NOTES

Antibacterial Activities of Antineoplastic Agents

C. ADRIEN BODET III,1,2 JAMES H. JORGENSEN,3,4 AND DAVID J. DRUTZ1,2

Departments of Medicine1 and Pathology,3 Division of Infectious Diseases, The University of Texas Health Science Center, and Division of Infectious Disease, Audie L. Murphy Veterans Administration Hospital,2 San Antonio, Texas 78284

Received 18 March 1985/Accepted 4 June 1985

Fourteen antineoplastic agents were examined for in vitro antibacterial activity against 101 aerobic and anaerobic bacterial isolates representing indigenous human microflora and selected opportunistic pathogens. Only 5-fluorouracil, mitomycin, and etoposide demonstrated inhibitory effects at achievable plasma concentrations, while the remaining drugs lacked appreciable antibacterial activities.

Altered host response by immunosuppression and interruptions in mucocutaneous barriers due to tumors, drug toxicity, and foreign bodies (catheters) are undoubtedly responsible for the increased susceptibility of cancer patients to infection. In addition to these predisposing factors, possible antibacterial activity of antitumor drugs has been suggested as a potential for influencing patterns of infection. Selective suppression of normal bacterial flora by antitumor drugs, thus altering colonization resistance (12), has been proposed as an explanation for Clostridium difficile-associated colitis in cancer patients (2, 3). Selective resistance of pathogens such as Pseudomonas aeruginosa to antineoplastic agents has been cited as an explanation for the prevalence of infection caused by this species in leukemic patients (4). Similar resistance of certain normal human microflora, such as Staphylococcus epidermidis and coryneform bacteria, could help to explain their occurrence as opportunistic pathogens in compromised hosts (13–15). To investigate the potential for alteration of normal bacterial ecology by antineoplastic agents, we determined the MICs of 14 antineoplastic drugs against a diverse group of 101 fresh clinical isolates or stock cultures of clinical origin representing both usual flora and selected bacterial pathogens.

Stock solutions of intravenous formulations of 5-fluorouracil (5-FU), mitomycin, etoposide (VP-16), bleomycin, carbustine, cisplatin, cyclophosphamide, cytosine arabinoside, dacarbazine, doxorubicin, methotrexate, thiopheta, vinblastine, and vincristine were prepared in sterile, preservative-free distilled water. The diluent used for the VP-16 parenteral formulation was prepared as described by Nissen et al. (11) and was tested to verify that it did not contribute any antibacterial activity. Agar dilution susceptibility tests were performed with the antineoplastic drugs by the methods of the National Committee for Clinical Laboratory Standards for aerobic (10) and anaerobic (9) bacteria. Sheep blood (5%) was added to Mueller-Hinton agar for testing fastidious aerobic species. Anaerobic bacteria were tested by using Wilkins-Chalgren agar without the addition of blood.

The antimicrobial susceptibility results with the antitumor drugs are summarized in Table 1. To assess the relevance of these results, the MIC obtained for each antineoplastic agent was compared with the peak plasma concentration expected after its intravenous administration (1). Only 3 of the 12 agents showed activity against 50% or more of the bacterial strains tested, i.e., 5-FU, mitomycin, and VP-16. The most active of the agents, 5-FU, inhibited >80% of the bacterial isolates tested at or below achievable plasma levels. Of 23 isolates of gram-negative aerobes, 17 were inhibited by concentrations less than 1/10 of the expected peak plasma concentration of 5-FU. Whereas all gram-positive anaerobic isolates were inhibited by 5-FU, the gram-negative anaerobes exhibited minimal susceptibility. Mitomycin, the second most active agent examined, inhibited most gram-positive aerobes and all anaerobic bacteria at expected peak plasma concentrations. The podophyllotoxin VP-16 inhibited only gram-positive bacteria at achievable blood levels of the drug. Gram-negative aerobes and anaerobes, as well as Streptococcus faecium, were markedly resistant to VP-16. No antibacterial activity was noted when the VP-16 diluent was tested separately.

