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Bactericidal activity of ceftaroline, vancomycin and daptomycin against methicillin-resistant *Staphylococcus aureus* isolates from cancer patients

Sir,

Bacterial infections are common in patients with cancer, especially among those with neutropenia. Staphylococci, including coagulase-negative staphylococci (CoNS) and *Staphylococcus aureus*, are frequent pathogens in this setting. At many cancer centres, including ours, ca. 50% of *S. aureus* isolates are resistant to methicillin. For several decades, vancomycin has been the preferred agent for the treatment of methicillin-resistant *S. aureus* (MRSA) infections. However, many recent studies have documented suboptimal responses and even overt treatment failures associated with vancomycin therapy. Ceftaroline fosamil, the prodrug of ceftaroline, is a novel oxyimino-cephalosporin with potent activity against many Gram-positive organisms, including MRSA [1]. We recently evaluated the in vitro activity of ceftaroline against clinical isolates recovered from cancer patients and confirmed the activity of ceftaroline against staphylococci [2]. Notably, it had potent activity against MRSA isolates with vancomycin minimum inhibitory concentrations (MICs) of ≥1.0 μg/mL. There is some evidence that bactericidal agents might be more effective than bacteriostatic agents in cancer patients with neutropenia [3]. Comparison of minimum bactericidal concentration (MBC) to MIC ratios is one way to evaluate the bactericidal activity of antimicrobial agents. Narrower ratios (≤1:4) are generally associated with better bactericidal activity than wider ratios (≥1:8). Time–kill studies are also used to determine bactericidal activity and can detect both the degree of killing and the rate or rapidity of killing. Consequently, we compared the bactericidal activity of ceftaroline with that of vancomycin and daptomycin against four randomly selected clinical MRSA isolates from cancer patients using both methods.

The MRSA isolates were recovered from blood culture samples of cancer patients treated at our institution during the years 2014 and 2015. Standard ceftaroline powder for in vitro testing was provided by Forest Laboratories, Inc. (New York, NY). Vancomycin and daptomycin were obtained commercially. MICs and MBCs for all three agents were determined using standardised broth microdilution testing as recommended by the Clinical and Laboratory Standards (CLSI). Time–kill studies were performed once on the four MRSA isolates using CLSI-approved broth microdilution techniques at concentrations of each agent that were equivalent to 1×, 4× and 8× the respective MICs [4].

Using MBC:MIC ratios, all three agents exhibited reliable bactericidal activity against the four MRSA isolates. The range of MBC:MIC ratios was 1:1 to 4:1 for ceftaroline, 1:1 to 2:1 for vancomycin and 1:1 to 4:1 for daptomycin. None of the four isolates was tolerant (MBC ≥32× the MIC) to any of the three test agents (data not shown).

Time–kill data for the four MRSA isolates are presented in Fig. 1. All three agents demonstrated excellent killing at 8× the respective MICs within 24 h. Killing of ≥99.4% was demonstrated at 4 × MIC for all agents. Defined bactericidal activity (99.9% killing) was achieved at 8 × MIC for each agent, except for 99.8% killing of isolate #2 by ceftaroline. Daptomycin demonstrated the most rapid rate of killing for each isolate.

Ceftaroline is a broad-spectrum cephalosporin with in vitro activity against various Gram-positive pathogens, including community- and healthcare-associated MRSA, methicillin-resistant CoNS and various streptococcal species (β-haemolytic streptococci, viridans group streptococci and *Streptococcus pneumoniae*). All of these organisms are common pathogens in cancer patients. MRSA, which now accounts for >50% of *S. aureus* isolates at many cancer centres, is of particular concern. A recent study from our institution, a National Cancer Institute-designated Comprehensive Cancer Center, demonstrated a high failure rate associated with vancomycin therapy for MRSA infections [5]. An independent risk factor for infection-related mortality was a vancomycin MIC of ≥2 μg/mL. Alternative agents, including linezolid, daptomycin and telavancin, are each associated with significant drawbacks such as declining susceptibility/emerging resistance (linezolid, daptomycin), lack of or unpredictable bactericidal activity (linezolid, telavancin), lack of efficacy in patients with pneumonia (daptomycin) and potential toxicity (myelotoxicity for linezolid; nephrotoxicity for telavancin). Whilst most extended-spectrum cephalosporins are active against methicillin-susceptible *S. aureus*, they are inactive against MRSA. With the development of ceftaroline, this gap in the coverage provided by cephalosporins has been closed. Ceftaroline has been approved by the US Food and Drug Administration (FDA) for the treatment of acute bacterial skin and skin-structure infections and for community-acquired bacterial pneumonia in adults and paediatric patients aged ≥2 months. Like other potential alternatives to vancomycin, ceftaroline has not formally been evaluated in neutropenic cancer patients. In a previous study, we documented the activity of ceftaroline against a wide spectrum of Gram-positive pathogens, including MRSA, isolated from cancer patients [2]. The current study demonstrates that ceftaroline has effective bactericidal activity against MRSA isolates from cancer patients using two different methods to determine bactericidal activity (i.e. MBC:MIC ratio and time–kill experiments). Based on these data, we believe that ceftaroline has a potential role in the treatment of

