Gram-negative bacterial infections are still among the most important causes of mortality during neutropenia in patients with hematological malignancies (19, 20), especially when related to Pseudomonas aeruginosa (3).

Due to its anti-Pseudomonas activity, ceftazidime represents one of the antibiotic of choice for the empirical treatment of bacterial infections in high-risk febrile neutropenic patients (10). According to its time-dependent antibacterial activity, the time that free drug concentrations remain above the MIC (10). According to its time-dependent antibacterial activity, the time that free drug concentrations remain above the MIC (t > MIC) is the main determinant for efficacy. Although a t > MIC of >50% of the dosing interval may suffice in immunocompetent patients (5), in immunocompromised ones concentrations four to five times the MIC may be needed for maximal bactericidal efficacy with ceftazidime (13). Accordingly, it may be speculated that during empirical treatment with ceftazidime maximized pharmacodynamic exposure against susceptible P. aeruginosa strains may be ensured when concentrations are four- to fivefold the sensitivity breakpoint (8 mg/liter) (13), namely, 32 to 40 mg/liter. Although these levels are difficult to obtain with intermittent administration, the application of continuous infusion may be beneficial, especially considering that in patients with acute leukemia several pathophysiological conditions may affect the pharmacokinetic behavior of hydrophilic antibiotics (15).

The pharmacokinetic-pharmacodynamic profile of continuous intravenous infusion of ceftazidime was assessed in 20 consecutive adult hematological patients (10 male, 10 female) with acute myeloid leukemia (AML) to determine whether a fixed 6-g daily dosage may ensure the maintenance of therapeutically relevant steady-state concentration in plasma (C_sst) in this subpopulation.

This study was approved by an internal review board, and informed consent was obtained from each patient. Patients were eligible for empirical monotherapy with ceftazidime if they had severe neutropenia (<100/μl; expected duration, >5 days) and a body temperature of >38.5°C on one occasion or >38°C on two occasions.

Exclusion criteria were an age of >75 years, an estimated creatinine clearance (CL_Cr) (4) of <50 ml/min, and the presence of effusions.

Fixed ceftazidime dosage (1-g intravenous [i.v.] loading dose plus a 5-g i.v. continuous infusion on day 1 and a 6-g/24 h i.v. continuous infusion on subsequent days) was administered for the first 72 h. Given the good stability of ceftazidime in solutions (18), 3 g ceftazidime dissolved in 250 ml saline was continuously infused every 12 h. Afterwards, if defervescence was documented and/or ceftazidime-susceptible bacteria were isolated from sterile sites, ceftazidime therapy went on. On the contrary, anti-gram-negative bacterial therapy was shifted to second line.

Blood samples to assess both ceftazidime C_sst (at 6 h and 24 h on day 1 and then every 24 h) and ceftazidime plasma decay over time (at 0, 0.5, 1, 2, 4, 6, 8, and 10 h after stopping therapy) were collected. To assess ceftazidime urinary concentrations, 24-h urine samples were collected at steady state. Plasma and urine samples were stored at −80°C until analysis.

Ceftazidime concentrations were analyzed by means of a high-performance liquid chromatography method based on that of Hanes et al. (9), with some modifications. Intra- and interassay coefficients of variation (CV) were <10%. The low limit of detection was 0.1 mg/liter.

Individual pharmacokinetic parameters were estimated by means of a two-compartment open model with first-order elimination (21) using WinNonlin (Pharsight Corporation, Mountain View, CA). Dose-related pharmacokinetic parameters (C_sst, area under the concentration-time curve during the 24-h
Dosing interval \( AUC_{0-24h} \) were normalized with respect to a 1-mg/kg daily ceftazidime dose. Urinary elimination of ceftazidime was estimated as follows: \( C_u/24h \) and \( V_u/24h \) (\( C_u/24h \) 24-h urinary concentration; \( V_u/24h \) 24-h urinary volume). According to normal or nonnormal distribution, the findings were expressed as the mean \( \pm \) standard deviation (SD) or the median and the range, respectively (8). Patients' characteristics are depicted in Table 1. The mean \( \pm \) SD plasma ceftazidime concentration-versus-time profile during continuous infusion is shown in Fig. 1. Although mean plasma ceftazidime concentrations were above 20 mg/liter at 6 h and the \( C_{ss} \) averaged around 40 mg/liter from day 2 on, significant variations over time in steady-state concentrations in plasma were observed, with which extent daily fluctuations in both intravenous fluid load (1.40 \( \pm \) 0.67 liters on day 1 versus 2.02 \( \pm \) 1.01 liters on day 8) and renal function (1.64 \( \pm \) 0.35 ml/min/kg on day 1 versus 2.11 \( \pm \) 0.47 ml/min/kg on day 5) might have concurred. Accordingly, large pharmacokinetic variability was documented (Table 1 and Fig. 2), with the CVs of pharmacokinetic parameters ranging between 28 and 41%. The linear relationship between ceftazidime clearance and the estimated CLCr was at the limit of significance (9). Ceftazidime's pharmacokinetic parameters are in agreement with other authors' findings showing that an enlarged volume of distribution and/or increased renal clearance may occur in patients with hematological malignancies (6, 14). Consistently, in order to maintain an appropriate \( \frac{t_{1/2}}{MIC} \) higher intermittent dosages were advocated (14).
Indeed, the application of a continuous infusion may be helpful in ensuring maximized pharmacodynamic exposure, often avoiding the need to increase the dosage. Additionally, in an in vitro pharmacodynamic model, ceftazidime at 6 g daily when administered as a continuous infusion was shown to ensure persistent bactericidal activity against resistant *P. aeruginosa* strains even at concentrations near the MIC (1). This means that in AML patients empirically treated with ceftazidime, the application of a continuous infusion might help to prevent therapeutic failure and resistance spreading also when borderline or intermediately sensitive pathogens are involved.

The large ceftazidime pharmacokinetic variability observed in this subpopulation might be partially attributed to the daily fluctuations in either the i.v. administered fluid load or high estimates of renal function. Accordingly, a higher initial loading dose of 2 g should be considered more appropriate with the
intent of rapidly achieving therapeutically relevant ceftazidime concentrations in AML patients.

Indeed, major changes in patients’ extracellular fluid content and glomerular filtration rate were shown to account for most of the pharmacokinetic variability of hydrophilic antibiotics, including ceftazidime, in critically ill patients (16). Consistently, altered pharmacokinetic behavior also of vancomycin (2, 7, 11), amikacin (17, 22), and teicoplanin (12, 15) was documented in hematological patients, and higher dosages were advocated for ensuring therapeutic concentrations.

In conclusion, after an initial loading dose, continuous infusion of 6 g daily may be helpful in maximizing pharmacodynamic exposure to ceftazidime in 72% of patients with AML and normal renal function. However, higher than currently suggested ceftazidime dosages may sometimes be necessary, and monitoring of concentrations in plasma may be useful in tailoring drug exposure.

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REFERENCES