Adequacy of high-dose cefepime regimen in febrile neutropenic patients with hematological malignancies

Fekade Bruck Sime, Michael S Roberts, Ing Soo Tiong, Julia H Gardner, Sheila Lehman, Sandra L Peake, Uwe Hahn, Morgyn S Warner, Jason A Roberts

School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, Australia; Therapeutics Research Centre, Basil Hetzel Institute for Translational Health Research, The Queen Elizabeth Hospital, Adelaide, Australia; Therapeutics Research Centre, School of Medicine, University of Queensland, Australia; Department of Haematology/Oncology, The Queen Elizabeth Hospital, Adelaide, Australia; SA Pathology and the University of Adelaide, Adelaide, Australia; Department of Intensive Care Medicine, The Queen Elizabeth Hospital, Adelaide, Australia; Royal Brisbane and Women’s Hospital, Herston, Brisbane, Queensland, Australia; Burns, Trauma, and Critical Care Research Centre, University of Queensland, Herston, Brisbane, Queensland, Australia; Institute of Translational Medicine, University of Liverpool, Liverpool, UK

Running title: Adequacy of cefepime dosing in febrile neutropenia

# Address correspondence to Fekade Bruck Sime, Fekade.Sime@mymail.unisa.edu.au
Abstract

Whilst guidelines recommend empiric cefepime therapy in febrile neutropenia, the mortality benefit of cefepime has been controversial. In light of this, recent reports on pharmacokinetic changes for several antibiotics in febrile neutropenia and the consequent sub-optimal exposure, call for a pharmacokinetic/pharmacodynamic evaluation of current dosing. This study aimed to assess pharmacokinetic/pharmacodynamic target attainment from a 2g intravenous (IV) eight-hourly cefepime regimen in febrile neutropenic patients with hematological malignancies.

Cefepime plasma concentrations were measured in the 3rd, 6th and 9th dosing interval at 60% of the interval and/or trough point. The selected pharmacokinetic/pharmacodynamic targets were proportion of the dosing interval (60% and 100%) for which free drug concentration remains above the minimum inhibitory concentration (MIC), $fT_{\text{MIC}}$. Target attainment was assessed in reference to the MIC of isolated organisms if available, or empiric breakpoints if not. %$fT_{\text{MIC}}$ was also estimated by log-linear regression analysis. All patients achieved > 60%$fT_{\text{MIC}}$ in the 3rd and 6th dosing intervals. 100%$fT_{\text{MIC}}$ was not attained in 6/12, 4/10 and 4/9 patients in the 3rd, 6th and 9th dose intervals respectively or in 14/31 (45%) of the dosing intervals investigated. On the other hand, 29/31 (94%) of trough concentration were at or above 4 mg/L. In conclusion, for patients with normal renal function, a high dose 2g IV eight hourly cefepime regimen appears to provide appropriate exposure if the MIC of the organism is $\leq$ 4 mg/L, but may fail to cover less susceptible organisms.

Key words: cefepime, pharmacokinetic, pharmacodynamic, febrile neutropenia, hematological malignancy
INTRODUCTION

The introduction of cefepime into clinical practice was widely accepted due to its broad spectrum activity. Cefepime is active against such organisms as *Acinetobacter baumannii, Pseudomonas aeruginosa* and Enterobacteriaceae with relatively low minimum inhibitory concentration (MIC) as compared to other broad-spectrum beta-lactam antibiotics (1, 2). Therefore, it is considered a good choice in the empiric management of febrile neutropenia, either as a monotherapy agent or as part of combination regimens (3, 4).

Whilst several comparative outcome trials suggest cefepime is clinically as effective as other beta-lactam antibiotics, meta-analyses (5, 6) of data from these trials report an increased risk of mortality associated with cefepime therapy, which was particularly high in febrile neutropenic patients (7). Conversely, a later meta-analysis by the United States’ Food and Drug Administration (FDA), which included several additional unpublished trials, concluded that there is no such association (8, 9). In addition, specific analysis of trials in febrile neutropenic patients did not show any statistically significant increase in mortality (9). The controversy continues as the methodological issues of the FDA’s and previous meta-analyses are challenged and debated (7, 10-12). However, there is little biological plausibility for the claimed risk of mortality, which was originally suggested to be related to unrecognised toxicity or poor *in vivo* antibiotic efficacy (6). Suboptimal antibiotic concentration and possible pharmacokinetic/pharmacodynamic (PK/PD) explanations were implicated.

