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Short communication

Efficacy and safety of daptomycin in the treatment of Gram-positive catheter-related bloodstream infections in cancer patients

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ABSTRACT

Excessive vancomycin usage has contributed to the emergence of vancomycin-resistant enterococci, and a high vancomycin minimal inhibitory concentration (MIC) >1.0 μg/mL has been associated with poor outcome in patients with meticillin-resistant *Staphylococcus aureus* (MRSA) infection. In view of these limitations, there is a need for an alternative agent. We evaluated the clinical efficacy and safety of daptomycin given as an alternative agent in the treatment of Gram-positive catheter-related bloodstream infections (CRBSIs) in cancer patients. Between June 2006 and March 2008, 40 patients with probable or definite CRBSI caused by Gram-positive organisms were prospectively enrolled to receive daptomycin intravenous 6 mg/kg/day for up to 4 weeks. In addition, 40 historical matched control patients treated with vancomycin were retrospectively identified. The control group was matched based on underlying disease, organism and neutropenic status. The daptomycin group was comparable with the vancomycin group in terms of neutropenia rate, complications, adverse events, length of hospital stay and death. However, more patients in the daptomycin group achieved symptom resolution at 48 h compared with the vancomycin group (76% vs. 53%; $P = 0.04$). Similarly, more patients in the daptomycin group achieved microbiological eradication at 48 h compared with the vancomycin group (78% vs. 34%; $P < 0.001$). Although not significant, nephrotoxicity was almost three-fold lower in the daptomycin group. The overall response was significantly better for daptomycin compared with vancomycin (68% vs. 32%; $P = 0.003$). In conclusion, compared with vancomycin, daptomycin treatment of Gram-positive CRBSI in cancer patients was significantly associated with earlier clinical and microbiological response as well as improved overall response.

1. Introduction

Gram-positive bacteria represent a leading cause of catheter-related bloodstream infection (CRBSI) in cancer patients [1].

Vancomycin is considered the agent of choice for the treatment of resistant Gram-positive cocci, including meticillin-resistant *Staphylococcus aureus* (MRSA) infections [2]. However, its excessive use has contributed to the emergence of vancomycin-resistant enterococci (VRE), vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA) [3]. In addition, vancomycin minimal inhibitory concentrations (MICs) >1.0 μg/mL have been associated with poor outcome in patients with MRSA infection [4]. Furthermore, because vancomycin has been shown to be ineffective in eradicating Gram-positive organisms embedded in the biofilm of infected central venous catheters (CVCs) in vitro, concerns have been raised as to whether vancomycin is the appropriate antibiotic for the treatment of CRBSIs [5].

Considering these limitations, there is a need for alternative agents. Daptomycin is a semisynthetic lipopeptide antibiotic that is active against various Gram-positive bacteria. Data from our laboratory showed that daptomycin is significantly more effective than vancomycin in eradicating MRSA embedded in the biofilm layer on catheter surfaces [5]. Furthermore, unlike vancomycin, daptomycin does not predispose to the emergence of VRE colonisation or infection and may be associated with a better safety profile, in particular lower nephrotoxicity [6,7].

In this study, we evaluated daptomycin as an alternative agent for the treatment of Gram-positive CRBSI.

2. Materials and methods

2.1. Study patients

Between June 2006 and March 2008, 40 patients with probable or definite CRBSI with Gram-positive organisms were prospectively

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enrolled to receive daptomycin intravenous (i.v.) 6 mg/kg/day for up to 4 weeks. These patients were compared with 40 historical matched control patients with CRBSI who were treated with vancomycin. The control group was matched by underlying disease, type of organism and neutropenic status.

Eligible patients were aged ≥18 years, with Gram-positive CRBSI, without a source for the bacteraemia other than the CVC, and at least two signs of sepsis within 48 h prior to daptomycin therapy.

Patients were ineligible if they had any one of the following: received therapy with an antibiotic such as vancomycin, linezolid, tigecycline or daptomycin for ≥48 h within 72 h of study medication initiation; pneumonia or possible complicated CRBSI (such as osteomyelitis, endocarditis or septic thrombosis); creatine phosphokinase exceeding five times the upper limit of normal; an estimated serum creatinine clearance of <30 mL/min (according to the Cockcroft–Gault formula); a bilirubin exceeding four times the upper limit of normal; or a history of hypersensitivity to lipopeptides.

Patients were not enrolled if they had pneumonia. If a patient developed pneumonia after study entry, linezolid or vancomycin was used as clinically indicated but not in combination with daptomycin. Daptomycin was then discontinued but the patient was still followed per protocol activities. These patients were excluded from efficacy evaluation.