Bleomycin, carmustine, cisplatin, cyclophosphamide, cytosine arabinoside, dacarbazine, doxorubicin, methotrexate, thiopheta, vinblastine, and vincristine demonstrated little or no activity at achievable plasma concentrations.

Based on the in vitro data presented here and the recent report of Hamilton-Miller (5), the direct influence of antineoplastic drugs on human microflora appears to be minimal. Few of the drugs showed appreciable antibacterial activities at achievable plasma levels, and there was no consistent pattern of inhibition of either usual flora or opportunistic pathogens. The possibility remains that antitumor drugs possess synergistic antimicrobial activity in combination with each other or with antibacterial therapeutic agents (7, 8). Greater antibacterial effect due to regional concentration of drugs, such as in the gastrointestinal tract, also cannot be excluded by our data. Unfortunately, little is known about gastrointestinal concentrations of these drugs after intravenous administration.

The suggestion that the presence of antitumor agents in blood samples for culturing may delay detection of bactere-
Aerobes

Corynebacterium spp. (2) 1-50 0.1-0.5 5-50 50->100 0.5-5 1
Corynebacterium sp. JK (1) 100 0.5 5 0.5 50 5
Lactobacillus sp. (1) 1-100 5 0.1 0.5 50 1
Escherichia coli (3) 1-5 5-50 0.5->50 2.5-5 10
Enterobacter aerogenes (3) 1-50 5-10 >100 >100 5 10
Enterobacter cloacae (3) 5-50 5-10 >100 >100 5 10
Klebsiella pneumoniae (3) 5-50 5 >100 >100 5 10
Salmonella enteritidis (2) 5 5 >100 >100 5 10
Serratia marcescens (3) 0.5-5 1-5 >100 >100 5 10
Shigella sp. (2) 5-50 5 >100 >100 5 10
Pseudomonas aeruginosa (4) 0.5-1 0.5 0.1-0.5 50-100 5-10 0.5
Branhamella catarrhalis (2) 1-50 0.5 5-50 >100 >100 5
Micrococcus sp. (2) 0.5-1 5-10 >100 >100 5 10
Staphylococcus aureus (4) 0.5-5 0.5 16-32 >100 5-50 10-50
Staphylococcus lugdunensis (methicillin resistant, conglutine negative) (2) 0.5-5 0.5 16-32 >100 5-50 10-50

Anaerobes

Peptococcus asaccharolyticus (2) 5-10 0.1 5-10 >100 >100 10-50
Peptostreptococcus anaerobius (2) 50 0.1 5-30-100 >100 5 30-100
Peptostreptococcus intermedius (1) 10 0.1 32 32 5 10
Clostridium butyricum (1) 10 0.1 5-30 32 5 10
Clostridium cadaveris (2) 1-100 0.1 32 32 5 10
Clostridium difficile (4) 10-50 0.5 5 5 10
Clostridium perfringens (2) 10-50 0.1-0.5 10-100 100-100 10-100
Actinomyces naeslundii (1) 5 0.05 5 5 0.05
Eubacterium limosum (1) 1-100 0.1 5-100 100 5 100
Bifidobacterium sp. (1) 100 0.1 5-100 100 5 100
Propionibacterium acnes (1) 100 0.1 5-100 100 5 100
Bacueroides bivius (1) 50 0.1 50 50 5 50
Bacueroides distasonis (1) 50 0.1 50 50 5 50
Bacueroides fragilis (2) 1-100 0.5 50-100 100 100 100
Bacueroides ovatus (2) 10-100 0.5 50-100 100 100 100
Bacueroides thetaiotaomicron (2) 1,000 0.1-0.5 50-1,000 100 100 100
Bacueroides vulgatus (1) 500 0.5 50-100 100 100 100
Pseudobacterium morgani (1) 1,000 1.0 500 100 100 100
Capnocytophaga sp. (2) 500-1,000 0.05 500 100 100 100

*Achievable plasma concentrations (micrograms per milliliter) are shown within parentheses.

LITERATURE CITED
dilution procedure for antimicrobial susceptibility testing of anaerobic bacteria. National Committee for Clinical Laboratory Standards, Villanova, Pa.