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MEROPENEM VERSUS CEFTAZIDIME PLUS AMIKACIN IN THE TREATMENT OF FEBRILE EPISODES IN NEUTROPENIC PATIENTS: A RANDOMIZED STUDY

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ABSTRACT

Background and Objective. Meropenem is the first of a new class of carbapenems which may be administered without cilastatin. This study was performed to assess the clinical efficacy and tolerability of meropenem monotherapy (1 g/8 h) compared with the standard combination of ceftazidime (2 g/8 h) plus amikacin (15 mg/kg/day) for the empirical treatment of infective febrile episodes in neutropenic cancer patients.

Methods. This was a three-center, randomized, non-blind parallel group trial. The primary objective was to compare the clinical efficacy of meropenem monotherapy with that of ceftazidime plus amikacin in the empirical treatment of febrile infective episodes in neutropenic patients. This was evaluated by the number of patients surviving on unmodified therapy at 72 h (primary end point) and by the clinical response at the end of therapy (secondary end point).

Results. A total of 93 febrile episodes (46 meropenem, 47 ceftazidime/amikacin) were evaluable. Bone marrow transplant patients accounted for 49.5% of all cases. There was a high incidence of Gram-positive infections but no pseudomonal infections. Microbiologically documented infections, clinically documented infections and unexplained fever accounted for 45%, 10% and 45% of episodes, respectively. There was a similar proportion of patients in the meropenem and ceftazidime/amikacin groups on unmodified empiric therapy at 72 h (80.4% vs 76.6%, p=0.65,) and cured at the end of therapy (37% vs 36.2%, p=0.9). No significant difference in tolerability was observed between the groups. Meropenem was well tolerated; of note, there were no cases of nausea/vomiting or seizure related to its use.

Interpretation and conclusions. Meropenem monotherapy was well tolerated and produced response rates similar to those obtained with ceftazidime/amikacin. The low overall success rates with both treatments concur with those of other recent studies and are probably due to a combination of several factors, including the adoption of strict assessment criteria.

Key words: Meropenem, ceftazidime, amikacin, neutropenia

The routine use of empirical broad-spectrum antibacterial combinations in the management of febrile neutropenia is a well-established practice which has steadily decreased early mortality from infection since the first studies were performed almost three decades ago.[1-3] The most commonly used antibacterial regimens comprise a β-lactam plus an aminoglycoside;[4,5] for example the combination of ceftazidime plus amikacin is presently considered by many to be the standard.

Improvements in the antimicrobial armamentarium have allowed the use of empirical monotherapy with agents which exhibit very wide antimicrobial spectra and good tolerability.[6,7] Third-generation cephalosporins and carbapenems have been the drugs employed for this purpose. Ceftazidime has been used extensively in this role and has been shown to be as efficacious as β-lactam/aminoglycoside combination regimens in the treatment of febrile neutropenic patients.[8,9] Imipenem/cilastatin was the first carbapenem to become commercially available. Used as monotherapy, it has proven as effective as several combination regimens[10] and ceftazidime monotherapy[11] in this setting. However, imipenem has certain metabolic and toxic disadvantages. It is metabolized by renal dehydropeptidases and its degradation products are potentially nephrotoxic.[12] In order to overcome this, it is necessary to co-administer imipenem with cilastatin, a specific dehydropeptidase I (DHP-I) inhibitor.

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Some studies have reported a relatively high incidence of nausea and vomiting with imipenem/cilastatin in neutropenic patients (up to 30%)[10,11,13] which contrasts with that reported in non-neutropenic patients (nausea 2.4%, vomiting 1.2%).[14] Also, imipenem/cilastatin produces seizures in a significant percentage of susceptible patients,[15] precluding its use in the treatment of meningitis and requiring caution in patients with renal and/or central nervous system (CNS) diseases.