PK/PD describes the relationship between the dose of antibiotics, the resulting concentrations achieved in biological fluids such as plasma or interstitial fluid, and the associated antibacterial activity. Characteristic relationships exist between plasma concentrations and antibacterial
activity. For beta-lactam antibiotics including cefepime, duration of the dosing interval for which the free drug concentration remains above the MIC ($f_{T>MIC}$), is the PK/PD index that guides dose selection and objectively measures dosing adequacy (13). For cefepime and other cephalosporins that exhibit the least post antibiotic effect among the beta-lactams, 60-70% $f_{T>MIC}$ is the conventional conservative PK/PD target (13) even though 100% $f_{T>MIC}$ may be required in immunocompromised hosts (14).

Any changes in the PK or PD properties of antibiotics demand adjustment of the dosing regimen to ensure attainment of the required PK/PD target (15). The PK of antibiotics is amenable to pathophysiological-driven alterations in some special patient populations with marked infections or inflammation, including those with neutropenic fever and malignancy. PK changes are observed as increases in the volume of distribution and/or clearance and subsequent low plasma and tissue concentrations. PD response may be affected due to changes in bacterial susceptibility. Such PK/PD changes in febrile neutropenic patients are documented for beta-lactam antibiotics, (16) although there is a dearth of information on cefepime. Navas et al. (17) have reported inadequate exposure from a traditional cefepime regimen (2g intravenous (IV) every 12 hours) in febrile neutropenic patients. However, a higher dosing regimen (2g IV every 8 hours) is now more commonly used in neutropenic patients with normal renal function. The objective of this work was, therefore, to assess PK/PD target attainment from an intermittent 2g IV eight-hourly cefepime dosing regimen in febrile neutropenic patients with hematological malignancies.
MATERIALS AND METHODS

Study setting, patients and drug administration. The study was conducted at The Queen Elizabeth Hospital (TQEH), Adelaide, South Australia. TQEH is an acute care teaching hospital providing emergency, inpatients (311 beds), outpatients and mental health services for over a quarter of a million population. Patients aged ≥ 18 years were pre-consented while receiving chemotherapy and/or stem cell transplant at the hematology unit of TQEH for the management of hematological malignancies. Thereafter, patients were enrolled when they developed febrile neutropenia which was defined as the presence of a single oral temperature of ≥ 38.3°C (101°F) or a temperature of ≥ 38.0°C (100.4°F) for >1 h, with a neutrophil count < 500 cells/mm³; or a count < 1,000 cells/ mm³, with a predicted decrease to < 500 cells/ mm³ (18). Additional inclusion criteria were prescription of cefepime for the management of febrile neutropenia and the presence of peripherally inserted central catheter (PICC) for blood sampling. Patients were excluded if they had known or suspected allergy to cefepime, did not have a PICC line, or if they were pregnant. The study was conducted in accordance with an Australian national statement on ethical conduct in human research as well as the declaration of Helsinki. Ethics approval was granted by the Human Research Ethics Committees of TQEH (HREC/13/TQEHLMH/301) and the University of South Australia (Application ID: 0000032581).

All patients received 2g cefepime administered every 8 hours via intermittent IV infusion over 30 minutes, followed by 15 minutes line flushing. In addition, all patients received gentamicin (7 mg/kg, once daily) for one to three days.

Data collection and blood sampling. Data describing patient characteristics were collected from electronic or paper-based medical records and included the following: demographic
characteristics, diagnosis of malignancies and infections, microbiological data, vital signs, and clinical hematological and chemistry data. Five blood samples were taken per patient over three days to monitor assumed steady-state cefepime concentrations. The first two samples were taken after the third dose; one at 60% of the dosing interval and the other as a trough 15 minutes before the next dose. The next two samples were taken similarly in the sixth dosing interval and finally, one trough sample was taken at the end of the ninth dosing interval.