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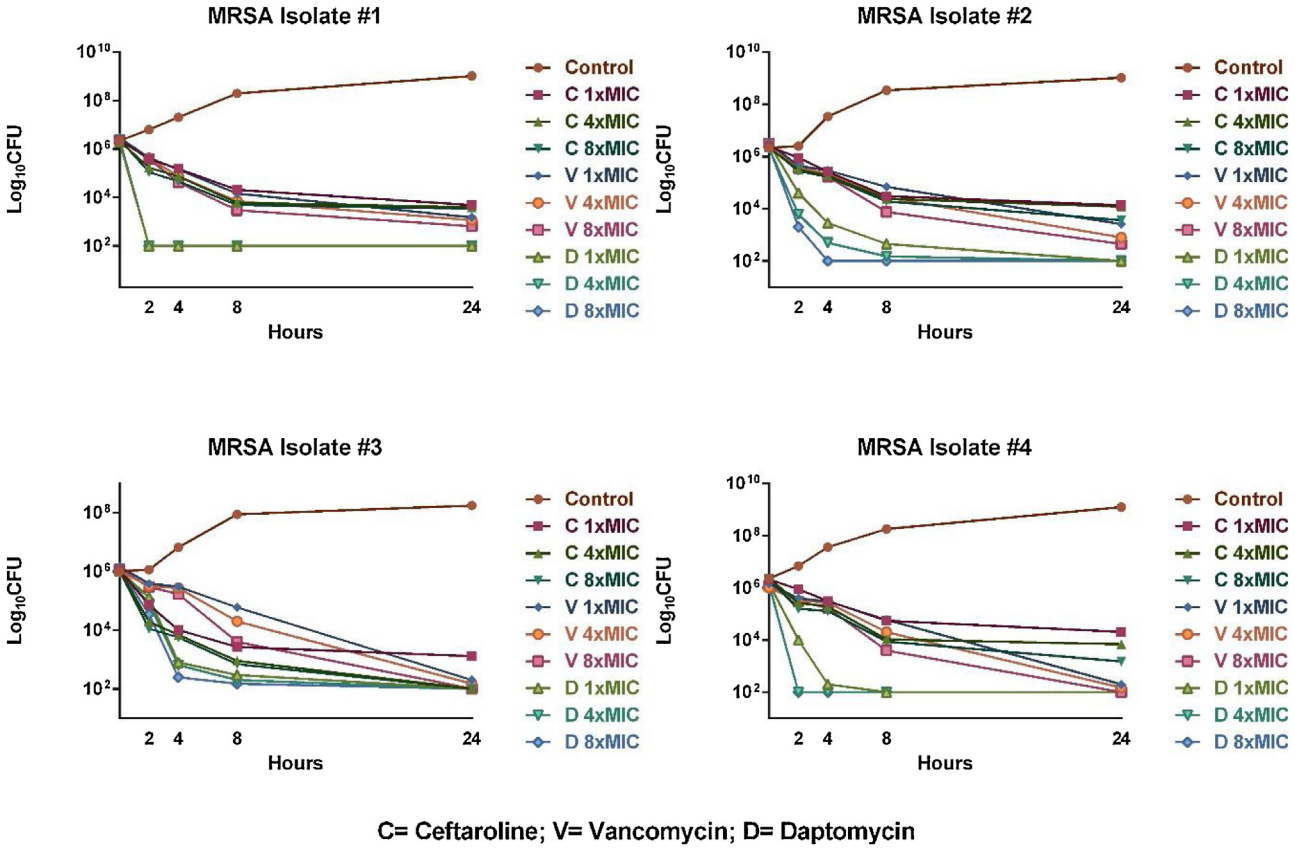

Fig. 1. Bactericidal activity of ceftaroline, vancomycin and daptomycin against four randomly selected methicillin-resistant *Staphylococcus aureus* (MRSA) isolates from cancer patients based on time–kill experiments.

staphylococcal infections, including those caused by MRSA, in cancer patients with or without neutropenia.

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Competing interests

None declared.

Ethical approval

Approval for this study was obtained from the Institutional Review Board of MD Anderson Cancer Center (Houston, TX) [MDACC protocol # PA-13-0970].

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