Meropenem is the first of a new class of carbapenems which, because of their relative stability to renal DHP-I, may be administered without cilastatin.[16,17] Meropenem possesses several other potential advantages over imipenem/cilastatin, such as improved activity against *Enterobacteriaceae*, *Haemophilus influenzae*, *Moraxella spp.*, *Neisseria spp.*, and most *Pseudomonas spp.*[18] and the flexibility of intravenous (IV) bolus administration. Furthermore, meropenem is well tolerated by the CNS and by the gastrointestinal system with regard to nausea and vomiting,[19] even in neutropenic patients.[20]

Therefore, meropenem would be expected to be an appropriate choice for empirical monotherapy of febrile neutropenic patients. Indeed, when this study was planned, preliminary data from a study involving 221 neutropenic patients (published subsequently[21]) showed meropenem to be as effective and as well tolerated as ceftazidime monotherapy. We undertook a multicenter, non-blind randomized study in cancer patients to compare the clinical efficacy of meropenem monotherapy with that of the combination of ceftazidime plus amikacin in this setting.

Patients and Methods

Participating centers and patient eligibility

Adult patients (≥16 years) with cancer admitted to the Hematology Department Inpatient Units of three Spanish University Hospitals were eligible for the study if they had neutropenia of <500 neutrophils/mm^3, serious fever (defined as a temperature of ≥ 38.5°C on one occasion, or two fevers of ≥ 38°C more than 30 min apart within a 12h-period) and had received no previous antibiotic treatment for at least 3 days before randomization (except selective intestinal decontamination which was discontinued before study therapy was started). Pathogens known at the time of entry had to be sensitive to both meropenem and either ceftazidime or amikacin. Written or verbal witnessed and informed consent was obtained prior to the administration of the study antibiotics. At the initiation of this trial, patients could re-enter the protocol if fever occurred in a different neutropenic episode and they had not received antibiotics for at least 7 days. Subsequently, after the inclusion of several cases, it was decided that re-entries should be excluded from the efficacy evaluation in order to preserve the validity of the statistical assumptions. Re-entries were, however, evaluated in the safety analysis.

Patients who were pregnant or breast-feeding, were allergic to any of the trial antibiotics or who had undergone allogenic bone marrow transplant (autologous transplants were allowed) were not eligible for inclusion. Also, patients who had a past history of seizures, CNS localized leukemia or cystic fibrosis or who were in hepatic failure or coma were excluded, as were those concurrently receiving any other investigational drug.

Study design, end points and sample size

This was a three-center, randomized, non-blind parallel group trial. The primary objective was to compare the clinical efficacy of meropenem monotherapy with that of ceftazidime plus amikacin in the empirical treatment of febrile infective episodes in neutropenic patients. This was evaluated by the number of patients surviving on unmodified therapy at 72 hours (primary end point) and by the clinical response at the end of therapy (secondary end point). Evaluation of the number of patients on unmodified therapy at 72 hours demonstrated whether meropenem can safely be given alone during this period when antibiotics are utilized in a truly empirical manner (i.e. before the causative organisms have been identified). Other secondary end points were the safety and tolerability of both treatments, assessed by the incidence of clinical adverse events and alteration of hematological and biochemical variables, and the necessity for treatment modification due to non-response of the infection to the initial therapy.

Assuming an evaluability rate of 95% and a satisfactory response rate of 85% in the ceftazidime/amikacin group, it was calculated that 50 patients per treatment group would be sufficient to detect a 25% lower response rate with meropenem (power = 72%, significance = 5%). Assuming these response rates, 50 patients per group would give an approximate 95% confidence interval (CI) for the difference between the treatments of 25±17%.