**Drug assay.** A liquid chromatography tandem mass spectrometry method (LC-MSMS) previously validated for simultaneous analysis of beta-lactam antibiotics (19) was extended to include cefepime on an ultra performance liquid chromatography system (Shi-madzu Corp., Kyoto, Japan) connected to API3200 mass detector (AB Sciex Pte. Ltd). Sample preparation procedures and mobile phase systems were as formerly described. Chromatographic separation was achieved on a C18 column (ZORBAX Eclipse XDB-C18, 2.1 mm × 150 mm, 3.5 μm; Agilent Technologies Inc.) via gradient elution. Multiple reactions monitoring (MRM) was performed in a positive mode using electrospray ionization. The masses of precursor and product ions monitored for cefepime were 481.1 and 125.0 respectively. Piperacillin was used as internal standard with MRM charge-to-mass ratios (m/z) of 518.16/143.10. Quadratic regression with a weighting scheme of $1 / (x \cdot x)$ best described the data for calibration curves over the concentration range of 0.25 to 50 mg/L ($r^2 > 0.9$). The lower limit of quantification was 0.25 mg/L. The inter-day and intra-day mean accuracies of quality control samples (QCs) ranged from 99%-105% and 99%-110%, respectively. Intra-day and inter-day coefficient of variations were less than 15% at all QC concentrations. The mean recovery was 95%. Stability data over three freeze-thaw cycles, for four hours on the bench top as well as for twelve hours post-preparation were within the requirement of guidelines (20).
Pharmacokinetic analysis. First, considering log-linear PK (21), concentrations at time 0.75 h, 2 h, 4 h and 6 h were estimated based on the two concentrations measured in the third dosing interval. Then the resulting concentration-time profiles including the measured concentrations were used to perform non-compartmental PK analysis using an MS Excel add-in program, PK Solver (22). 0.5 h was entered for the (bolus) infusion time and the linear trapezoidal method was selected for calculation of area under the curve from 0 to infinity (AUC$_{0\text{--}inf}$).

Statistical Analysis. IBM® SPSS® Statistics version 19.0 (SPSS Inc., Chicago, IL) software was used to execute statistical analysis. Characteristics of study participants were summarised using descriptive statistics. As appropriate, the Mann–Whitney U test or Kruskal–Wallis test was used to compare observed concentrations among the dosing intervals. p-value less than 0.05 was considered as statistically significant.

Pharmacodynamic assessment. The blood sampling times were selected to enable assessment of the achievement of 60\% $f_{T>MIC}$ and 100\% $f_{T>MIC}$ without calculating the exact duration for which the free concentration remains above MIC. Free cefepime concentrations were calculated from total plasma concentration assays considering 19\% protein binding (23, 24). When culture tests were positive, specific MICs for the isolated organisms were used if available. When there were no organisms identified, the highest MIC of all susceptible organisms (8 mg/L) was used according to the Clinical Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC breakpoints (25, 26). Additionally, $f_{T>MIC}$ was estimated for the third and sixth dosing intervals by means of log-linear regression analysis based on the two concentrations measured in the terminal elimination phase.
RESULTS

Twelve patients with neutropenic fever and malignancy were enrolled in the study. Characteristics of these study participants are presented in Table 1. Most patients exhibited slight hypoalbuminemia and did not have renal dysfunction. Blood cultures tested positive for four patients. Two patients were obese, four patients were overweight and the rest had normal body weight.

Fifty-three plasma concentrations were analysed from the 12 patients in 31 assumed steady-state dosing intervals. For two patients, only two concentrations each were measured during the third dosing interval, and for one patient a concentration was not measured after the sixth dosing interval because cefepime was discontinued by clinicians treating the patient. PK parameter estimates for all patients are summarized in Table 2. Figure 1 depicts the distribution of free plasma cefepime concentrations measured at 60% of the dosing interval in the third and sixth dosing intervals. All concentrations were above the highest MIC of susceptible organisms (8 mg/L), and hence > 60% $f_{T>MIC}$ was attained in all patients. A comparison of unbound trough cefepime concentrations from all participants in the third, sixth and ninth dosing intervals is presented in Figure 2. No statistically significant difference in trough concentrations was noted among the three dosing intervals ($p=0.975$), although the median value was relatively higher in the sixth dosing interval. Nearly half of the unbound trough concentrations, 14/31 (45%), were below 8 mg/L (highest MIC). In contrast, 29/31 (94%) of trough concentration were at or above 4 mg/L. No trough concentration less than 2 mg/L was observed. The distribution of % $f_{T>MIC}$ estimates in the third and sixth dosing interval is depicted in Figure 3. Six of the twelve patients during the third interval, 4/10 patients during the sixth interval, and 4/9 patients in the ninth
interval did not achieve 100% $f_{T>MIC}$. However, $\% f_{T>MIC}$ was greater than 70% and 60% for all patients in the third and sixth dosing intervals respectively.

