.3	56.6
Linezolid	-	0.5	0.0	0.0	2	38.1	99.5	100.0	100.0	-	2	2	99.5	0.0
Quinupristin/dalfopristin	-	0.0	0.0	1.5	20.3	35.5	40.6	53.3	91.9	-	4	8	35.5	59.4
Teicoplanin	-	-	0.0	68.5	79.7	80.2	80.2	80.2	81.2	84.8	0.25	>16	81.2	15.2
Vancomycin	-	-	0.5	0.5	5.1	57.9	76.1	78.7	78.7	78.7	1	>16	78.7	21.3
viridans group streptococci (70)														
Garenoxacin	15.7	61.4	81.4	82.9	92.9	95.7	100.0	100.0	-	-	0.06	0.5	100.0[d]	-
Gatifloxacin	0.0	1.4	10.0	50.0	75.7	80.0	82.9	95.7	-	-	0.25	4	80.0	17.1
Linezolid	-	0.0	0.0	1.4	20.0	92.9	100.0	100.0	100.0	-	1	1	100.0	0.0
Quinupristin/dalfopristin	-	0.0	4.3	15.7	100.0	100.0	100.0	100.0	100.0	-	0.5	1	100.0	0.0
Teicoplanin	-	-	0.0	98.6	98.6	100.0	100.0	100.0	100.0	100.0	≤0.12	≤0.12	-	-
Vancomycin	-	-	0.5	5.7	91.4	100.0	100.0	100.0	100.0	100.0	0.5	0.5	100.0	0.0
S. pneumoniae (52)														
Garenoxacin	38.5	92.3	100.0	100.0	100.0	100.0	100.0	100.0	-	-	0.06	0.06	100.0[d]	-
Gatifloxacin	0.0	0.0	13.5	86.5	98.1	100.0	100.0	100.0	-	-	0.25	0.5	100.0	0.0
Linezolid	-	0.0	0.0	0.0	26.9	88.5	100.0	100.0	100.0	-	1	2	100.0	0.0
Quinupristin/dalfopristin	-	0.0	0.0	32.7	98.1	100.0	100.0	100.0	100.0	-	0.5	0.5	100.0	0.0
Teicoplanin	-	-	0.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	≤0.12	≤0.12	-	-
Vancomycin	-	-	0.0	65.4	100.0	100.0	100.0	100.0	100.0	100.0	0.25	0.5	100.0	0.0

a. Susceptibility criteria of the NCCLS [2002].
b. Underlined value indicates that proportion of strains susceptible at the breakpoint concentration.
c. - = indicates untested MIC or that no interpretive criteria are published by the NCCLS.
d. Susceptibility for garenoxacin was that recommended by the manufacturer [Fung-Tomc et al., 2000].

CONCLUSIONS

- During the initial year of the CANCER Program, the prevalence of Gram-positive pathogens was slightly lower than those reported previously by other investigators. However, the rank order of occurrence of specific Gram-positive organisms parallels those reported by other investigators and from chemotherapy guidelines.
- Linezolid demonstrated a wide spectrum against the top Gram-positive pathogens, and the overall rank order for susceptibilities was: Linezolid (100%) > vancomycin (96%) > teicoplanin (94%) > garenoxicin (90% at ≤ 4µg/ml) > quinupristin/dalfopristin (86%) > garenoxicin (81% at ≤ 2 µg/ml) > gatifloxacin (71%).
- Continued evaluation for antimicrobial resistance as well as changes in the prevalence of Gram-positive pathogens (or their occurrence versus Gram-negative bacilli) requires the use of longitudinal surveillance programs such as the CANCER Program. Such initiatives allow the development of therapeutic strategies for coping with changes in resistance and pathogen prevalence in this dynamic at-risk patient environment.

ACKNOWLEDGEMENTS

The CANCER Program has been funded by the Wyeth-Ayerst Pharmaceutical Company. Members of The CANCER Study Group include: T Fritsche, (University of Washington, Seattle, WA), P Iwen, (Nebraska Medical Center, Omaha, NE), J Jorgensen, (University of Texas Health Science Center, San Antonio, TX), A Keating, (Princess Margaret Hospital Ontario Cancer Institute, Toronto, Ontario), K Ralston (MD Anderson Cancer Center, Houston, TX), M Saubolle, (Good Samaritan Medical Center, Phoenix, AZ)

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