Antibiotic treatment

Patients were randomly allocated to one of the treatment arms using consecutive computer-generated sealed envelopes. Randomization was stratified by center. Meropenem was provided in glass vials containing 500 mg and was administered at a dosage of 1 g/8 h. The antibiotic was reconstituted in 10 mL of water and then diluted up to 100 mL with 0.9% saline solution and infused intravenously over 20-30 min. Ceftazidime (Kefamin®) was administered following the manufacturer's recommendations at a dosage of 2 g/8 h. Amikacin (Amikacina Normon®) was administered at a dosage of

15 mg/kg/day, given either in two or three separate doses. It was recommended that amikacin dosages be adjusted according to serum concentrations as indicated by the manufacturer. Dosages were adjusted in patients with renal insufficiency according to the manufacturers' recommendations for ceftazidime and amikacin and, as previously published,[19] for meropenem. The minimum recommended duration of therapy was 7 days and the maximum was 28 days. In order for study treatment to be stopped, the patient had to be afebrile for at least 4 days and have a neutrophil count of > 500 cells/mm^3. In the event of non-response to the study treatment, other antimicrobials could be added if clinically indicated. Any previously prescribed antibacterials (including those for prophylactic selective gut decontamination) were stopped prior to randomization.

Assessment criteria

All isolated bacteria were tested for antibiotic susceptibility by using the zone diameter interpretative standards and equivalent minimum inhibitory concentrations (MICs) recommended by the *National Committee for Clinical Laboratory Standards*:[22] breakpoints for resistance were an inhibitory zone diameter of ≥14 mm for ceftazidime and amikacin, and ≥ 10 mm for meropenem. Disks for meropenem were supplied by Zeneca Pharmaceuticals with 10 μg of antibiotic per disk. Commercial disks were used for ceftazidime and amikacin.

Bacteremia was defined as fever with at least one positive pre-therapy blood culture, with or without other symptoms of systemic infection. Two positive pre-therapy blood cultures were required for coagulase-negative staphylococci or coryneforms.

Primary febrile episodes were classified as either microbiologically documented infections (with or without bacteremia), clinically documented infections, unexplained fever, or unevaluable (if the patient was not neutropenic, not febrile, exhibited non-infectious fever e.g. due to transfusion or underlying disease, received concomitant antibiotics at entry or violated other entry criteria).

Each febrile neutropenic episode was clinically assessed and classified as a cure if the signs and symptoms of the infection were resolved without any change to the allocated antibacterial therapy, and without recurrence thereafter. Failures were classified as unchanged/worse (no improvement or deterioration of signs and symptoms of the infection) and cure with modification (complete remission of local and systemic signs and symptoms of infection following the addition of another antibacterial). If any additional antibiotic was given before 72h, the response was always classified as unchanged/worse. The addition of an antibacterial or antifungal agent was considered as failure if the patient had an unexplained fever. In cases of microbiogically or clinically proven infection, the addition of antifungal agents did not constitute failure of the study regimen.

Deaths due to infection were classified as treatment failures unless the patient received only one or two doses of the study antibiotic. For the efficacy evaluation a patient was evaluated as a cure (as described above) or as a failure, which included death due to the primary infection, unchanged/worse and cure with modification.

Tolerability

Appropriate hematological and biochemical tests were performed at least once before the beginning of the study antibiotic treatment, once during therapy or as clinically indicated, and within 24 h after the end of treatment. All adverse events were recorded with a description of the event, severity, duration, any action taken, outcome and the investigator's assessment of the relationship to study medication. All treated patients have been included in the summary of adverse events.

Statistical analysis

Statistical analyses were performed using the SAS statistical program (SAS Institute Inc., Cary, Nc, USA). Demographic characteristics were compared to confirm homogeneity. The primary end point was the number of patients remaining on unmodified randomized treatment at 72 h; the principal secondary endpoint was the clinical response at the end of study therapy.

For each of these end points, the differences in proportion of success between the treatment arms were estimated together with 95% confidence intervals, calculated using a normal approximation (without correction of continuity), and statistical significance determined by using Chi-squared Pearson tests (without correction of continuity). Any differences in the response levels in the centers were examined and taken into account in the analysis, if appropriate.