**DISCUSSION**

In the context of the growing evidence of altered antibiotic PK and subsequent underexposure in febrile neutropenia, a high dose cefepime regimen (2g IV 8-hourly) has not been widely subjected to PK/PD assessment. Further to this, a clear picture is lacking with regard to the underlying causes of the controversial claims of increased risk of mortality associated with cefepime therapy, except the thoughts of potential role of toxicity as well as underexposure from conventional dosing (6, 27). Although this study did not aim to describe cefepime toxicities, it evaluated PK/PD exposure from a 2g dose administered 8-hourly via intermittent IV infusion in febrile neutropenic patients with malignancies.

The median volume of distribution of cefepime estimated in this study is higher than that reported for healthy individuals from a Phase I study (34 L vs 18 L) (21). Similarly high mean/median volumes of distribution have been previously reported for critically ill patients (27) (= 29 L), burns patients (28) (= 26 L) and general ward patients with normal renal function (29) (= 32 L). The observed significant expansion in volume of distribution may be attributable to a combination of various factors including capillary fluid extravasation, high volume fluid therapy, and the markedly increased BMI/obesity observed in our cohort (Table 1) (16, 30, 31). On the other hand, previous estimates of total clearance and half-life in healthy volunteers (21) (8.4 L/h; 2.3 hrs) and critically ill burns patients (28) (= 9 L/h; 2.45 hrs) are comparable with this study (8.7 L/hr; 2.5 hrs). Given that cefepime is predominantly eliminated unchanged via glomerular filtration (21), the similarities with healthy individuals’ data are sensible as all patients in this
study exhibited normal renal function (Table 1). However, augmented renal clearance is not uncommon in febrile neutropenic patients with normal renal function; therefore, higher than usual clearance of cefepime is a possibility in such cases (32).

Considering the conservative PK/PD target of 60% fT>MIC, unbound cefepime concentrations were greater than the highest anticipated MIC of susceptible organisms (8 mg/L) for all patients in this study. The median free concentration at 60% of the dosing interval was 17 mg/L, a value greater than four-times the MIC of cefepime for the majority organisms, including many P. aeruginosa clinical isolates for which cefepime MIC values may be ≤ 4 mg/L (29). For beta-lactam antibiotics including cefepime, maximal bacterial killing is expected to occur at concentrations of about 4 to 5 times the MIC (33). However, a more pragmatic PK/PD target for beta-lactam antibiotics in immunocompromised neutropenic patients may be 100% fT>MIC, which was attained in 55% of the dosing intervals assessed in this study, when considering the empiric MIC breakpoint 8 mg/L. The median unbound trough cefepime concentrations were just below or above 8 mg/L for three consecutive days at steady state (Figure 2), and consistent with previous findings in critically ill patients (27).

Therefore, if considering PK/PD targets, a high dose cefepime regimen (2g IV 8-hourly) appears to be adequate for the majority of patients and organisms. This dose provided 100% fT>MIC coverage for 94% of the dosing intervals in this study for organisms with MIC breakpoints of ≤ 4 mg/L. The high dose regimen is also supported by previous studies with less frequent dosing schedules (2g IV 12-hourly) that have shown that trough concentrations can be low for the majority of febrile neutropenic patients (17). Similar findings in critically ill patients suggest that, such low dosing regimens are inadequate when considering empiric therapy against less
susceptible Gram negative organisms (27, 34). Median trough concentrations in this study were also marginally close to the 8 mg/L breakpoint (Figure 2), suggesting that de-escalation from the current high dose therapy may result in sub-optimal exposure in patients with normal renal function.

