SUPPLEMENTARY MATERIAL

MATERIAL AND METHODS

Definitions

The Multinational Association for Supportive Care in Cancer (MASCC) score was calculated as described elsewhere. Neutropenia was defined as an absolute neutrophil count <500/mm^3. The presence of comorbidities was described as the presence of at least one of the following conditions: i) diabetes mellitus, ii) chronic pulmonary obstructive disease, iii) chronic miocardiopathy, iv) chronic liver disease, and v) chronic renal disease. Shock was defined as a systolic pressure <90 mmHg that was unresponsive to fluid treatment or required vasoactive drug therapy. Low-risk bloodstream infection (BSI) was considered when the infection originated in the urinary tract, or was secondary to catheter infection or to gut translocation (endogenous source). Episodes of BSI originating in any other source were considered complex BSI.

Treatment with a β-lactam/β-lactamase inhibitor (BLBLI) or a carbapenem was considered as monotherapy if no other drug with activity against Gram-negatives was coadministered, irrespective of isolate susceptibility

Case-fatality rates were defined as death by any cause within 7, 14 and 30 days of the BSI episode. Persistent BSI was defined as positive blood cultures beyond the first 48 hours of adequate antibiotic therapy. Relapse of BSI was defined as positive blood cultures for the same microorganism occurring within 7 days of treatment discontinuation.

Statistical analysis

The variables included in the propensity score analysis of the empirical therapy cohort (ETC) were age, sex, acute leukemia, hematopoyetic stem cell transplant, comorbidities, previous corticosteroids, previous antibiotics, previous hospitalization, profound neutropenia (<100/mm^3), days of previous neutropenia, MASCC score <21, previous episode of BSI, complex BSI, coinfection, septic shock at presentation, and empirical combination therapy. The variables inlcuded in the propensity score analysis of the definitive therapy cohort (DTC) were age, sex, comorbidities, acute leukemia, hematopoyetic stem cell transplant, previous episode of BSI, previous corticosteroids, profound neutropenia (<100/mm^3), days of previous neutropenia, MASCC score <21, complex BSI, coinfection, septic shock at presentation, source control, adequate empirical combination therapy, active targeted combinaton therapy and empirical monotherapy with an aminoglycoside.

RESULTS

Microbiological studies

The MIC for BLBLIs was not available for six isolates from six patients who received these regimens; these isolates were considered either susceptible or resistant on the basis of local laboratory reports.

In the ETC, the MICs provided for patients who received PTZ were as follows: ≤ 16 mg/L (11 isolates), ≤ 8 mg/L (16 isolates), ≤ 4 mg/L (10 isolates), 2 mg/L (two isolates), and < 1 mg/L (one isolate). In the same cohort, the two available MICs for cefoperazone-sulbactam (C-S) were 16 mg/L, and the only available MIC for amoxicillin-clavulanate (AMC) was 8 mg/L. In the DTC, the MICs provided for patients

who received PTZ were as follows: ≤ 16 mg/L (one isolate), ≤ 8 mg/L (six isolates), ≤ 4 mg/L (two isolates), and 2 mg/L (two isolates). The available MICs for AMC were 8 mg/L (four isolates) and ≤ 16 mg/L (one isolate).

Antibiotic data

Empirical therapy cohort

Dosage regimens were available for 123 patients receiving carbapenems and for 44 patients treated with BLBLIs. Among them, >80% of patients received the following doses (adjusted in cases of renal failure): meropenem 1 g/8 h; imipenem 500 mg/6 h; ertapenem 1 gr/24 h. Two patients received meropenem in prolonged-infusion (2 g/8 h and 1 g/6 h each, the latter combined with colistin). For PTZ, the great majority of patients received 4 g/8 h (44.1%), followed by 4.5 g/6 h (23.2%), 4 g/6 h (16.2%), and 4.5 g/8 h (16.2%). The two patients treated with C-S received 2 g/12 h and the remaining two received 1 g/8 h of AMC.

Fifty-four patients received a second active antibiotic in combination with the administered β-lactam for ≤ 48 hours: carbapanem + aminoglycoside (26 patients), carbapenem + colistin (14 patients), PTZ + aminoglycoside (12 patients), carbapenem + ciprofloxacin (one patient) and carbapenem + colistin + aminoglycoside (one patient).

For patients who received empirical therapy with BLBLI, 30-day case-fatality rate was 26.4% (9/34) for those whose regimen was changed to a carbapenem. No deaths were recorded in the 12 patients continuing to receive a BLBLI or in the only patient who received ciprofloxacin. The remaining patient treated empirically with PTZ died within 48 hours of BSI. In patients empirically treated with carbapenems who continued with carbapenem, mortality was 15.5% (19/122 patients). One of the two

patients whose therapy was changed to tigecyclin died, whereas neither of the patients whose therapy was changed to BLBLI died.

Definitive therapy cohort

The dosage regimens were similar to those specified for the ETC. Two patients received meropenem in prolonged-infusion (1 g/6 h one patient, and 2 g/6 h one patient, combined with tigecyclin and aminoglycoside). An active combination therapy with the β-lactam was administered in 24 patients: carbapenem + aminoglycoside (19 patients), carbapenem + colistin (three patients), PTZ + aminoglycoside (one patient), and carbapenem + tigecyclin + aminoglycoside (one patient).

Sixty-one patients in this cohort had received inadequate initial empirical antibiotic therapy: PTZ (n=32), cefepime (n=17), ceftazidime (n= 4), aztreonam (n=2), ceftriaxone (n=1), AMC (n=1), levofloxacin (n=1), C-S (n=1), ticarcillin-clavulanate (n=1), and no empirical therapy (n=1). Twenty-five patients had received monotherapy with an aminoglycoside. Among them, of the 23 patients whose therapy was changed to carbapenems, five died (21.7%). The two remaining patients were switched to ciprofloxacin and PTZ, and neither died.