Results

Patients and underlying infections

A total of 122 febrile episodes occurring in 102 patients were included in the study. Twenty-nine episodes were considered unevaluable for response due to the following reasons (number of meropenem and ceftazidime/amikacin patients, respectively): re-entries, 20 (11 vs 9); no fever, 2 (1 vs 1); no neutropenia, 2 (2 vs 0); concomitant non-protocol antibiotics at randomization, 2 (1 vs 1); less than 6 doses of protocol antibiotic, 2 (2 vs 0); study drugs underdosed, 1 (0 vs 1). Therefore, 93 febrile episodes corresponding to 93 patients (91% of patients) were evaluable; of these patients, 46 received meropenem and 47 received ceftazi-

Table 1. Patient demographic characteristics.

	Meropenem	*Ceftazidime + Amikacin*
No. of patients	46	47
Age*	42.2 (17-71)	41.6 (16-66)
Sex (male/female)	22/24	27/20
Underlying disease		
Acute leukemia	19	21
Lymphoma	14	15
Multiple myeloma	8	7
Breast cancer	2	4
Other°	3	0
Bone marrow transplant	22 (47.8%)	24 (51.1%)
Acute leukemia	9	6
Lymphoma	9	8
Multiple myeloma	2	6
Breast cancer	2	4
Oral antibacterial prophylaxis	31 (67.4%)	31 (65.9%)
Quinolones	18	21
Trimethoprim/sulfamethoxazole	13	10
Central line	44 (95.6%)	46 (97.8%)
Prior to therapy	44	43
After therapy initiation	0	3
Parenteral nutrition	17 (36.9%)	19 (40.4%)
Prior to therapy	15	11
After therapy initiation	2	8
Duration of neutropenia (days)* (since antibiotic treatment began)	12 (4-42)	10 (3-55)
G-CSF use	5 (10.9%)	2 (4.3%)
At randomization	2	2
After randomization	3	0

**Median (range). °Others were: RAEB, RAEB-T, plasmatic cell leukemia. Abbreviations: G-CSF = granulocyte colony stimulating factor; RAEB = refactory anemia with excess blasts; RAEB-T = RAEB in transformation.*

Table 2. Classification of febrile episodes.

	Meropenem (n=46)	*Ceftazidime + Amikacin (n=47)*
Bacteriologically documented	23 (50.0%)	19 (40.4%)
Bacteremic	22	19
Non-bacteremic	1	0
Clinically documented	5 (10.9%)	4 (8.5%)
Unexplained fever	18 (39.1%)	24 (51.1%)

dime/amikacin. The characteristics of evaluable patients are shown in Table 1. It is noteworthy that 76% of patients presented leukemia or had received a bone marrow transplant (49% were bone marrow transplant patients and 27% were leukemic non-transplant patients).

Table 3. Bacteremia isolated.

	Meropenem	*Ceftazidime + Amikacin*
Gram-positive	18 (78.3%)	15 (78.9%)
Coagulase-negative staphylococci	13	12
Staphylococcus epidermidis	12	8
Staphylococcus hominis	0	2
Staphylococcus hemolyticus	0	1
Staphylococcus capitis	0	1
Staphylococcus warneri	1	0
Streptococci	2	3
Streptococcus faecalis	1	2
Streptococcus sanguis	1	0
Streptococcus pneumoniae	0	1
Other Gram-positive	2	0
Listeria monocytogenes	1	0
*Polymicrobial**	1	0
Gram-negative	5 (21.7%)	4 (21.1%)
Escherichia coli	3	2
Acinetobacter lwoffi	1	0
Capnocytophaga	0	1
Alcaligenes xyloxidans	0	1
Gram-negative rods, NOS	1	0
Total	23	19

*NOS = not otherwise specified. *S. epidermidis + viridans streptococci (NOS).*

The type of infections observed were: microbiologically documented infections with or without bacteremia in 42 patients (45%); clinically documented infections in 9 patients (10%); unexplained fever in 42 patients (45%), with a similar distribution between both treatment groups (Table 2). The majority of the microbiologically documented infections were bacteremias without a clinical focus. Of the bacteremias, 32/41 (78.0%) were caused by Gram-positive bacteria and 9/41 (22.0%) by Gram-negative bacteria (Table 3). Of the Gram-positive bacteremias, 78.1% were due to coagulase-negative staphylococci.