Since most organisms have a relatively low MIC breakpoint for cefepime (MIC ≤ 2), with the exception of few Gram negative isolates (e.g. *P. aeruginosa*) (25), the trough concentrations achieved in this study (Figure 2) will also meet a more aggressive PK/PD target of 100% $fT_{>4\times MIC}$ for most patients. 100% $fT_{>4\times MIC}$ has been recommended for cefepime in order to maximize microbiological success in treatment of Gram negative infections (33). However, this may require high trough concentrations for pseudomonal infections (> 32 mg/L), risking toxicity. Lamoth et al. (35) previously suggested that the threshold for cefepime-induced neurotoxicity, including those other than seizure, may be as low as 15 to 20 mg/L (total concentration); although convulsive seizures are more likely to occur at concentrations of about 70 mg/L or higher (36). Six out of thirty-one trough concentrations in this study (19%) fall within the 15 to 20 mg/L range, though no neurological toxicities were observed. Given high variability in concentrations (coefficient of variation of trough concentrations was about 50% in this study), the high dose therapy is likely to result in concentrations beyond these ‘low thresholds’ even in patients with normal renal function. Indeed there are some case reports of neurotoxicity in patients with normal renal function (37, 38). If the aforementioned thresholds can be validated in large trials, the range from empiric coverage to ‘toxicity’ (trough concentrations 8 to 20 mg/L) would amount to a narrow therapeutic index warranting regular therapeutic drug monitoring (TDM).
The high dose regimen (2g IV 8-hourly) was used in most of the published comparative clinical trials in adult febrile neutropenic patients (about 60%) included in the meta-analyses that initially suggested increased mortality with cefepime therapy; while low dose regimens (1-2 g twice daily) were used in the rest (5, 6). Whereas studies that monitored cefepime concentrations from the low dose regimens (17, 27, 34) suggest that underexposure is likely, measured concentrations from this and other studies (27) of the high dose therapy indicate that this may occur only if high MIC organism are involved. Given the sample size limitation of this study, more data from large trials may be necessary to exclusively rule out underexposure against usually susceptible organisms in the presence of variable and continually changing susceptibility to current antibiotics. Further to this, for some special population groups such as those with high creatinine clearance and obesity, concentrations are likely to be far below the empiric break points. The lowest unbound trough concentrations among our patients were observed for the participant with high creatinine clearance (2 mg/L for P12) and those with marked obesity (3 mg/L for P10 and 11) (Table 1, Figure 2). In such patients, extended infusion over half of the dosing interval may significantly improve the probability of target attainment without increasing the total dose administered, and thus minimising the apparent toxicity concerns (15, 39). Clinical studies have reported increased % fT>MIC with prolonged infusion, for cefepime (39, 40) and other beta-lactam antibiotics (15, 41). Current PK/PD understanding is that, improved exposure can potentially translate into improved clinical outcome. In support of this, a retrospective study by Bauer et al. (42) reported a mortality benefit from the use of extended infusion cefepime regimen. However, a recent systematic review, by Burgess et al. (43) suggests that, despite the accumulating evidence of improved PK/PD target attainment, the correlation of this with optimal
clinical outcome is yet to be demonstrated in a well designed randomised prospective study, given the methodological limitations of existing studies.

A similar limitation of this study is that, no outcome assessment was performed to describe if achievement of adequate PK/PD exposure was associated with favourable patient outcomes. It was not possible to perform any preliminary assessment because of the small sample size and also the variability in the type and schedule of concomitant antibiotic therapy (gentamicin for 1 to 3 days; or vancomycin). In addition 4 out of 12 patients did not complete cefepime therapy due to persisting fever. Even though this observation does not allow any conclusion (small sample size) a recent study also reported clinical failure with cefepime therapy despite achievement of 100 % $fT > \text{MIC}$ (44). In addition to this, a previous study has challenged the ability of existing cefepime breakpoints to predict clinical outcomes (45). Taken altogether, there seems to be accumulating evidence suggesting a need for critical re-evaluation of PK/PD properties of cefepime to confirm if the current dosing targets correlate with optimal clinical outcomes.