The decision whether to remove or exchange the CVC within 96 h of the onset of bacteraemia was left to the discretion of the primary physician and the patient. In neutropenic patients where pneumonia could not be definitely excluded or in patients who developed pulmonary infection after study entry, a broad-spectrum β-lactam with good penetration into the lungs could be added.

Polymicrobial bacteraemia with Gram-negative organisms was treated with other antimicrobial agents.

2.2. Follow-up and outcome

All patients in the daptomycin arm were evaluated during treatment, at the end of treatment and post-treatment at 32 ± 7 days after the last dose of study drug.

The primary endpoints were clinical and microbiological response. Secondary endpoints, including late complication, infection-related death and relapse within 3 months following the initial bacteraemia were also studied.

2.3. Definitions

CRBSI was classified according to the current Infectious Diseases Society of America (IDSA) criteria guidelines [2].

Clinical response was defined as resolution of clinical signs and symptoms within 48 h of initiating appropriate study antibiotic therapy.

Microbiological resolution was defined as eradication of the microorganism from the bloodstream within 48 h of initiating appropriate study antibiotic therapy. Patients who did not have a repeat blood culture within the first 2 weeks of initiating appropriate study antibiotic therapy were excluded from the analysis.

Persistence was defined as continued isolation of the Gram-positive organism from the blood 72 h after initiation of appropriate antibiotic therapy.

Relapse was defined as the recurrence of bacteraemia within the first 3 months.

An infection-related complication was defined as the development of deep-seated infection that was not present or suspected at the onset of bacteraemia but was subsequently diagnosed after 1 week from initiation of study antibiotic therapy.

Overall response was defined as clinical and microbiological resolution within 72 h of initiation of appropriate (study drug) antibiotic therapy, without evidence of relapse, infection-related complications or infection-related mortality.

Nephrotoxicity was defined as an increase of 0.5 mg/dL or ≥50% from baseline serum creatinine level at any time during therapy.

2.4. Statistical analysis

χ^2 test or Fisher's exact test were used to compare categorical variables, as appropriate. Continuous variables were compared by Wilcoxon rank sum test owing to deviation of the data from a normal distribution. All tests were two-sided and statistical significance was set at $P \leq 0.05$. Statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC).

3. Results

During the study period, 575 patients with probable or definite Gram-positive CRBSI were screened. In total, 40 patients were prospectively enrolled in the daptomycin arm. In this cancer setting, most of the ineligible patients had received therapy with an antibiotic such as vancomycin for more than 48 h within 72 h of study medication initiation. The analysis included 38 patients who received daptomycin: 2 patients were excluded from analysis because they were diagnosed with pneumonia at study entry and received concomitantly daptomycin, vancomycin and linezolid. One patient was also diagnosed with thrombophlebitis prior to study entry.

The organisms included *S. aureus* (MRSA and meticillin-sensitive *S. aureus*), coagulase-negative staphylococci, α-haemolytic streptococci, *Enterococcus*, *Corynebacterium* and *Bacillus* spp.

Daptomycin was comparable with vancomycin in terms of neutropenia rate, duration of antibiotic treatment and catheter management, complications, length of hospital stay and infection-related death (Tables 1 and 2). At baseline, all organisms in the vancomycin group and most of the organisms in the daptomycin group were susceptible to vancomycin, with a MIC ≤2 μg/mL. The majority of causative organisms had a MIC between 1 μg/mL and 2 μg/mL (Table 1). In the daptomycin group, isolates were available for 22 patients and all were susceptible to daptomycin.

The two groups were also comparable in terms of clinical and microbiological response after 1 week from initiation of daptomycin and vancomycin. However, after 48 h of initiating the study drug, significantly more patients in the daptomycin arm achieved symptom resolution (76% vs. 53%; $P = 0.04$) (Table 2; Fig. 1) and microbiological eradication (78% vs. 34%; $P < 0.001$) (Table 2) compared with the vancomycin arm.

Similarly, overall response to daptomycin as defined above was significantly greater than that for vancomycin (68% vs. 32%; $P = 0.003$).

The two groups were comparable in terms of overall safety and relapse. Nineteen patients developed 45 adverse events; 3 of the adverse events were drug-related, 2 were mild in severity and 1 was moderate. Only one patient in the daptomycin group had a significant increase in serum creatinine kinase that necessitated discontinuation of daptomycin. This patient expired secondary to a massive gastrointestinal bleed that was related to his relapsed acute myelogenous leukaemia but not to the daptomycin.

The two groups had similar creatinine levels at baseline and at the end of therapy (Table 1).

Although the rate of nephrotoxicity was not significantly different for the two groups, it was almost three-fold lower in the daptomycin group versus the vancomycin group (8% vs. 23%; $P = 0.12$) (Table 1).