There were 33 Gram-positive and ten Gram-negative isolates. Respective percentages susceptible to meropenem, ceftazidime and amikacin were: 50%, 38.7%, 45.1% for all Gram-positive bacteria; 44%, 36% and 52% for coagulase-negative staphylococci; and 90%, 90% and 70% for Gram-negative bacteria.

Efficacy

Analysis of treatment modification at 72 h was the primary end point and there were no significant differences between the treatment groups in this regard, with 80.4% vs 76.6% of the evaluable meropenem and ceftazidime/amikacin recipients, respectively, remaining on unmodified therapy (p=0.65; 95% CI -12.8 to 20.5%).

Table 4. Clinical response in evaluable patients.

	Meropenem (n=46)	*Ceftazidime + Amikacin (n=47)*
Cure	17 (37.0%)	17 (36.2%)
Failure		
Cure with modification	24 (52.2%)	16 (34.0%)
No change/worse	5 (10.9%)	14 (29.8%)

Similarly, an intent-to-treat analysis of all episodes (including re-entries) found no difference between meropenem (57 episodes) and ceftazidime/amikacin (55 episodes) [76.5% vs 76.5%; p > 0.99].

The clinical responses at the end of therapy are shown in Table 4. The proportions with a satisfactory response at the end of therapy were similar in the two groups: 37.0% in the meropenem group vs 36.2% in the ceftazidime group (p=0.9; 95% CI -18.8 to 20.4%). Overall, at the end of therapy, more patients were cured/improved with or without the use of additional antibacterials in the meropenem group than in the ceftazidime/amikacin group (89.1% vs 70.2%).

The type of antimicrobial most frequently added to the protocol regimens was a glycopeptide, which was added in 25 cases (54.3%) in the meropenem group and in 20 cases (42.5%) in the ceftazidime/amikacin group. The addition of other antimicrobials or antifungals was less common (used in 6% and 4% of all cases, respectively).

The cure rates in patients with bacteremia (with meropenem and ceftazidime/amikacin, respectively) were 36.4% vs 26.3% (p = 0.49) at the end of therapy. In patients with unexplained fever, the respective rates were 50% vs 41.7% (p=0.59). The number of patients with clinically documented infections was too small to merit an analysis.

The rate of defervescence and the time on unmodified therapy, plotted by the Kaplan-Meier method and compared by the log-rank test, showed no difference between the treatment groups.

Tolerability

All 122 febrile episodes, irrespective of whether or not they were evaluable for efficacy, were included in the tolerability analysis. Overall, regardless of the investigators' assessment of a causal relationship to study therapy, there were 28 (44.4%) patients with 54 adverse events in the meropenem group and 23 (39.0%) patients with 53 adverse events in the ceftazidime/amikacin group.

Table 5. Drug-related adverse events*.

	Meropenem (n=62 episodes)	*Ceftazidime + Amikacin (n=60 episodes)*
Erythema multiforme	1°	0
Alkaline phosphatase increase	2	0
SGOT/SGPT increase	1	0
Renal function alteration	0	1°
Rash	0	1
Deafness	0	1
Tinnitus	0	1

**Some patients had more than one adverse event. °Adverse events that led to withdrawal of the study antibiotic.*
Abbreviations: SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamate pyruvate transaminase.

Three patients in each treatment group experienced one or more adverse event that was judged to be related to study therapy (Table 5). In one case in each group the investigator considered it necessary to stop study treatment. In each case the patients completely recovered from the adverse event. It is notable that there were no reports of nausea, vomiting or seizures related to study treatment in either group; likewise, no serious drug-related adverse effects were reported.