**CONCLUSIONS**

A high dose cefepime regimen (2g IV 8-hourly) appears to provide appropriate antibiotic exposure in febrile neutropenic patients with normal renal function given the MIC of anticipated organisms is $\leq 4 \text{mg/L}$. However, based on current PK/PD recommendations, it may frequently fail to achieve maximum targets against higher MIC Gram negative organisms. Plasma concentrations are highly variable among patients, suggesting that, in the absence of well defined therapeutic range and common toxicity/treatment-failure concerns, monitoring cefepime concentration would be advantageous to support rational clinical decisions. The correlation of
current PK/PD recommendations with favourable patient outcomes deserves ongoing thorough clinical investigation.
ACKNOWLEDGMENT

Jason Roberts is funded by a Career Development Fellowship from the National Health and Medical Research Council of Australia (APP1048652).

We acknowledge the support from the clinical staff of the Department of Haematology, and Cancer Clinical Trials, The Queen Elizabeth Hospital, Adelaide, South Australia.

We declare no competing interests.
REFERENCE


Nonconvulsive status epilepticus due to cefepime in a patient with normal renal function. Epilepsy Behav 8:312-314.


Table 1. Characteristics of study participants

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Weight (Kg)</th>
<th>BMI (kg/m²)</th>
<th>Hematological malignancy</th>
<th>CrCL (ml/min/1.73m²) Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Serum albumin value (g/L) Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Blood culture result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>54</td>
<td>75</td>
<td>21.3</td>
<td>Hodgkin’s Lymphoma</td>
<td>87</td>
<td>79</td>
<td>70</td>
<td>23</td>
<td>24</td>
<td>27</td>
<td>Staphylococcus spp</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>79</td>
<td>86</td>
<td>28.9</td>
<td>Diffuse large B-cell lymphoma</td>
<td>89</td>
<td>68</td>
<td>72</td>
<td>31</td>
<td>30</td>
<td>32</td>
<td>Bacillus spp</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>52</td>
<td>96</td>
<td>27.7</td>
<td>Acute myeloid leukaemia</td>
<td>66</td>
<td>74</td>
<td>81</td>
<td>30</td>
<td>28</td>
<td>30</td>
<td>Klebsiella pneumoniae</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>59</td>
<td>67</td>
<td>23.5</td>
<td>Follicular lymphoma</td>
<td>88</td>
<td>73</td>
<td>68</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>Enterococcus faecium</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>76</td>
<td>64</td>
<td>23.8</td>
<td>Acute myeloid leukaemia</td>
<td>61</td>
<td>61</td>
<td>66</td>
<td>25</td>
<td>26</td>
<td>28</td>
<td>Negative</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>50</td>
<td>75</td>
<td>25.4</td>
<td>Diffuse large B-cell lymphoma</td>
<td>64</td>
<td>55</td>
<td>55</td>
<td>29</td>
<td>31</td>
<td>29</td>
<td>Negative</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>56</td>
<td>88</td>
<td>23.6</td>
<td>Mantle cell lymphoma</td>
<td>72</td>
<td>72</td>
<td>81</td>
<td>30</td>
<td>28</td>
<td>30</td>
<td>Bacillus spp</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>57</td>
<td>77</td>
<td>25.7</td>
<td>Multiple myeloma</td>
<td>72</td>
<td>63</td>
<td>72</td>
<td>32</td>
<td>29</td>
<td>31</td>
<td>Negative</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>66</td>
<td>86</td>
<td>29.8</td>
<td>Multiple myeloma</td>
<td>69</td>
<td>69</td>
<td>60</td>
<td>29</td>
<td>27</td>
<td>31</td>
<td>Negative</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>39</td>
<td>184</td>
<td>46.9</td>
<td>Diffuse large B-cell lymphoma</td>
<td>65</td>
<td>65</td>
<td>65</td>
<td>30</td>
<td>31</td>
<td>32</td>
<td>Negative</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>68</td>
<td>101</td>
<td>33.7</td>
<td>Anaplastic large cell lymphoma</td>
<td>75</td>
<td>83</td>
<td>83</td>
<td>29</td>
<td>24</td>
<td>24</td>
<td>Negative</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>40</td>
<td>73</td>
<td>29.4</td>
<td>Acute myeloid leukaemia</td>
<td>106</td>
<td>101</td>
<td>101</td>
<td>27</td>
<td>27</td>
<td>27</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Median 57 82 26.7 72 70 70 29 29 30
Interquartile range 52-67 74.5-90 23.8-29.5 66-88 65-75 66-77 28-30 27-30 28-32