Serious adverse events considered to be unrelated to the study antibiotics were observed in 14 patients: four meropenem recipients with four serious adverse events (sclerosing cholangitis, lung hemorrhage, severe organic psychosis, and a congestive heart failure related to anthracycline use) and 10 ceftazidime/amikacin recipients with 12 serious adverse events (thrombosis related to a central intravascular line, invasive pulmonary aspergillosis, digestive system hemorrhage, dyspnea, pneumonia, cerebral hemorrhage, esophagitis, mucous membrane disorder, renal failure, two lymphoma-like reactions and a severe hemorrhagic cystitis related to viral infection).

There were no differences between treatment groups in relation to changes in hematological and biochemical values. Three patients had creatinine clearance values of < 51 mL/min (38.2-50.6 mL/min) at randomization and none had a deterioration of their renal function during the study treatment.

A total of four patients died (one in the meropenem and three in the ceftazidime/amikacin group), of whom three died during the study and one died in the month following the end of therapy. Three of these patients were evaluable and one was unevaluable (due to re-entry). No patient died during the first 4 days of treatment; the earliest death occurred on day 8.

In one case in each treatment group, the primary infectious episode was considered as being a contributory cause of death. Of these, the patient in the meropenem group had septicemia due to a *Staphylococcus epidermidis* that did not respond to the protocol antibiotic. Eight days after starting treatment, the patient died as a result of pulmonary hemorrhage. The patient in the ceftazidime/amikacin group also had septicemia due to *S. epidermidis* and gastroenteritis that was cured, with modification, at the end of therapy, but at day 15 a fatal bilateral pneumonia developed that was not microbiologically documented. The other two causes of death were a disseminated fungal superinfection and the progression of a refractory lymphoma.

Discussion

The results of this study show that monotherapy with meropenem appears to be as clinically effective as the combination of ceftazidime/amikacin in the empirical treatment of febrile episodes in neutropenic patients with cancer. The proportion of patients on unmodified therapy at 72h and cured at the end of therapy was similar in both groups. This indicates that meropenem can safely be given alone as empirical therapy for the first 72h, before the causative organisms have been identified. Similarly, there were no differences between the two groups in the rate of defervescence, the time on unmodified therapy, or the response of patients with bacteremia or fever of unknown origin. Additions to the protocol drugs were comparable in the meropenem and ceftazidime/amikacin groups, with glycopeptides being the most frequently added antimicrobials. The mortality rate was 3.9%; only two deaths were related to the primary infectious episode and no deaths occurred in the first 7 days of treatment. With respect to tolerability (including nephrotoxicity), no significant differences were observed between treatment groups. Meropenem was well-tolerated and there were no cases of nausea/vomiting or seizures related to its use.

These findings differ from those reported with imipenem/cilastatin, the most frequently used carbapenem.

Some studies of imipenem/cilastatin in neutropenic patients have reported an incidence of nausea/vomiting of 10-30%,[10,11,13] and in one study this necessitated discontinuation of the drug in 10% of recipients.[11] In addition, imipenem/cilastatin is associated with a relatively high incidence of seizures, which may be up to 20% in patients with impaired renal function and/or underlying CNS disease,[15] and has reached 10% in neutropenic patients without these risk factors (when a dose of 4 g/day was used).[10]

In our study, relatively low success rates were observed with both treatments. For instance, the cure rate obtained with ceftazidime/amikacin (36%) was much lower than those obtained with this regimen in studies published between 1987-93 (71%, 63%, and 74%).[4,5,23] This may be explained by the differences between our patients and neutropenic patients in other studies. In our study, a considerable proportion of patients had undergone bone marrow transplant (49.5%); almost all patients (97%) had central venous catheters; nearly 40% were receiving parenteral nutrition, and 66% had received prophylactic trimethoprim/sulfamethoxazole or quinolones. Also, the distribution of the type of infection was different in our study compared to other studies; we observed a similar proportion of unexplained fever (45%), but a lower proportion of clinically documented infection (10% vs reported incidence of 25-30%) and a higher incidence of bacteriologically documented infections (45% vs reported incidence of 25-37%). Most previous studies have reported a lower response rate for bacteriologically documented infections and usually for clinically documented infections, compared with unexplained fevers. In this study, 78% of bacteremic episodes were caused by Gram-positive bacteria, of which 78% were coagulase-negative staphylococci. Approximately 60% of the coagulase-negative staphylococci isolated were resistant to the protocol antibiotics. The universal use of central venous catheters and the frequent use of antibiotic prophylaxis may explain this high incidence of Gram-positive infections in general, and coagulase-negative staphylococci in particular. However, the three most recent studies of ceftazidime/amikacin reported relatively low response rates of 32%, 52% and 54%,[20,24,25] which are similar to our results, probably because of a combination of the factors previously suggested.

Two other trials have investigated meropenem monotherapy in the empiric treatment of febrile neutropenia.

In a large *European Organization for Research and Treatment of Cancer* (EORTC) study involving 958 evaluable cancer patients in which meropenem was compared with ceftazidime/amikacin, meropenem monotherapy was as effective as the combination therapy.[20] A significantly lower incidence of nephrotoxicity and ototoxicity (taken together) was observed in meropenem recipients compared with ceftazidime/amikacin-treated patients. Our success rates with meropenem monotherapy in the whole group (37%), in Gram-positive bacteremic episodes (23.5%), and in patients with fever of unknown origin (50%) are lower than those observed in the EORTC study (56%, 31% and 66%, respectively).[20] However, the EORTC trial involved a lower proportion of bone marrow transplant patients, microbiologically documented infections, and Gram-positive bacteremias. In another randomized study, the suc-

cess rate with meropenem was 44% (67/153 episodes) vs 41% (63/151 episodes) with ceftazidime monotherapy.[21]

The high incidence of Gram-positive infection observed in our study is in line with what is now occurring in most centers, where approximately 70% of bacteremias are caused by Gram-positive bacteria.[26] For example, in the two most recent studies performed by the EORTC, 67% and 69% of single-organism bacteremic episodes were caused by Gram-positive bacteria.[20,24] We observed only one case of pseudomonal infection (in an unevaluable patient), which reflects the low and decreasing incidence of infection with this bacteria in neutropenic patients today (1.4% and 0.8% in the EORTC studies[20,24]). Nonetheless, the risk of life-threatening infection with *Pseudomonas* remains a cause for concern and empirical antibiotic therapy should still provide antipseudomonal coverage.

Compared with β-lactam/aminoglycoside combination regimens, monotherapy with an agent such as meropenem may be associated with a number of potential benefits, including more convenient administration and a lower risk of nephrotoxicity and ototoxicity. A potential problem with all other monotherapies may be the emergence of resistant organisms, especially *P. aeruginosa*. However, this was not a problem in this or other published studies with meropenem monotherapy in neutropenic patients. It has been suggested that the development of resistance may be avoided by using a combination regimen (e.g. β-lactam plus aminoglycoside). However, at least in non-neutropenic patients, the addition of an aminoglycoside to imipenem/cilastatin did not prevent the emergence of resistant *P. aeruginosa* compared with imipenem/cilastatin alone.[27] Therefore, in neutropenic patients, it has yet to be shown that a combination of meropenem with an aminoglycoside will reduce the emergence of resistant pathogens compared with monotherapy. Until such information becomes available, the empirical addition of an aminoglycoside appears unnecessary.

In summary, we and other clinicians have observed a significant change in the microbiology of infections in neutropenic cancer patients, namely a high incidence of Gram-positive infection and a dramatic decrease in infections caused by *P. aeruginosa* (with fungal infections representing a major problem in particular settings[28]). This study shows monotherapy with meropenem to be as clinically effective as the combination of ceftazidime plus amikacin in the empirical treatment of febrile episodes in such patients. The relatively low success rates achieved reflect other recent studies in similar populations and are probably due to a combination of factors. In our opinion, however, they do not merit the empirical use of glycopeptides, and the use of meropenem monotherapy in these high-risk patients is justified.

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