BMI, Body mass index; CrCL, creatinine clearance (Cockcroft-Gault)
Table 2. Non-compartmental pharmacokinetic parameter estimates of cefepime from twelve febrile neutropenic patients with hematological malignancies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Mean</th>
<th>Median</th>
<th>Interquartile range</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{ss}$</td>
<td>litres (L/kg)</td>
<td>33.4</td>
<td>34</td>
<td>24.8 - 42.7</td>
</tr>
<tr>
<td>CL</td>
<td>litres/h</td>
<td>8.6</td>
<td>8.7</td>
<td>6.8 - 10.8</td>
</tr>
<tr>
<td>$t_{1/2}$</td>
<td>h</td>
<td>2.7</td>
<td>2.5</td>
<td>2.4 - 3.0</td>
</tr>
<tr>
<td>MRT</td>
<td>h</td>
<td>3.9</td>
<td>3.6</td>
<td>3.5 - 4.4</td>
</tr>
<tr>
<td>$AUC_{0\text{-}inf}$</td>
<td>mg/litres.h</td>
<td>269</td>
<td>232</td>
<td>186 - 294</td>
</tr>
<tr>
<td>$K_{el}$</td>
<td>1/h</td>
<td>0.3</td>
<td>0.3</td>
<td>0.2 - 0.3</td>
</tr>
</tbody>
</table>

$V_{ss}$, volume of distribution at steady state; CL, total clearance; $t_{1/2}$, half-life; MRT, mean residence time; $AUC_{0\text{-}inf}$, area under the concentration versus time curve from time zero to infinity; $K_{el}$, terminal elimination rate constant
List of figures

Figure 1. Box-and-whisker plot of unbound cefepime plasma concentrations at 60% of the third and sixth dosing interval in febrile neutropenic patients with hematological malignancy receiving 2g IV 8-hourly dosing. The whiskers extend to 1.5 times the interquartile range from Q1 or Q3, or the highest/lowest point within the range. Outlier points are those that are away from the interquartile range by greater than 1.5 times from Q1 or Q3.

Figure 2. Unbound cefepime plasma concentrations from trough samples in the third, sixth and ninth dosing interval in patients with neutropenic fever and hematological malignancy receiving 2g IV 8-hourly dosing. MIC, minimum inhibitory concentration.

Figure 3. Box-and-whisker plot of proportions of the dosing interval that the free cefepime concentration remained above the minimum inhibitory concentration of 8 mg/L in twelve febrile neutropenic patients with hematological malignancy receiving 2g IV 8-hourly dosing. The whiskers extend to 1.5 times the interquartile range from Q1 or Q3, or the highest/lowest point within the range.
Figure 1. Box-and-whisker plot of unbound cefepime plasma concentrations at 60% of the third and sixth dosing interval in febrile neutropenic patients with hematological malignancy receiving 2g IV 8-hourly dosing.

The whiskers extend to 1.5 times the interquartile range from Q1 or Q3, or the highest/lowest point within the range. Outlier points are those that are away from the interquartile range by greater than 1.5 times from Q1 or Q3.
Figure 2. Unbound cefepime plasma concentrations from trough samples in the third, sixth and ninth dosing interval in patients with neutropenic fever and hematological malignancy receiving 2g IV 8-hourly dosing.

MIC, minimum inhibitory concentration.
Figure 3. Box-and-whisker plot of proportions of the dosing interval that the free cefepime concentration remained above the minimum inhibitory concentration of 8 mg/L in twelve febrile neutropenic patients with hematological malignancy receiving 2g IV 8-hourly dosing. The whiskers extend to 1.5 times the interquartile range from Q1 or Q3, or the highest/lowest point within the range.